II International Conference on Cancer Research and Targeted Therapy

October 26-28, 2017

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II International Conference on
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Committee Members

Wlodek Lopacynski  
Bethesda  
MD, USA

Myron R Szewczuk  
Queen's University, Kingston  
Ontario, Canada

Chellappan Srikumar  
Moffitt Cancer Center & Research Institute, USA

Appu Rathinavelu  
Rumbaugh Goodwin Institute for Cancer Research, FL, USA

Simon C. Robson  
Dana-Farber Harvard Cancer Center, MA, USA

Mousa Shaker  
Albany College of Pharmacy and Health Sciences, NY, USA

Anupam Bishayee  
Larkin University  
FL, USA

Sudhakar Yakkanti  
Former Associate Director, Center for Cancer Metabolism, SRI, CA, USA
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The Cancer Cell

- Cancer Metabolism
- Cancer Metastasis
- Cancer Stem Cell Biology
- Cell Signal Transduction in Development and Cancer
- Molecular Oncology

Cancer Immunology

- Checkpoint Inhibitors in Treating Cancers
- Monoclonal Antibodies to Treat Cancer
- Cancer Vaccines
- Antitumor Immunity

Cancer Microenvironment

- Tumor Biomarkers
- Tumor Angiogenesis
- Tumor Imaging
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- Cancer Genomics

Organ Specific Cancer

- Gynecological Cancer
- Pediatric Cancer
- Breast Cancer
- Lung Cancer
- Gastric Cancer
- Oral Cancer
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Hypothalamic Hormones: From Neuroendocrinology to Therapy of Cancer and Other Diseases

Andrew V. Schally
Veterans Affairs Medical Center Miami, FL, USA
Dept. of Medicine, Dept. of Pathology, and Sylvester Comprehensive Cancer Center, University of Miami Medical School, FL, USA

Abstract

The discovery, isolation, elucidation of structure, synthesis, and clinical testing of the neuropeptide hypothalamic luteinizing hormone-releasing hormone (LHRH), which regulates reproduction, and of other hypothalamic hormones will be summarized. The synthesis and experimental and clinical testing of agonistic analogs of LHRH will be reviewed focusing on the development of new methods for the treatment of prostate cancer. Subsequent development of antagonistic analogs of LHRH and cytotoxic analogs of LHRH conjugated to doxorubicin will be reviewed, with special emphasis on therapy of prostate cancer. In 1982, we introduced a new hormonal therapy for prostate cancer based of agonists of LH-RH and demonstrated its efficacy in inducing androgen deprivation in men with advanced prostate cancer. Therapy with these agonists of LHRH is still presently the preferred world-wide treatment for men with advanced prostate cancer. Antagonists of Gastrin Releasing Peptide (GRP), which inhibit various tumors, will be also reported.

The synthesis and evaluation of antagonists of growth hormone-releasing hormone (GHRH) for treatment of various cancers will be described. The efficacy of these GHRH antagonists has been demonstrated in models of androgen-independent prostate cancer, pancreatic, colorectal, gastric, renal, and bladder cancer, brain tumors, lung cancer (SCLC and non-SCLC), melanoma and hepatoama. Antitumor effects of GHRH analogs have also been demonstrated in vivo in nude mice bearing human breast cancer, including the triple negative variety, and ovarian and endometrial cancer lines, and recently in human acute myeloid leukemia and papillary thyroid cancer. The pathophysiologic basis underlying the response to GHRH antagonist is explained by the presence of GHRH and GHRH receptors in a variety of tumors. Tumor inhibition produced by these GHRH antagonists is associated with suppression in the expression of VEGF, bFGF, pAKT and EGF-/HER receptor family and interference in PKC and MAPK signaling. We determined that GHRH antagonists, LHRH antagonists, and GRP antagonists inhibit Benign Prostatic Hyperplasia (BPH) in vitro and in vivo and reduce prostate cell volume.

In view of powerful inhibitory action of GHRH antagonists on human cancers, we chose to evaluate the stimulatory and pathophysiologic effects of GHRH agonists. We therefore synthesized new GHRH agonists and tested them. We showed that our earlier GHRH agonists, and new agonists of MR class stimulate cardiac myocytes and accelerate regeneration of the heart in rats and in swine after myocardial infarct. New GHRH agonist MR-409 also stimulated fibroblasts and speeded up wound healing in mice. We demonstrated stimulatory effects of GHRH agonist on pancreatic β-islet cells of rats and diabetic mice before and after transplantation of islets. GHRH agonists exert beneficial effects on diabetes, including an elevation in insulin levels and a lowering of glucose levels. In addition, we are evaluating therapeutic effects of GHRH agonists in eye diseases including diabetic retinopathy. In collaboration, we demonstrated the presence of hypothalamic hormones and their receptors in various structures of the human eye. This may allow the use of peptide analogs for the treatment of eye diseases. Various experimental studies are also continued, on beneficial effects of GHRH antagonists for therapy of Alzheimer’s disease.

The overall program has provided extensive new information on the application of hypothalamic peptide analogs for treatment of cancers and other diseases and conditions for which present therapies are inadequate.
Biography

Dr. Andrew V. Schally, endocrine oncologist, is the discoverer of hypothalamic hormones. For his work in Neuroendocrinology he was awarded the Nobel Prize for Medicine in 1977. Dr. Schally’s discoveries laid the foundation for modern endocrinology. Subsequently he pioneered the application of analogs of hypothalamic hormones for cancer treatment, including the present method for therapy of prostate cancer based on agonists of LHRH. He is VA’s, Miami University’s and the South’s only Nobel Laureate. Today, thousands of cancer patients worldwide are benefiting from Dr. Schally’s work.

Dr. Schally received his training in England and Canada. He became a naturalized citizen of the United States in 1962 and joined the staff of the Veterans Administration Hospital in New Orleans. He was also Professor of Medicine at Tulane University School of Medicine. After hurricane Katrina in August 2005, Dr. Schally was transferred to the VA Medical Center at Miami Florida. He is at present, Chief of the new Endocrine, Polypeptide and Cancer Institute at the VA Medical Center in Miami, Distinguished Medical Research Scientist of the Veterans Affairs Department and Distinguished Miller Professor of Pathology and Professor of Medicine in the Division of Hematology/Oncology at the University of Miami, Miller School of Medicine.

Fluent in several languages, Dr. Schally has 33 awards and 22 honorary degrees to his credit and belongs to more than 40 scientific organizations worldwide. In 1978 he was listed as the most cited author in the field of endocrinology. Since 1978, Dr. Schally has been working intensively on hormone-dependent tumors and developing peptide analogs for cancer treatment. The experience from animal research is rapidly translated to clinical research and patient care. In Miami Dr. Schally is continuing his research on the control of cancer and other diseases, applying his discoveries over the last 30 years.

Dr. Schally is author or co-author of more than 2,500 publications and a recipient of many Honors: including Nobel Prize in Physiology or Medicine, 1977; Membership of US National Academy of Sciences, 1978; Lasker Award, 1975; Borden Award in Medical Research, 1975; Gairdner Award, Mickle Award 1974; and The French “Legion d’Honneur” in 2004.
Contributions of Mitochondrial DNA to Metastatic Efficiency

Danny R. Welch
Department of Cancer Biology and Cancer Center, The University of Kansas Medical Center, KS, USA

Abstract

Mitochondrial Nuclear Exchange (MNX) mice, created by transferring an oocyte nucleus from strain x into an enucleated oocyte from strain y, show that mammary tumor formation and metastasis are regulated by inherited mitochondrial polymorphisms (PMID: 26471915). Since stromal compartments also possess changed mitochondria, we hypothesized that mitochondrial polymorphisms in non-cancer compartments could exert effects on tumor formation or metastasis in addition to genetic (cell autonomous) changes. Syngeneic tumor cells were injected into MNX mice with the same nuclear, and therefore same MHC, background. Experimental metastasis was compared between wild-type and MNX mice (i.e., with same or different mtDNA backgrounds, respectively). E0771 mammary carcinoma and B16-F10 melanoma cells (both syngeneic to C57BL/6J), formed significantly (P<0.01) more lung metastases in C57BL/6J-mtMNX (C3H/HeN). K1735-M2 melanoma cells (syngeneic to C3H/HeN) formed significantly (P<0.05) fewer lung metastases in C3H/HeNmtMNXC57BL/6J. These results have been replicated 3 times using >10 mice per experiment. C57BL/6J mitochondria confer resistance to metastasis in both cell autonomous and non-cell autonomous experiments. Basal metabolic and ROS differences comparing mouse embryonic fibroblasts isolated from wild-type and MNX mice are among mechanisms being explored. Together, our findings highlight the striking influences that mitochondrial haplotypes can exert on tumorigenicity and metastasis via both intrinsic and extrinsic mechanisms. Support: Susan G. Komen for the Cure (SAC11037), Natl Fndn Cancer Res, P30-CA168524.

Biography

Dr. Welch received his Ph.D. from the University of Texas Houston. Following a brief stint in pharma, he rose through the faculty ranks at Penn State and UAB before joining the faculty at the University of Kansas Medical Center as founding chair of the Department of Cancer Biology.

His lab is recognized as discover of 8/30 known metastasis suppressor genes. He is a Komen Scholar and Hall Family Professor of Molecular Medicine; Deputy Editor of Cancer Research and serves on numerous grant and journal review boards. He is also the recipient of numerous mentoring and teaching awards.
Conversion of Androgen Receptor Signaling from a Growth Suppressor in Normal Prostate Epithelial Cells to an Oncogene in Prostate Cancer Cells Involves a Gain of Function in c-Myc Expression and DNA Replication Licensing

John T Isaacs
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, The Johns Hopkins School of Medicine, MD, USA

Abstract


An additional unique gain of oncogenic AR functions in prostate cancer cells involves AR binding to replication complexes (RC) at origin of replication sites in early G1 associated with licensing/restricting DNA for a single round of duplication during S-phase (Litvinov I et al. PNAS 2006; 103: 15085). Castrate resistant prostate cancer (CRPC) cells characteristically increased their nuclear AR level. Thus when CRPC cells are acutely exposed to supraphysiologic androgen, their adaptively increased nuclear AR is over-stabilizes preventing sufficient degradation in mitosis inhibiting DNA re-licensing and thus death in the subsequent cell cycle (Vander Griend D et al. Cell Cycle 2007; 6:647 and Isaacs J et al. Prostate 2012; 72: 1491). These mechanistic results provide a paradigm shifting rationale for bipolar androgen therapy (BAT) in patients progressing on chronic androgen ablation. BAT involves giving sequential cycles alternating between periods of acute supraphysiologic androgen followed by acute ablation to take advantage of vulnerability produced by adaptive auto-regulation and binding of AR to RC in CRPC cells (Schweizer M et al. Sci Transl Med 2015; 7:269ra2).

Biography

Dr. Isaacs has been a faculty member in the Johns Hopkins School of Medicine (JHSOM) since 1980. He is Professor of Oncology, Urology, and Cellular and Molecular Medicine (CMM) in the JHSOM and is a Professor of Chemical and Biomolecular Engineering, The Whiting School of Engineering, The Johns Hopkins University. He has served as member of the Experimental Therapeutics Study Section of NIH, on 11 editorial boards, is the Editor-In-Chief of THE PROSTATE, and has served as a past director of the CMM graduate program in JHSOM. He is a member of the National Academy of Inventors and past President of the Society for Basic Urologic Research (SBUR).

Dr. Isaacs’ long-term goal is to develop effective therapies to decrease the death rates due to cancer, particularly prostate cancer. Presently, a series of agents that his group invented/developed are currently in various phases of clinical testing. These include: (1) the orally active antiangiogenic agent, tasquinimod; (2) the intravenously delivered Prostate Specific Membrane Antigen (PSMA) activated cytotoxic thapsigargin prodrug, G202 as therapy for hepatocellular cancer and metastatic castration resistant prostate cancer; and (3) the intraprostatic injectable Prostate Specific Antigen (PSA) activated pro-aerolysin cytotoxin, PRX302, for the treatment of localized prostate cancer and for Benign Prostatic Hyperplasia.
Estrogens and Inflammation- New Insights into the Increased Risk of ER+ Post-Menopausal Breast Cancer with Obesity

Manuel Picon-Ruiz¹, Cynthia Morata-Tarifa¹, Hyunho Yoon¹, Rehana Qureshi¹, Kibeom Jang¹,², Minsoon Kim¹,², Dorraya El-Ashry¹,³ and Joyce M. Slingerland¹,²,³*

¹Braman Family Breast Cancer Institute, UM Sylvester Comprehensive Cancer Center, FL, USA
²Department of Biochemistry & Molecular Biology, University of Miami Miller School of Medicine, Miami, FL, USA
³Department of Medicine, University of Miami Miller School of Medicine, Miami, FL, USA

Abstract

Obesity increases the risk and adverse prognosis of estrogen receptor-positive (ER+) breast cancers after menopause, but mechanisms thereof are not fully known. In obesity, adipocyte maturation is reduced leading to an increase in immature preadipocytes. Obesity mediates a chronic inflammatory state through NF-κB pathway driven pro-inflammatory cytokine expression. Here, we identified one mechanism whereby obesity contributes to tumor progression. Cancers contain a subset of self-renewing stem cells that mediate treatment resistance and metastasis. We showed prolonged co-culture of breast tissue adipocytes together with breast cancer lines or cultured primary dissociated human breast cancer cells increases secretion of pro-inflammatory cytokines IL6, IL8, CCL2, CCL5 and IP10. Prolonged exposure to fat cells or to each cytokine increased the proportion of both ER+ and ER- breast cancer cells that form mammospheres and express ALDH1 activity in vitro and that can initiate primary tumors and metastasis in vivo. Preadipocyte or cytokine exposures activate Src, and Src family kinase activity induced Sox2, cMyc and Nanog upregulation and miR302b induction. miR302b upregulation is Sox2-dependent, promotes cytokine-driven sphere formation, and in turn, stimulates cMYC and SOX2 expression. Finally, Src was not only activated by preadipocyte or cytokine exposures, it was also required to sustain cytokine induction, since Src inhibitors decreased cytokine production after co-culture. Thus, cancer cell invasion into local fat would establish feed-forward loops to activate Src, maintain pro-inflammatory cytokine production and increase tumor initiating cell abundance, tumor growth and metastasis.

Biography

Dr. Slingerland has a longstanding track record in funded breast cancer research. She founded and directs the Braman Family Breast Cancer Research Institute at UMSCCC. Her work has focused on cell cycle regulation and signal transduction via the TGF-MEK, Src and PI3K pathways. She discovered the cell cycle inhibitor p27, and has contributed to understanding the G1 to S phase transition and how aberrant signal transduction, including Src, MEK, and PI3K pathways, disrupt cell cycle regulators in cancer cells. She has investigated use of targeted therapies with MEK and Src inhibitors to reverse anti estrogen resistance in breast and ovarian cancer and brought these to clinical trials. Recent work has focused on understanding how hierarchies in breast cancer stem cells may contribute to chemo-resistance and may be killed by novel targeting agents.
Epigenetic Approaches in Cancer Risk Assessment and Etiology

Mukesh Verma

Epidemiology and Genetics Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute (NCI), National Institutes of Health (NIH), Medical Center Drive, Rockville, MD, USA

Abstract

Several approaches are applied to identify risk of developing cancer in different ethnic and racial groups. One of the approach is epigenetics that facilitates cancer control throughout the cancer core continuum. To understand current progress and trends in the inclusion of epigenetics in cancer epidemiology, we evaluated the published literature and the National Cancer Institute (NCI) supported research grant awards in this field to identify trends in epigenetics research. We present a summary of the epidemiological studies in NCI’s grant portfolio and in the scientific literature published irrespective of support from NCI. Biomarkers identified in the analysis might be useful in risk prediction of different cancers. Breast cancer was the most frequently studied cancer type in grants and publications. Blood cells and tumor tissue were the most commonly used biospecimens in these studies, although buccal cells, cervical cells, sputum, and stool samples also were used. DNA methylation profiling was the focus of the majority of studies, but several studies also measured microRNA profiles. We illustrate here the current status of epidemiologic studies that are evaluating epigenetic changes in large populations. Some research needs include developing improved strategies for epigenetic data analysis and interpretation; determining the stability of epigenetic marks in repeated biospecimen samples from the same people over time; and studies that examine the relationship between epigenetic marks in germline DNA and tumor DNA. While there are limitations to the broad application of epigenomics to epidemiology research, there are situations where this type of research is appropriate and it should be considered.

Biography

Dr. Mukesh Verma is a Program Director and Chief in the Methods and Technologies Branch (MTB), Epidemiology and Genomics Research Program (EGRP) of the Division of Cancer Control and Population Sciences (DCCPS) at the National Cancer Institute (NCI), National Institutes of Health (NIH) with expertise in implication of epigenome, microbiome, metabolome, and genomic information for risk assessment and understanding disease etiology. He represents NCI in Common Fund Programs on (1) Epigenomics, (2) Metabolomics, and (3) Molecular Transducers of Physical Activity. Before coming to the DCCPS, he was a Program Director in the Division of Cancer Prevention (DCP), NCI, providing direction in the areas of biomarkers, early detection, risk assessment and prevention of cancer, epigenetics, epidemiology, and cancers associated with infectious agents. Since joining the NCI, he has sought to champion the visibility of and investment in cancer epigenetics research both within the Institute and across other federal and non-governmental agencies, and to raise public awareness about controlling cancer. Dr. Mukesh Verma holds a M.Sc. from Pantnagar University and a Ph.D. from Banaras Hindu University. He did postdoctoral research at George Washington University and was a faculty member at Georgetown University Medical Center. He has published 161 research articles and reviews and edited five books in cancer biomarkers, epigenetics and epidemiology field.
Cell Type Based Classification of Breast Cancer
Tan A. Ince
Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, FL, USA

Abstract

Nearly three quarters of breast cancers are estrogen hormone dependent. These patients are initially treated with drugs that block estrogen hormone, such as Tamoxifen. However, between one third to half of these patients eventually become resistant to this treatment. For these patients and those whose tumors are not estrogen dependent to begin with, there are no alternative hormone treatment options. We found that approximately three quarters of estrogen-dependent tumors and two thirds of estrogen-independent tumors express hormone receptors for vitamin D and testosterone receptor.

We studied more than 15,000 normal breast cells and discovered eleven previously undefined normal cell subtypes, which are grouped into four new hormonal differentiation groups (HR 0, 1, 2, 3), which were characterized by vitamin D, androgen and estrogen hormone receptor expression. Next, we examined 3,157 human breast tumors and found that each patients’ tumor could also be grouped into four new hormonal differentiation groups (HR 0, 1, 2, 3), which are characterized by vitamin D, androgen and estrogen hormone receptor expression.

Importantly, the patients with these triple HR-positive tumors (HR3) were up to seven times more likely to survive compared to patients with triple HR-negative tumors (HR0). Compared to many existing genetic/molecular tests with 2-3 fold survival differences, this cell-type based approach can become a powerful new tool in predicting patient outcomes. Moreover, these findings offer the possibility of expanding hormone therapy to patients who are otherwise treated with chemotherapy.

Biography

Dr. Ince is an Associate Professor of Pathology, Director of Tumor Stem Cell Division at the Interdisciplinary Stem Cell Institute, Scientific Director, Live Tumor Culture Core and member of the Braman Family Breast Cancer Institute at the University of Miami Miller School of Medicine.

Smart Active Tumor Targeting Drug Delivery Systems
Myron R. Szewczuk
Queen's University, Kingston, Ontario, Canada

Abstract

Conventional chemotherapies targeting tumor suffer from limitations such as poor aqueous solubility, causing elevated toxicity, lack of selectivity toward cancer cells, and multiple drug resistance against treatments. Here, we engineered “smart” drug carrier systems with three delivery strategies that allow drug carriers to initiate the enhanced permeability and retention (EPR) effects at tumor sites, actively and specifically targeting cancer cells with prolonged circulation time and controlled drug release, and thirdly, stimuli-responsive drug carriers. Firstly, the metronomic therapy of a slow-released oseltamivir phosphate (OP) encapsulated in a biodegradable poly(lactic-co-glycolic acid) (PLGA-OP) cylinder implanted at the tumor site without the need for repeated drug administration impeded tumor neovascularization, growth, and metastasis in heterotopic xenografts of tumors growing in a mouse model of human pancreatic cancer. Secondly, OP-conjugated polymeric micelles prepared by RAFT living radical polymerization specifically targeted and halted tumor growth followed with the cancer cell internalization of the micelle loaded with a cytotoxic chemotherapeutic. Thirdly, a pH-responsive, active targeting delivery system was designed using folic acid functionalized amphiphilic alternating copolymer poly(styrene-alt-maleic anhydride) (FA-DABA-SMA) via a biodegradable linker 2,4-diaminobutyric acid (DABA). This latter study revealed that the novel interactions between the modified FA-DABA-SMA polymers with the cells could lead to enhanced hydrophobic drug delivery efficiency as a probe for cancer chemotherapeutics.

Biography

For the past 35 years, Dr. Szewczuk is Full Professor of Immunology and Medicine, Queen's University, Kingston, Ontario Canada. He received his B.Sc. (Hon) in Chemistry (U. of Guelph), M.Sc. in Biochemistry (Guelph), Ph.D. in Immunochemistry (U. of Windsor) and post-doctoral training with Gregory W. Siskind, M.D. in cellular immunology at Cornell University Medical College, NYC. Dr. Szewczuk's recent research has focused on the role of glycosylation in receptor activation with a particular focus of TOLL-like, nerve growth factor Trk, EGFR and insulin receptors. He has discovered a novel receptor-signaling platform and its targeted translation in multistage tumorgenesis and engineered drug delivery systems.
Clinical Implications of the GALNT14-rs9679162 Genotype Polymorphism – A Therapeutic Outcome Predictor for Multiple Gastrointestinal Cancers

Chau-Ting Yeh
Liver Research Center, Chang Gung Memorial Hospital, Taoyuan, Taiwan

Abstract

A recent GWAS study, aiming at identification of SNP markers capable of predicting chemotherapy responses in advanced Hepatocellular Carcinoma (HCC) patients, has accidentally discovered and SNP that can predict therapeutic outcomes of multiple gastrointestinal cancers. The SNP, Rs9679162, is located in the intron of the N-Acetylgalactosaminyltransferase 14 (GALNT14) Gene. To date, this SNP has been found to associate with clinical outcomes of advanced HCC patients receiving chemotherapy (5FU + Cisplatin + Mitoxantrone), advanced HCC patients receiving chemoembolization (Adriamycin + Embolization), advanced colon cancer patients receiving surgical resection plus adjuvant chemotherapy (5FU + Oxaliplatin), advanced cholangiocarcinoma patients receiving surgical resection, advanced esophageal squamous carcinoma cancer patients receiving concurrent chemotherapy (5FU + Cisplatin) and radiotherapy and signet ring cell gastric cancer patients receiving surgical resection (Unpublished). GALNT14 is an Enzyme Responsible of the Initial Step of O-Glycosylation in many proteins including Mucin, the most abundant protein in gastrointestinal tract. Our recent study has indicated that the intron region where the Rs9679162 is located serves as a transcription enhancer or suppressor for GALNT14 promoter, dependent on which HCC cell line is used. The differential expression levels of GALNT14 are linked to distinct degrees of chemotherapy sensitivity. Besides serving as an outcome predictor of gastrointestinal cancer, other clinical application has been explored. Combining GALNT14 -Rs9679162, an SNP on WWOX intron, and an intergenic SNP, a particular triple SNP pattern can identify a subgroup of advanced HCC patients (In About 1/10 Of All HCC Patients), In whom chemotherapy can achieve > 30% of complete (not partial) response. In an ongoing clinical trial, GALNT14-Rs967916 genotype is used to pre-stratify advanced HCC patients into favorable and unfavorable responder groups. Only patients in the unfavorable responder group are randomized to receive either chemoembolization alone or Chemoembolization + Sorafenib targeted therapy. Interim analysis has revealed a significant difference in time-to-tumor progression between the two randomized groups, indicating that this concept/strategy can potentially improve the chance of success for a new anticancer drug when launching an expensive clinical trial. At this time, it is still unclear whether inhibition or enhancement of the GALNT14 enzyme function can alter anticancer drug sensitivity. However, in recent study, a GALNT14 expression assay has been proposed in clinical trials to identify patients potentially more sensitive to pro-apoptotic receptor agonists, Dulanermin and Drozitumab. In summary, O-Glycosylation is believed to play an important role in carcinogenesis of gastrointestinal cancers. Despite the molecular and cellular mechanisms remain largely unclear, An SNP located on an o-glycosylation enzyme gene (GALNT14) has been shown to associate with clinical outcomes of multiple gastrointestinal cancers. At this time, oncologists can make use of this property to improve their anticancer strategies in treating these cancer patients.
Biology of Cell-Free Nucleic Acids and Their Role in Initiation and Metastasis of Cancer

Professor Indraneel (Neel) Mittra
Dr. Ernest Borges Chair in Translational Research and Professor Emeritus, Department of Surgical Oncology, Tata Memorial Centre, Advanced Centre for Treatment, Research & Education in Cancer (ACTREC), Mumbai, MH, India

Abstract

Several hundred billion to a trillion cells die in the adult human body daily, and a considerable amount of fragmented cell-free nucleic acids (cfNAs) from dying cells are released into the circulation. Our research has shown that circulating cfNAs can freely enter into healthy cells, accumulate in their nuclei, trigger a DNA damage repair response (DDR) and integrate into host cell genomes by an unique mechanism. Similarly, at the tissue level, locally generated cfNAs from dying cells can be taken-up by healthy bystander cells to induce DDR that facilitates their integration into recipient cell genomes. Genomic integration of cfNAs leads to dsDNA breaks, inflammation, chromosomal instability, senescence and apoptosis of recipient cells. cfNAs from cancerous cells can cause oncogenic transformation of NIH3T3 cells which are tumourigenic in immune-deficient mice. These findings raise a new hypothesis of cancer metastasis which posits that metastasis arises from de novo oncogenic transformation of cells of target organs induced by cfNAs arising from apoptotic circulating tumour cells (CTCs). This hypothesis challenges the current dogma that metastasis is produced by growth of CTCs that are lodged in distant organs.

