

2018 November 2
**Jensen
Symposium**

***Celebrating the 60th Anniversary
of the Discovery of Estrogen Receptor***



SYMPOSIUM ORGANIZERS

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Department of Cancer Biology
University of Cincinnati College of Medicine

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Department of Internal Medicine
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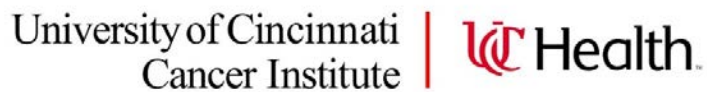
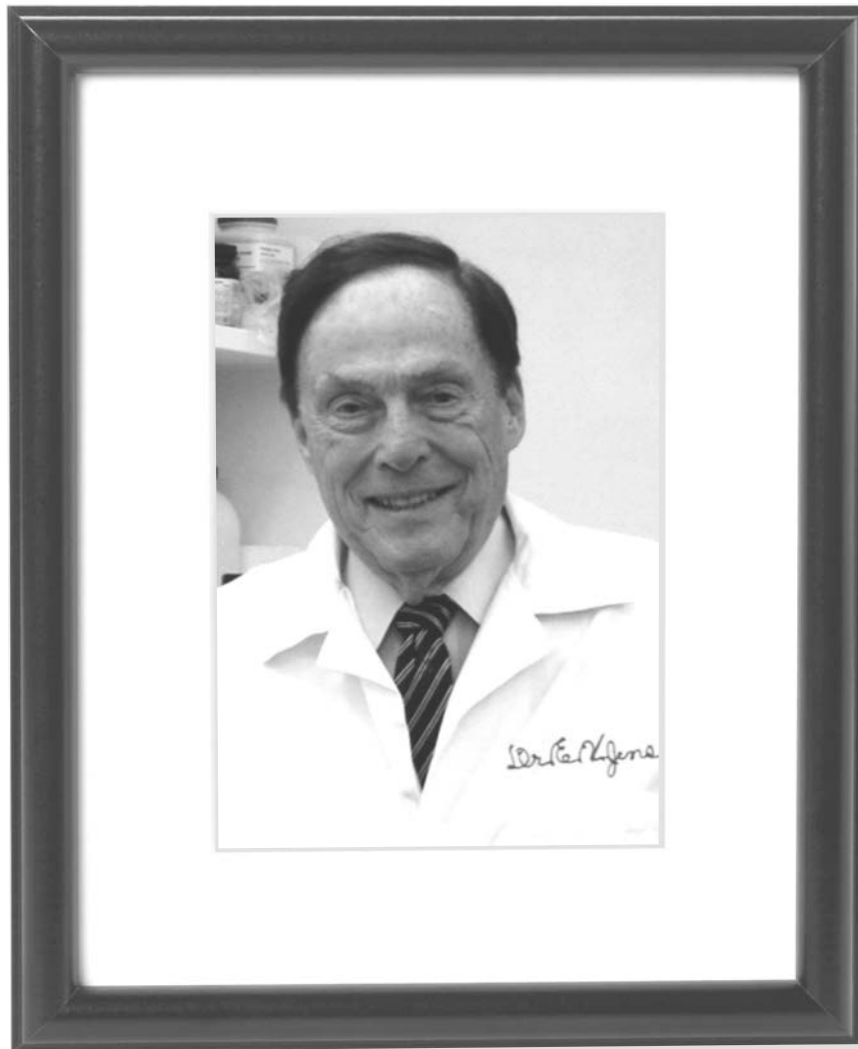


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Cover design by Glenn Doerman, Department of Cancer Biology, University of Cincinnati College of Medicine

A complete PDF of this 2018 Jensen Symposium Abstract booklet can be found at
<http://med.uc.edu/docs/default-source/default-document-library/2018-Jensen-Symposium-Abstract-booklet.pdf?sfvrsn=4>



Dr. Elwood Jensen served as the University of Cincinnati Distinguished University Professor from 2002 - 2012. He gifted his collection to UC College of Medicine. Please visit the exhibit on Elwood Jensen at the Henry R. Winkler Center for the History of the Health Professions. The exhibit contains many items from the Elwood V. Jensen, Ph.D. Papers, such as the Lasker Award and other commendations, photographs, professional and personal correspondence, and much more. The displays are located in the Winkler Center on the R-Level of the Donald C. Harrison Health Sciences Library. From the library stairwell take a LEFT and walk straight ahead. If using the library elevator, take a left upon exiting, then another left and proceed to the glass doors.

PROGRAM AGENDA

FRIDAY, NOVEMBER 2

LOCATION: KRESGE AUDITORIUM*

- 8:00 – 9:00AM **Registration and Breakfast**
- 9:00 – 9:15AM **WELCOME & OPENING REMARKS**
- Melanie T. Cushion, Ph.D.**, Senior Associate Dean for Research,
University of Cincinnati College of Medicine
- Jun-Lin Guan Ph.D.**, Chair and Professor, Department of Cancer Biology,
University of Cincinnati College of Medicine
- 9:15 – 10:00 **Inaugural Jensen Lifetime Achievement Award**
- Bert W. O'Malley, M.D.**
Baylor College of Medicine
Talk Title *"A Warburg Pathway Enzyme Directly Activates SRC-3 Coactivator to Promote Breast Cancer Metastasis"*
- 10:00 – 10:45 **Jensen Memorial Lecture**
- W. Lee Kraus, Ph.D.**
UT Southwestern Medical Center
Talk Title *"Nuclear Receptors, Transcriptional Enhancers, and Gene Regulation in Cancer and Reproduction"*
- 10:45 – 11:00 **Coffee Break**
- 11:00 – NOON **SHORT TALKS** (Session Chairs: Atsuo Sasaki & Vladimir Bogdanov)**
- 11:00 – 11:15 Cristina Andreani (Poster #43: "KDM6B Histone Demethylase Promotes Acquired Resistance to FASNi in Mutant KRAS NSCLC Cells")
- 11:15 – 11:30 Syn Yeo (Poster #35 *"Warping Developmental Space-Time: A Perspective from Single-cell RNA-seq of Mammary Tumors"*)
- 11:30 – 11:45 Haixia Niu (Poster #37: *"Retinoid X Receptor is a Positive Regulator of Normal Hematopoietic Stem Cell Activity Through Cell-autonomous and Non Cell-autonomous Signaling"*)
- 11:45 – Noon Carol Mercer (Poster #3: *"CALCOCO1 has a Novel Role in Selective Autophagy Induced by Inhibition of mTOR: Is this Good or Bad for Breast Cancer?"*)
- NOON – 2:00PM **Lunch and Poster Session****