Biography

Professor Mittra obtained his medical degree from University of Delhi and is a Fellow of the Royal College of Surgeons of England and holds a PhD degree from University of London. He did his post-doctoral training with Dr Renato Dulbecco, Nobel Laureate, at the Imperial Cancer Research Laboratories in London. Professor Mittra is a multi-faceted personality. He is a breast cancer surgeon while at the same time being deeply involved in public health and basic research in cancer. Professor Mittra's current research interests lie in the area of biology of extracellular nucleic acids and their role in ageing, inflammation, degenerative disorders and initiation and metastasis of cancer.

GPCR Regulate RTK Transactivation in NSCLC

Terry W. Moody
NIH/NCI, MD, USA

Abstract

Peptide GPCR for bombesin (BB), endothelin (ET), neurotensin (NTS) and pituitary adenylate cyclase activating polypeptide (PACAP) regulate transactivation of the EGFR in NSCLC cells (Moody et al., Curr Drug Targets 2016). Because the EGFR may form homodimers with itself or heterodimers with HER2, the ability of peptides to cause transactivation of the EGFR and HER2 was investigated. Two minutes after addition of ET-1 to NSCLC cell lines NCI-H838 (wild type EGFR) or NCI-H1975 (EGFR L858R/T790M double mutant) tyrosine phosphorylation of the EGFR, HER2 and ERK was increased 4-, 3- and 2-fold, respectively (Moody et al., Peptides 2017). ETAR, EGFR and HER2 mRNA was present in all NSCLC cell lines tested. Because ET-1, ZD4054, BQ123 but not BQ788 or ET-3 bound with high affinity to NCI-H838 or NCI-H1975 cells, ETAR but not ETBR predominates. Within seconds after addition of ET-1 to NSCLC cells, the cytosolic Ca2+ increased and the increase was blocked by BQ123 (ETAR antagonist) but not BQ788 (ETBR antagonist). The increase in EGFR, HER2 and ERK tyrosine phosphorylation caused by ET-1 was inhibited by BQ123 or the tyrosine kinase inhibitors (TKI) gefitinib or lapatinib. The increase in the EGFR and HER2 transactivation regulated by the ETAR was inhibited by PP2 (Src inhibitor), Tiron (antioxidant) and GM6001 (MMP inhibitor). The increase in reactive oxygen species (ROS) caused by ET-1 addition to NSCLC cells may impair protein tyrosine phosphatase activity resulting in increased EGFR and HER2 phosphorylation. ET-1 stimulated whereas gefitinib, lapatinib and BQ123 but not BQ788 inhibited NSCLC growth. BQ123 increased the cytotoxicity of gefitinib or lapatinib using NCI-H838 or NCI-H1975 cells. Trastuzumab inhibited the growth of NSCLC cells in vitro and the increased the response rate of NSCLC patients with HER2 mutations (Mitri et al., Chemother Res Pract 2012). The results indicate that GPCR agonists stimulate the growth of NSCLC cells in an EGFR and HER2-dependent manner.
Revitalizing the Metabolic Activity of Tumor Associated T Cells

Pearlie Epling-Burnette*, Rebecca Swearingen and Matthew S. Beatty
H. Lee Moffitt Cancer Center and Research Institute, FL, USA

Abstract

Studies reveal that T-cells activated in the tumor microenvironment display distinct metabolic programs that impact their ability to detect and eradicate tumor cells. Checkpoint molecules such as PD-1, at least in part, activate these suppressive programs by limiting the influx of glucose and other important nutrients. In general, checkpoint blocking therapies have dramatically changed the pharmacological landscape in melanoma and are rapidly expanding in many cancers. There is, however, an important unmet clinical need to develop novel therapeutic combinations that target additional mechanism of tumor-associated immune suppression. It is important to understand additional checkpoint molecules that are responsible for suppressed caused by changes in metabolic pathways or nutrient deprivation. We found that cereblon (Crbn), an E3-ubiquitin ligase substrate receptor for the DDB1/Cul4A/Roc1 complex controls the metabolic state of effector T-cells in the B16 melanoma mouse model. T-cells present in this hostile tumor microenvironment are exposed to hypoxia, high lactic acid, and poor amino acid availability that suppress their anti-tumor cytotoxic potential. Tumor-bearing Crbn−/− mice have a higher proportion of CD44+ melanoma reactive (TRP2+) tumor infiltrating lymphocytes (TIL) that express PD-1 receptor and retain their ability to influx and metabolize glucose, arginine, and glutamine. Importantly, CRBN is the molecular target of thalidomide and immunomodulatory drugs including lenalidomide, and pomalidomide that have been shown previously to potentiate T-cell function. Additional experiments are required to understand the detailed mechanism of CRBN-associated immune regulation and to determine if treatment with immunomodulatory compounds that bind CRBN may act to overcome a metabolic checkpoint induced through nutrient restrictions or metabolic re-programming in the tumor microenvironment.

Biography

Dr. Pearlie K. Epling-Burnette, PharmD, PhD (PD/PI) is a Senior Member at the H. Lee Moffitt Cancer Center and a Professor at the University of South Florida (USF). Her mission is to contribute to the prevention and cure of cancer and to be a leader in cancer immunotherapy. She is recognized as expert in immunology of chronic hematologic malignancies including Large Granular Lymphocyte (LGL) Leukemia, Myelodysplastic Syndrome (MDS), other rare bone marrow failure diseases and myeloproliferative neoplasms (MPNs). Close collaborations with clinical investigators has allowed her to translate her research into several clinical trials targeting abnormal immune functions. For many years, she has conducted research that required patient sample collection and processing and now she is the Director and PI of the NHLBI-sponsored National Biorepository for Myelodysplastic Syndrome. This project will actively recruit 2,000 MDS cases and 500 comparators for baseline and longitudinal biospecimen collection for a period spanning 7 years. Future translational studies to enhance anti-tumor immune function with broad applications in cancer will be supported by studies on a novel metabolic checkpoint protein.
Beta-Arrestin 1 Targets in Nicotine-Mediated Lung Cancer Metastasis and Angiogenesis

Srikumar P. Chellappan
H. Lee Moffitt Cancer Center and Research Institute, FL, USA

Abstract

Smoking is highly correlated with lung cancers of all histologies, since tobacco-specific nitrosamines and other carcinogenic agents present in tobacco smoke act as genotoxic agents. Nicotine, the addictive component of tobacco smoke, is not thought to be carcinogenic; at the same time, it can induce cell proliferation, invasion and migration, thus acting as a strong tumor promoter. These effects of nicotine occur through the nicotinic acetylcholine receptors; these receptors, which are mainly present on neurons and neuromuscular junctions, are also expressed on a variety of non-neuronal cells, mediating the tumor promoting functions of nicotine. Our earlier studies had shown that nicotine could induce the expression of a variety of genes involved in epithelial-mesenchymal transition; these include ZEB1, ZEB2, vimentin, fibronectin etc. Nicotine could also induce multiple matrix metalloproteinases, promoting metastasis. These effects of nicotine required the mediation of the scaffolding protein, beta-arrestin-1. Our recent studies show that nicotine as well as e-cigarette extracts can promote the self-renewal of stem-like cells from lung cancer, through the mediation of the transcription factor Sox2 and the transcriptional co-activator, YAP1. YAP1 was found to promote the expression of various genes involved in angiogenesis, through its physical interaction with HIF1α. The role of beta-arrestin-1 and its downstream targets in these processes will be discussed.

Biography

Dr. Srikumar Chellappan obtained his Ph.D. in Biochemistry from Indian Institute of Science, Bangalore in 1987. After a highly productive post-doctoral stint at Duke University Medical Center, he started his independent laboratory at Columbia University in 1992, and continued to work on the links between cell surface signaling and transcriptional regulation in cancer. He moved to H. Lee Moffitt Cancer Center and Research Institute in 2001, where he is a Moffitt Distinguished Scholar and Chair of the Department of Tumor Biology. Dr. Chellappan works on smoking related cancers, with an emphasis on the molecular mechanisms underlying EMT, stemness and metastasis.

Induction of Synthetic Lethality in Glioblastoma

Markus Siegelin
Columbia University Medical Center, NY, USA

Abstract

Glioblastomas are notoriously resistant to treatment and display a resistant phenotype towards apoptosis. Our research has identified a unique selective vulnerability of IDH1 mutated glioblastoma cells for a special type of apoptosis inducing drugs. We have evaluated this concept in various state-of-the art model systems of glioblastoma, including stem cell-like glioma cells. In addition, we have determined the mechanisms involved in this synthetic lethality, linking tumor cell apoptosis with metabolism. This concept might offer a novel therapeutic opportunity for malignant glial brain tumors.
Day - 2

October 27, 2017
Scanning the Tumor Microenvironment for Targetable Mediators of Cancer Stem Cell Plasticity

Mark W. Jackson1,2, Benjamin L. Bryson1, Damian J. Junk1, Jacob Smigiel1, Neetha Parameswaran1, Mary R. Doherty1 and Courtney A. Bartel1

1Department of Pathology, Case Western Reserve University, OH, USA
2Case Comprehensive Cancer Center, Case Western Reserve University, OH, USA

Abstract

Increasing evidence suggests that tumor cell plasticity promotes metastasis and tumor recurrence, resulting in cancer patient mortality. While it is clear that the tumor microenvironment (TME) contributes to tumor cell plasticity, the specific TME factors that actively generate tumor cell plasticity are largely unknown. Here, we identify TME cytokines that promote epithelial-mesenchymal plasticity, and acquisition of cancer stem-cell (CSC) properties. A screen of 27 TME cytokines identified multiple Interleukin-6 family members as inducers of mesenchymal/CSC properties, with Oncostatin M (OSM) being the most potent. Importantly, OSM induced plasticity was mediated by STAT3, but also dependent on TGF-β signaling and downstream SMAD3. Inhibition of functional TGF-β/SMAD3-signaling prevents the OSM-induced mesenchymal/CSC properties. The epithelial-mesenchymal transition induced by the STAT3/SMAD3 axis results in a highly invasive and metastatic phenotype and the emergence of CSC properties, including therapeutic resistance. We propose that, targeted blockade of the OSM/STAT3/SMAD3 axis in tumor cells may represent a novel therapeutic approach to prevent the plasticity associated with metastasis and tumor recurrence. We have completed a small molecule screen for drugs that prevent OSM-mediated plasticity, and are assessing their roles in preventing or reversing aggressive cancer cell properties.

Biography

Dr. Mark W. Jackson is an Associate Professor in Pathology and the Case Comprehensive Cancer Center. The Jackson laboratory focuses on genetic events that contribute to epithelial cell transformation and progression. Using forward genetic strategies, his research has identified novel proteins that regulate cancer cell signaling pathways (NFκB, EGFR, MAPK and PI3K/AKT) and confer resistance to cancer therapy. In addition, his research has identified the contribution of tumor microenvironmental cytokines to the transformation process, epithelial-mesenchymal plasticity, and the acquisition of cancer stem cell (CSC) properties.

Acidity as a Resistance Mechanism to Targeted Therapies in Cancer

Olivier Dormond
Department of Visceral Surgery, Lausanne University Hospital, Switzerland

Abstract

Tumor cells preferentially use glycolysis despite the presence of oxygen generating an increased quantity of acidity. Consequently, the tumor microenvironment is classically acid and profoundly influences the biology of tumors. For instance, acidity favors tumor progression by increasing tumor cell mobility and metastasis. In addition, it also confers a growth advantage to cancer cells since, in contrast to other cell types present in tumors, they possess all the enzymatic machinery necessary to keep a physiological intracellular pH in acidic conditions. Besides, acidity also modifies the efficacy of anti-cancer therapies including chemo- radio- and immunotherapy. Here, the effect of acidity on anti-angiogenic drugs, including mTOR inhibitors and anti-VEGF therapies will be presented.

Detection of Tumors by Ptpmu Molecular Imaging Agents

Susann Brady-Kalnay
Case Western Reserve University, OH, USA

Abstract

Currently, surgeons do not have reliable markers to distinguish where tumors end and normal tissue begins. Glioblastoma (GBM), the most common primary brain tumor, has median patient survival of little more than one year. Surgical resection of all enhancing tumor prolongs survival, yet successful resection is challenging because GBM tumors are not well circumscribed and diffusely infiltrate the brain, which results in >90% local recurrence. Development of next-generation optical fluorescent molecular imaging agents to help surgeons specifically differentiate cancerous from normal tissue intraoperatively will reduce the rate of local recurrence and increase patient survival.

An extracellular fragment of the cell surface adhesion molecule PTPmu is a unique imaging biomarker of the tumor microenvironment. The PTPmu fragment arises from cleavage of the receptor protein tyrosine phosphatase (PTPmu),
a proteolytic event seen in multiple tumor types including GBM. An agent that binds to this PTPmu fragment, SBK2, recognizes human tumors. Systemic delivery of the SBK2 agent results in binding to tumor cells within minutes in vivo, and can label 99% of all dispersing brain tumor cells several millimeters away from the main tumor mass.

We are translating this highly selective fluorescent SBK2 agent for pre-surgical systemic delivery to GBM patients to render the cancerous GBM tissue visible in real-time using current surgical microscopy. Fluorescent molecular imaging will enhance the efficacy and efficiency of cancer surgery by allowing real-time decisions between palliative and curative treatment for improved surgical resection of all tumors.

**Biography**

Dr. Brady-Kalnay received her Ph.D. from the University of Cincinnati. She was a Postdoctoral Fellow in the laboratory of Nick Tonks at Cold Spring Harbor Labs. She joined the faculty at Case Western Reserve University in 1995 and is Professor of Molecular Biology and Microbiology. She discovered a key change in proteolysis of cell-cell adhesion molecules and receptor protein tyrosine phosphatases in human cancer, which she exploited to develop molecular imaging agents and theranostic targeting agents for tumors. Her imaging research uses cutting edge approaches such as cryo-imaging to detect cell migration and invasion in the tumor microenvironment.

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**Heme and Mitochondrial Function in Non-small Cell Lung Cancer**

Li Zhang*, Sarada Preeta Kalainayakan, Poorva Ghosh, Sanchareeka Dey, Purna Chaitanya Konduri, Keely Fitz Gerald and Li Liu
The University of Texas at Dallas, TX, USA

**Abstract**

In 1920s, Otto Warburg made the observation that cancer cells utilize significantly more glucose than normal, healthy cells, which led him to believe that cancer cells relied on glycolysis more than healthy cells. However, many subsequent studies have shown that glucose is not only necessary for glycolysis but also for oxidative phosphorylation and production of building blocks for the synthesis of many biomolecules. Lung cancer is the leading cause of cancer-related death in the US and the world, and non-small cell lung cancer represents 85% of lung cancer cases. There are many challenges associated with studying and treating lung cancer, and there is a diverse set of metabolic factors influencing the tumorigenesis and metastasis of lung cancer. Recent studies have shown that lung cancer cells rely heavily on mitochondrial respiration and that inhibiting mitochondrial function may be an effective method to combat lung cancer. Further, more research has noted increased levels of heme flux and function as critical to intensified oxygen consumption and accompanying amplified pathogenesis and progression of lung cancer. The upregulation of mitochondrial DNA and biogenesis genes are also correlated with lung cancer. Recent experimental data will be presented to show that targeting tumor cell bioenergetics via inhibition of heme and mitochondrial functions can effectively suppress lung tumorigenesis and progression.

**Biography**

Professor Li Zhang completed her PhD from UCLA and postdoctoral studies from MIT department of Biology. She is the Cecil H. and Ida Green Distinguished Chair in Systems Biology Science at the University of Texas at Dallas. Professor Zhang's laboratory has worked on studying heme signaling and function for 20+ years. She has published many original research articles and a book entitled "Heme Biology: The Secret Life of Heme in Regulating Diverse Biological Processes" on this subject. Professor Zhang's laboratory has also made important contributions in understanding the roles of molecular chaperones in cellular signaling, molecular mechanisms of oxygen signaling, and the actions of neurotoxins. Recently, Professor Zhang's lab focuses on investigating heme function in lung cancer. She and colleagues have provided a unifying view of cancer bioenergetics in a review article entitled "A Holistic View of Cancer Bioenergetics: Mitochondrial Function and Respiration Play Fundamental Roles in the Development and Progression of Diverse Tumors," published in the journal "Clinical and Translational Medicine."

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**MDM2 Oncogene: A New Biomarker for Metastatic Cancers**

Appu Rathinavelu
Rumbaugh Goodwin Institute for Cancer Research, Health Professions Division College of Pharmacy, Nova Southeastern University, FL, USA

**Abstract**

Many types of cancers contain mutations of p53 or defects in the pathways that are regulated by this tumor suppressor gene as one of the major causes of tumor growth induction. In the last fifteen years, overexpression of MDM2 that can also lead to similar consequences by inactivating p53, has emerged as equally important pro-oncogenic mechanism. MDM2 is overexpressed in nearly 30-40% of carcinomas and regulates the p53 levels through a negative feedback loop by involving ubiquitination and subsequent degradation. Because of its prevalent expression and its interactions with p53 and many other
signaling molecules, MDM2 has been gaining a central role in the regulation of cancer development and progression. Both genetic and biochemical evidence indicate that MDM2 and one of its isoforms called MDMX can also perform distinct yet co-operative functions in the process of p53 inactivation. Several small molecules that can antagonize the interaction between MDM2-p53, by blocking the N-terminal transactivation domain and preventing the negative regulation of p53, have come into clinical trials. In the last fifteen years, a prototype of this pharmacological family called Nutlin-3 was studied extensively using various in vitro models. However, many other entities of the same pharmacological family are currently undergoing pre-clinical and clinical testing and are steadily advancing towards approval for the treatment of leukemia and other forms of cancers. Accumulation of evidence in the literature clearly indicates that MDM2 can function beyond the grips of p53 and therefore, antagonizing MDM2 represents an attractive approach to combat tumor growth and expansion. Numerous findings have strongly indicated that MDM2 overexpression can promote tumor angiogenesis through multiple pathways and thereby enhance the metastatic potential of cancer cells. Therefore, it is evident that MDM2 overexpression could increase angiogenesis, enhance metastatic potential, and trigger drug resistance via both p53 dependent and independent mechanisms. Several experiments with sarcoma, prostate and breast cancer cells show results that support the speculation related to the enhancement proliferative and pro-angiogenic mechanisms by MDM2. Given the importance of MDM2 in regulating multiple pathways that are related to cancer progression, we are speculating greater importance for MDM2 in the process of making therapeutic decisions (Research was supported by the Royal Dames of Cancer Research Inc., Ft. Lauderdale, Florida and by the grant from the Community Foundation of Broward, Ft. Lauderdale, Florida).

Biography

Dr. Rathinavelu received his Ph.D., M. Phil., M.S., and B.S. from the University of Madras in India and conducted his Post-Doctoral work at Purdue University. He joined NSU’s College of Pharmacy in 1992 and he is currently the Executive Director of the Rumbaugh Goodwin Institute for Cancer Research of NSU. Dr. Rathinavelu has been involved in cancer research for more than two decades with great interest and expertise in drug discovery, pharmacogenomics, signal transduction, gene expression and natural products research. Dr. Rathinavelu holds 5 new patents for the discovery of novel anti-angiogenic compounds that are nearing completion of pre-clinical testing. Dr. Rathinavelu serves on the Governmental Affairs Committee of Bio Florida and was a member of the Center of Excellence for Marine Biology and Biotechnology consortium that included scientists from NSU, Florida Atlantic University and Florida International University. Dr. Rathinavelu has published, co-authored, and reviewed research articles and textbooks extensively. Dr. Rathinavelu is the recipient of the 'Fulbright Award for Excellence in Teaching and Research' for the year 2015 from the Council of the International Exchange of Scholars of the United States of America (USA).

Emerging Role of HPIP Signaling in Cancer Cell Survival, EMT and Metastasis under Metabolic Stress

Bramanandam Manavathi1, Saratchandra Singh Khumukcham1, Anju Dwivedi1, Vasudevarao Penugurti1, Uppala Veena1 and Vijaya Lakshmi Malisetty2

1University of Hyderabad, TS, India
2Acharya Nagarjuna University, AP, India

Abstract

Unlike a normal cell, a transformed or cancer cell acquires survival ability even under stressful conditions like hypoxia and low serum by exploring minor modifications of regulatory signaling circuits inside the cells. Two of the most important survival signaling cascades frequently deregulated in cancer are Src/MAPK and PI3K/Akt/mTOR pathways. Therefore, understanding the mechanism of action and the role of upstream regulators of these pathways is important because it provides a therapeutic option for cancer treatment. PBXIP1/HPIP, an estrogen receptor interacting protein, has been reported to act as an upstream regulator of PI3K/Akt/mTOR signaling in cancer cells. Here we report that HPIP expression is induced under hypoxia in breast cancer cells. HIF1alpha, hypoxia inducible transcription factor, directly binds to HRE elements that harbors in HPIP promoter to activate its transcription. Silencing of HPIP by HPIP shRNA rendered MDA-MB231 cells to lose the cancerous properties such as survivability, invasion, epithelial to mesenchymal transition (EMT) and anchorage independent growth ability under hypoxia. HPIP promoted cancer cell survival and invasion under hypoxia by modulating the expression of carboxic anhyderase (CAIX) expression and activation of matrix metalloproteinases (MMPs) in MBA-MD231 cells. Clinical studies indicated that HPIP and HIF1alpha expressions correlate in triple negative breast cancer (TNBC) specimens. Together these results suggest the involvement of a novel signaling pathway in the development of triple negative breast cancer (TNBC) and influence of hypoxic microenvironment. This pathway could be a potential therapeutic target to treat TNBCs.