- 2:00 – 2:45 **Jensen Memorial Lecture**
Carol A. Lange, Ph.D.
University of Minnesota Masonic Cancer Center
Talk Title “*A Tale of Two Receptors: Regulation of Breast Cancer Cell Fate via Phospho-SRs*”
- 2:45 – 3:30 **Jensen Memorial Lecture**
C. Kent Osborne, M.D.
Baylor College of Medicine
Talk Title “*Molecular Mechanisms for Endocrine Resistance in Breast Cancer and Therapeutic Implications*”
- 3:30 – 4:15 **SHORT TALKS (Session Chair: Jiajie Diao)**
- 3:30 – 3:45 Chinmayee Goda (Poster #8: “*FOXF1 in Endothelial Cells Prevents Lung Cancer Progression*”)
- 3:45 – 4:00 Brian Hunt (Poster #9: “*RON-mediated Metabolic Reprogramming in the Breast Tumor Microenvironment*”)
- 4:00 – 4:15 Kara Wolfe (Poster #22: “*Localized GTP Biosynthesis Fuels Renal Cell Carcinoma Migration and Metastasis*”)
- 4:15 – 4:20 **CLOSING REMARKS**
Pier Polo Scaglioni M.D., Chief, Division of Hematology/Oncology,
Department of Internal Medicine, University of Cincinnati College of Medicine
- 4:20 – 5:00PM **Awards/Happy Hour**

***KRESGE AUDITORIUM** is located in the Medical Sciences Building

** **Short talk** includes 10-12 minutes talk and 3-5 minutes discussion.

*** **Posters with odd numbers** will be judged from 12:50PM to 1:20PM; **even numbered posters** will be judged from 1:20 to 1:50PM.

INAUGURAL JENSEN LIFETIME ACHIEVEMENT AWARD

Bert W. O'Malley, M.D.

**Thompson Professor of Molecular and Cellular Biology
Chancellor of Baylor College of Medicine**

Dr. Bert O'Malley is the Tom Thompson Distinguished Leadership and Service Professor of Molecular and Cellular Biology and Chancellor at Baylor College of Medicine. He graduated medical school at U. Pittsburgh, followed by periods at Duke, NIH, and Vanderbilt. He was first to discover that nuclear receptors are transcription factors that regulate mRNA production in target cells in response to intracellular hormones. He uncovered mechanisms for activating steroid receptors, and discovered the existence of 'coregulators', the coactivators and corepressors of gene transcription. The coregulators turned out to be the long sought 'master regulators' of mammalian gene function. His work led to a molecular understanding of how hormonal antagonists work and had major importance to reproduction, genetic disease, metabolism, and especially cancers. Dr. O'Malley is the founding father of the field of Molecular Endocrinology and a member of the National Academy of Sciences and the National Academy of Medicine, and has received over 60 honors and awards for his work, including the National Medal of Science (White House, 2008). He has trained over 250 scientists and published over 700 papers and holds 26 patents in the fields of Gene Regulation, Molecular Endocrinology and Steroid Receptor and Coactivator Action. He developed a later interest in the impressive cooperation of nuclear proteins in dysfunctional processes of transcription in cancer, metabolic disease, and heart damage. This interest was fueled by his recent many studies of the entire coregulatome of mammals detailing the crossover roles of transcription/repair coactivator proteins. In very recent work, he developed the concept that small molecules can regulate coactivators to produce therapeutic outcomes for diseases such as cancer.

A Warburg Pathway Enzyme Directly Activates SRC-3 Coactivator to Promote Breast Cancer Metastasis

S. Dasgupta and B. W. O'Malley Laboratory, MCB Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX

Alterations in both cell metabolism and transcriptional programs are hallmarks of cancer that sustain rapid proliferation and metastasis. However, the mechanisms that control the interaction between metabolic Warburg glycolysis reprogramming and transcriptional regulation remain unclear. Here we show that the Warburg enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 4 (PFKFB4) regulates transcriptional reprogramming by activating the oncogenic steroid receptor coactivator-3 (SRC-3). PFKFB4, a regulatory enzyme that synthesizes a potent stimulator of glycolysis², was found to be a robust stimulator of SRC-3 that coregulates estrogen receptor. PFKFB4 phosphorylates SRC-3 at serine 857 and enhances its transcriptional activity, whereas either suppression of PFKFB4 or ectopic expression of a phosphorylation deficient Ser857Ala mutant SRC-3 abolishes the SRC-3-mediated transcriptional output. Mechanistically, phosphorylation of SRC-3 at Ser857 increases its interaction with the transcription factor ATF4 by stabilizing the recruitment of SRC-3 and ATF4 and other target gene promoters. Ablation of SRC-3 or PFKFB4 suppresses breast tumor growth in mice and prevents metastasis to the lung from an orthotopic setting, as does the Ser857Ala-mutant SRC-3. PFKFB4 and phosphorylated SRC-3 levels are increased and correlate in estrogen receptor-positive tumors, whereas, in patients with the basal subtype, PFKFB4 and SRC-3 drive a common protein signature that correlates with the poor survival of patients with breast cancer. These findings suggest that the Warburg pathway enzyme PFKFB4 acts as a molecular fulcrum that couples sugar metabolism to transcriptional activation by stimulating oncogenic SRC-3 to promote aggressive metastatic tumors.

JENSEN MEMORIAL LECTURE

W. Lee Kraus, Ph.D.

**Cecil H. and Ida Green Distinguished Chair in Reproductive Biology Sciences
Director of the Cecil H. and Ida Green Center for Reproductive Biology Sciences
University of Texas Southwestern Medical Center**

Dr. W. Lee Kraus is the Director of the Cecil H. and Ida Green Center for Reproductive Biology Sciences at University of Texas South Western Medical Center. He is also Professor and Vice Chair for Basic Sciences in the Department of Obstetrics and Gynecology, and Professor of Pharmacology. Dr. Kraus received his Ph.D. in 1994 from the University of Illinois, Urbana-Champaign, where he studied gene regulation by steroid hormone signaling pathways. He completed his postdoctoral work at UC San Diego in 1998, where he studied the mechanisms of estrogen-regulated transcription from chromatin. Dr. Kraus was on the faculty at Cornell University in Ithaca, NY from 1999 to 2010, rising through the ranks to full professor. Since July 2010, he has been at UT Southwestern. He is also a founder of Ribon Therapeutics, Inc., a biopharmaceuticals startup focused on PARP monoenzymes, which began operations in 2015.