Biography

Dr. Manavathi received Ph.D. degree in Biochemistry from SK University, India in 2002. Thereafter he joined the MD Anderson Cancer Center, USA as a Postdoctoral Fellow and worked on understanding the molecular basis of breast cancer...
until 2007. In the same year, he joined University of Hyderabad, India where he is now working as an Associate Professor in Biochemistry. He is also a visiting scientist of Terry Fox Laboratory, Canada. He has been working in the field of breast cancer. He received awards like IYBA, BOYSCAST and Novartis Cancer Award. He has published over 30 research articles of high impact.

**Anti-Cancer Chemotherapeutics Having High Efficacy in Acidified Cancer Nests**

**Hiroshi Kobayashi**  
*Chiba University, Japan*

**Abstract**

It was found more than 80 years ago that solid cancer nests are acidified, but *in vitro* studies under acidic conditions had not been focused for a long time. We started *in vitro* experiments with mammalian cancer cells under acidic conditions in 1996. After the protocol for culturing cancer cells in acidic medium had been established, we examined the anti-proliferation efficacy of approximately 280 compounds under acidic conditions and found that the anti-cancer efficacy of 4 drugs, lovastatin, cantharidin, manumycin A and ionomycin, increases dramatically at acidic pH. These drugs specific to acidic nests are expected to have less of effects on normal tissues whose pH is slightly alkaline. In the case of statins prescribed for hyperlipidemia patients, no serious side effects, such as dysfunction of immune system, pain, diarrhea, nausea, and hair loss, have been reported. Anti-cancer activity of statins in animal models have been reported from many groups. On the basis of data obtained *in vitro* experiments and animal studies, clinical usages of anti-cancer drugs specific to acidic nests are discussed.

**Biography**

Dr. Hiroshi Kobayashi received his Ph.D. in Biochemistry from University of Tokyo in 1974. After his postdoctoral training at Colorado University Medical Center, he started to study adaptation strategies of microorganisms to acidic environments at Chiba University in 1978. His research has been focused on mammalian cell functions under acidic conditions from 1996 at Graduate School of Pharmaceutical Sciences, Chiba University. His current challenge is to develop cancer chemotherapy specific to acidic nests. He retired in March 2012 and is now a professor emeritus at Chiba University. He works as an associate editor of International Immunopharmacology published by Elsevier from 2014.

**Phgdh Defines a Metabolic Subtype in Lung Adenocarcinomas with Poor Prognosis Displaying Unique Metabolic Dependencies**

**Boxi Zhang**, **Adi Zheng**, **Per Hydbring**, **Gorbatchev Ambroise**, **Michel Goiny**, **Sophie Erhardt**, **Helin Vakifahmetoglu-Norberg** and **Erik Norberg**

1*Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden*

2*Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden*

**Abstract**

Although molecular signatures are emerging determinants of choice of therapy for lung adenocarcinomas, additional tumor specific dependencies might have tremendous impact of the outcome of treatment. An evolving therapeutic approach includes targeting metabolic dependencies in cancers. Here, we have dissected the metabolic fingerprints of lung adenocarcinomas and show that phosphoglycerate dehydrogenase (PHGDH), the rate-limiting enzyme in serine biosynthesis, is highly upregulated in an adenocarcinoma subset with poor prognosis. By using an integrative approach, we describe the molecular mechanism underlying the metabolic subtypes and show that genetic depletion of PHGDH shows potent and selective toxicity to this subset. Our integrative analysis provides evidence that a unique metabolic program is activated in lung adenocarcinoma subsets, described by PHGDH, which confers growth and survival signaling and may have therapeutic implications.

**Biography**

Asst. Professor Erik Norberg obtained his Ph.D. from Karolinska Institute in 2011. He then moved on and performed his Post-doctoral training at the Dana-Farber Cancer Institute, Harvard Medical School in Boston, MA, USA in the Nika Danial Lab. In 2013, he was recruited back to Karolinska Institute as an Asst. Professor at the Institute of Environmental Medicine, Karolinska Institute. In 2016, he moved his lab to the Department of Physiology and Pharmacology also at the Karolinska Institute.
Evaluation of Cytotoxicity of Phosphoethanolamine Drug toward Human Cancer Cell Lines

Herman Mansur¹, Zélia Lobato, Maria de Fátima Leite, Alexandra Mansur, Sandhra Maria de Carvalho and Lorena Mansur

Federal University of Minas Gerais, Brazil

Abstract

Cancer, a complex group of diseases characterized by the uncontrolled growth and spread of abnormal cells, has long been the leading cause of death in many countries. Despite undeniable advances in recent decades, it remains one of the world’s most lethal diseases with millions of new cases every year. Recently, phosphoethanolamine (PEA) has raised great concerns and debates reaching the Brazil’s Supreme Federal Court as a promising drug on cancer therapy, but with controversial results and no definitive decision yet. Herein, we evaluated in vitro the toxicity effect of PEA using MTT cell viability assay toward 5 human cancer cell types (lymphoma, glioma, breast cancer, osteosarcoma, and cervical cancer) and human embryonic kidney cell type (control normal cell line) compared to anticancer drug doxorubicin (DOX) as the reference standard. The results demonstrated no detectable toxicity of PEA against all cancer cell types tested based on the mitochondria activity compared to the high killing rate verified for doxorubicin control samples known as an effective anticancer drug. Moreover, novel fluorescent quantum dots were designed and synthesized for tracking the pathway of the PEA internalization by tumor cells and assisting on elucidating the possible toxicity mechanisms involved in the cell metabolism.

Biography

Dr. Herman Mansur is a Metallurgical and Materials Engineer (1985) and Master in Chemistry (1992) from Federal University of Minas Gerais (UFMG, Brazil). He did his PhD in Chemistry of fluorescent nanomaterials from Melbourne University (Australia)/UFMG (1996) and Post-Doctoral at Clarkson University (NY, USA) in bio-nanotechnology and bioconjugates. He joined the Materials and Metallurgical Dept. at UFMG (1998, Brazil) and currently holds a Full Professor position. He has over 150 peer-reviewed papers in high quality journals, 400 presented in conference proceedings (H=29; 2700 citations) with 6 patents, in nanomaterials for nanomedicine and biomedical applications. He attended over 20 international conferences as invited speaker and chaired 15 international scientific sections.

SALL4 is an Essential Regulator in MLL-Rearranged Leukemogenesis

Jianchang Yang*, Ji Li Li’, Hong Gao 1,2, Li Liu’, Jaya Pratap Pinnamaneni’, Deepthi Sanagasetti’, Vivek P. Singh1, Megumi Mathison1, Qianzi Zhang1, Fengju Chen’, Qianxing Mo4 and Todd Rosengart1

1Department of Surgery, Baylor College of Medicine, TX, USA
2Department of Pathology, Stony Brook University Medicine, NY, USA
3Department of Medicine, Baylor College of Medicine, TX, USA
4Dan L Duncan Cancer Center, Baylor College of Medicine, TX, USA

Abstract

The stem cell factor SALL4 plays important roles in normal hematopoiesis and leukemogenesis. We previously reported that SALL4 exerts its effect via recruiting important epigenetic factors such as DNA methyltransferases DNMT1 and lysine-specific demethylase 1 (LSD1/KDM1A), -both are critically involved in the mixed lineage leukemia (MLL)-rearranged (MLL-r) leukemia. Recently, the SALL4’s functions were further linked with MLL/HOXA9 pathway. However, it remains unclear whether SALL4 is indeed a key player in the pathogenesis of MLL-r leukemias, which have a very poor prognosis in clinic. Using mouse bone marrow (BM) retroviral transduction/transplantation approach combined with tamoxifen-inducible, CreERT2-mediated Sall4 gene deletion, here we report that SALL4 expression is indispensable in leukemogenesis induced by MLL-AF9, -one of the most common MLL-r oncoproteins found in patients. Through gene expression and chromatin immune-precipitation assays, we show that SALL4 impacts the levels of histone modification markers H3K79me2/3 and H3K4me3 at MLL-AF9 target gene promoters by interacting with at least DOT1-like histone H3K79 methyltransferase (DOT1l) and LSD1/KDM1A, which leads to down-regulated transcript expressions. Surprisingly, normal Sall4f/f/CreERT2 mice treated with tamoxifen, or vav-Cre mediated Sall4-/- mice were healthy and displayed no significant hematopoietic defects. Our study thus identifies critical roles of SALL4 and their underlying molecular/epigenetic mechanisms in MLL-AF9 leukemia, suggesting that selectively targeting the SALL4 pathway as an ideal approach in treating human MLL-r leukemias.

Biography

Dr. Jianchang Yang received his MD from XinJiang University of Medical Sciences, MS of Medical Biochemistry from Sun Yat-sen University in China, and his doctorate degree in Molecular Cardiology from Charite University Medicine (Berlin)–magna cum laude. His research interests include normal and leukemic hematopoietic stem cell regulation, cardiac progenitor cell and cellular reprogramming, epigenetic control of gene expression, ES cells, generation of patient-specific pluripotent progenitor cells for clinical therapies.
Development of Novel Pateamine A Derivatives as First-In-Class Translation Initiation Inhibitors Targeting the Vulnerabilities of Cancer

Kenneth G. Hull1, Rong Chen2, Yu Ri Kim3a, Maryam Safari3b, Mingzhao Zhu1, Yuling Chen3, Wesley Skillern3, Qun Qin3, William Wierda4, Changchun Deng3b, Susan Bates3b, William Plunkett2,5 and Daniel Romo3

1Department of Chemistry and Biochemistry & CPRIT Synthesis & Drug-Lead Discovery Laboratory, Baylor University, TX, USA
2Department of Experimental Therapeutics, The University of Texas M.D. Anderson Cancer Center, TX, USA
3Program in Cellular and Molecular Medicine, Boston Children’s Hospital, MA, USA
4The Center for Lymphoid Malignancies, 5Division of Medical Oncology and Hematology, Columbia University Medical Center, NY, USA

Abstract

The development of an effective therapeutic is dependent upon disabling an aspect of the pathophysiology of a malignancy that is critical to its survival and proliferation. This could at once block further progression and preferentially kill the tumor while minimizing harming of normal tissues. Dysregulation of protein translation is a common feature of cancer. Because many oncoproteins turn over rapidly and have relatively short half-lives, the translation of these oncogenes represents a cancer-specific vulnerability, which may be exploited by novel targeted therapies. Among the processes of eukaryotic protein translation: including initiation, elongation, termination and ribosome recycling, initiation is the most regulated and rate-limiting. The formation of the eukaryotic translation initiation factor 4F (eIF4F) complex, which prepares mRNA for incoming 40S ribosomes, is the essential step for initiation, and thus an attractive target for developing therapeutics that are directed at protein translation. eIF4F is comprised of the scaffold protein eIF4G, the cap-binding protein eIF4E, and the helicase eIF4A. The natural product pateamine A (PatA) has been shown to be a potent inhibitor of translation initiation through binding to eIF4A. Subsequent medicinal chemistry identified des-methyl, des-amino pateamine A (DMDAPatA) a simplified analog of the natural PatA that is easier to synthesize and exhibits potent anti-proliferative activity in vitro against >30 human cancer cell lines. Xenograft studies in mice showed DMDAPatA has high activity in models of human leukemia and melanoma leading to significant tumor reduction. However, preliminary data on DMDAPatA suggests that it is highly protein bound in human plasma and may lack sufficient in vivo potency required for clinical development. To address this, we designed several new PatA analogs with the goal of improving the physical properties and potency against cancer cells. This led to the identification of three novel derivatives that met these criteria. The new PatA analogs reduce the levels of intrinsically short-lived anti-apoptotic protein Mcl-1 in chronic lymphocytic leukemia (CLL). One of the new PatA analogues, namely MZ-735, was comprehensively investigated in diffuse large B-cell lymphoma (DLBCL), double hit lymphoma (DHL), and pancreatic ductal adenocarcinoma (PDAC). DLBCL is the most common aggressive lymphoma, DHL is the most chemoresistant lymphoma, and PDAC remains the most lethal malignancy to date. Despite these three malignancies differ vastly in the treatment regimens, the response to chemotherapy, outcome, and histological origin, they all are associated with highly dysregulated c-Myc. Our results demonstrate that MZ-735 was significantly more potent than DMDAPatA, as MZ-735 induced apoptosis in DLBCL, DHL, and PDAC, with an IC50 below 5 nanomolar (nM) in most cell lines. MZ-735 potentiated suppressed the expression of the c-Myc oncprotein in these cancer cell lines. Importantly, MZ-735 failed to induce any significant cytotoxicity in normal blood cells, suggesting this PatA analogue may be safe to human hematopoietic system. Our goal is to identify a primary drug “lead” from the three discovery compounds based on in vivo efficacy, pharmacokinetics and preliminary in vitro toxicity screening. These studies will provide proof-of-principle data for developing a PatA derivative for the treatment of B-cell malignancies and pancreatic cancer. Furthermore, PatA analogues may also be active in other cancers, where the driver oncogenes are highly dependent on eIF4F.

Role of Aging-Associated Genes in Regulating Breast Cancer Malignancy

LuZhe Sun

Department of Cell Systems & Anatomy, University of Texas Health Science Center, TX, USA

Abstract

Although age is a major risk factor for breast cancer incidence and mortality, we don’t know what genes are positively or negatively associated with age that also positively or negatively regulate the transforming activity of tumor-initiating cells and consequently breast cancer development and progression. Revelation of these genes should have a significant impact on aging and cancer research, and yield molecular targets for breast cancer prevention. We identified 82 breast cancer patients in the TCGA (The Cancer Genome Atlas) dataset with information on their age, menopause status, and RNA-seq data from paired adjacent normal and cancer tissues. Using a linear regression analysis for gene transcripts increased or decreased in the TCGA dataset with information on their age, menopause status, and RNA-seq data increased or decreased in the TCGA dataset with information on their age, menopause status, and RNA-seq data, we obtained 14 upregulated and 24 downregulated genes that are associated with both Age and Breast Cancer (ABC genes). Significantly, using the KM-Plotter dataset, we found that high levels of the 14 up-regulated ABC genes and low levels of the 24 down-regulated ABC genes are significantly associated with worse relapse free survival from breast cancer suggesting that they play a tumor-promoting or tumor-suppressing roles respectively. Knockdown of a number of up-regulated ABC genes led to decreased proliferation of breast cancer cells. Some of them also promote breast cancer cell
migration and anchorage-independent growth. We have selected a couple of up- and down-regulated ABC genes for more
detailed analyses of their role in the regulation of breast cancer cell proliferation in soft agar, migration through transwells,
and tumorigenicity and metastasis in xenograft models.

Epigenetic Therapy for HPV-Associated Cancer

Natalia Issaeva1,2, Asel Biktasova1, Michael Hajek1, Andrew Sewell1, Cyril Gary1, Gary Bellinger1 and Wendell G
Yarbrough1,2

1Department of Surgery, Division of Otolaryngology, Yale University, New Haven, CT, USA
2Yale Cancer Center, Yale University, New Haven, CT, USA

Abstract

5-azacytidine (5-aza) is synthetic cytidine analog that is used in clinic to treat myelodysplastic syndromes and acute
myeloid leukemia. 5-aza is currently being studied in a window clinical trial for head and neck squamous cell carcinoma
(HNSCC) at Yale Cancer Center. While generally accepted that human papilloma virus (HPV) associated HNSCC
represents a distinct clinical disease from tobacco-associated HNSCC in terms of prognosis and treatment responsiveness,
current guidelines state that the HPV status should not influence treatment paradigms. We sought to further understand
the mechanism of therapeutic demethylation effects in HPV+ cancers in an effort to develop an effective treatment with less
morbidity for this subset of HNSCC.

In this study, we investigated the effects of 5-azacytidine on head and neck cancer cells, xenografted tumors, and tumors
from patients enrolled in a window 5-aza trial. We demonstrated that 5-azacytidine induces double strand breaks (DSBs)
at the sites of hypomethylated DNA only in HPV-associated head and neck cancer cells. We found that these DSBs are
dependent on active transcription and replication. Our data revealed that 5-aza significantly decreased expression of all
HPV genes in head and neck cancer cells and in tumors. Importantly, 5-aza was effective in inducing p53-dependent
apoptosis in HPV-positive cells and tumors from a clinical trial, as well as in inhibiting tumor growth and reducing cancer
cell invasion in vivo in mouse model.

Our data suggest that demethylating agents may provide effective therapy for HPV-associated HNSCC as an alternative
to standard cytotoxic therapy or for recurrent tumors.

Biography

Dr. Natalia Issaeva received PhD in 2005 in Karolinska Institute (Stockholm, Sweden), and she is currently an Assistant
Professor working at the Yale Medical School (New Haven, CT, USA). Her ongoing research projects are focused on
the understanding the role of human papilloma virus (HPV) in head and neck squamous cell carcinoma (HNSCC)
development and progression and designing novel therapeutic strategies to target head and neck tumors exploiting their
various defects and “Achilles’ heels”.

Cytoskeleton-Associated Proteins as Targets for Tumor Therapy

Sabine Windhorst1, Adi Gazdar2 and Yuan-Na Lin3

1Department of Biochemistry and Signal Transduction, University Medical Center Hamburg-Eppendorf, Martinistrasse 52,
D-20246 Hamburg, Germany
2Department of General, Visceral and Thoracic Surgery, University Medical Center Hamburg-Eppendorf, Martinistrasse 52,
D-20246 Hamburg, Germany
3Hamon Center for Therapeutic Oncology Research, University of Texas Southwestern Medical Center, TX, USA

Abstract

Metastasis is the leading cause of cancer death. In order to form distant metastasis, cancer cells need to proliferate
and have to be motile. A promising approach to block metastasis is thus to specifically inhibit both, proliferation and
motility of cancer cells. Since, cytoskeleton-associated proteins control both, these proteins are very interesting targets for
specific inhibition of metastasis. We have identified an actin bundling protein (ITPKA) as well as an actin-nucleator and
microtubule stabilizer (DIAPH2) as cytoskeleton-associated proteins essential for metastasis of lung or colon carcinoma.
ITPKA is already discussed as prognostic marker for patients with lung carcinoma. Under physiologic conditions ITPKA
is mainly expressed in neurons of the central nervous system (CNS). ITPKA-inhibitors that do not pass the blood-brain-
barrier, thus should only slightly affect cells outside the CNS. In addition to ITPKA, we aim to identify further cytoskeleton-
associated proteins that are essential for tumor progression but show limited expression in normal tissue. Our goal is to
identify signatures of cancer related cytoskeleton-associated proteins in different tumor types and develop specific inhibitors
against these proteins.
Biography

Dr. Sabine Windhorst has her expertise in elucidating the role of cytoskeleton-associated proteins in tumor progression. Her group had identified two proteins (ITPKA and DIAPH1) essential for metastasis of lung or colon cancer (Windhorst and Gazdar, 2017; Lin et al., 2015). Her goal is to identify the set of cytoskeleton-associated proteins essential for tumor progression as well as to develop highly select small molecule inhibitors against these proteins.

Enhancing the Efficacy of JAK2 Inhibitors for Myeloid Neoplasms

Gary W. Reuther1, Lucia Mazzacurati and Que T. Lambert

H. Lee Moffitt Cancer Center and Research Institute, FL, USA

Abstract

While it is evident from genetic and pre-clinical models that aberrant JAK2 signaling plays a role in the etiology of myeloproliferative neoplasms (MPNs), JAK2 inhibitors have had limited success in patients. While there may be some long-term survival improvement in patients undergoing treatment with ruxolitinib, the only FDA-approved JAK2 inhibitor for MPN patients, the need to improve the efficacy of such drugs at decreasing the neoplastic allele burden in patients remains a priority of anti-MPN research. Importantly, the quality of life improvements afforded by JAK2 inhibitors in MPN patients suggests JAK2 inhibitors, such as ruxolitinib, will remain a mainstay in the treatment of MPNs. We have been working to improve anti-MPN therapies by developing novel JAK2 inhibitors as well as assessing combinations of signal transduction inhibitors with JAK2 inhibition. In addition, we have been assessing the ability of JAK2-driven cells to rapidly and reversibly develop resistance to JAK2 inhibitors (JAK2 inhibitor persistence) in order to identify potential novel targets for upfront combination therapies that will thwart the development of drug persistence. More specifically, we have been utilizing rationally designed polypharmacology to develop novel dual inhibitors that simultaneously target JAK2 kinase activity as well as BET domains. We have also been assessing the PIM family of serine threonine kinases as therapeutic targets for MPNs. Our current studies demonstrate that a novel PIM inhibitor (INCB053914) displays impressive synergistic effects with ruxolitinib in pre-clinical models of MPN and supports the development of a clinical trial to test this combination in MPN patients.

Biography

Dr. Gary Reuther is an associate member in the Department of Molecular Oncology at the Moffitt Cancer Center in Tampa, Florida. He received his Ph.D. from Duke University in 1997 and did his post-doctoral training at the University of North Carolina at Chapel Hill. His research focuses on developing novel therapeutics to improve the lives of patients with myeloproliferative neoplasms, a family of disorders that affects about 300,000 people in the U.S. Throughout his career, Dr. Reuther has received research funding from the NIH, ACS, Jimmy V Foundation, Leukemia and Lymphoma Society, and MPN Research Foundation, among others.

Anticancer Activities of Newer Tetraoxane Analogs

Arvind Kumar1, Kantha Chindera2, Smita T Karegodar2, Martin Widschwendter2 and Satish K. Awasthi3

1Chemical Biology Laboratory, Department of Chemistry, University of Delhi, DL, India
2Department of Women's Cancer, UCL EGA Institute for Women's Health, London, UK

Abstract

Ovarian cancer is the most lethal gynaecological cancer. Though several risk factors are associated with ovarian cancer, presence of germline BRCA1 and BRCA2 mutations predispose a woman for more than 45% risk of developing high grade serous ovarian cancer. Inflammation is one of the important driving factors for ovarian carcinogenesis. Use of compounds that could block inflammation or downstream signaling pathways can be treated as potential prevention strategies for population at high risk. Despite massive efforts, none of the current drugs have been shown to improve ovarian cancer survival rate. Platinum based compounds are the main line of therapy for ovarian cancer. However, rapid resistance against platinum compounds further complicates treatment in recurrence cases. There is an unmet need for alternative therapeutics as well as novel preventive strategies. Trioxane and tetraoxane compounds used for antimalarial activity can be screened anticancer activity if they target inflammatory pathways leading to ovarian cancer.

In this study, we screened tetraoxane-based compounds for anticancer activity against SKOV3 and HOC7 cells and evaluated their potential as preventives as well as therapeutics for ovarian cancer. The MTT assay was used to study the growth inhibitory effects. Gross microscopic changes and influence on cell proliferation were examined. We found five active lead compounds showing promising anti-proliferative activity. We hypothesized that tetraoxane-based compounds block inflammatory pathways responsible for ovarian cancer, thus inhibiting proliferation of ovarian cancer cells. Elaborate experiments are underway to elucidate their mechanism of action. We anticipate that our preliminary findings on the
potential use of tetraoxane compounds as promising preventive or therapeutic alternatives for high grade serous ovarian cancer will have immense clinical implications.

**Biography**

Prof. Satish Kumar Awasthi did D. Phil from University of Allahabad, Allahabad, UP, India in 1991. He is recipient of several National and International awards. It includes TIT-UNICEF fellowship in Japan, INSA Visiting Fellowship, in Germany, the Commonwealth Academic Award in UK etc. Dr Awasthi has published more than 75 papers in various journals, six book chapters and one national patent. His current research interest is design and synthesis of small molecules to various targets including cancer and malaria and antisense studies of peptide-nucleic acid (PNA).