Dr. Kraus' research has led to new information about the connections between hormone-regulated gene expression and the gene-regulating effects of chromatin, which has implications for understanding and treating breast cancers. His recent work has helped to characterize the estrogen-regulated transcriptome and identify thousands of novel non-coding RNAs. It has also led to some surprising new conclusions about the activity of poly(ADP-ribose) polymerase-1 (PARP-1), an NAD⁺-regulated nuclear factor that connects cellular NAD⁺ levels to nuclear signaling, chromatin structure, and gene expression.

Dr. Kraus has served as an editor for Molecular Endocrinology and Molecular Cancer Research. He is the founding organizer of the Cold Spring Harbor Laboratory meeting on the PARP family and has been an organizer of two Keystone Conferences on nuclear receptors. He has been recognized for his outstanding research by the Endocrine Society with the Richard E. Weitzman Memorial Award for research excellence in 2007 and the Ernst Oppenheimer Award for research excellence in 2014. Dr. Kraus holds the Cecil H. and Ida Green Distinguished Chair in Reproductive Biology Sciences at UT Southwestern Medical Center.

Nuclear Receptors, Transcriptional Enhancers, and Gene Regulation in Cancer and Reproduction

Transcriptional enhancers, which function as nucleation sites for the assembly of transcription-regulating complexes across the genome, drive cell type-specific patterns of gene expression that underlie the distinct biological properties of different cell types. Although many features of active enhancers (e.g., H3K4me1, H3K27ac, enrichment of p300/CBP and Mediator, and enhancer RNA production) have been defined by genomic assays, the roles of these features in ER α enhancer function are not well understood. The Kraus lab has had a long-standing interest in enhancer biology, in particular the molecular mechanisms and kinetics of enhancer assembly in signal-regulated systems. In particular, we are interested in cell type-specific enhancers that drive biological outcomes in reproductive tissues and in hormone-dependent cancers. We have focused on enhancers formed by estrogen receptor alpha (ER α), a ligand-regulated, sequence-specific DNA-binding transcription factor that nucleates de novo enhancer formation in cells in response to estrogen signaling, as well as other transcription factors (TFs), such as Sox2, FOSL1, and PLAG1. We have used a variety of molecular, biochemical, genomic, genetic, and computational approaches to determine (1) where enhancers are formed by specific TFs across the genome, (2) the kinetics of enhancer formation and disassembly, (3) the influence of genetic variation on enhancer formation and function, and (4) the role of the specific enhancer features noted above, especially enhancer transcription, in enhancer function. In addition, we have developed new computational tools to study enhancer function, such as the Total Functional Score of Enhancer Elements (TFSEE), a robust and unbiased computational pipeline that simultaneously identifies putative subtype-specific enhancers and their cognate TFs by integrating the magnitude of enhancer transcription, TF mRNA expression levels, TF motif p-values, and enrichment of H3K4me1 and H3K27. Collectively, our analyses are providing new insights into the role of nuclear receptors and other TFs in enhancer complex assembly and function in a variety of biological systems.

This work is supported by grants from the U.S. National Institutes of Health (DK058110; HD087150) and the Cancer Prevention and Research Institute of Texas (RP160319, RP110471-P1) to W.L.K.

JENSEN MEMORIAL LECTURE

Carol A. Lange, Ph.D.

**Professor of Medicine (Division of Hematology, Oncology, and Transplantation) and Pharmacology
Tickle Family Land Grant Endowed Chair
Co-Lead, Cellular Mechanisms Program
University of Minnesota Masonic Cancer Center**

Dr. Carol A. Lange is the Tickle Family Land Grant Endowed Chair of Breast Cancer Research and Professor of Medicine and Pharmacology at the University of Minnesota Masonic Cancer Center (MCC) in Minneapolis, Minnesota, where she serves as Director of the Cancer Biology Training (NIH/NCI T32) Program and Co-Leader of the Cellular Mechanisms of Cancer Program within the MCC. Her research is focused on steroid hormone receptor action and signal transduction in breast and ovarian cancer. Her lab studies mechanisms of gene regulation by cross talk between growth factor-mediated signaling pathways and steroid hormone receptors, using the human progesterone receptor (PR) as an understudied model receptor that is highly relevant to ER+ women's cancer and stem cell biology. Additional research focus is aimed at targeting stress-activated signaling pathways (p38 MAPKs, ERK5, HIFs, cortisol and glucocorticoid receptors (GR)) as inputs to GR-target gene expression in breast cancer progression. A key phospho-GR target gene discovered in the Lange lab, known as breast tumor kinase (Brk/PTK6), drives advanced breast and ovarian cancer phenotypes (invasion, metastasis, changes in cancer stem cell biology). Dr. Lange has served on numerous NIH and DOD study sections. She is Editor-in-Chief of the journal *Hormones and Cancer* (Springer/Nature) and a Scientific Advisor to the NIEHS.

A Tale of Two Receptors: Regulation of Breast Cancer Cell Fate via Phospho-SRs

Estrogen receptors (ERs) remain the premier target in ER+ breast cancers. However, both ER+ and ER-negative breast cancers also frequently contain progesterone (PR), androgen (AR), and/or glucocorticoid receptors (GR). The complexity of co-expressed and functionally redundant SRs and the significance of their interactions has only recently begun to be appreciated. Despite what we know about the hallmarks of cancer and modern surgical techniques to remove all traces of SR+ primary breast tumors, cancer targeted therapies are still primarily aimed at blocking cancer cell proliferation (i.e. tamoxifen is a cytostatic agent). These treatments are initially very effective, but also simultaneously stimulate and enable alternative cancer cell fates. Steroid hormones are potent morphogens that primarily act via paracrine mechanisms in the breast and reproductive tissues. Although they are expressed in a minority of cells within a given hormonally regulated normal tissue, resident SRs are master transcription factors whose developmental role is to orchestrate massive changes in cell fate over the reproductive lifespan. We propose that similar mechanisms are at play in heterogeneous SR+ breast tumors. Notably, all aspects of SR action are tightly linked to protein kinase (PK) pathways frequently elevated or activated in women's cancers. Historically, our studies have revealed that PKs and SRs are co-dependent in SR+ cancer cells. In this context, oncogenic PKs phosphorylate SRs, profoundly altering SR gene promoter selection and cell fate. Phospho-SR-driven mechanisms allow non-proliferating or otherwise stressed cancer cells to continue living via genetic reprogramming. In these viable survivors, phosphorylation events enable the activation of phospho-SR target gene programs that permit cellular transitions that function as an escape valve, endowing a few talented cells, known as cancer stem or stem-like cells (CSCs herein), with the latent potential to escape hormone blockade and repopulate entire tumors at distant sites. The emergence of CSCs out of the selection pressure of hormone ablative cancer treatment is a significant problem. Understanding how related SRs govern this process, their potential for functional redundancy, and the impact of local growth factors and inflammatory cytokines or other local factors that phosphorylate SRs and thereby effectively mimic the effects of SR ligand-binding during hormone ablation, is a major challenge that if overcome, will prevent loss of life and livelihood in breast cancer patients with SR+ metastatic disease.

JENSEN MEMORIAL LECTURE

C. Kent Osborne, M.D.

**Director, Dan L Duncan Comprehensive Cancer Center
Tina and Dudley Sharp Chair in Oncology
Professor of Medicine and Molecular and Cellular Biology
Baylor College of Medicine**

Dr. C. Kent Osborne was born in 1946 in St. Louis, Missouri. He received his AB and MD degrees from the University of Missouri, both with honors. He completed his internship and residency at Johns Hopkins Hospital in 1974, and then spent three years as a clinical associate at the Medicine Branch, Breast Cancer Section of the National Cancer Institute in Bethesda, Maryland. In 1977, he took his first faculty position at The University of Texas Health Science Center at San Antonio, where he rose to the rank of Professor and became Director of the Division of Medical Oncology in 1992. In 1999, Dr. Osborne and his team moved to Baylor College of Medicine to develop a new multidisciplinary Breast Center and in 2005 he was named Director of the new Dan L Duncan Cancer Center at Baylor College of Medicine which achieved “comprehensive” designation under his leadership in 2015.

Dr. Osborne is a physician scientist who has focused on breast cancer his entire career. His research interests include understanding the biology of breast cancer and then developing new treatment approaches for the disease. He has published extensively on the mechanisms by which hormonal therapies such as tamoxifen inhibit breast cancer growth and how breast cancers become resistant to these therapies. He has also studied the role of various growth factors in breast cancer development and progression, and more recently how these other growth factors can interact with estrogen to stimulate tumor growth. His laboratory is also focusing on the mechanisms by which breast cancers develop resistance to HER2-targeted therapies. For more than a decade Dr. Osborne was Chairman of the Breast Cancer Committee for the Southwest Oncology Group, where he directed numerous nationwide clinical trials investigating new treatment strategies for breast cancer patients. He is currently the Principal Investigator of the Baylor Breast Cancer Specialized Program of Research Excellence grant which has been funded since the Program began in 1992.

Dr. Osborne has received many awards for his accomplishments. Among his awards are the Komen Foundation Award, the Brinker International Award for Breast Cancer Research, the European Institute of Oncology Annual Breast Cancer Award, the ASCO Bonadonna Award for Breast Cancer Research, The William L. McGuire Memorial Lectureship from the SABCS Symposium and most recently, The 2018 AACR Distinguished Investigator Award for Extraordinary Scientific Achievement and Leadership in Breast Cancer Research. At Baylor College of Medicine, he is currently the Director of the Dan L Duncan Comprehensive Cancer Center and Professor of Medicine and Molecular and Cellular Biology and holds the Tina and Dudley Sharp Chair in Oncology at Baylor College of Medicine.

Molecular Mechanisms for Endocrine Resistance in Breast Cancer and Therapeutic Implications

Endocrine therapy to block estrogen signaling is the most potent treatment for patients with estrogen receptor (ER) positive breast cancer. However, its effectiveness is limited in some patients by de novo or acquired resistance. We demonstrated that crosstalk between ER and growth factor receptor pathways plays a role in endocrine therapy resistance by altering ER activity. These pathways include insulin, the IGFs, the HER family of tyrosine kinase receptors, integrins and stress kinase pathways which can activate ER and its coregulators by phosphorylation. Signaling through several of these pathways is enhanced by blocking ER activity thereby facilitating the development of resistance. Blocking growth factor signaling with mTOR or CDK4,6 inhibitors has dramatically improved progression free survival when combined with endocrine therapy but resistance to these therapies eventually develops. Mutations in ESR1, the gene encoding ER, also activate ER and are a cause for resistance in patients with metastatic breast cancer previously treated with aromatase inhibitors.

Recently we reported that acquired resistance is associated with high levels of the pioneer factor FOXA1. High FOXA1 plays a vital role in altering enhancer and transcriptional programs, activating multiple growth factor pathways and the expression of cancer secretome components that promote resistance to endocrine therapy and enhance metastases. Recent clinical studies show increased FOXA1 activity due to amplification or mutation in 20% of metastatic breast cancers. Genetic alterations in FOXA1 are largely mutually exclusive of ESR1 mutations suggesting that they are independent causes of resistance.

Recent studies in our group suggest that HIF-2a is a mediator of high FOXA1 and growth factor receptor signaling in endocrine resistance. HIF-2a is the top super-enhancer target of high FOXA1-induced enhancer reprogramming. Knockdown of HIF-2a or FOXA1 or a HIF-2a small molecule inhibitor represses growth of endocrine resistant cells suggesting the need to further investigate this approach in appropriately selected patients in the clinic.

POSTERS

1.

Requirement for Autophagic Lipid Metabolism to Sustain mTORC1 in TSC-Deficient Neural Stem Cells

Chenran Wang*, Michael A. Haas, Fuchun Yang, Syn Yeo, Takako Okamoto, Song Chen, Jian Wen, , Pranjali Sarma, David R. Plas and Jun-Lin Guan*

Department of Cancer Biology, University of Cincinnati College of Medicine, Cincinnati

While mTORC1 negatively regulates autophagy in cellular homeostasis, much less is understood on how autophagy impacts on mTORC1 signaling in vivo. By creating and analyzing a mouse model with double conditional knockout of Tsc1 and an essential autophagy gene Fip200 in neural stem/progenitor cells (NSCs), we describe mechanisms by which autophagy controls mTORC1 hyper-activation and the neurodevelopmental lesions of Tuberous Sclerosis Complex (TSC) including defective NSC maintenance, differentiation and tumorigenesis. We show that TSC-deficient cells require autophagy to maintain mTORC1 hyper-activation under energy stress conditions. Autophagy of lipid droplets (i.e. lipophagy) is used as an alternative energy source to fuel OXPHOS, ATP generation, and mTORC1 during energy stress. In vivo, targeting lipophagy or its downstream catabolic pathway reverses defective phenotypes caused by Tsc1-null NSCs and blocks their tumorigenesis in mouse models. These results reveal a cooperative function of selective autophagy in coupling energy availability with TSC pathogenesis, providing potential new therapeutic strategies to benefit TSC patients driven by mTORC1 hyper-activation.

POSTERS

2.