**1,2,3 Triazole Tethered Chalcone and Flavone Hybrids as Potential Cytotoxic & Antimicrobial Agents**

Alka Agarwal  
*Department of Medicinal Chemistry, Banaras Hindu University, Varanasi, UP, India*

**Abstract**

The organic compounds containing chalcone and flavone scaffold as a core unit exhibit various biological and pharmaceutical activities. Chalcones containing several functional groups showed a wide spectrum of biological activities such as antimicrobial, antimalarial, anticancer, anti-inflammatory, antileishmanial, antiprotozoal, anti-HIV, antioxidant and antiulcer activities. Flavones and their derivatives have also been found to display antioxidant, antimicrobial, anticancer, antimalarial, anti-inflammatory, antiulcer, antileishmanial and anti-HIV properties.

In recent years, 1, 2, 3-triazoles have gained special attention in the drug discovery because several drug molecules contain 1, 2, 3-triazole group such as Tazobactam, Cephalosporin and Cefatrizine. They are clinically used for the treatment of bacterial infections. It is well known that the combination of two or more types of pharmacophores into one molecule could afford a new entity with increased bioactivities. In present work we designed and synthesized a small library of 1, 2, 3-triazole linked chalcone and flavone conjugates for their antimicrobial, antiplasmodial and cytotoxic activities.

The compounds of chalcone series showed promising antibacterial activity with MIC 6.25 μg/mL against *S. aureus* (ATCC 25323), *E. faecalis* (ATCC 29212), *E. coli* (ATCC 35218) and *S. boydii* (clinical isolate) which is similar to ciprofloxacin MIC 6.25 μg/mL. The compound contain two triazole moieties in chalcone series showed promising antibacterial activity with MIC 6.25 μg/mL against *E. faecalis* (ATCC 29212), *E. coli* (ATCC 35218) and *S. boydii* (clinical isolate). Compound containing two triazole moieties in flavones series showed potent antifungal activity with MIC 6.25 μg/mL against *C. albicans* (ATCC 90028) One of chalcone compound showed IC₅₀ 2.74 μg/mL *in vitro* against the erythrocytic stages of *P. falciparum* (3D7 strain).

**Biography**

Dr. Alka Agarwal’s research group is mainly working on design, synthesis and characterization of novel molecules against various microbes including bacteria, fungi, malaria and cancer. Recently they have made significant contribution in applied science. Their research is much diversified from single x-ray crystal analysis to modern drug discovery to cure microbial infection and cancer which is more prevalent in India. Dr. Agarwal have DST funded INDO-UK International Project in collaboration with University of Delhi, Delhi. She got Indian National Science academy (INSA) award – International Exchange Visiting Scientist Award and visited Ruhr University Bochum, Germany. She has delivered many lectures in National and International Universities have published more than 60 papers in reputed journals.
Immunomodulating Drugs (Imids) for the Treatment of Chronic Lymphocytic Leukemia - The Complete Story

Asher A. Chanan-Khan
Mayo Clinic Cancer Center, NCI Designated Comprehensive Cancer Center, FL, USA

Abstract

TIMIDs are novel therapeutic agents that have made significant impact in various B cell cancers. In CLL thalidomide and its derivative lenalidomide demonstrated interesting anti-leukemic effects that seems to be through modulation of the immune microenvironment. From the first report of its clinical activity in CLL to the most recently published Phase III clinical trial it is now evident that lenalidomide may have an important role as a CLL therapeutic and that this effect on the CLL cell is mediated through both modulation of the CLL cell as well as its microenvironment.

Renal Toxicities in Targeted Therapies

Tendulkar Ketki
University of Nebraska Medical Center, NE, USA

Abstract

A wide variety of toxicities associated with incorporation of targeted therapies in routine cancer therapy, are now well-recognized. Management of these toxicities are distinct from those seen with conventional cytotoxic agents all of which are a part of our armamentarium against cancer. Anti-vascular endothelial growth factor (VEGF) agents including the monoclonal antibody bevacizumab, aflibercept (VEGF trap), and anti-VEGF receptor (VEGFR) tyrosine kinase inhibitors (TKIs) can all cause elevated blood pressure and proteinuria needing close monitoring. Monoclonal antibodies against the human epidermal growth factor receptor (HER) family of receptors, can cause electrolyte imbalances due to the direct nephrotoxic effect of the drug on renal tubules needing high dose supplementation. The TKIs, can lead to long term chronic kidney disease. Rituximab, an anti-CD20 monoclonal antibody, can cause more acute injury with tumor lysis syndrome. Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, can cause acute kidney injury with proteinuria. Streamlining relatively safe treatment strategies depending on the renal adverse effects resulting from these agents is essential for, the well-being of patients particularly in those with multiple medical comorbidities. Feasibility of continuation of therapy inspite of renal toxicities for the overall benefit remains a challenge. Such dilemmas in clinical practice, highlights the need for discussion of kidney biopsy which can reveal type and acuity of injury to facilitate management decisions, not only of the kidney disease, but also of the underlying malignancy.

Biography

Dr. Ketki Tendulkar is an assistant professor with the Division of Nephrology at the University of Nebraska Medical Center. Her research interests include malignancy related chronic kidney disease and acute kidney injury. She is also actively involved in the kidney donor evaluation at the University hospital.

Engineering Pancreatic Cancer from Normal Human Tissue

Jun Liu1, Naoki Akanuma1, Michael Nipper1, Ming Gao1, Kaitlyn R. Bejar1, Xue Yin1, Francis E. Sharkey3, Aatur D. Singhi1, Huamin Wang4, Howard C. Crawford1 and Pei Wang1

1Department of Cellular and Structural Biology, The University of Texas Health Science Center at San Antonio, SA, USA
2Department of Pathology, The University of Texas Health Science Center at San Antonio, SA, USA
3Department of Pathology, University of Pittsburgh Medical Center, PA, USA
4Department of Pathology, The University of Texas M.D. Anderson Cancer Center, TX, USA
5Department of Molecular and Integrative Physiology & Internal Medicine, University of Michigan Health System, MI, USA

Abstract

Over the past thirty years, the survival rate for many cancers has improved, but pancreatic ductal adenocarcinoma (PDAC) continues to be the most deadly common cancer with a five-year survival rate of less than 7%. Few models are available to study the molecular mechanisms of human PDAC tumorigenesis. Lineage tracing experiments in mouse PDAC models demonstrated that pancreatic intraepithelial neoplasia (PanIN) lesions are mainly derived from acinar cells undergoing acinar to ductal metaplasia (ADM), suggesting that ADM might be an early event that promotes KRAS-driven PDAC tumorigenesis. We have developed a flow cytometry based system to identify and separate acinar and ductal cells from normal human pancreatic tissue. We showed that, unlike mouse acinar cells, human acinar cells undergo ADM though TGFβ signaling. This system allows us for the first time to isolate and culture human acinar and ductal cells, providing an experimental method to investigate whether human acinar and ductal cells can be transformed to PDAC. To model
human PDAC development, we introduced the four most frequent mutations in PDAC, KRAS, p16, p53, and SMAD4, into human acinar and ductal cells. Two million of the genetically modified acinar derived ductal like cells (AD cells) or ductal cells were transplanted subcutaneously or orthotopically into NOD-SCID mice. The xenografts were harvested two months after transplantation. Pathological analysis found that invasive PDAC was generated from both acinar and ductal cells. However, only acinar derived PDACs had liver metastasis. Thus, for the first time, we have generated PDAC from normal human acinar and ductal cells, suggesting that both cell types can be the origin of PDAC. Our model provides a unique system to study many aspects of human PDAC development including investigating early tumor initiation events, identifying early detection markers, testing the driver and passenger mutations found in patients, and evaluating the drugs and treatments for PDAC.

Grant Support: Jun Liu was supported by a post-doctoral fellowship through Cancer Prevention Research Institute of Texas (CPRIT) Research Training Award RP140105. Ming Gao and Yue Yin are supported by a pre-doctoral fellowship through CPRIT Research Training Award RP 170345. Pei Wang is CPRIT scholar and funded by First time faculty award from CPRIT.

Biography

Dr. Pei Wang received Ph.D from Baylor College of Medicine in 2004. She did her postdoctoral training in Seung Kim lab at Stanford University. After that she joined University of Texas Health Science Center at San Antonio in 2012 as a tenue track assistant professor working on pancreas related diseases including pancreatic cancer, pancreatitis and diabetes. She received CPRIT first time faculty award in 2012. She was awarded an R21 from NCI to study pancreatic cancer and RO1 from NIDDK to study Hippo signaling pathway in pancreas.

E3 Ubiquitin Ligases as Drug Targets in Human Cancer

Chia-Hsin (Lori) Chan*, Hong-Jen Lee, Diane Ruan and Jiabei He
Department of Pharmacological Sciences, Stony Brook University, NY, USA

Abstract

Cancer stem cells (CSCs) are pluripotent with a self-renewal capacity that allows a small number of cells to give rise to numerous, differentiated progeny. CSCs resist cytotoxic chemotherapy and drive metastasis. Thus, finding a way to target CSCs is important for developing effective cancer adjuvant therapy. Cell-based and animal studies have established that Twist is fundamental regulator of CSC feature and progression. Twist is an appealing drug target for CSC; however, the strategy to directly target Twist remains elusive because it lacks a drug-binding domain as a transcription factor. Ubiquitination conjugated through ubiquitin lysine 63 (K63) is a recently identified regulatory modification of proteins that is distinct from the canonical K48-linked ubiquitination for protein degradation. My laboratory now has recently reported that K63 ubiquitination as an important posttranslational modification that controls Twit activation and subsequent CSC phenotypes. K63 ubiquitination of Twist is mediated by specific E3 ubiquitin ligases; thus identifying the E3 ubiquitin ligases for EMT-TF activation offers a class of molecular targets for mechanism-driven drug discovery.

†This work is supported by New York State Department of Health (DOH01-G31845GG-3450000), National Institute of Health (K22CA181412) and TRO Carol M. Baldwin Award.

Biography

Dr. Lori Chan is an Assistant Professor of Pharmacological Sciences at SUNY-Stony Brook University. She earned her BS and PhD degrees at National Taiwan University, Taiwan. Dr. Chan undertook postdoctoral studies at M.D. Anderson Cancer Center, USA. Dr. Chan received a number of accolades, which includes the Odyssey Outstanding Research Publication Award, AMGEN Award in Basic Science Research, Breast Cancer SPORE Career Development Award, Komen Postdoctoral Fellowship Award, Feldstein Medical Foundation Award and recently the Komen Career Catalyst Research Award. The Chan lab focuses on identification and characterization of cancer-promoting E3 ubiquitin ligases as new drug targets by suing a series of complementary approaches including biochemical studies, preclinical animal models and clinical specimens. Currently, we are undertaking the questions regarding the roles of cancer-associated E3 ligases in cancer metabolic reprogramming, metastasis and stemness.
Regulatory Role of ADAM10 Protease and It’s Substrates in Pancreatic Cancer

Jaya Padmanabhan  
Dept. of Tumor Biology, H. Lee Moffitt Cancer Center and Research Institute, FL, USA

Abstract

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers with a 5-year overall survival rate of ~6%. Currently there are no effective therapies to treat this cancer and it is expected that by 2030 PDAC will rise from 4th to 2nd rank as the leading cause of cancer-related deaths in the United States. The absence of early detection methods and the aggressiveness of the disease at the time of detection contribute to the increased lethality in PDACs. Additionally, the dense desmoplastic nature of the PDAC stroma prevents drug accessibility to the tumor thus contributing to the failure in current therapies. PDAC stroma mainly consists of cancer-associated fibroblasts (CAFs) and immune cells and the growth of tumor is supported by secreted factors, including growth factors, in the tumor microenvironment. An understanding the molecular mechanisms that contribute to the enrichment of tumor microenvironment would enable us to target these for novel drug development. Recently we showed that ADAM10 (A Disintegrin and Metalloprotease 10), a protease involved in ectodomain cleavage of many membrane-targeted growth factors and receptors, contribute to the drug resistance in pancreatic cancer cells. We showed that inhibition of ADAM10, as well as its knockdown, prevented ectodomain shedding of its substrates and enhanced the sensitivity of cancer cells to gemcitabine. Furthermore, since ADAM10 is activated in response to calcium influx, we tested the efficacy of calcium channel blockers on PDAC cells and found that in addition to enhancing the cytotoxicity, these agents affected the vesicular trafficking and membrane targeting of ADAM10 and its substrates. These cells also showed reduced migration and invasion as well diminished colony formation on soft agar, indicative of a potential role for ADAM10 and its substrates in metastasis of PDAC cells. Preliminary studies indicate that Rab GTPases would be responsible for the altered trafficking of ADAM10 and its substrates and interfering with their function would reduce the growth and metastasis of cancer cells. These novel findings imply that an understanding of the molecular machinery involved in the intracellular trafficking and membrane targeting of ADAM10 and its substrates would enable the development of novel targeted therapies that would enhance tumor response to established treatment strategies in PDAC.

Biography

Dr. Jaya Padmanabhan obtained her Ph.D. in Biochemistry from the University of Kerala, India, in 1988. After successful post-doctoral training at Duke University Medical Center and Columbia University, she joined the University of South Florida. She became an Assistant Professor in the Dept. of Molecular Medicine in 2010. She currently works at the Moffitt Cancer Center, with a joint appointment in the University of South Florida. Her work focuses on the common molecular events that drive neurodegeneration as well as pancreatic cancer, with an emphasis on targeting cell cycle regulatory pathways to combat cancer as well as certain neurodegenerative diseases.
Pomegranate Phytochemicals Target Inflammatory Signaling to Confer Prevention of Mammary Carcinogenesis

Anupam Bishayee
Department of Pharmaceutical Sciences, College of Pharmacy, Larkin University, FL, USA

Abstract

Pomegranate (*Punica granatum* L.), an ancient, mystical and distinctive fruit, represents a reservoir of bioactive phytochemicals with extraordinary medicinal value. Pomegranate fruits have been used for centuries for prevention and treatment of various diseases, including inflammation-driven ailments. Various *in vitro*, *in vivo* and clinical studies demonstrate chemopreventive and therapeutic actions of pomegranate-derived substances, including juice, extracts as well as phytoconstituents, against colon, lung, prostate and skin cancer. Based on our earlier study, a characterized pomegranate emulsion (PE) containing various phytochemicals including, caffeic acid, ellagic acid, gallic acid, protocatechuic acid, punicalagins, 17-α-estradiol and γ-tocopherol, was found to exert a striking inhibition of dimethylbenz(a)anthracene (DMBA)–initiated rat mammary tumorigenesis via antiproliferative, proapoptotic and estrogen receptor signaling-modulatory mechanisms. The aim of the present work was to investigate anti-inflammatory mechanism of action of PE during DMBA-induced rat mammary tumorigenesis by analyzing the expression of cyclooxygenase–2 (COX–2), heat shock protein 90 (HSP90), nuclear factor–κB (NF–κB) and nuclear factor erythroid 2p45-related factor 2 (Nrf2). Mammary tumor samples from our previous chemopreventive study were utilized to detect the expressions of COX–2, HSP90, NF–κB, inhibitory κBα (IkBα) and Nrf2 by immunohistochemical techniques. PE lowered the expression of COX–2 and HSP90, reduced the degradation of IkBα, blocked the translocation of NF–κB from cytosol to nucleus, and elevated the expression and nuclear translocation of Nrf2 during DMBA-induced mammary carcinogenesis. These interesting findings in conjunction with our previous data clearly indicate that pomegranate phytochemicals suppress DMBA--initiated mammary tumorigenesis through anti-inflammatory mechanisms mediated through two interrelated molecular pathways, namely NF–κB and Nrf2 signaling.

Biography

Dr. Anupam Bishayee is a Professor and Chair at the Department of Pharmaceutical Sciences, College of Pharmacy, Larkin University, Miami, Florida. Dr. Bishayee has 25 years’ experience in pharmaceutical education, research, teaching, and administration. Dr. Bishayee’s research focuses on elucidation of mechanism–based cancer preventive and therapeutic effects of medicinal plants, natural products, dietary, and synthetic agents using several pre-clinical models of cancer. Various projects of Dr. Bishayee are funded by the National Institutes of Health as well as private pharmaceutical/biotechnological companies. Dr. Bishayee has published nearly 150 original research papers and review articles, mostly in high-impact journals, 12 book chapters, and 65 abstracts as well as delivered more than 30 invited presentations. Dr. Bishayee is the Editor-in-Chief of the *Journal of Natural Products in Cancer Prevention and Therapy* and is serving as an editorial board member and reviewer of more than 60 reputed journals.

Anticancer Mechanisms of a Supercritical CO2 Extract of Mango Ginger (*Curcuma amada* Roxb.)

Steven J. Melnick* and Cheppail Ramachandran2
1Nicklaus Children’s Hospital, FL, USA
2Dharma Biomedical, L.L.C. FL, USA

Abstract

Mango ginger (Curcuma amada Roxb.) is among the less-investigated species of Curcuma for anticancer properties. We have investigated the *in vitro* and *in vivo* anticancer mechanisms of a supercritical CO2 extract of mango ginger (CA) in human glioblastoma (U-87MG) and human alveolar (SJRH30) and embryonal (RD) rhabdomyosarcoma cell lines. The labdane diterpene, (E)-Labda-8(17),12-diene-15,16 dial (LDD) is most abundant compound followed by other terpenoids. *In vitro* cytotoxicity with CA is greater than temozolomide, etoposide, irinotecan and curcumin in the U-87MG cells and greater than vinblastine, cyclophosphamide and curcumin in SJRH30 and RD cells. Synergy analysis with CompuSyn software reveals synergism between CA the chemotherapeutic drugs used in each cell line. *In vivo* studies in U-87MG and SJRH30 xenograft mice demonstrated comparable or greater efficacy in reduction of tumor growth and increased survival compared to the chemotherapeutic drugs (irinotecan and vinblastine respectively) and synergy with CA-drug combinations. *mRNA* and protein expression studies showed that CA modulates expression of genes associated with apoptosis (Bax, Bcl-2, Bcl-X, BNIP3, caspase-3, mutant p53, and p21), cell proliferation (Ki67) and angiogenesis (VEGF), *in vitro* and *in vivo* and down regulation of AMPKα and AKT phosphorylation, HSP90 and inhibition of cell migration in a dose-dependent manner. Exploration of mechanisms attributed to the Warburg effect demonstrated that the combination of CA with glycolytic inhibitors; 2-deoxy-D-glucose (2-DG) and sodium oxamate (SO) inhibits growth, proliferation and migration in U-87MG cells. Preliminary studies evaluating mechanisms of the reverse Warburg effect describe interactions between cancer cells and cancer-associated and reactive fibroblasts.
Biography

Dr. Steven Melnick currently serve as Chief, Department of Pathology and Clinical laboratories at Nicklaus Children’s Hospital. His academic background includes a B.Sc. in Physics (McGill) and Ph.D. in Chemistry (McGill) in the fields of nuclear quadrupole resonance and theoretical chemistry. Dr. Melnick completed his M.D. from Queens University, Kingston, Ontario and have since pursued cell and molecular biology in the fields of cancer and medicinal product development based on natural sources. This led to the establishment of a research laboratory dedicated to ethnobotanical medicinal research that has produced peer-reviewed publications, intellectual property and an extensive pipeline of botanical-based products for future development.

Dietary Polyphenols as Epigenetic Modulators: Progress and Challenges

Sanjay Gupta
Department of Urology, Case Western Reserve University & The Urology Institute, University Hospitals Cleveland Medical Center, Cleveland, OH, USA

Abstract

Diet and lifestyle factors contribute to cancer development by inducing both epigenetic and genetic changes that, in combination with genetic make-up, result in the disruption of key cellular processes leading to neoplastic progression. Dietary polyphenols have been reported to demonstrate many interesting biological activities, including induction of epigenetic changes and cancer prevention. We have recently demonstrated that polyphenols derived from green tea and dietary flavones abundantly present in common fruits and vegetables have ability to reactivate several tumor suppressor genes which has relevance to cancer. In searching the mechanism of the anticancer properties of dietary polyphenols, we observed that these promising compounds alter epigenetic mechanisms at various levels. The presentation will discuss these epigenetic modifications elicited by dietary polyphenols, current progress made in this area along with challenges encountered. Understanding the mechanism(s) of epigenetic regulation and its reversibility by dietary polyphenols will result in the development of new strategies for the prevention and/or treatment of cancer.

An Immunomodulatory Role of Bitter Melon Extract in Inhibition of Head and Neck Squamous Cell Carcinoma Growth

Ratna B. Ray
Department of Pathology, Saint Louis University, St. Louis, MO, USA

Abstract

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer and leading cause of cancer related mortality worldwide. Despite the advancement in treatment procedures the overall survival rate of patients has not considerably enhanced in the past few decades. Therefore, new strategies to achieve a favorable response for the improvement in the prognosis of HNSCC are urgently needed. In this study, we examined the role of bitter melon extract (BME) in HNSCC tumor microenvironment. Mouse head and neck cancer (SCCVII) cells were subcutaneously injected into the flanks of syngeneic mice. We observed that oral gavage of BME significantly inhibits the tumor growth in mice as compared to control group. We next investigated the role of BME as an immunomodulator in HNSCC model. Forkhead box protein P3+ (FoxP3+) T cells suppress tumor immunity. We observed that BME treatment decreases the infiltrating regulatory T (Treg) cells by inhibiting FoxP3+ populations in the tumors and in spleens. Additionally, BME treatment reduces Th17 cell population in the tumor. However, BME treatment did not alter Th1 and Th2 cell populations.

The role of BME in NK-cell modulation against HNSCC remains unknown. We observed that treatment of human NK-cell line (NK3.3) with BME enhances ability to kill HNSCC cells. BME increases granzyme B accumulation and translocation/accumulation of CD107a in NK3.3 cells exposed to BME. An increase in cell surface expression of CD16 and NKp30 in BME-treated NK3.3 cells was observed when co-cultured with HNSCC cells. Interestingly, we did not observe NK cell modulation in HNSCC mouse model. Together, our findings offer a new insight into how bitter melon extract inhibits HNSCC growth by modulating NK cell activation and Treg populations, implicating an immunomodulatory role of BME.

Biography

Dr. Ratna Ray is a professor of Pathology at the Saint Louis University, Missouri in USA. Ratna did her MS and PhD from the Calcutta University. She did her post-doc at the University of Alabama in Birmingham in cancer research. She moved to Saint Louis University and joined as an assistant professor and rose to professor in 2005. She is also a member of the Cancer Center of Saint Louis University and Washington University. Dr. Ray’s laboratory is well funded by NIH. She is interested in cancer prevention and therapy related work, as well as HCV mediated liver disease progression. She has more than 120 peer-reviewed publications. Ratna is member several scientific societies and editorial board member of several journals.
Targeting the Proteasome Pathway for Cancer Treatment: Lessons from Mother Nature

Rahul R. Deshmukh
LECOM–School of Pharmacy, Bradenton, FL, USA

Abstract
Ubiquitin proteasome system (UPS) has an important role in maintaining normal cellular functions. Unfortunately, it is exploited by the cancer cells for survival and proliferation. This led to emergence of UPS as a valid therapeutic target resulting in the development of proteasome inhibitors (PIs). So far, very few PIs such as bortezomib, carfilzomib, and ixazomib got approval by the Food and Drug Administration. However, inherent and acquired resistance and toxicities for PIs have been observed in cancer patients. There is an urgent, unmet need for novel PIs that are better than existing agents in terms of safety and efficacy. Natural compounds have great potential in this regard. Whether these natural compounds could be used as it is or as templates to design and develop novel PIs needs to be seen.