Estrogen Receptor Alpha is a Novel Tumor Suppressor in Osteosarcoma

Susan A. Krum¹, Gustavo A. Miranda-Carboni², and Maria Angeles Lillo Osuna¹

¹Department of Orthopaedic Surgery and Biomedical Engineering, University of Tennessee Health Science Center, Memphis, TN; ²Department of Medicine, University of Tennessee Health Science Center, Memphis, TN

Osteosarcoma is a malignant tumor in the bone that originates from normal osteoblasts or osteoblast precursors. Normal osteoblasts express estrogen receptor alpha (ER); however, osteosarcomas do not due to promoter DNA methylation. Treatment of 143B osteosarcoma cells with Decitabine (DAC, 5-Aza-2'-deoxycytidine) induced expression of ER, leading to a decrease in proliferation and a concurrent induction of osteoblast differentiation, as marked by alkaline phosphatase expression and activity and expression of bone sialoprotein (BSP). 17-estradiol (E2) further decreases the DAC-induced reduction in proliferation. Over-expression of ER also inhibits proliferation and induces osteoblast differentiation and silencing of ER prevents the effects of DAC, demonstrating that ER is both necessary and sufficient for DAC-mediated suppression of osteosarcoma. In an orthotopic model of osteosarcoma in vivo, 143B cells were injected into the tibia of NSG mice and DAC inhibited tumor growth and metastasis. Together, these experiments suggest that the FDA-approved DNA methylation inhibitor DAC can be used to treat osteosarcoma patients to decrease proliferation and induce osteoblast differentiation.

POSTERS

3.

CALCOCO1 has a Novel Role in Selective Autophagy Induced by Inhibition of mTOR: Is this Good or Bad for Breast Cancer?

Stefely JA^{1,2}, Thomas HE¹, Zhang Y¹, Freiburger EC³, Kwiecien NW³, Coon JJ^{3,4}, Pagliarini DJ^{4,5}, Mercer CA¹

¹University of Cincinnati; ²School of Medicine and Public Health, Madison, WI; ³Genome Center of Wisconsin, Madison, WI; ⁴Morgridge Institute for Research, Madison, WI; ⁵University of Wisconsin-Madison

Autophagy is a pathway that sequesters cellular cargo into vesicles that are destined for lysosomal digestion. The capture of autophagy cargo is not always random, but is often selective, using selective autophagy receptors (SARs) to tether cargo to LC3/GABARAP autophagy proteins. Inhibitors of the mammalian target of rapamycin (mTOR), which are FDA approved for breast cancer and other tumor types, have been well-studied for their ability to induce autophagy. However, the role of autophagy in cancer is in debate, with widely disparate reports showing that autophagy may suppress or enable tumorigenesis. We began our study with the hypothesis that mTOR inhibitors (mTORis) induce selective autophagy, and that cargo selection defines whether autophagy is pro- or anti-tumorigenic. Using high resolution mass spectrometry proteomics in autophagy-deficient mouse embryo fibroblasts (MEFs) treated with an mTORi, we found that Lc3b, Gabarapl2, and several known SARs were among the most significantly increased hits, validating our approach. We also identified the calcium coiled coil domain-containing protein 1 (CALCOCO1), a protein known primarily as a transcriptional coactivator for nuclear sterol receptors, including the estrogen receptor (ER). CALCOCO1 was a prime candidate as a novel SAR based on domain structure homology to its paralogs and known SARs: NDP52 and TAX1BP1. We confirmed that CALCOCO1 levels were regulated by mTORis in an autophagy-dependent manner in Hep3B cells; that CALCOCO1 interacts exclusively with LC3C in human cells; and that CALCOCO1 is essential for endoplasmic reticulum selective autophagy (ER-phagy), thus validating that CALCOCO1 is a bona fide SAR regulated by mTOR. In breast cancer cells, our preliminary data suggest that CALCOCO1 is a SAR primarily in ER-negative cells, and that LC3C may be limiting in ER-positive cells. Future studies are designed to determine the significance of CALCOCO1-dependent ER-phagy in tumorigenesis.

POSTERS

4.

Attenuated Compartmentalization of 3D Chromatin Organization in Meiosis and its Maturation in Sperm Development

Alavattam KG, Maezawa S, Sakashita A, Barski A, Kaplan N, Namekawa SH

University of Cincinnati, Cincinnati Children's Hospital Medical Center, and Technion - Israel Institute of Technology

Germ cells manifest a unique gene expression program and regain totipotency in the zygote. Here, by performing Hi-C (genome-wide chromosome conformation capture), we reveal the unique 3D chromatin organization of male germ cells, which is distinct from the organization of interphase nuclei and mitotic chromosomes. We show that highly compartmentalized 3D chromatin organization, a prominent feature of interphase nuclei, is largely attenuated in meiotic prophase. Instead, meiotic prophase is dominated by short-range intrachromosomal interactions, representing a condensed form akin to mitotic chromosomes. However, in stark contrast to mitotic chromosomes, we observe weak genomic compartmentalization as well as large, weak topologically associating domains (TADs) in meiotic prophase. In postmeiotic round spermatids, genome organization undergoes strengthening and consolidation, forming highly compartmentalized 3D chromatin organization in mature sperm. During meiotic sex chromosome inactivation, the X chromosome lacks any domain organization in the transcriptionally repressed XY body, revealing distinct 3D chromatin organization between autosomes and the X chromosome. We propose that male meiosis occurs amidst the global reprogramming of 3D chromatin organization, the maturation of which takes place in sperm development to prepare the next generation of life.

POSTERS

5.

Scribble Controls HSC Self-Renewal through Polarity-dependent Activation of Hippo Signaling

Mark J Althoff^{1,2,3}, Ramesh C Nayak¹, Shailaja Hegde^{1,3}, Ashley M Wellendorf¹, Fatima Mohmoud³, Mei Xin^{1,2}, Q Richard Lu^{1,2}, Maria T Diaz-Meco⁴, Jorge Moscat⁴ and Jose A Cancelas^{1,3}

¹Cincinnati Children's Hospital Medical Center, Cincinnati, OH; ²Cancer & Cell Biology Graduate Program, University of Cincinnati, Cincinnati, OH; ³Hoxworth Blood Center, University of Cincinnati College of Medicine, Cincinnati, OH; ⁴Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA.

Hematopoietic stem cell (HSC) transplantation is used in cancer therapy and represents the cornerstone of ex vivo cell/ gene therapy for HSC driven diseases. Search of molecular targets to expand functional HSC for translational applications remains paramount. HSC respond to extrinsic cues and either self-renew or differentiate according to changes in cellular polarity. While the mechanisms underlying polarity establishment and maintenance are well characterized in neuronal stem cells and epithelial cell populations, the role that polarity regulators have on the polarization and function of HSC remains elusive. Scribble, a multi-modular scaffolding protein, coordinates the spatial organization of intracellular proteins. By using a combination of constitutive and inducible hematopoietic-specific Scribble-deficient animal models, hematopoietic reconstitution assays, structure-function mutants of Scribble and intracellular protein trafficking analysis, we identified the functional relevance of Scribble in HSC activity. Scribble-deficient HSC are prone to cell cycle entry, have increased hematopoietic potential during stromal-dependent cultures or after chemotherapeutic stress in vivo and display increased self-renewal following serial transplantation. Mechanistically, SCRIBBLE polarizes LATS1 and YAP1 of the Hippo Signaling Pathway in HSC. Deletion of Scribble disrupts the LATS1/YAP1 complex and permits YAP1 nuclear translocation. Notably, cytoplasmic polarization of YAP1 can be restored in Scribble deficient HSC by reintroducing full-length Scribble or a PDZ domain-containing mutant. The Hippo-YAP1 axis has been argued to be dispensable in HSC, but our most recent data suggests this pathway, in conjunction with Scribble polarization, may play an essential role in regulating HSC self-renewal. Understanding this connection will allow us to exploit novel targets such as these during HSC-based gene-therapy for the successful treatment of cancers and hematologic diseases.

POSTERS

6.

The Link Between Mitochondrial Morphology and Hematopoietic Stem Cell Function

James Bartram¹, Jose Javier¹, Ashwini Hinge², Juying Xu², Marie-Dominique Filippi²

¹Cancer & Cell Biology Graduate Program, University of Cincinnati, Cincinnati, OH; ²Cincinnati Children's Hospital Medical Center, Cincinnati, OH

For many hematological disorders bone marrow transplantation is the only curative therapy. However, one-in-four patients will endure bone marrow failure. Maintenance of a functional hematopoietic stem cell (HSC) pool is crucial for successful transplantations. HSCs undergo stepwise differentiation to produce myeloid and lymphoid progenitors, as well as self-renewal to maintain a functional stem cell pool; however, HSCs become dysfunctional i.e. unable to properly regulate their self-renewal and differentiation potential after transplantation. One cause is the deregulation of proper mitochondrial organization i.g. Transplanted (1T) HSCs acquire fused and polarized mitochondria while non-transplanted (NT) HSCs maintain healthy dispersed mitochondria. This deregulation of mitochondrial organization is due to the loss of function of the fission regulator Drp1 in 1T HSCs. Here we show this with single cell RNA seq data from 1T and NT HSCs in conjunction with analysis of mitochondrial morphology of 1T HSCs compared with Drp1 deficient HSCs. Transplanted donor HSCs are required to leave quiescence and undergo division to regenerate the recipients bone marrow, therefore, we wanted to analyze mitochondrial morphology of NT HSCs pre and post division. In order to do this, we used the widely established H2B mouse model where mice are treated with doxycycline for two weeks and then chased for 18 weeks and then sacrificed and analyzed. FACS analysis was used to sort HSCs that had not undergone division i.e. GFP high expressing cells and HSCs that had undergone division i.e. GFP low expressing cells. Next, the mitochondrial morphology of these populations was analyzed. We were able to show that HSCs that underwent division had hyper fused mitochondria while cells that had not undergone division still had healthy dispersed mitochondria. In all, we were able to conclude that mitochondrial morphology is linked to the functional status of HSCs and that divisional history plays a role.

POSTERS

7.

Differentiation of Novel GFP:FOXF1 Embryonic Stem Cell Line into FOXF1-positive Endothelial Progenitor Cells

Flood HM and Kalinichenko, VV

Center for Lung Regenerative Medicine, Cincinnati Children's Research Foundation, Cincinnati, OH

Pulmonary endothelial cells (ECs) are critical for endothelial barrier maintenance and lung homeostasis. Acute lung injury (ALI) increases endothelial permeability resulting in edema and inflammation. ALI can develop into the life-threatening complication acute respiratory distress syndrome. Recent advances in treatment of human lung diseases have introduced cell replacement strategies to contribute to lung regeneration. Preliminary studies have shown that the introduction of endothelial colony forming cells prior to ALI in mice reduces the extent of injury and improves survival. However, the cells utilized in the preliminary studies did not express a fluorescent tracer for monitoring in vivo integration, and were additionally negative for FOXF1, a transcription factor which has been shown to be expressed in lung ECs and important for proper lung function. The current study sought to first develop a traceable cell line to determine if the transplanted cells integrate into the lung barrier to rescue function and phenotype, and second to differentiate into a sub-population of endothelial progenitor cells (EPCs) that express FOXF1. Using the CRISPR/Cas9 system, we have successfully generated a novel embryonic stem cell line where we knock GFP in to the *Foxf1* locus. We have reviewed recently published EC differentiation protocols to develop a novel differentiation method which yields ~95.2% ECs. These ECs are positive for stemness marker C-Kit, suggesting they have successfully differentiated into an EPC population. Further analysis demonstrates that our EPC population is ~51.5% FOXF1-positive as detected by GFP:FOXF1. Altogether, we have successfully developed a differentiation protocol which yields ~51.5% FOXF1-positive EPCs. Further work needs to be done to determine if the EPCs described in the current study function as ECs and if they are able to integrate into the host lung endothelial system and successfully rescue mouse models of lung injury.

POSTERS

8.

FOXF1 in Endothelial Cells Prevents Lung Cancer Progression

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Lung cancer is the leading cause of cancer-related mortality worldwide. The 5-year survival rate is less than 20%, emphasizing a need to improve existing therapies. Solid tumors, including lung tumors are characterized by abnormal vasculature that plays a crucial role in tumor progression. Through whole transcriptomic analysis, we identified that lung tumor-endothelial cells (TECs) undergo biological reprogramming, however the factors that regulate the reprogramming are not well defined. Identification of these factors will improve our understanding of tumor vascular biology and aid in designing novel therapeutic targets to normalize the tumor vasculature. Forkhead Box F1 (Foxf1) is a transcription factor expressed by normal lung ECs. We observed that Foxf1 mRNA and protein levels are down regulated in TECs in lung cancer patient samples and mouse models of lung cancer. Furthermore, lower Foxf1 expression correlated with poor overall survival of lung cancer patients. Based on this, we hypothesized that Foxf1 in ECs promotes lung tumor progression. To test our hypothesis, we used inducible EC-specific Foxf1 heterozygous mice (endFoxf1^{+/-}) and inducible EC-specific Foxf1 overexpression (endFoxf1OE) mice. Using an orthotopic model of lung cancer, we observed that Foxf1 in ECs inhibited lung tumor growth and metastasis in mice. Gene expression and immunohistological analysis demonstrated that Foxf1 indirectly regulates angiogenesis in tumors. Through immunohistological analysis, we observed that Foxf1 regulates vascular maturity, thereby vascular perfusion and hypoxia within lung tumors. To determine the mechanism by which Foxf1 regulates lung tumor vasculature, we performed RNA-seq, and observed down-regulation of Wnt/ β -catenin signaling pathway in Foxf1-deficient TECs. Using in vitro assays, we found that Foxf1 regulates Wnt/ β -catenin signaling pathway in ECs. Overall, our data shows that Foxf1 in ECs prevents lung tumor progression through vascular normalization.