Biography
Dr. Rahul Deshmukh received his Bachelor of Pharmacy degree from University of Pune and Master of Pharmacy degree from Bharati Vidyapeeth University, India. He also received his Master of Science in Pharmaceutical Sciences degree from University of Maryland, Baltimore. He completed his PhD from Wayne State University. His PhD research was focused on the study of crosstalk between 5’-AMP-activated protein kinase (AMPK) and ubiquitin proteasome system (UPS) as well as novel ways to sensitize solid tumors to proteasome inhibitors.

With more than 15 years of research experience, his research focuses on ‘drug design and discovery’, ‘natural products’ and ‘repurposing the FDA approved drugs for the treatment of cancer’. Dr. Deshmukh has contributed to 12 publications including original research, review articles and a book chapter. Currently, he works as an Assistant Professor of Pharmaceutical Sciences at LECOM–School of Pharmacy. He also serves as an ad hoc reviewer and editorial board member for several peer reviewed scientific journals.

Targeting Glioblastoma Stem Cells with Curcumin and Curcumin Analogs

Regina M. Graham*, Zachary Gersey, Gregor Rodriguez, Winston Walters, Nadia Myrthil, Denis Ortega Loni, Wanda Gonzalez, Eduardo Veliz, Roger M. LeBlanc and Steven Vanni
University of Miami, FL, USA

Abstract
Glioblastoma is one of the worst diagnoses a patient can receive with an overall survival of 15 months. This poor outcome is attributed to the presence of radio and chemotherapy resistant glioblastoma stem cells (GSCs), which drive tumor regrowth following therapy. Curcumin is a bioactive compound known to have anti-tumor activity in multiple types of cancers. Here we investigated the effects of curcumin and several novel curcumin analogs on GSCs.

GSC lines were derived from patient tumor specimens and characterized by multiple putative stem cell markers. Curcumin induced dose-dependent cell death with an average IC50 (five GSC lines) of approximately 25mM. Furthermore, curcumin increased reactive oxygen species (ROS) levels, induced robust MAPK activation, inactivated STAT3 and down-regulated the STAT3 target and pro-survival protein survivin. All these effects were reversed with the ROS inhibitor N-acetylcysteine. Furthermore, treatment with low-dose curcumin (2.5mM) significantly inhibited neurosphere formation in the GSC lines. Examination of the14 curcumin analogs, synthesized via Claisen-Schmidt reaction, revealed 4 that were approximately 5-10 fold more effective than curcumin (IC50’s ranging from 2.7-5.8mM) in inducing GSC death. Similar to curcumin, these analogs induced apoptosis, however the mechanism of action appears to be different than that of curcumin.

These results indicate that curcumin induces ROS mediated down-regulation of STAT3 and survivin, two proteins important for GSC survival and self-renewal. Clinically relevant doses of curcumin significantly inhibited the self-renewal properties of GSCs—important for the chemotherapy targeting GBM relapse. Curcumin and curcumin based analogs warrant further study for GBM treatment.

Biography
Dr. Regina M. Graham received her undergraduate degree from Stony Brook University and her Ph.D. from Tulane University. She performed her postdoctoral training at the University of Miami in pharmacology before receiving a faculty position in Neurological Surgery. Dr. Graham is Director of the University of Miami Brain Tumor Initiative (UMBTI) Research Laboratory and Director of Research for the Mystic Force Foundation, which supports childhood cancer research. Research interests include development of natural products and natural product derivatives for cancer therapy, nanoparticles as a platform to target and deliver chemotherapies to cancer cells, and tumor metabolism as a therapeutic target.
Targeting Growth Factors by the Cures of Mother Nature

Mükerrem Betül Yerer Aycan
University of Erciyes, Faculty of Pharmacy, Pharmacology Department, Kayseri, Turkey

Abstract

Growth factors are one of the main factors responsible from the uncontrolled cell progress in cancer. Up to date many scientists have focused on these factors either as the marker or as the targets in several cancer types. Mainly the drugs are designed to target these factors are monoclonal antibodies. Nerve growth factor (NGF), epidermal growth factor (EGF), hepatocyte growth factors (HGF), fibroblast growth factors (FGF), vascular endothelial growth factors (VEGF), platelet derived growth factor (PDGF), transforming growth factor (TGF-β) are some of these factors not only increasing the ability of cell proliferation but also playing crucial roles in triggering the invasion and metastasis of the cells.

The herbs that are traditionally used for anticancer treatment and target multiple interdependent processes. Given the multiple effects of these agents, their future use for cancer therapy probably lies in synergistic combinations. For instance, Artemisia annua, Viscum album, Curcuma longa, Camellia sinensis, Vitis vinifera, Angelica sinensis, Taxus brevifolia, are some of the herbs that has shown to affect VEGF and those which have additional effects on the molecules related to cancer progress and further can target other growth factors. During active cancer therapy, they should generally be evaluated in combination with chemotherapy and radiation. In this role, they act as modifiers of biologic response, potentially enhancing the efficacy of or reducing the resistance to the conventional therapies. The tumor microenvironment may be more sensitive to a cocktail of natural products administered continuously at relatively low doses than to single-agent pharmaceutical compounds administered intermittently at higher dose levels alone.

Biography

Dr. Mukerrem Betül Yerer Aycan, is an Assoc. Prof. and Chief of Pharmacology Dept. at University of Erciyes, Faculty of Pharmacy. Prior to this she had held the position of Vice-Dean of the same Faculty for 8 years. Dr. Yerer Aycan is a pharmacist and she has been completed around 40 research projects up to date. Subsequently, she is a group leader of a research team working especially on inflammation and inflammation related diseases such as neurodegeneration and cancer. She is still a board member of the Drug Research and Development Center of the Erciyes University and mainly working on the personalized medicine applications in cancer.

Nanoparticulate Drug Delivery in Cancer Therapy

Yeşim Aktaş
Erciyes University, Faculty of Pharmacy, Department of Pharmaceutical Technology, Turkey

Abstract

Conventional therapeutic applications have significant shortcomings since the cytotoxic drug is distributed nonspecifically in the body affecting both cancer and healthy cells. For this reason several attempts have been done for the active and passive targeting of the therapeutic molecule to the tumor tissue, thus minimizing the drug amount and adverse effects in the normal tissue. Drug delivery systems such as micelles, dendrimers, liposomes, solid lipid carriers, gold carriers, viral carriers, nanotubes and magnetic carriers are developed for the efficient delivery of the cytotoxic molecules with minimum undesired effects in cancer therapy. In order to improve the biodistribution of therapeutic molecules, drug carriers have been designed in optimal size and modified surface properties. These nanosized carriers are able to diminish the toxicity of the therapeutic agents in the neighborhood cells and selectively increase the drug accumulation within the cancer cells. Besides these advantages, nanodrug carriers have the opportunity to overcome the solubility and the stability problems of the drug molecules.

Biography

Dr. Yeşim AKTAŞ graduated from Hacettepe University Faculty of Pharmacy in Turkey. She received her M.Sc degree in the same university. She finished her Ph.D. thesis in Hacettepe University and Paris Sud University as “co-tutelle” in pharmaceutical technology. She has 15 original research articles, 3 book chapters and approximately 30 oral and poster presentations in international scientific meetings about micro/nanoparticulate drug delivery systems. Currently she is working in Erciyes University as the head of department of pharmaceutical technology and head of Pharmaceutical Product Application and Research Center.
Structure Activity Relationship Studies of Limonoids and their Derivatives as Potential Anti-Cancer Agents

Kalyan C. Nagulapalli Venkata
Department of Pharmaceutical Sciences, College of Pharmacy, Larkin University, Miami, FL, USA

Abstract

Plants have evolved through time and developed numerous defense mechanisms to thwart pests and pathogens for their survival. In order to overcome this innate pressure, plants synthesize unique and diverse molecules. The biochemical synthesis of vast array of phytochemicals is one such employed mechanism. There are many classes of compounds with insecticidal and anti-feedant activities, and limonoids are prime examples of this group. Limonoids are one of the major classes of phytochemicals along with flavonoids, coumarins, and carotenoids in Meliaceae and Rutaceae families. Limonoids are oxygenated triterpenoids derived from a precursor with furanylsteroid skeleton, which is prone to oxygenation and rearrangement reactions. It has been demonstrated in number of secondary metabolites, including limonoids, which small changes in basic structure due to chemical transformations would result in significant alterations in their biological activities. Number of biological studies have advanced our understanding about the disease prevention and therapeutic properties of limonoids. Due to their ability to suppress cell proliferation and induce apoptosis, limonoids have been investigated for their potential anti-cancer properties. The aim of this presentation is to analyze the chemistry, structure activity relationships and rational design efforts towards the development of limonoid analogs as anti-cancer molecules.

Biography

Dr. Kalyan C. Nagulapalli Venkata is an Assistant Professor at Department of Pharmaceutical Sciences of Larkin University College of Pharmacy, Miami, Florida, USA. Dr. Venkata has more than 10 years combined experience in pharmaceutical industry and academia. Dr. Venkata's research interests encompass the isolation, identification and synthesis of natural products relevant to inflammation and cancer. Dr. Venkata has expertise in computational modelling methods and utilizing advanced spectroscopic techniques towards identifying novel natural products. Dr. Venkata has published his work related to cancer in high-impact peer-reviewed journals, such as Molecular Cancer Therapeutics, British Journal of Cancer and Seminars in Cancer Biology.

Withaferin A Causes Reduction of Key Stem-Cell Regulators Inducing Neuroblastoma Differentiation

1Mystic Force Foundation, Department of Neurosurgery, University of Miami, FL, USA
2Miami Children's Hospital, Miami, FL, USA

Abstract

Neuroblastoma (NB), the most common extra-cranial solid tumor in children, originates from the precursor neuroblasts of the sympathetic nervous system. NB accounts for approximately 7-10% of childhood cancers and 15% of childhood cancer death. Despite an aggressive treatment regimen, the 5-year survival for high-risk NB remains less than 50%. The differentiation of NB cells into mature cells represents a promising strategy for NB therapy. Withania somnifera has been used for centuries in Ayurvedic medicine, and its derivatives have been shown to affect multiple pathways important for cancer progression in breast, prostate and pancreatic cancers.

Our data indicates that WA induces NB stem-like cell death, and promotes ROS-mediated NB cell differentiation. WA promoted morphologic alterations (neurite outgrowth) in dose-dependent manner. Immunocytochemistry and western blot analysis indicated an increase in neuronal markers, as well as a decrease in stem cell markers. WA also promoted ROS induction, which could be prevented with NAC pretreatment. NAC also prevented morphological changes and inhibited changes in stem cell and differentiation marker expression seen with WA treatment – suggesting ROS induction to be the likely mechanism of WA-induced differentiation. WA also induced NB stem-like cell death in a dose-dependent manner, and significantly inhibited neurosphere formation at concentrations as low as 50nM, which did not exhibit cytotoxicity in regular cell culture conditions. Differentiation therapy aims to reduce tumor regrowth following high-dose chemotherapy and stem cell transplant in patients classified as high-risk. WA holds great promise as a novel alternative NB treatment strategy for children with persistent minimal residual disease.

Biography

Gregor is a 4th year Medical Student at University of Miami Miller School of Medicine. He has been researching anticancer therapies for 6 years now, since he was a junior in college, mainly focusing on natural treatments such as Curcumin and Withaferin A on glioblastoma, neuroblastoma, and other CNS malignancies under the guidance and vision of Dr. Regina Graham. He is currently applying to residency in Internal Medicine with future plans of specializing in Hematology/Oncology, and continuing research on novel anticancer therapies, especially natural treatments such as Curcumin and Withaferin A.
Organ Specific Cancer

Functional Genomics in Gastroesophageal Cancer: Can We Target?

Wael El-Rifai
Sylvester Comprehensive Cancer Center, University of Miami, FL, USA

Abstract
Over the past few years, we have come to appreciate the extent of molecular complexity and heterogeneity in cancer cells as important factors in determining response to therapy. The standard first-line chemo-radiotherapy approaches in gastric and esophageal cancer (GEC) patients have shown high toxicity with limited efficacy in the treatment of a significant number of GEC patients. The molecular analysis of cancer cells has uncovered key genetic and epigenetic alterations underlying the development and progression of tumors. Cancers with chromosomal instability are characterized by massive DNA copy number gains and losses across their genome. Gastric and esophageal adenocarcinomas fit this profile where genomic amplifications are frequently detected. The emerging understanding of the molecular mechanisms of carcinogenesis has helped to identify key molecular pathways and druggable targets in cancer. These drugs inhibit or interfere with key molecules or signaling pathways that regulate cell growth and proliferation, angiogenesis, apoptosis, invasion and metastasis, and inflammation. Several oncogenic pathways are activated due to genomic amplifications or mutations of key signaling molecules such as RTKs, KRAS, and AURKA are present in these cancers. However, targeting many of these signaling pathways has been less effective than anticipated. The recent identification of Aurora kinase A (AURKA), at the 20q region, as an important molecular player in these cancers suggest that targeting AURKA may be an effective approach in gastric and esophageal cancers. Mechanistic and pre-clinical studies have shown that aberrant overexpression and cellular localization of AURKA in cancer cells leads to activation of several important signaling effectors such β-catenin, NF-κB, STAT3, and EIF4E. Our results from several mechanistic and preclinical studies have shown that targeting AURKA can be effective in KRAS activated cancers as well as for overcoming drug resistance to mTOR and platinum therapy in GECs.

Role of Dietary Broiler Chicken and Milk in the Causation of Breast Cancer- A study conducted in Goa, India

Roque Gabriel Wiseman Pinto
Department of Pathology, Goa Medical College, Goa University, Bambolim, Goa, India

Abstract
Breast Cancer is the commonest cancer in women, in Goa, India. A study was conducted in Goa Medical College to ascertain the role of Dietary Chicken Broilers and milk in the causation of Breast Cancer. 594 Breast Cancer Women were studied. The Microscopic types were Infiltrating Duct Carcinoma, Infiltrating Lobular Carcinoma, Mixed Carcinoma, Medullary Carcinoma, Colloid Carcinoma, Papillary Carcinoma, Metaplastic Carcinoma. Bilateral Breast Cancers were also studied. The incidence of Breast cancer in Goa was 22.9%. The youngest patient was 18yrs old and the oldest 90yrs. The risk factors were studied. 50 women normal controls were also studied. It was concluded in the study that the excess consumption of Chicken Broilers and milk is the significant cause of Breast Cancer. Hence these dietary factors play an important role in the prevention and control of Breast Cancer.

NQO1-Mediated Reduction of the ALDH+ Cancer Stem Cell Phenotype Suppresses the Growth of Lung Cancer Cells

Erik A. Bey
WVU Cancer Institute & Department of Pharmaceutical Sciences, West Virginia University, WV, USA

Abstract
Lung cancer is the leading cause of cancer related deaths in the U.S. and throughout the world. Tumor recurrence in cancer patients occurs when cancer stem-like cells from primary tumors escape therapy because of their innate quiescent phenotype or other adaptive epigenetic changes that allow their survival. ALDH+ lung cancer cells have been reported to have cancer stem-like properties, including self-renewal and resistance to chemotherapy. In our laboratory we have recently shown that reduction in NQO1 expression reduces the ALDH+ tumor population in a heterogenous tumor population. This reduction in ALDH+ tumors by, NQO1 expression reduction, inhibited growth in soft agar, reduced tumor invasion and prolonged survival in an in vivo mouse model of lung cancer. Thus, our future goals are to develop novel therapeutics including siRNA nanoparticles targeting NQO1 to reduce lung cancer burden in NQO1+ lung cancer patients.
Comparative Cytological Techniques in the Diagnosis Non-Neoplastic and Neoplastic Bronchopulmonary Lesions

Meenakshi Gundewar1, Pragati J. Karmarkar and Sadhana D. Mahore
NKP Salve Institute of Medical Sciences and Research Centre, Nagpur, India

Abstract

Diagnostic cytoLOGY is one of the suitable modality for both non-neoplastic and neoplastic conditions of the lung. Cytologic examination of specimens obtained from the respiratory tract is a primary and frequently the initial diagnostic technique performed in patients with respiratory symptoms or in those presenting with a pulmonary abnormality. The use of different cytological methods in the diagnosis of lesions of the respiratory tract has been generally acclaimed as one of its most successful application in the evaluation of patient with suspected lung malignancy.

Material and methods: It’s a prospective study of 127 cases. The present study is conducted in the department of pathology at a tertiary care hospital. It is a cross-sectional study, carried out on all patients who were admitted with lung diseases during a period of 2 years (2013-2015). Total of 127 symptomatic patients, both male and female, of all age group with the specified complaints were evaluated in the study. Patients with respiratory tract complaints with cough, breathlessness, hemoptysis, fever and chest pain were subjected to bronchoscopic examination.

Results: There were 81 males and 46 females. Male:female ratio was 1.76:1. The mean age was 50±16.14 years. The lowest age was 14 years and the oldest age was 85 years. It was included in both the non-neoplastic and neoplastic study groups. Most of the patients (17) were in the age group of 41-50 years (21.79%). Sensitivity of BB was 91.8%; while that of BAL was only 59.2%. Specificity of BB was 87.5% and that of BAL was 75%. Accuracy of brush cytology was 90.7% while that of BAL was 63.1%

Conclusions: Bronchial brushing is a much superior technique in the diagnosis of bronchopulmonary lesions. It demonstrates far better sensitivity, specificity and accuracy in comparison to BAL/bronchial washings. Combination of various cytohistological techniques complements each other and enhances the diagnostic efficacy of various non-neoplastic and neoplastic lung diseases.

New Therapeutic Approaches to Tackling Bone Metastatic Disease

Conor C. Lynch
H. Lee Moffitt Cancer Center and Research Institute, FL, USA

Abstract

Bone metastatic prostate cancer is common in men with advanced disease. In bone, prostate cancer promotes the formation of lesions composed of areas of extensive bone formation and destruction driven by mesenchymal stromal cell (MSC) derived osteoblasts and myeloid derived osteoclasts respectively. Our studies show that prostate cancer cells drive this process via parathyroid hormone related peptide (PTHrP) and post-translational modification of PTHrP by matrix metalloproteinases (MMPs). Reciprocally, we have found that bone marrow MSCs can drive the evolution of apoptosis resistant prostate cancer cells via the secretion of interleukin-28 (IL-28). Chronic exposure to IL-28 results in a rewiring of the prostate cancer cell circuitry with heightened phosphorylated STAT3 noted in the resistant cancer cell sub-populations. STAT3 activity has been noted in the majority of bone metastatic prostate cancers and may offer an opportunity for therapeutic intervention to treat this disease.

Biography

Dr. Lynch is an Associate Professor at the Moffitt Cancer Center in Tampa, Florida focusing on skeletal malignancies using genetic and pharmacological approaches.

The Role of Simvastatin in Inhibiting Migration and Proliferation of Breast Cancer Cells through Rho/Rock Signaling Pathway

Erwin Danil Yulian1*, Arleni Bustami2 and Ricky Dosan2
1Surgical Oncology Division, University of Indonesia, Indonesia
2Integrated Laboratory, University of Indonesia, Indonesia

Abstract

The Rho/Rho-Associated Coiled-Coil Containing Protein Kinase (ROCK) pathway is involved in breast cancer metastasis via its role in regulating cancer cell migration and proliferation, making it a potential target therapy. Cholesterol is implicated in cancer metabolism, both as energy source and as building blocks for lipid rafts formation in cell membrane that harbors oncogenic receptors. By inhibiting HMG-CoA Reductase (HMGCR), statins reduce cholesterol biosynthesis and decrease the formation of isoprenoid intermediates, which are essential for Rho/ROCK signalling.
Simvastatin 40 mg/d were administered to 30 breast cancer subjects for 4-6 weeks followed by mastectomy. Changes in migration (migration index, ROCK activity, and mRNA levels of RhoC, CXCR4 and CD44) and proliferation (Ki67 expression) from biopsy and surgical specimen were obtained before and after intervention. Simvastatin 40 mg/d significantly reduced migration index (p=0.006), ROCK activity (p=0.002), mRNA levels of CXCR4 (p=0.045) and Ki67 expression (p<0.001). Decrease was also observed in mRNA levels of RhoC (p=0.163) and CD44 (p=0.094).

Biography
Dr. Erwin Danil Yulian is a Surgical Oncologist from University of Indonesia and frequent speaker at oncological events in Indonesia. For the past 10 years, Dr. Erwin has been researching breast and thyroid cancer. He inspires many of his students to do research in oncology. Since 2016, he has been promoted to be the head of Breast Cancer Research in Indonesian Medical Education and Research Institute (IMERI). Dr. Erwin heads up the Fellow Program for Surgical Oncology and the Doctoral Program of Medicine at University of Indonesia. His current research and publications focus on metastasis prevention in Breast Cancer.

A New Strategy to Increase Proteotoxic Cell Death in Prostate Cancer
Carlos Perez-Stable1,2,3* and Alicia De Las Pozas1
1Miami VA Healthcare System/GRECC, FL, USA
2University of Miami Miller School of Medicine, FL, USA
3Sylvester Comprehensive Cancer Center, FL, USA

Abstract
Prostate cancer is a leading cause of death in men and when unresponsive to androgen deprivation therapy, it is known as castration-resistant prostate cancer (CRPC). Enzalutamide is an approved drug that inhibits androgen receptor activity and increases overall survival for CRPC. However, most responding patients develop resistance indicating that new therapies are required. We propose a new strategy that increases proteotoxic stress with cyclophilin + proteasome inhibitors to promote apoptotic cell death in CRPC without toxic side effects. Inhibition of cyclophilins (required for proper protein folding) will increase misfolded proteins, which further accumulate when combined with proteasome inhibitors to amplify proteotoxic stress and lead to cell death in cancer but not in normal cells. Combination of CRV431 (ContraVir Pharmaceuticals; new non-immunosuppressive analog of cyclosporine A that inhibits cyclophilins) and carfilzomib (new proteasome inhibitor approved for multiple myeloma) increases poly-ubiquitinated proteins and apoptotic cell death in CRPC cells. Stable shRNA knockdown of cyclophilin A or D increases CRV431 + carfilzomib or carfilzomib cell death suggesting that cyclophilins are viable targets for chemotherapy. The proteotoxic stress inhibitor cycloheximide strongly antagonizes CRV431 + carfilzomib cell death in CRPC cells. CRV431 + carfilzomib also increases poly-ubiquitinated proteins and apoptotic cell death in lung, melanoma, and liver cancer cells whereas a non-cancer cell line is resistant. Targeting the essential proteotoxic stress response survival pathway by combining cyclophilin and proteasome inhibitors may be a useful strategy to selectively kill CRPC without causing excessive side effects to normal cells and tissues.

Biography
Dr. Perez-Stable is a Research Chemist at the Miami VA and a Research Associate Professor at the University of Miami Miller School Of Medicine. He earned a Ph.D. in Genetics from the University of California, Davis and completed post-doctoral work at Columbia University. In Miami, Dr. Perez-Stable has devoted research interests to experimental therapeutics of prostate cancer using transgenic mouse and human cell line models. In addition, there are interests in the mechanisms of chemotherapy induced cell death and the identification of novel anti-cancer agents that specifically kill prostate cancer cells without harming normal cells.

Understanding Women’s Choice of Mastectomy Versus Breast Conserving Therapy in Early-Stage Breast Cancer
Jeffrey Gu1, Gary Groot2, Lorraine Holtslander3 and Rachel Engler-Stringer1
1Community Health and Epidemiology, Department of General Surgery, University of Saskatchewan, Saskatoon, Saskatchewan, Canada
2Community Health and Epidemiology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada
3College of Nursing, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Abstract
Background and Aims: Between 2007 and 2010 65% of all newly diagnosed breast cancer patients in Saskatchewan had a mastectomy, the second highest mastectomy rate in Canada. Although there are quantitative studies looking at factors that influence mastectomy choice, this literature is fairly limited, largely retrospective, and mostly conducted in counties outside Canada. It is not known if the same factors apply in Saskatchewan, especially given its large rural population. This study’s purpose was to understand why Saskatchewan women choose mastectomy as opposed to BCT.
Methods: A qualitative approach using Interpretive Description was used. Purposeful sampling was aimed at capturing diversity and variation of the phenomenon under the study. 13 mastectomy and 12 BCT patient semi-structured interviews were conducted. Data was analyzed using thematic analysis and presented in thematic maps.