POSTERS

9.

RON-mediated Metabolic Reprogramming in the Breast Tumor Microenvironment

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Despite advances in clinical detection, breast cancer (BC) is the second leading cause of cancer-related deaths in women. Existing therapies to treat BC show efficacy in destroying bulk tumor cells but fail to address components of the tumor microenvironment such as breast cancer stem cells (BCSCs), which show tumor-repopulating qualities, and macrophages, which show the capacity to directly dictate the anti-tumor immune response. Recurrent BC is frequently treatment resistant and has poor survival outcomes and is thought to be a consequence of incomplete eradication of tumor-repopulating cells. The RON receptor tyrosine kinase (RTK) overexpressed in more than half of all BCs independent of molecular subtype. Importantly, RON has been shown to be a predictor of BC recurrence, metastasis and poor prognosis in patients with BC. Our previous data suggest overexpression of RON leads to ligand-independent activation, and when transgenically overexpressed in the mouse mammary epithelium leads to aggressive, metastatic BC in 100% of female mice. Ongoing studies looking into cell type-specific consequences of RON signaling in BC demonstrate roles of epithelial RON signaling in supporting M2 (anti-inflammatory, pro-tumorigenic) polarization of macrophages and enhanced BCSC phenotypes. Here, we describe the novel function of RON signaling in facilitating metabolic reprogramming with enhanced 'Warburgian' phenotypes. Further, we demonstrate contribution of RON-mediated metabolic reprogramming on macrophage polarization and BCSC phenotypes, suggesting novel mechanisms by which tumor epithelial RON signaling resists treatment. Using a pre-clinical model of BC recurrence, we seek to test rationally devised therapeutic strategies to prevent and treat recurrent BC.

POSTERS

10.

Up-regulated TGF- β Signaling Drives MDS-like Bone Marrow Failure Following Acute Viral Inflammatory Stress

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Hematopoietic stem cells (HSCs) self-renew or differentiate to produce mature circulating blood cells after transplant or viral infection. However, how signaling pathways regulate these decisions is still unclear. Dysregulation causes either leukemia or bone marrow failure. Myelodysplastic syndromes (MDS) are a group of bone marrow failure syndromes defined by cytopenias in ≥ 1 blood lineage, myeloid dysplasia and hematopoietic stem and progenitor cells (HSPCs) clonal expansion, with some types more likely to transform into acute myeloid leukemia. Our lab has published that transplanted murine HSCs have a TGF β signaling autocrine loop that accelerated bone marrow failure after transplant, reversible by using TGF β pharmacological inhibitors. We decided to further explore the effect of TGF β signaling during stress using a mouse model conditionally overexpressing transgenic aTGF β 1 in the hematopoietic system (Tg-Cre $^{+}$). Preliminary data show that stress induced by polyinosinic:polycytidilic acid (pIC) to mimic viral infection causes persistent pancytopenia and increased progenitor dysplasia up to 9 months after stress in Tg-Cre $^{+}$ mice compared to controls. Flow cytometry of Tg-Cre $^{+}$ bone marrow revealed an expanded HSPC compartment, and RNA-seq of Tg-Cre $^{+}$ HSCs revealed that pathways related to mitochondrial regulation and cell cycling were up-regulated compared to controls 3 months after stress. Tg-Cre $^{+}$ pIC-stressed HSCs had higher mitochondrial membrane potential, and immunofluorescence analysis showed altered mitochondrial distribution in Tg-Cre $^{+}$ mice 3 months after stress. Distribution of MAVS, a mitochondrial membrane protein that effects response to viral stress, was altered in Tg-Cre $^{+}$ after aTGF β 1 overexpression, and remains after pIC stress. Results therefore suggest that up-regulated TGF β signaling alters mitochondrial architecture, function and MAVS cellular distribution to pre-dispose towards MDS-like bone marrow failure triggered after acute viral stress.

POSTERS

11.

Passenger Deletion Vulnerability in Glioblastoma

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Glioblastoma multiforme (GBM) is the most common, aggressive and lethal primary brain tumor in humans. Despite aggressive therapy the median survival of GBM patients is approximately 15 months. Monoallelic loss of PTEN occurs in ~70% of GBM. Through experimental validation studies in patient-derived primary GBM cell lines, we discovered that the lipogenic gene SCD undergoes unintended co-deletion as a passenger to PTEN, resulting in hemizygous loss of SCD in a subset of GBM. Additional *in silico*, genetic and biochemical analysis lead to the identification of two distinct PTEN-deleted subgroups: one with hemizygous co-deletion of PTEN and SCD (hereafter SCD-expressing), and another with very little or no PTEN/SCD expression due to PTEN mutation/homozygous loss and epigenetic suppression of the remaining SCD allele (hereafter SCD-non-expressing). SCD is an integral membrane protein of the endoplasmic reticulum (ER), involved in mediating the rate-limiting step of unsaturated fatty acid biosynthesis. SCD catalyzes the desaturation of the saturated fatty acids stearic (C18:0) and palmitic acids (C16:0) to the monounsaturated fatty acids oleic (C18:1) and palmitoleic acids (C16:1), respectively. We showed that the SCD-expressing lines are highly sensitive to SCD inhibition in the absence of dietary oleate and that the SCD-non-expressing lines are resistant to SCD inhibition. *In vivo*, we showed that mice treated with the SCD inhibitor survive longer than mice treated with vehicle. We also showed that SCD-expressing GBM lines acquire inhibitor resistance upon long-term exposure to the inhibitor *in vitro*. To understand the mechanism of resistance, we performed Reverse Phase Protein Array (RRPA) and RNA-Seq. Results illustrated the up-regulation of SCD among other genes.

POSTERS

12.