Results: Women chose mastectomy because of one of three main themes (Figure 1): worry about cancer recurrence, perceived consequences of BCT treatment, or breast-tumor size perception. In contrast, women chose BCT because of three different themes (Figure 2): mastectomy being too radical, surgeon influence, and feminine identity.

Conclusions: Although the individual reasons found in this study have been seen in the literature before, choice of mastectomy or BCT has not previously been understood as having different reasons underlying each choice of therapy. These results are also novel in identifying interdependent subthemes or secondary reasons for each choice. Furthermore, the thematic maps created are useful additions to the literature in providing a visual depiction of decision-making factors for patients and health care workers.

TGF-Β1 as A Prognosis Marker and Its Down regulation in Childhood Acute Lymphoblastic Leukemia Patients

Carlos Eduardo Coral de Oliveira1*, Alberto Yoichi Sakaguchi2, Carlos Hiroji Hiroki3, Gustavo Aliano Gâmbaro4, Glauco Ackelington Freire Vitiello5, Marla Karine Amarante2 and Maria Angelica Ehara Watanabe6
1State University of Londrina, Brazil and Pontifical Catholic University of Paraná, Brazil
2State University of Londrina, Brazil
3University of São Paulo, Brazil
4Pontifical Catholic University of Paraná, Brazil

Abstract

Acute lymphoblastic leukemia (ALL) is a malignant hematologic disorder and the most common cancer in children up to 2 and under 5 years old. The transforming growth factor-beta (TGF-β) is an important cytokine that mediates regulatory functions in cellular biology and tumor environment. In the hematopoietic system, TGF-β signaling exerts cytostatic effects on hematopoietic stem cells, but its role in hematological malignancies remains elusive. Here, we examined the association study of four TGFB1 gene polymorphisms, and TGF-β1 plasma expression levels in 104 children with ALL, comparing with 115 age-related controls. The case-control study of TGFB1 gene polymorphisms (rs1800468, rs1800469, rs1800470 and rs1800471) revealed they were not associated with ALL susceptibility or risk of relapse, and their different genotypes did not alter TGF-β1 plasma levels. Decreased plasma expression was found in children with ALL (mean 8.18 ng/mL, s.e.m= 1.18 vs. controls= 15.88 ng/mL ± 1.08; p<0.0001). TGF-β1 plasma levels were downregulated in newly diagnosed children (3.01 ng/mL ± 0.83), comparing to children receiving chemotherapy (8.52 ng/mL ± 1.77; p= 0.004), and to children in complete remission (14.81 ng/mL ± 2.86; p< 0.0001). Surprisingly, in children with relapsed disease TGF-β1 plasma levels were downregulated (3.00 ng/mL ± 0.87). Thus, it is reasonable that the loss of TGF-β1 may be a critical marker of relapse with potential prognostic value. Finally, this marker must now be tested in a large prospective study to assess its precise clinical relevance in ALL.

Financial support: National Council for Scientific and Technological Development (CNPq).
Abstract

The heterogeneity within cancer is proposed to be driven by the population of cells within the tumor mass endowed with stem cell characteristics, called cancer stem cells (CSCs). These CSCs have been attributed to resistance towards conventional cancer treatment, leading to treatment failure and thus poor therapeutic outcome. Intriguingly, CSCs exhibit heterogeneous phenotypes and behavior driven by diverse biological events in the tumor microenvironment. During cancer progression and therapeutic pressures, these complex biological events confer different cellular fates and provide characteristics to cancer cells such as self-renewal, proliferation, quiescence, cell death, differentiation as well as de-differentiation. Different CSCs' fates may be linked to distinct cellular programs governed by specific molecular switch and axes in a context-dependent manner, leading to tumor resistant phenotype. Thus, developing CSC-targeting therapies is of major interest which requires insight understanding of the unique molecular circuitry that regulates the CSCs and their cellular fates.

Our current work focuses on the elucidation of cellular and molecular characteristics that are associated with CSCs associated with their resistance behavior and stemness characteristics. *In vitro* models of CSC were established mimicking different *in vivo* biological events throughout cancer progression leading to CSC formations. These models were characterized for their cellular fates and their phenotypic heterogeneity, demonstrated through analysis of gene expression associated with stemness, proliferation, epithelial-mesenchymal transition (EMT) and resistance and quiescence. Our results revealed distinct expression pattern exhibited in the CSC-associated gene expression pattern which is associated with different cellular fates in different *in vitro* models. Based on our findings, we propose that there exist key regulators that act as molecular switches to regulate the dynamics of their cellular fates throughout oncogenesis. CSCs utilize this program to their advantage in response to the constant changes in their microenvironment in favoring their survival, proliferation and heterogeneity. In particular, the acquisition of CSC-phenotypes may be facilitated by intricate cellular program through the reprogramming of their cellular metabolism, known as onco-metabolic reprogramming/metabolic switch. Specifically, Lin28 has been previously identified as a possible regulator that governs the stem cell fate through metabolic reprogramming, which was exclusively associated with stemness and resistance characteristics. It also found to be involved in regulating CSC metabolic pathways. Investigation on the role of Lin28 and other molecular regulators may provide a better insight of the complexity of CSCs' dynamic characteristics. Our works on *in vitro* CSC models may provide a system that would likely facilitate further investigation into the molecular circuitry of the heterogeneous CSC phenotypes, possibly via onco-metabolic reprogramming and stemness regulatory axis, and thus this axis would be important target for the treatment of cancer. In summary, our research would likely have a significant impact on designing and developing novel approaches for targeting the key regulators in CSCs as novel targeted approach for the inhibition of cancer progression and treatment with better therapeutic outcome.

Biography

Dr. Ramasamy earned her PhD in Clinical Medicine Research Programme (Human Embryonic Stem Cell Research) from Imperial College London, UK. Currently, she serves as the Head of Cell & Molecular Biology Laboratory, Central Research Facility and as a Senior Lecturer at the Department of Molecular Medicine, Faculty of Medicine, University of Malaya (UM). She has been actively engaged in stem cell research for a decade now and recently embarked on cancer stem cell research, the research fields that she has so much of passion. Her research group has set their focus to strive for innovative and creative cutting edge research in developing effective stem cell therapy and target cancer stem cells by developing scientific programs of exceptional merit in collaboration with multiple institutions at national and international level. She has been invited to present the research findings in many national/international meetings. Currently, she also serves as the President of Tissue Engineering and Regenerative Medicine Society of Malaysia and an active member of Research Development and Enhancement Programmes at UM. She acts as a Sub-editor and Peer-Reviewer of many academic journals.

Dr. Carlos E. C. Oliveira is currently Assistant Professor of Medical School at Pontifical Catholic University of Paraná, Londrina, Brazil, and Research Fellow in the Department of Pathological Sciences, State University of Londrina. Dean of the School of Pharmacy (2008-2011) and Professor of Human Pathology at the Assis Gurgacz Faculty. Member of the Editorial Board of Journal of Hematology Research, Blood Research and Transfusion Journal, and Biochemistry and Biotechnology Reports. His main research activities focus on the immunopathology of cancer, particularly in acute leukemia, and molecular and immunological markers of chronic diseases. Expertise in Immunological and Molecular Biology Techniques.
Chemotherapy-Sensitizing Effects of Aspirin, Metformin, and Oseltamivir Phosphate in Pancreatic Cancer

Bessi Qorri	extsuperscript{1*}, Manpreet Sambi	extsuperscript{1}, William Harless	extsuperscript{2} and Myron R Szewczuk	extsuperscript{1}

	extsuperscript{1}Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada
	extsuperscript{2}ENCYT Technologies, Inc., Membertou, Nova Scotia, Canada

Abstract

Pancreatic ductal adenocarcinoma (PDAC) is characterized by a highly inflammatory microenvironment, contributing to its exceptionally poor prognosis. This inflammation is implicated in the formation of an extremely dense extracellular matrix (ECM), resulting in pronounced desmoplasia, both further exacerbating chemoresistance. Cancer-associated inflammation also promotes the phenotypic changes associated with epithelial-to-mesenchymal transition (EMT), contributing to the invasive and metastatic nature of the disease. Due to the inherent resistance of PDAC cells and drug resistance developed from gemcitabine (Gem) monotherapy, non-steroidal anti-inflammatory drug (NSAID), aspirin (Asp/A) has shown to increase the efficacy of Gem on pancreatic cancer cells. Metformin (met), a common anti-diabetic drug, has demonstrated a decrease in overall cancer mortality; however, some cell lines have developed resistance to treatment. Oseltamivir phosphate (OP) has been shown to reverse the phenotypic changes of EMT associated with chemoresistance and cancer progression by targeting neuraminidase-1 (Neu-1). Pancreatic cancer PANC-1 and Gem-resistant PANC-1 (PANC-1/GemR) cell lines were analyzed for cell viability via WST-1 assays upon treatment with each drug and drug combinations. Tumor tissue samples from immunocompromised mice that received no treatment, only Gem, or combined therapy with Asp/Met/OP/Gem were analyzed using immunohistochemistry for E- and N-cadherin to determine the presence of EMT. Sialidase assays were performed to elucidate a common mechanism of action for the various drugs in preventing cancer cell growth. A combination of Asp, Met, and OP work synergistically as chemotherapy-sensitizing agents in the treatment of pancreatic cancer.

Therapeutic Targeting Human Pancreatic Cancer Stem Cells

Manpreet Sambi	extsuperscript{1*}, William Harless	extsuperscript{2} and Myron R Szewczuk	extsuperscript{1}

	extsuperscript{1}Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada
	extsuperscript{2}ENCYT Technologies, Inc., Membertou, Nova Scotia, Canada

Abstract

Cancer stem cells (CSCs) are a small subset of cells found within tumors and are the proposed driving force behind cancer relapse. CSCs are resistant to chemotherapy because they remain dormant at the time of treatment. However, they can be activated to proliferate under the influence of inflammatory cytokines released by the host body upon any injury that requires tissue remodeling. We hypothesize that chemotherapeutics in combination with oseltamivir phosphate (OP) and aspirin can interfere with the development of stem cell enrichment and corresponding chemoresistance by blocking distinct repair pathways upregulated after treatment with chemotherapeutics. We tested the proliferative capacity of CSCs through exogenous exposure of PANC-1 and MDA-MB 231 gemcitabine resistant cancer cell lines to Interleukin-6 (IL-6) and Hepatocyte Growth Factor (HGF) at concentrations that reflect serum levels measured during surgical procedures. Following treatment with HGF and IL6, cancer cells were exposed to multi-target drug therapy for 72 hours, after which the cell proliferative capacity was analyzed using the WST-1 assay. Preliminary data showed that the combination therapy was more potent after initial exposure to cytokines when compared with cancer cells without pretreatment. Furthermore, in order to investigate the efficacy of the combination therapy RAGxCy double mutant mice model of human pancreatic cancer was given combination therapy over the course of 90 days. Preliminary data have shown a difference in the proliferative capacity of cultured primary tumor and liver metastatic nodules of treated versus untreated cohorts.

Biography

Manpreet Sambi is currently a PhD trainee under the direct supervision of Dr. Myron R. Szewczuk in the Department of Biomedical and Molecular Sciences, Queen's University, Kingston ON, Canada and co-supervision of Dr. William Harless, MD, PhD, certified Medical Oncologist and CEO of Encyt Technologies, Inc., Sydney NS to work on therapeutic targeting cancer stem cells (CSC). To do this, Manpreet is working towards characterizing and understanding the mechanisms of cancer stem cell activation and proliferation. This knowledge will improve the potency of conventional chemotherapeutic treatment options with aspirin and oseltamivir phosphate in a multimodal targeted approach.
Day - 3

2017

October

28
Targeting the Neurotransmitter Receptor-Driven Regulation of Cancer Stem Cells in Cancer of the Lungs and Pancreas

Hildegard M. Schuller
Experimental Oncology Laboratory, College of Veterinary Medicine, University of Tennessee, Knoxville, TN, USA

Abstract
The leading type of lung cancer, pulmonary adenocarcinoma (PAC), and the leading type of pancreatic cancer, pancreatic ductal adenocarcinoma (PDAC), are stimulated in their growth, angiogenesis, metastasis and drug resistance by agonists for beta-adrenergic receptors (ARs). The stress neurotransmitters norepinephrine (Nor) and epinephrine (Epi) are the physiological agonists for these receptors. Nor and Epi are released by exocytosis from the autonomic nervous system, the adrenal gland as well as PAC and PDAC and their normal cells of origin in response to nicotinic acetylcholine receptor (nAChR)-mediated Ca\textsuperscript{2+}-influx induced by smoking or psychological stress, both of which are risk factors for these cancers. The mechanisms of b-AR-driven cancer stimulation has been extensively studied in animal models and in vitro systems comprised predominantly of differentiated cancer cells. However, the potential regulation of cancer stem cells by neurotransmitter receptors is poorly understood. Using cancer stem cells isolated by selective culture conditions from human PAC and PDAC cell lines and commercially available cancer stem cells isolated by cell sorting from human cancers, we have shown that the stem cells from both types of cancer synthesize and release the neurotransmitter acetylcholine that continuously stimulates their self-renewal via the induction of the synthesis and secretion of Nor and Epi regulated by nAChRs expressing the subunits α7, α3, and α5. In turn, binding of both stress neurotransmitters to Ga\textsubscript{s}-coupled b-ARs activated adenyl cyclase, resulting in the formation of intracellular cAMP and activated protein kinase a that activated the sonic hedgehog pathway and Notch pathway. Chronic exposure of the cells to nicotine or its nitrosated carcinogenic derivative N-nitroso-nicotine ketone (NNK) upregulated the α7nAChR, thus greatly increasing stress neurotransmitter-induced self-renewal of cancer stem cells. At the same time, the α4nAChR which regulates the synthesis and release of the inhibitory neurotransmitter g-aminobutyric acid (GABA) by these cells was desensitized, thereby suppressing the cancer inhibiting effects of GABA. In vivo experiments with subcutaneous mouse xenograft models further emphasized the important regulatory role of Nor and Epi as potent stimulators of cancer stem cells and GABA as important inhibitor. Exposure of the animals to chronic social stress or chronic nicotine significantly increased xenograft sizes, an effect accompanied by increased systemic and tumor levels of Nor, Epi and the activation of multiple cAMP-dependent signaling pathways whereas GABA was suppressed. Treatment of the animals with GABA completely reversed all of these effects. By contrast, stress reduction by environmental enrichment showed strong tumor inhibiting effects in these mouse models, effects associated with decreased stress neurotransmitter levels and increased levels of GABA and opioid peptides, both of which inhibit the formation of cAMP in vitro via the G\textsubscript{i}-mediated inhibition of adenylyl cyclase activation downstream of their respective G-coupled receptors. Collectively, these data identify strategies that restore cAMP homeostasis by inhibiting G\textsubscript{s}-signaling as promising tools for the prevention and adjuvant therapy of PAC and PDAC.

To Determine Whether Smoking, in any Form, is a Risk Factor in the Development of Cervical Cancer (CC) Among Urban Chinese Women

Jingmei Jiang
Institute of Basic Medical Sciences Chinese Academy of Medical Sciences, School of Basic Medicine Peking Union Medical College, China

Abstract
Purpose: To Determine Whether Smoking, In Any Form, Is a Risk Factor in the Development of Cervical Cancer (CC) Among Urban Chinese Women.

Methods: We ascertained retrospectively the smoking habits of 1,865 women (aged 35+) who had died from CC (cases) and 48,781 who had died from causes unrelated to smoking (controls) in 24 cities using data from a large national survey of smoking and mortality in 1989-1991. We assessed the risk of smoking on CC mortality with and without considering passive smoke exposure from a spouse using a proportional mortality study design.

Results: Overall, there was a 51.0% excess risk of death from CC among smokers. When the spouse’s exposure was further considered, the RR (95%CI) for exposed vs. unexposed women was 1.28 (1.04-1.57) for passive smokers, 1.49 (1.02-2.20) for active smokers, and 1.69 (1.27-2.26) for women with both exposure (all P<0.001). Significant dose-response associations were observed between smoking and CC for all categories of exposure. For example, individuals with both smoking exposure had the highest risk of CC mortality with moderate (RR=1.67 (1.18-2.38)) and high (RR=1.88 (1.04-3.41)) daily cigarette consumption, and they also had the highest risk with ≤15 years exposure (RR=1.73 (1.19-2.52)) and >15 years exposure (RR=1.95 (1.15-3.32)), compared with the active and passive groups (P for trend <0.001).
**Conclusions:** Younger trend of CC death and the rapid increase in smoking among young women may have a profound impact on future incidence of CC. Our findings emphasize the need for preventive efforts among both women and men in China.

**Biography**

Dr. Jingmei Jiang, as a professor of biostatistics, has been working in the department of epidemiology and biostatistics, Institute of Basic Medical Sciences Chinese Academy of Medical Sciences, School of Basic Medicine Peking Union Medical College since 1990. She is the current head of statistics section and principal investigator of statistical research. She focuses her research on the application of statistical methods in medical research. Since 2012, she has been in charge of projects of National Natural Science Foundation of China, as a Co-PI, in charge of National projects in different fields. So far, she has published more than 70 papers and published 4 books (as an editor in Chief or Chapter editor), two of books published in English. She is now, as an editor, serving for several English journals and has become a life member of the UICC Fellows.

**Role of AMPK in Ovarian Cancer: An Immune Perspective**

**Ramandeep Rattan**

1Division of Gynecology Oncology, Henry Ford Health System, MI, USA

2Department of Pathology, Wayne State University, MI, USA

3INSERM, Institut Cochin, Paris, France, CNRS, Paris, France, Universite Paris Descartes, Sorbonne Paris Cite, Paris, France

4Department of Neurology, Henry Ford Health System, MI, USA

**Abstract**

AMP-activated protein kinase (AMPK) plays a critical role in the regulation of cell growth by regulating various pathways like protein synthesis, lipid metabolism, growth factor signaling and cell cycle. We and others have shown that AMPK activation inhibits the growth of ovarian cancer. To gain insight into the role of AMPK in restraining epithelial ovarian cancer (EOC), especially its modulation in the host immuno-environment, we studied the progression of ovarian cancer in AMPKa1 knockout (KO) compared to wild type (Wt) mice. The ID8 syngeneic mouse EOC cells were injected intraperitoneally into mice to recapitulate high-grade EOC. The AMPKa1 KO mice with ID8 tumors had significantly decreased survival (median survival 50 days vs. 80 days in Wt mice). KO mice displayed increased ascites and extensive peritoneal dissemination compared to Wt mice. Immune profiling showed CD4 and CD8 T cells were decreased in the KO mice, with a concomitant 3-fold increase in MDSCs compared to Wt in ascites, tumor, PBMCs, and spleen. KO MDSCs expressed higher levels of immunosuppressive markers and suppressed T cell proliferation more significantly than Wt, as observed by lower levels of IFNg. Overall, our data suggests that AMPK deficiency promotes an immune-suppressive atmosphere by altering the function of MDSC, which results in an extremely permissive growth environment for EOC. Our study will provide a new dimension to understanding the immunosuppressive environment encountered by EOC and provide new therapeutic strategies to impact treatment of EOC patients, primarily to improve the effectiveness of current immunotherapy approaches.

**Biography**

Dr. Ramandeep Rattan holds a joint position of Assistant Professor at Henry Ford hospital in the Gynecologic Oncology division and the Department of Oncology at Wayne State University, Detroit, MI. Her field of research is ovarian cancer, focused on the role of the metabolic enzyme AMPK in ovarian cancer. She has received various grant awards during her postdoc at Mayo Clinic, from AACR, OCRF, Marsha Rivkin, MOCA and MIOCA. As an independent PI, she has received grants from the DOD OCRP.
**Disease Associated Sialoglycoproteins of Non-Small Cell Lung Cancer**

Sujata Ghosh  
Department of Experimental Medicine and Biotechnology, Post Graduate Institute of Medical Education & Research, Chandigarh, India

**Abstract**

Lung cancer is the most common cause of cancer-related death worldwide. Incidence of lung cancer is rising at an alarming rate. The major histological sub-type, non-small cell lung cancer (NSCLC) accounts for ~ 85% of all the human lung carcinoma cases. Metastasis and drug resistance are the major contributors to the poor prognosis of NSCLC. Despite major advances in cancer treatment in the past decade, the prognosis of patients with lung cancer has improved only minimally. Therefore, the need of the hour is to develop newer strategies of better diagnostic and therapeutic potential for this disease.

Lung cancer is characterized by a complex array of biomolecular alterations that drive uncontrolled growth and metastatic spread. Altered glycosylation especially aberrant sialylation is one of the prominent biomolecular alterations in cancer cells. During oncogenesis, wide variation has been found in the quantity, derivatization and type of linkage of terminal sialic acids to the sub-terminal sugar residues. Sialylation influences tumor cell behavior at different levels including cell motility, invasion, dissemination and inhibition of apoptosis. Altered sialylation in cellular glycans has been reported in case of lung cancer. However, the disease associated sialoglycoproteins of lung cancer have not received much attention. My group is engaged to explore the sialoglycoproteome of NSCLC. We have identified and characterized several disease associated sialoglycoproteins of NSCLC. Further, we have found the potential of these sialoglycoproteins in the disease progression. Hence, such sialoglycoproteins may be the potential targets for developing clinically useful strategies of better diagnostic and therapeutic significance.

**Biography**

Dr. Ghosh is working as a Professor in the Department of Experimental Medicine & Biotechnology, Post Graduate Institute of Medical Education and Research, Chandigarh, India. She graduated from the University of Calcutta with a Bachelor of Science degree in Chemistry in 1979 and completed her Masters of Science degree from Calcutta University in 1981. Further, she pursued her research in the area of Protein Biochemistry and achieved her Ph.D. degree from Jadavpur University, Calcutta in 1988. She has vast teaching experience in the area of Biochemistry and Medical Biotechnology. She is a member of several scientific societies. The thrust areas of her research include ‘Cancer Glycobiology’ and ‘Molecular basis of host- pathogen interaction’. She has guided 27 students for their Ph.D. degree and presently three Ph.D. students are working under her direct supervision. She has 76 publications in the journals of international repute. The main aim of her laboratory is to develop clinically useful targeted strategies in view of glycobiology, for the treatment of non-small cell lung cancer. The goal of the other area of her research is to explore the mechanism of host - enteropathogen interaction with an aim to have a better understanding of the disease pathogenesis.

**Inflammatory Biomarker in Predicting Breast Cancer Radiotherapy-Induced Early Adverse Skin Reactions**

Jennifer J. Hu*, Cristiane Takita¹, Jean L. Wright¹, Omar L. Nelson¹, Isildinha M. Reis¹, Wei Zhao¹ and Eunkyung Lee¹  
¹University of Miami Miller School of Medicine, FL, USA  
²Johns Hopkins University, MD, USA

**Abstract**

**Background:** Breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer death in American women. Post-surgery adjuvant radiotherapy (RT) significantly improves local control and survival. However, many patients develop early adverse skin reactions (EASRs) that impact quality of life and clinical outcomes.

**Methods:** We evaluated an inflammatory biomarker, highly-sensitive C-reactive protein (hsCRP) in predicting RT-induced EASRs in 499 breast cancer patients. In each patient, we measured pre- and post-RT hsCRP levels using an ELISA kit. RT-induced EASRs were assessed at post-RT using the NCI Common Toxicity Criteria (v3.0). Association between EASRs and CRP levels were assessed using logistic regression models after adjusting for potential confounders.

**Results:** RT-induced grade 2+ EASRs were observed in 290 (58%) patients at the end of RT. In multivariable analysis, patients with the highest quartile of pre-RT hsCRP have a significantly higher risk for RT-induced 2+ EASRs (OR=1.75; 95%CI=1.06-2.90) after adjusting for confounders. More importantly, grade 2+ EASRs were significantly associated with increasing pre-RT hsCRP levels particularly combined with high propensity score (PS) derived from 12 patient and clinical
risk factors. There was significant improvement of the area under the ROC curve from 0.80 (PS third quartile) to 0.85 (PS third quartile and pre-RT hsCRP third quartile).

**Conclusion:** We validate that the inflammatory biomarker hsCRP can predict RT-induced EASRs, particularly combined with other patient/clinic risk factors.

**Impact:** Our results suggest the potential application of hsCRP to predict RT-induced EASRs, impact RT decision making, and target for precision intervention.

**Biography**
Dr. Hu is a professor of Public Health Sciences at the University of Miami School Of Medicine. She has training in basic sciences and epidemiology. Her research mainly focuses on the molecular/genetic mechanisms of breast cancer risk/survival disparities and precision oncology. Her major contribution to cancer research includes: (1) deficient DNA damage/repair in human breast and prostate cancer risk; (2) functional implication of DNA repair genotypes in human cancer risk and targeted therapies; (3) gene-diet interactions in human colon and breast cancer risk; and (4) impact of genomics on radiosensitivity and disparities in breast cancer treatment outcomes.

**Restoration of Anti-Oncodriver Th1 Responses in Breast Cancer**
Krithika Kodumudi*, Cynthia Rosemblit, Doris Wiener and Brian Czerniecki
Breast Oncology Program and Department of Immunology, H. Lee Moffitt Cancer Center and Research Institute, FL, USA

**Abstract**
Breast cancer is the most commonly diagnosed cancer and major cause of cancer death among women. Our group has shown progressive loss of the anti-HER2 Th1 immune response in HER2 positive breast cancer patients. Targeting or correction of the cellular immune response against HER2 may prevent the recurrence in high-risk patients with Ductal Carcinoma In-situ (DCIS) and IBC. We have developed an HER2 peptide-pulsed dendritic cell (DC1) vaccine to induce a strong anti-HER2 immune response in breast cancer patients. Administration of HER2/neu pulsed DC1 in patients with DCIS and early invasive breast cancer (IBC) resulted in strong CD4 Th1 immune responses. The pathologic complete response (pCR) was higher in patients with DCIS than in patients with stage I IBC. In addition, high and intermediate HER2-expressing breast cancer cell lines treated with CD4+ Th1 cells, or Th1 cytokines TNF-α and IFN-γ induced tumor senescence and apoptosis in a dose dependent manner. Blockade of HER2/HER3 in combination with Th1 cytokines, TNF-α and IFN-γ resulted in an increased senescent and apoptotic phenotype with increased CXCL10 secretion in vitro. Overall, correcting the anti-HER2 Th1 response may have a significant impact in improving response to HER2 targeted therapies. Immunotherapeutic strategies with adoptive cell therapy in combination with targeted therapies are currently being explored in our laboratory.

**Biography**
Dr. Krithika Kodumudi senior research scientist in Breast Oncology and Immunology program at Moffitt Cancer Center and an assistant professor in Oncological Sciences department, University of South Florida. She received her doctorate in Biochemistry from Mahatma Gandhi Institute of medical sciences, Nagpur University in 2007. At the end of my training and after receiving Ph.D. degree, she joined Moffitt Cancer Center. Her primary research interest is to develop therapeutic approaches to block immunosuppression within the tumor microenvironment and the use of specific combinatorial approaches to enhance anti-tumor immunity and complete regression for the treatment of cancer.

**New Insight into Targeting the WEE1 Signaling Axis**
Gabriela Wright, Volha Golubeva, Lily Remsing Rix, Ankita Jhuraney Fumi Kinose, Norbert Berndt, Yunting Luo Grace Ward, Ernst Schonbrunn, Eric Haura, Jhanelle Gray Harshani Lawrence, Alvaro Monteiro and Uwe Rix*
H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA

**Abstract**
BRCT (BRCA1 C-terminal) domain proteins are critical components of the DNA damage response (DDR), targeting of which may enhance DNA damaging chemotherapy. Through a small molecule compound screen in lung cancer cells against kinases that interacted with BRCT domain proteins we identified synergy of the WEE1 kinase inhibitor AZD1775 with cisplatin. WEE1 directly interacted with the BRCT domain protein PAXIP1, which regulated WEE1-mediated phosphorylation of CDK1. PAXIP1 overexpression enhanced caspase 3-mediated apoptosis in cells treated with AZD1775. Furthermore, cell lines and patient-derived xenograft models expressing high levels of PAXIP1 and WEE1 exhibited synergistic effects of AZD1775 and cisplatin suggesting that WEE1 and PAXIP1 levels may be used as mechanism-
based biomarkers of response when WEE1 inhibitor AZD1775 is combined with DNA damaging agents. In addition, we observed that AZD1775 also exhibited anticancer activity in lung cancer cells as a single agent without DNA damaging chemotherapy. Using a chemical proteomics approach, we identified several previously unknown targets in addition to WEE1. In particular, we observed polo-like kinase 1 (PLK1) as a new target of AZD1775, which was inhibited with similar potency as WEE1. Gene silencing of WEE1 and PLK1 suggested that targeting PLK1 enhances the pro-apoptotic and antiproliferative effects observed with WEE1 knockdown. In summary, we show that PAXIP1 and PLK1 are critical components in the WEE1 signaling pathway and make important contributions to the activity of the WEE1 inhibitor AZD1775 either in combination with chemotherapy or as a single drug, respectively.

Biography

Dr. Uwe Rix Uwe received his Ph.D. in pharmaceutical sciences under the mentorship of Juergen Rohr at the Medical University of South Carolina before joining Giulio Superti-Furga’s group at the Center for Molecular Medicine (CeMM) in Austria as a postdoctoral fellow. In 2011, Uwe joined the Moffitt Cancer Center in Tampa, FL, as an Assistant Member Faculty in the Chemical Biology and Molecular Medicine (CBMM) Program. Here, his research focuses on characterizing pleiotropic drug effects, targets and mechanisms in cancer cells using systems chemical biology approaches, in particular small molecule phenotypic screening in combination with drug target identification by affinity-based chemical proteomics.

Blocking Mechanisms of Obesity Dependent Pancreatic Cancer Progression

F. Messaggio, N. Nagathihalli, N. Merchant and M.N. VanSaun*
Department of Surgery, University of Miami Miller School of Medicine, Sylvester Comprehensive Cancer Center, FL, USA

Abstract

Obesity is an escalating epidemic in the world, posing a risk factor for multiple forms of cancer. Of those, pancreatic cancer has carried a survival rate of less than 5% for the past 30 years. Our results have demonstrated that murine models of pancreatic cancer support a direct correlation between dietary intake, obesity and disease development. The causal factors and cellular signaling pathways altered in obese individuals are under investigation to determine mechanisms driving of obesity dependent pancreatic cancer progression. Dysregulation of adipose secreted cytokines, or adipokines, is coincident with obesity associated inflammatory responses. In obese individuals, serum levels of leptin significantly increase while adiponectin levels decrease. Cytokine dysregulation typically contributes to mitogenic activation and the development of acquired drug resistance in cancers. We have demonstrated that obesity potentiates PDAC by increasing leptin secretion, which in turn activates STAT3 and ERK to directly contribute to in vitro proliferation, migration, and in vivo tumor growth. In contrast, the adipose derived cytokine, adiponectin, has been shown to inhibit growth and invasive phenotypes in multiple cancers including PDAC. Our studies have shown that adiponectin or AdipoRon, an adiponectin receptor agonist, blocks leptin and IL-6 induced ERK and STAT3 activation, which in turn decreases PDAC tumor growth both in vitro and in vivo. While pharmacologically increasing levels of adiponectin/AdipoRon can effectively inhibit PDAC cell growth, we have found that both adiponectin receptors (AdipoR1 and AdipoR2) are decreased in human and murine PDAC tissues. It had been previously demonstrated that activation of the nuclear hormone receptor PPAR increased adiponectin receptor expression in mouse white adipose tissue. Importantly, treatment with PPAR gamma agonists increased the expression of AdipoR2 and also inhibited proliferation in PDAC cell lines. Overall, our studies establish that adiponectin receptor activation is important for the suppression of cytokine induced tumorigenic signaling in PDAC.

The Enhancement of Combination of Berberine and Metformin in Inhibition of DNMT1 Gene Expression through Interplay of SP1 and PDPK1 in Lung Cancer

Shou Wei Han
Laboratory of Tumor Biology, Department of Medical Oncology, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou University of Chinese Medicine, Guangzhou, Guangdong Province, China

Abstract

Berberine (BBR), an isoquinoline alkaloid found in the rhizome of medicinal plants, exhibited anti-cancer property. We previously showed that BBR inhibited growth of non-small cell lung cancer (NSCLC) cells through p38 mitogen-activated protein kinase (MAPK)–mediated induction of forkhead box O3a (FOXO3a). However, the detailed mechanism underlying this still remained to be elucidated. Herein, we further confirmed that BBR not only induced cell cycle arrest, but also reduced the migration and invasion of NSCLC cells. Mechanistically, we observed that BBR reduced 3-phosphoinositide dependent protein kinase-1 (PDPK1) and SP1 protein expressions. Exogenously expressed SP1 overcame BBR-inhibited PDPK1 expression. Moreover, BBR inhibited DNA methyltransferase 1 (DNMT1) gene expression and overexpressed DNMT1 resisted BBR-inhibited cell growth. Intriguingly, overexpressed PDPK1 antagonized BBR-inhibited SP1 and
DNMT1 expression. Finally, metformin enhanced the effects of BBR both in vitro and in vivo. Collectively, our results show that BBR inhibits growth of NSCLC cells through inhibition of SP1 and PDPK1; this results in a reduction of DNMT1 expression. The interplay of PDPK1 and SP1 converge on the inhibition of DNMT1 in response to BBR. In addition, there is a synergy of BBR and metformin. This study reveals a novel mechanism of BBR in combination of metformin for NSCLC therapy.

Biography

Dr. Swei (Sunny) Hann obtained his MD and PhD from Sichuan University, China, did his postdoctoral training at Duke University, USA. Now is the full Professor of Medicine, Director of Laboratory of Tumor Biology, Second Clinical Medical Collage, Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, P. R. China. Published over 100 articles and obtained multiple funding both in USA and in China.

Neuropeptide Prp-1 as a Potent Regulator of Tumor Suppressors and Oncoproteins in Human Chondrosarcoma

Karina Galoian*, Amir Qureshi†, and H.T Temple†

1University of Miami, Miller School of Medicine, FL, USA
2Nova Southeastern University, FL, USA

Abstract

Metastatic chondrosarcoma is a bone malignancy and does not respond either to chemotherapy or radiation; therefore, the search for new therapies is urgent. Disruption of cellcell junctions, down regulation of tumorsuppressive adherens junctions and desmosomes represent hallmark phenotypes for cancer cells and may directly contribute to tumorigenesis. The cell junction pathway array data indicated downregulation of desmosomal proteins, such as desmoglein (1,428fold), desmoplakin (620fold) and plakoglobin (442fold) in human chondrosarcoma JJ012 cell line. In our early publications we demonstrated powerful antiproliferative cytostatic effect of mTORC1 inhibitor, neuropeptide PRP-1. Western blot experiments demonstrated restoration of the expression of the above mentioned desmosomal tumor suppressor proteins after treatment with PRP1. The peptide was able to restore the expression of tumor suppressors SOCS3 and TET1/, 2 involved in inflammatory pathway as well. However, the peptide did not have any effect on tumor suppressors of Hedgehog and Hippo pathways, indicating that there is selectivity of action depending what signaling pathway the tumor suppressor belonged to. PRP-1 proved that it can downregulate some of the key oncoproteins. In western blot and luciferase assay experiments we demonstrated drastic downregulation of c Myc and pMyc. The embryonic stem cell marker Nanog, which is a target for miR302c-367 cluster, is expressed in many cancers. Nanog expression was substantially decreased after the treatment with 10μg/ml PRP-1 in dose response manner. miRNA may be tumor suppressor or onco miRNA depending on cellular context. Exiqon microarrays indicated that PRP-1 significantly upregulated tumor suppressor miRNAs and downregulated onco miRNA.

Biography

Dr. Karina Galoian is a research associate professor of University of Miami, Miller School of Medicine. After International Fogarty fellowship at National Institute of Health, Bethesda, MD and postdoctoral fellowship in the University of Pennsylvania, Philadelphia, she joined University of Miami in 2001 and became faculty member in 2007. She is research director of Sarcoma Disease site group at Sylvester Comprehensive Cancer Center, Head and Principle investigator of Musculoskeletal Oncology signal transduction laboratory of the Department of Orthopedic surgery. D. Galoian is recipient of prestigious 2017 Albert Nelson Marquis Lifetime Achievement Award in biochemistry by (Marquis Whos Who) USA.
Control of Differentiation in Lymphoma and Breast Cancer

Feng Bai1, Shiqin Liu1,2, Ho Lam Chan1, Alexandria Scott1, Ping Zhu2 and Xin-Hai Pei1,3*

1Molecular Oncology Program, Department of Surgery, University of Miami Miller School of Medicine, FL, USA
2Department of Hematology, Peking University First Hospital, Beijing, China
3Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, FL, USA

Abstract

Aberrant cell differentiation has long been observed during tumorigenesis and poor differentiation is strongly associated with worse prognosis. The molecular mechanism of how altered differentiation is linked to tumorigenesis is poorly understood. This study uses two well-defined in vivo cell differentiation systems, blood and mammary gland, to determine how altered differentiation by loss-of-function of GATA3 contributes to tumor development and progression.

GATA3, a transcription factor, is required for the development of multiple organs, including the mammary glands and hematopoietic system. In humans, GATA3 is undetectable in hyperproliferative diseases of hematopoietic B cells and mammary basal epithelial cells. Deletion of Gata3 in mice causes early lethality or severe growth defects, making it difficult to study its role in vivo in tumorigenesis. We have previously demonstrated that p18INK4c (p18), a cell cycle inhibitor, is a direct downstream target of GATA3. We discovered that heterozygous germline deletion of Gata3 in mice reduced cell proliferation with induction p18 in hematopoietic T and mammary epithelial cells. We found that loss of p18 restored Gata3-deficient proliferation of T and mammary epithelial cells. We showed that deficiency of Gata3 in p18 null background increased populations of hematopoietic B and mammary basal epithelial cells, and resulted in B cell lymphomas and basal-like mammary tumors. Gata3-deficient lymphomas and mammary tumors were poorly differentiated and capable of rapidly regenerating tumors when transplanted. In conclusion, this study reveals that Gata3 is a tumor suppressor specifically in B cell lymphomagenesis and basal-like breast tumorigenesis.

Biography

Dr. Pei has a broad background in both clinical and basic cancer research. As a physician, he devoted himself to clinical cancer research for 9 years. He received his Ph.D in Japan and postdoctoral training on cell cycle control in North Carolina. Since becoming a tenure track assistant professor in 2011, he has have published 15 research papers. His research has been focused on how cell cycle is controlled in vivo, and how altered cell differentiation is linked to tumorigenesis.

BikDD and Doxorubicin Delivery to AU565 Breast Cancer Cell line by Targeted Lipid Based Nanovesicles

Zeynep Busra Bolat1, Burcu Devrim1, Ongun Mehmet Saka1, Sevgi Gulyuz3, Ozgur Yilmaz1, Asuman Bozkir2, Dilek Telci1 and Fikrettin Sahin1

1Department of Genetics and Bioengineering, Yeditepe University, Turkey
2Department of Pharmaceutical Technology, Ankara University, Turkey
3Materials Institute, Marmara Research Center, TUBITAK, Turkey

Abstract

Breast cancer, a heterogeneous disease, has the highest incidence rate and major cause of death in females worldwide. Lipid based vesicles are known to have enhanced accumulation ability in tumors with longer systemic circulation. Poly (2-ethyl-2-oxazoline) (PetOx) polymers conjugated with other lipids were used as to prepare lipid based nanovesicles. Peptide 18, a tumor homing peptide, shown to have high potential in targeting breast cancer cells was used in labelling the lipid based nanovesicles. Toxicology studies performed on the cell panel composed of human osteoblasts, hepatocytes, mesenchymal stem cell, endothelial cells, fibroblasts and kidney cell lines showed that lipidic nanocarriers did not affect the cell survival hence they would pose little toxicity if any to the tissues. Attachment of peptide 18 to the lipid based nanovesicles' surface specifically targeted the construct to AU565 breast cancer cell line with lower binding affinity recorded for the healthy epithelial MCF10A. Pro-apoptotic BikDD gene and doxorubicin delivery by peptide 18 labelled lipidic nanovesicles to AU565 cells led to apoptosis which was detected using Annexin V/PI staining and caspace 3 activation. The increased Bik mRNA expression and protein expression in AU565 cell line along with apoptotic cell death indicate a high effectiveness for these targeting lipidic nanovesicles Our results suggest that BikDD gene and doxorubicin loaded peptide18-targeted lipidic nanovesicles may be promising drug carriers worth to be tested further in preclinical studies.

Keywords: Breast cancer, apoptotic gene BikDD, doxorubicin

Biography

Zeynep Busra Bolat has completed her B.Sc from Fatih University and M.Sc from Yildiz Technical University. She is currently a Ph.D candidate and Teaching Assistant in Yeditepe University. She has published a paper in reputed journal during her master studies.
Metabolomics in Predicting Radiotherapy-induced Normal Tissue-Toxicities in Breast Cancer Patients

Joshua J. Kleinman¹, Eunkyung Lee¹, Cristiane Takita¹, Jean L. Wright⁴ and Jennifer J. Hu¹
¹Department of Public Health Sciences, University of Miami Miller School of Medicine, FL, USA
²Department of Radiation Oncology, Johns Hopkins University, MD, USA

Abstract

Purpose: Early adverse skin reactions (EASRs) are a symptomatic side effect of adjuvant radiotherapy (RT) often experienced by breast cancer patients after breast-conserving surgery. We evaluated global metabolomic profiles of breast cancer patients to identify metabolic pathways and biomarkers associated with RT-induced EASRs.

Methods and Materials: Pre-RT urine samples from 60 female breast cancer patients receiving adjuvant RT (45–50.4 Gy) after breast-conserving surgery were metabolically profiled. Patients were frequency matched after RT by race/ethnicity and BMI to low-EASR (n=30) and high-EASR (n=30) subgroups. Web-based MetaboAnalyst 3.0 was employed to perform metabolomic data analysis, visualization, and interpretation of 478 biochemical compounds. Pathway enrichment and topology analyses, correlation analyses, and Student’s t-tests were conducted to identify pathways and biomarkers significantly associated with RT-induced EASRs and to evaluate differences between high-EASR and low-EASR subgroups.

Results: The study population consisted of 24 AA (40%), 18 NHW (30%), 14 HW (24%), and 4 “other” (7%) patients with a median BMI of 36.78 and median age of 58.20 years. Seven metabolic pathways were significantly associated with RT-induced EASRs. The alanine, aspartate and glutamate metabolism pathway had the highest pathway impact value (0.60) and most significant FDR-adjusted p-value (p=0.0028). Furthermore, 13 metabolic biomarkers were significantly associated with RT-induced EASRs, including glutamate, a compound of special interest.

Conclusions: Global metabolomic profiling can be used to identify biochemical markers of radiosensitivity in breast cancer patients receiving adjuvant RT. Given the identified role of glutamate in RT-induced EASRs, we speculate that glutaminase inhibitors may be useful in preventing RT-induced EASRs.

Biography

Mr. Kleinman is a second-year undergraduate student at the University of Miami and an alumnus of the Illinois Mathematics and Science Academy. He is pursuing a Bachelor of Science in Public Health and Bachelor of Arts in Latin American Studies with a concentration in Pre-medical studies. His academic and research interests include epidemiology, health disparities, and the history of science and medicine as well as cultural anthropology and international studies. He is a distinguished recipient of the Stamps Family Charitable Foundation Leadership Scholarship and is an academic Foote Fellow at the University of Miami’s College of Arts and Sciences.

Inflammatory Biomarker in Radiotherapy-Related Pain

Gavin Ajami¹, Eunkyung Lee¹, Cristiane Takita¹, Jean L. Wright⁴, Omar L. Nelson†, Isildinha M. Reis¹, Wei Zhao¹ and Jennifer J. Hu¹
¹University of Miami Miller School of Medicine, Miami, FL, USA
²Johns Hopkins University, MD, USA

Abstract

Introduction: More than half of cancer survivors report pain and it negatively impacts quality of life. Radiotherapy (RT)-induced inflammation was proposed as a mediator of normal tissue toxicities, however, its relation to pain has not been determined.

Methods: In a prospective study of 366 breast cancer patients undergoing RT, plasma C-reactive protein (CRP) concentration was measured using ELISA kits, and pain score was assessed with four pain severity items (i.e., pain at its worst, least, average, and now) from the Brief Pain Inventory (0=no pain to 10=worst pain) at pre- and post-RT. Pain scores of 4-10 were considered clinically-relevant pain, and RT-related pain outcomes (pre- and post-RT pain, RT-associated pain and extreme pain increase) were defined, and their associations with CRP were evaluated using multivariable logistic regressions.

Results: The study consists of 235 Hispanic whites (64%), 73 African Americans (20%), and 58 non-Hispanic whites (16%). The prevalence of pain was 17% at pre-RT and 30% at post-RT. About 19% experienced RT-associated pain, and 9% showed extreme pain increase. More than half of patients had elevated CRP levels (>3 mg/L) either at pre-RT or post-RT, and 27% had CRP change of >1 mg/L after RT. The multivariable analyses showed that CRP change was associated with higher risk of RT-associated pain (Odds ratio [OR] =2.04, 95%CI=1.04-4.02) and extreme pain increase (OR=3.24, 95%CI=1.33-7.88).

Discussion: The study outcome suggests that RT-induced inflammatory response, as defined by CRP change, was associated with RT-associated pain. Intervention with anti-inflammatory measures may ameliorate RT-related pain in breast cancer survivors.

Biography

Mr. Ajami is a graduate student of Public Health Sciences at the University of Miami School of Medicine. He has training in basic sciences and epidemiology. His research project will focus on the molecular/genetic mechanisms of breast cancer survival disparities and precision oncology.
Abstract

CDK1 Promotes Angiogenesis via Regulating HIF-1α Activity in MDM2 Overexpressed Prostate Cancer

Saad Alobid1, Khalid Alhazzani1,2, Thanigaivelan Kanagasabai1,2, Ali Alaseem1,2, and Appu Rathinavelu1,2
1College of Pharmacy, Nova Southeastern University, Plantation, FL, USA
2Nova Southeastern University, FL, USA

F16 is a Novel New Candidate for Brain Tumors

Mohammad Algahtani1,2, Khalid Alhazzani1,2, Sivanesan Dhandayuthapani1,2 and Appu Rathinavelu1,2
1College of Pharmacy, Nova Southeastern University, Plantation, FL, USA
2Nova Southeastern University, FL, USA

Glioblastoma multiforme (GBM) is one of the most aggressive and lethal type of all cancers with a median survival of about one year and a very low 5-year survival rate of 5% among the patients. Therefore, development of effective treatment for GBM is urgently needed. Since GBM is one of the most highly vascularized solid tumors, and its growth is angiogenesis-dependent, antagonizing tumor angiogenesis by using angiogenesis inhibitors seems to be a promising strategy to be evaluated for GBM. However, one of the difficulties that limit the usage of angiogenesis inhibitor in brain tumor treatment is the presence of the BBB. In this context, F16, a novel anti-angiogenic agent developed at the Rumbaugh Goodwin Institute for Cancer Research of Nova Southeastern University, has shown promising results so far. Intensive preclinical evaluation of F16 has exhibited potent anti-angiogenic and anti-tumor activities via selectively antagonizing VEGFR2. More importantly, we evaluated F16 pharmacokinetic distribution patterns using BALB-c mice. After a single i.p injection, F16 concentration was the highest in the brain indicating that F16 was transported across BBB and slowly accumulates into the brain regions with an apparent Tmax (12 h). Even though F16 was accumulated in the brain, no signs of cognitive change were observed in the treatment groups. Assessment of biochemical parameters that are reflecting vital organ functions showed no signs nor elevation in injury related biomarker levels of liver, heart, kidney, and pancreases after F16 treatment. In addition, our preliminary in vitro studies of F16 on U87MG cell lines showed that F16 exhibited a potent cytotoxic against U87MG cell lines (IC50 26μM). Furthermore, western blot results of U87MG showed an increase in the expression of BAX, p53 and p21 after 10μM and 20μM of F16. Also, F16 inhibited the migration of U87MG cells after 24 h of treatment. Therefore, our results suggest that F16 could reduce tumor growth as monotherapy and improve response to chemotherapeutic agents in GBM. (This research was supported by the generous funds provided by the Community Foundation of Broward, Florida and the Royal Dames of Cancer Research Inc., Ft. Lauderdale, Florida).

Abstract

MDM2 is an oncogene amplified in approximately 40% of all human prostate carcinoma which is correlated with aggressive tumor phenotype, poor outcomes, distant metastasis and overall mortality. Moreover, hypoxia, by activating several survival pathways, drives tumor cells to proliferate rapidly, metastasize, and resist chemo and radiotherapy. Thus, the transcription factor, hypoxia inducible factor -1 alpha (HIF-1α) is activated to facilitate adaptation of cancer cells to the harsh microenvironment through inducing gene expression of the downstream genes to modify vital biological processes and ensure tumor survival and progression. In this regards, our previous findings showed that even under normoxic conditions, MDM2 overexpression can induce the protein levels of HIF-1α significantly and its downstream target gene VEGF in MDM2 transfected cell line (LNCaP-MST) compared to LNCaP leading to angiogenesis and other detrimental effects. However, the underline cellular mechanism that leads to HIF-1α activation in response to MDM2 overexpression is yet to be elucidated. Therefore, identifying the mechanisms by which HIF-1α implicates prostate cancer progression represents an opportunity for cancer treatment. Interestingly, our preliminary data demonstrate a positive correlation between MDM2 and cyclin dependent kinase 1 (CDK1) in LNCaP-MST compared to LNCaP, and utilizing the MDM2 inhibitor (Nutlin-3) reduced CDK1 levels significantly indicating that CDK1 plays an important role in HIF-1α activation in MDM2 overexpressed cells under normoxia. Subsequently, we postulated that the upregulation of HIF-1α is most likely regulated by MDM2 through CDK1. In this study, we aimed to investigate the impact of MDM2 overexpression on HIF-1α levels and to explore how MDM2 regulates HIF-1α activity in prostate cancer cells under normal oxygen tension. (This research was supported by the generous funds provided by the Community Foundation of Broward, Florida and the Royal Dames of Cancer Research Inc., Ft. Lauderdale, Florida).
MDM2 Overexpressing Cancer Cell Lines Control MMPs Activity

Ali Alaseem1,2, Thiagarajan Venkatesan1, Priya Dondapati1,2, Saad Alobid1,2, Khalid Alhazani1,2 and Appu Rathinavelu1,2
1 College of Pharmacy, Nova Southeastern University, FL, USA
2 Nova Southeastern University, FL, USA

Abstract

MDM2 (Murine Double Minute), a multi-domain protooncogene, is overexpressed and considerably linked with poor prognosis in a large number of tumor types including sarcomas and carcinomas. Through p53 dependent and independent mechanisms, MDM2 is directly associated with the loss of control of cell cycle, increased proliferation, pro-angiogenesis, and metastatic ability. The matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidase with mainly proteolysis activity and found to impact physiological and diseased conditions. More than 24 types of MMPs promote invasion, angiogenesis, metastasis, and proliferation and eventually poor cancer prognosis. Predominately, MMP-9 plays a central role in various processes concerning the regulation of inflammation involved in wound healing and tissue remodeling. To date, a growing number of studies have examined the role of MMP-9 in promoting the tumor progression. In fact, MMP-9 releases cytokines and pro-angiogenic and pro-metastatic factors and thereby facilitate angiogenesis and metastasis. The tissue inhibitor of metalloproteinases (TIMP-1) is a negative regulator of MMPs, and independent of MMPs regulation, TIMP-1 regulates a broad range of biological activities ranging from apoptosis, cell growth and angiogenesis. Besides, TIMP-1 dysregulation displayed an impact towards extracellular matrix (ECM) integrity and positively potentiates a metastatic capability. Our research group investigated the role of MDM2 overexpression in modulating MMP-9/TIMP-1/THBS-1 pathway in prostate cancer cells (LNCaP) and MDM2 transfected (LNCaP-MST). Functional assays were performed including the MMP fluorescence activity assay, zymography assay or measuring the activity of MMP-9/2 to examine the significance of MMPs activity in MDM2 overexpressing cancers. Protein expression analysis was used to detect and compare the levels of MDM2, MMPs, and TIMP-1 in MDM2 overexpressing cell lines in a control and Nutlin-3 (20 μM) treated cells. Our findings suggested that MMP activity is increased in LNCaP-MST compared to LNCaP. Surprisingly, the level of MMP activity was increased after treating LNCaP and LNCaP-MST with Nutlin-3 by four and two folds in LNCaP and LNCaP-MST respectively. Constant increase effect of MMP activity was observed in osteosarcomas (SJSA-) and breast cancer (GI-101A) models seven and three folds respectively. Unlike LNCaP cells, in SJSA-1 and GI-101A, TIMP-1 expression strikingly up regulated which suggest a contextual effect of MDM2 in regulating the examined pathway. In conclusion, our results that indicate MDM2 regulate MMP/TIMP pathway in a context fashion and thereby increase metastatic ability (The financial support from the Royal Dames of Cancer Research Inc., Ft. Lauderdale is gratefully acknowledged).

Evaluation of Antitumor Effects of a Novel Inhibitor of VEGFR-2 in a Colorectal Xenograft Model

Khalid Alhazzani1,2, Sivanesan Dhandayuthapani1, Ali Alaseem1,2, Saad Alobid1,2 and Appu Rathinavelu1,2
1 College of Pharmacy, Nova Southeastern University, FL, USA
2 Nova Southeastern University, FL, USA

Abstract

Purpose: Colorectal cancer (CRC) is the third most diagnosed type of cancer in the United States. Angiogenesis is one of the fundamental processes driving CRC progression, and thereby antiangiogenic therapy has been successfully applied to treat CRC. In this study, we examined whether F16, a novel vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitor, suppresses tumor growth and tumor vasculature in a mouse CRC model.

Methods: Athymic nude mice developed CRC xenografts subcutaneously after being inoculated with COLO 320 DM adenocarcinoma cells. Tumor-bearing mice were intraperitoneally injected with vehicle, F16, or 5-Fluorouracil for 21 days. Changes in body weight, tumor volume, food intake, survival time, and behavior were monitored. At the end of the experiment, tumor masses were excised and subjected to immunohistochemistry analysis to investigate vascular changes.

Results: Growth of CRC xenografts were significantly inhibited upon F16 treatment (p <0.001). The inhibition ratio was 91.89 ± 1.33, 95.43 ± 6.37 for F16 and 5-FU respectively. No significant change in body weight was observed among treatment groups (p >0.05). No change in food intake, nor behavior were observed. At the end of the experiment, the average tumor weight was significantly reduced in F16 compared to control (357.1 mg Vs 1608 mg; p <0.001). Immunohistochemistry analysis of tumor tissue sections revealed a significant reduction of CD31, an endothelial marker, in F16 treatment group in compared to control.

Conclusions: Treatment with F16 reduces tumor growth and increases survival rate in CRC tumor-bearing mice compared with untreated controls. Also, F16 treatment also reduces microvessel density which suggests F16 anticancer effects is mediated through inhibition of angiogenesis. In consent with previous in vitro, F16 mediates antiangiogenic effects through inhibition of ectoderm of VEGFR2. These results justify further evaluation of F16 as a potential new therapeutic strategy for treating CRC. (This research was supported by the generous funds provided by the Community Foundation of Broward, Florida and the Royal Dames of Cancer Research Inc., Ft. Lauderdale, Florida).
RPS3 Fucosylation in Melanoma Cell Biology

Gregory Watson1, Lancia Darville2, John Koomen2 and Eric Lau1

1Department of Tumor Biology, H. Lee Moffitt Cancer Center, FL, USA
2Department of Molecular Oncology, H. Lee Moffitt Cancer Center, FL, USA

Abstract

Global fucosylation is reduced in progressive melanoma and increasing fucosylation slows tumor growth and decreases metastatic burden in vivo. However, the proteins or pathways that are influenced by fucosylation and therefore contribute to tumor growth and dissemination are unknown. The aim of this work is to identify fucosylated proteins in melanoma cells and to characterize the role their fucosylation plays in melanoma growth, behavior and response to therapy.

We identified fucosylated proteins in melanoma cells by UEAI lectin-pulldown followed by LC-MS/MS identification. Over 200 unique proteins are recognized by UEAI. Ribosomal protein S3 (RPS3) was found to be fucosylated in a panel of melanoma cells. RPS3 protein is elevated in malignant cells in culture and in human melanoma cells as assessed by tissue microarray. Forcing RPS3 expression in melanoma cells confers a growth advantage in 3D culture, supporting a role for RPS3 in melanoma progression. The fucosylated form of RPS3 is found only in the cytoplasmic fraction, and RPS3 fucosylation is altered in response to cellular stressors, suggesting fucosylation of RPS3 is involved in stress response.

RPS3 expression and localization are altered during melanoma development and therapeutic resistance. RPS3 is a fucosylated protein and its fucosylation level responds to stress. These findings suggest that RPS3 and the post-translational fucosylation of RPS3 may contribute to melanoma progression and have a role in the cellular response to therapeutic stress.

Biography

Gregory is an early-stage postdoctoral fellow in the Lau Lab at the H. Lee Moffitt Cancer Center. He is currently exploring the role of fucosylation in melanoma cell biology, response to cellular stressors, and the potential for the development of the proteins that influence fucosylation as novel therapeutic targets for downstream development.

Evaluation of Crosstalk between FAK and MDR1 in Platinum Resistant Ovarian Cancer Cells

Keerthi Thallapureddy1, Arkene Levy2 and Appu Rathinavelu2

1Department of Biological Sciences, Halmos College of Natural Sciences and Oceanography, Farquhar Honors College, Nova Southeastern University, Fort Lauderdale, FL, USA
2Rumbaugh-Goodwin Institute for Cancer Research, Nova Southeastern University, FL, USA

Abstract

Patients have experienced the recurrence of ovarian cancer due to chemotherapy resistance. These new tumors have developed resistance to taxane and platinum chemotherapy. Platinum resistance continues to be a major challenge in the chemotherapeutic management of ovarian cancer. This project serves to understand a gene that may be a potential target to treat platinum resistant ovarian cancer. Preliminary studies have shown that a protein kinase known as the Focal Adhesion Kinase (FAK) has been implicated in the development of this platinum resistance. FAK is known to play an important role in cell adhesion and metastasis. A multidrug resistant gene (MDR1) codes for the P-glycoprotein, an ATP-dependent efflux pump known to play an important role in chemotherapeutic resistance. Tumor cells expressing P-glycoprotein are resistant to an array of anticancer drugs because the protein transports drugs out of the cell. Anticancer drugs have been found to induce the MDR1 gene, thus P-glycoprotein can serve as a potential target for anticancer therapy. An intracellular link between FAK and MDR1 has been determined through protein and apoptosis analysis of treatment with an FAK inhibitor, Y15, which targets the Y-397 site of FAK. Western blot analysis was conducted to evaluate cell death and protein expression in control and Y15-treated platinum sensitive cell lines and control and Y15-treated platinum resistant epithelial ovarian cancer cell lines. DNA fragmentation was also conducted to test for apoptosis resulting from the Y15 drug treatment. This study provides insight in confirming a potentially targeted approach through the crosslink between FAK and MDR1 in platinum resistant ovarian cancer. This study is the first to link the FAK dependent cytotoxic mechanism of Y15 to the MDR1 gene in platinum resistant ovarian cancers. I would like to thank Rumbaugh Goodwin Institute for Cancer Research, NOVA Southeastern University Honors College, and the Royal Dames for providing financial support to conduct this research study.
Check Point Inhibitor Technique to Treat Breast Cancer

Department of Biophysics and Pharmacology, UFRN, Natal-RN, Brazil

Abstract

During immunosurveillance, the immune system is capable to recognise and destroy tumour cells by the activation of the so-called immunological brakes, essential to avoid autoimmune events, creating barriers to T-cell activation and tumour rejection. One of the foremost inhibitory pathway is done by the protein PD-1, whose activation is exploited by several cancer types, including breast cancer, being considered nowadays an important novel therapeutic approach for treating cancer.

Several immune checkpoint inhibitor antibodies are already approved by the FDA to bind the protein PD-1, disrupting its interaction with the PD-L1 and PD-L2 ligands, thereby attenuating inhibitory signals and augmenting the host anti-tumour response. Among them, the drug pembrolizumab, an immune checkpoint inhibitor antibody, is being widely used to efficiently blocks a protective mechanism on cancer cells, triggering the T-cells to destroy them.

Our aim in this work is to describe the interaction energies between the protein PD-1 and its drug inhibitor pembrolizumab, taking advantage of their X-ray crystal structure. The interaction energy between each PD-1 molecule and the drug was calculated in silico through quantum chemistry approaches considering any significant attractive and repulsive drug’s amino acid residues. Although it was observed few repulsive interactions, the attractive ones were predominant, pointing out to a strong inhibition of the programmed cell death receptor. Besides, several biochemical aspects were analyzed, especially those related to the immune checking points. Our results show a great qualitative step for immunotherapy to become one of the standard tool in cancer therapy.

Biography

Mr. E.L. Albuquerque is a PhD student at the Department of Biophysics and Pharmacology, Universidade Federal do Rio Grande do Norte (UFRN), in Natal-RN, Brazil.

Quantum Biochemistry Approach to Investigate the Binding Energy Features of a Cilengitide RGD- Integrin Compound

Department of Biophysics and Pharmacology, UFRN, Natal-RN, Brazil

Abstract

Integrins are proteins of alpha and beta subtypes that function mechanistically by attaching the cell cytoskeleton to both bind to and respond to the extracellular matrix (ECM). They are crucial to the initiation, progression and metastasis of cancerous tumors. Among them, the vitronectin receptor αVβ3 is the most studied, mainly due to its role in tumor growth, progression and angiogenesis.

On the other hand, after RGD (Arg-Gly-Asp) cilengitide peptides have been found to promote cell adhesion, numerous biomaterials have been RGD functionalized for medical applications. Accordingly, RGD-based drugs and peptides containing RGD sequences are used in association with drugs in therapies of cancer and anti-angiogenesis. Its design and production require a precise knowledge not only of its biochemical structure, but also its binding mechanism with the integrin.

In view of that, by employing quantum biochemistry methods based on the Density Functional Theory (DFT) within the Molecular Fractional with Conjugate Caps (MFCC) approach, we investigate the binding energy features of RGD cilengitide interacting with the integrin vitronectin receptor, using a CPCM (Conductor-like Polarizable Continuum Model) scheme to represent the electrostatic environment through a dielectric constant. We have taken into account all ligand-residue interactions within a radius of 1 nm from the ligand, showing the most important regions of the ligand and the residues affecting the binding mechanism. Our computational results allow us to provide a detailed energy profile of the cilengitide-integrin binding mechanisms, providing an efficient alternative towards the development of RGD-based drugs, leading to new bio-engineering devices for cancer therapy.

Biography

Mr. U.L. Fulco is a PhD student at the Department of Biophysics and Pharmacology, Universidade Federal do Rio Grande do Norte (UFRN), in Natal-RN, Brazil.
Mouse Prostate Organoids Reveal an Essential Role for PI3K Alpha in Mouse Prostate Cancer Growth, Metabolism and Tumorigenesis and its Regulation by the Ph Level of the Tumour Microenvironment

Barzan A Sadiq
Babraham Institute, University of Cambridge, Cambridge, UK

Abstract

Globally, there is over a million new annual cases of prostate cancer. In approximately 70% of the cases, at least one copy of the tumour suppressor gene, phosphatase and tensin homolog deleted on chromosome 10 (PTEN), is found to be lost at diagnosis. PTEN is a phosphatase that works in contrast to the class I PI3Ks (phosphoinositide 3-kinase). Class I PI3Ks are heterodimers composed of a catalytic subunit (p110α, p110β, p110δ, or p110γ), which lend their names to the different PI3K complexes, and a regulatory subunit (p85α, p85β, p84, or p101). These heterodimers are expressed differently and seem to assume specific roles in different cellular functions, both within different tissues and single cell types, and are able convey spatially restricted signals, by phosphorylating the PI(4,5)P2 (phosphatidylinositol 4,5-bisphosphate) to produce PI(3,4,5)P3 (phosphatidylinositol 3,4,5-trisphosphate) in the inner leaflet of plasma membrane. These lipids belong to a complex signalling network widely implicated in human pathophysiology. PI(3,4,5)P3 activates vital downstream effector proteins, namely Akt, which is crucial for many cellular processes such as glucose metabolism, transcription, cell proliferation, cell migration, and apoptosis. The PI(3,4,5)P3 pool is controlled by the dephosphorylating abilities of PTEN, to produce PI(4,5)P2, and SHIP to produce PI(3,4)P2, respectively. PI(3,4)P2 is an important second messenger itself that can also activate Akt. The loss of PTEN causes unregulated PI3K/Akt signalling, which allow survival of prostate cancer cells and prevent apoptosis.

We have utilised an established system to culture mouse prostate organoids, which has been isolated from a mouse model of prostate cancer that has a site-specific deletion of the PTEN phosphatase gene. The prostate-specific deletion of PTEN results in a significant reduction in the PTEN gene and protein expression in the mouse prostate tissue and cultured organoids. The animals display hyperplasic intraepithelial neoplasia by 6–8 weeks, and eventually to adenocarcinoma by 4 months of age. Whilst, cultured organoids grow to a condensed yet sizable cell mass, in comparison to the wild type controls. This presented a good opportunity to study the PI3K signalling mechanisms of prostate cancer, and the tumour microenvironment in isolation. Our data indicates that there is a substantial increase in the accumulated levels of PI(3,4,5)P3 and PI(3,4)P2 lipids. This may offer a route in which these lipids play a role in the development and survival of prostatic cancerous cells. We show that this increased level of signalling is primarily driven by the PI3Ka isoform. We further report that the aberrant signalling is dependent on the pH level of the tumour microenvironment, as raising the pH of the organoids medium dramatically increases accumulation of PI(3,4,5)P3 and PI(3,4)P2, although the cause of this effect was unclear, we hypothesise the pH of the local environment may influence signalling via class I PI3Ks.

Furthermore, the vast accumulation of PI(3,4)P2 seen suggest that PTEN may also negatively regulate the PI(3,4)P2 signal, in addition to that of PI(3,4,5)P3. Our findings further our knowledge in understanding the mechanisms of this disease and contribute to the development of more targeted treatments.

Targeting of Prostate Cancer with Polymeric Nanocarriers Labelled with PMSA-Binding Peptide

Ayca Ece Nezir¹, Umut Can Oz², Polen Kocak³, Umut Uğur Özkose¹, Ozgur Yilmaz¹, Asuman Bozkir², Fikrettin Sahin¹ and Dilek Telci¹

¹Department of Genetics and Bioengineering, Yeditepe University, Turkey
²Department of Pharmaceutical Technology, Ankara University, Turkey
³Materials Institute, Marmara Research Center, TUBITAK, Turkey

Abstract

Prostate cancer is the second most common cancer type among men with 37.6% incidence worldwide. It is a type of cancer that cannot be treated with only a single approach and chemotherapy is not very effective for cancer cells that have become hormone-independent. To overcome the limitations of conventional chemotherapy and its damage on healthy cells, we used polymeric nanocarrier constructs formulated via highly biocompatible/biodegradable poly(2-ethyl-2-oxazoline)-b-poly(L-lactide) (PetOx-b-PLA) based polymers with a prostate-specific membrane antigen (PMSA)-targeting peptide as a targeting moiety. Since docetaxel is the most effective chemotherapeutic against prostate cancer, this microtubule stabilizing drug was loaded into our peptide targeted nanoconstructs to be specifically addressed to prostate cancer cells. BikDDA, an effective pro-apoptotic gene, was also encapsulated within the same constructs and its expression in transfected prostate cancer cells were shown with real-time PCR and Western blotting. Cell death induced by both drug- and gene- carrying constructs was analyzed using Annexin V-PI staining. Our data demonstrated that peptide 563 effectively targeted PMSA expressing 22Rv1 prostate cancer cells when compared to the healthy PNT1A control cell line suggesting that the delivery of the cargo within nanocarriers was specific to the prostate cancer cells. This targeted therapy may potentially become a strong substitute for the conventional approaches due to the reduced side-effects it may offer.

Keywords: Prostate cancer, pro-apoptotic gene BikDDA, docetaxel

Biography

Ayca Ece Nezir has completed her BSc from Yeditepe University and MSc from T.C. Istanbul Kultur University. She is currently a PhD student and Teaching Assistant in Yeditepe University.
Evaluation of Oncolytic Activity the TRUYO’s Rotavirus in MES-OV Cell Line of Ovarian Cancer

Gutiérrez-Castañeda Luz D¹ and Guerreo Fonseca Carlos A²
¹Biology Molecular of Virus (Group of Investigation), Faculty of Medicine, Institute of Biotechnology, National University of Colombia, Fundación Universitaria de Ciencias de la Salud, St. José Hospital, Genetics Department (Bogotá, Colombia)
²Biology Molecular of Virus (Group of Investigation), Faculty of Medicine, National University of Colombia

Abstract

Introduction: At the Biology molecular of virus’ laboratory from the National University of Colombia it has been working about the study of the oncolytic potential of five rotaviruses. One of them is a rotavirus called TRUYO (1). The tropism of the oncolytic virus by the tumor cell in a specific way is determined in part by the presence of receptors on the cell membrane, which allows its entry and subsequent replication in it, for this reason we get the conclusion that it is important during the evaluation of the oncolytic virus determine which tumors are susceptible to the infection. The oncolytic potential of TRUYO rotavirus has not been evaluated in ovarian cancer cell lines yet.

Objective: To evaluate if TRUYO’s rotavirus has the capacity or the ability to infect, replicate and induce cell death of the MES-OV (ATCC) cell line of ovarian cancer.

Methodology: The MES-OV cell line was inoculate with TRUYO rotavirus during 12 or 24 hours to 37°C, 5% CO₂. The infection was evaluated and inspected with immunohistochemical, flow cytometry, the replication was evaluated with ELISA, and the death cell with flow cytometry and immunofluorescence.

Results: After 12h post-inoculate with TRUYO’s rotavirus the viral antigens were detected within MES-OV cells. The virions were found in the supernatant and those were capable to infect MES-OV cells. The replication cycle was between 8 and 10 hours. Cell death markers were detected. The TRUYO’s rotavirus had the ability to infect and replicate in ovarian cancer cells.

Keywords: Oncolytic virus, ovarian, cancer rotavirus

Biography

Luz Dary Gutierrez Castañeda is a bacteriologist and has a master degree in human genetics from National University of Colombia. She is a current PhD candidate in Biotechnology at the same university. She is also a part time lecturer of Human genetics at the department of medicine of the Health Sciences University Foundation.
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