Spliceosome Mutant MDS and AML Cells Activate Innate Immune Signaling by Regulating the Expression of Therapeutically Targetable IRAK4 Isoforms

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Alternative RNA splicing and mutations in spliceosome genes are common features of MDS and AML, however which misspliced genes contribute the malignant state remains unclear. A global analysis of intron and exon usage in AML revealed enrichment of alternatively spliced genes associated with inflammatory and immune pathways in leukemic cells as compared to normal cells. The gene with the greatest differential isoform expression was IRAK4, a serine/threonine kinase downstream of toll-like receptor (TLR) signaling. RNA sequencing revealed that normal cells preferentially express an IRAK4 isoform resulting from exclusion of the exon 4, which encodes a protein lacking the N-terminal death domain (IRAK4-Short). In contrast, MDS/AML samples expressed increased full-length IRAK4 isoform (IRAK4-Long) that retains exon 4. Of all somatic genetic mutations associated with AML, mutation of U2AF1 (S34F) significantly correlated with inclusion of exon 4. Examination of IRAK4 exon 4 usage in CD34+ cells from patient samples revealed that nearly all MDS patient samples with mutations in U2AF1 exhibited increased inclusion of exon 4 as compared to WT U2AF1 MDS samples or healthy controls. Ectopic expression of U2AF1-S34F in AML cells resulted in significant retention of IRAK4 exon 4 and expression of IRAK4-Long protein. Importantly, U2AF1-S34F AML cells were more sensitive to pharmacologic inhibition of IRAK1/4 as compared to isogenic cells with WT U2AF1. CA-4948, a potent oral small-molecule inhibitor of IRAK4, blocked IRAK4-mediated signaling in TLR-stimulated THP1 AML cells, and decreased leukemic burden in xenografted mice. Finally, CA-4948 treatment led to reduced leukemic engraftment of primary patient MDS/AML samples with expression of IRAK4-Long. Taken together, we find that mutations in U2AF1 induce expression of therapeutically targetable "active" IRAK4 isoforms and provide a genetic link to chronic innate immune signaling and IRAK1/4 activation in MDS and AML.

POSTERS

13.

Genomic Variants Enriched in Patients with Plexiform Neurofibroma

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In Neurofibromatosis type 1, NF1 gene mutations characterize benign plexiform neurofibroma (PNF) Schwann cells (SC), but no other genomic changes have been identified to explain patient-to-patient variability in tumor formation. Whole exome sequencing data from SC and fibroblast DNA from the same resected PNFs confirmed SC biallelic NF1 mutations. We identified frequent, possibly damaging, germline alterations in OBSCN, PKHD1, CUBN, CELSR2, COL14A1 and ATM. Germline variants in 16 genes, including ATM, were cross-validated in cohorts of dermal NF (DNF) and PNF, and many also showed decreased gene expression. In contrast, somatic SC variants were present at low read number, in few tumors, and are of uncertain relevance to tumorigenesis. ATM-relevant DNA repair defects were present in a subset of neurofibromas, and in neurofibroma SC. In mice, genetic Atm loss promoted Schwann cell precursor self-renewal and increased tumor formation in vivo. Genomic variants may contribute to neurofibroma initiation, growth, and/or progression.

POSTERS

14.

Inducible Correction of a RUNX1 Mutation of Human AML Causes a Switch of AML to B-ALL

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The RUNX1 mutations are found frequently associated with MLL-partial tandem duplication (MLL-PTD) in AML. We have developed two complementary mouse models that express a MLL-PTD knock-in mutation together with a RUNX1 S291fsX300 mutation found in AML patients: in the first model RUNX1 S291fsX300 was introduced into the bone marrow cells of the MLL-PTD knock-in mice by retrovirus transduction, while in the second model the tetracycline-inducible RUNX1 S291fsX300 mutation was knock-in at the Collagen a1 locus and the mice was crossed to MLL-PTD knock-in. Under tetracycline induction, the RUNX1 S291fsX300 and MLL-PTD double mutation bearing mice developed a spontaneously AML and had a survival time 6-10 months after transplantation, and they showed symptoms of MDS/AML or AML. We transplanted the AML mouse bone marrow to secondary recipient. The c-Kit⁺ AML cells cultured from the RUNX1 mut-off mice showed reduced viability and significantly reduced CFU-C activities, which are accompanied by a lineage switch in a decrease in expression of Mac1 and an increase in expression of B220. An analysis of the lineage distribution in their peripheral blood and bone marrow revealed that the RUNX1 mut-off AML mice underwent a dramatic lineage switch from myelocytes to lymphocytes. Pathological analysis also showed a drastic decrease of the myeloid marker MPO and increased lymphoid marker B220 in the RUNX1 mut-off mice. Consistently, a RT-PCR test of the BM c-Kit⁺ cells further showed that upon turning off the RUNX1 mut, critical B cell regulatory genes including TCF3, EBF1, PAX5, CD79A were significantly up regulated whereas myeloid regulatory genes such as PU.1 were downregulated. In addition, RUNX1 S291fsX300 expression in the AML cells confers a resistance to chemotherapy (Ara-C) treatment compared with that of WT RUNX1 expression, indicating that the RUNX1 mutation is responsible for the AML resistance to therapy.

POSTERS

15.

Elucidating the Cell Type-Specific Mechanisms of the Ron Receptor in the Prostate Tumor Microenvironment

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The incidence of advanced prostate cancer (PCa) in American men has grown by 72% within the last decade yet current treatments fail to effectively treat advanced disease. We study the Ron receptor tyrosine kinase as a novel target for PCa treatment. Ron is expressed in macrophages and epithelial cells and is found overexpressed in PCa. Ron expression increases with disease severity in humans and mouse models, suggesting Ron drives progression to advanced PCa. We have shown that loss of Ron signaling in prostate epithelial cells or in myeloid cells markedly reduces tumor growth and modulates the tumor microenvironment, particularly the functions of macrophages and CD8+ T cells. We hypothesize that the Ron receptor utilizes cell type-specific mechanisms to suppress the antitumor immune response. To explore these mechanisms, we employed Cre-Lox technology and the well-established TRAMP PCa mouse model to generate transgenic PCa mice containing ablation of Ron signaling in prostate epithelial cells or myeloid cells. We observe that Ron signaling in either cell type is critical for prostate tumor growth in our transgenic models. Furthermore, loss of Ron in either cell type leads to increased macrophage and CD8+ T cell tumor infiltration, and our in vitro data show that loss of Ron in either cell type suppresses antitumor M1 macrophage activation and promotes tumor-supporting M2 macrophage activation. Additionally, preliminary data suggest loss of Ron in either cell type leads to increased activation of CD8+ tumor-infiltrating lymphocytes. Overall, our data suggest the Ron receptor coordinates immunosuppressive mechanisms in both the malignant tumor cells and the host macrophages to dampen antitumor immunity and promote prostate cancer. These studies implicate Ron targeting as a powerful therapeutic tool with broad utility for understanding and refining therapeutic strategies to treat advanced PCa.

POSTERS

16. Dissecting Mechanistic Basis for Differential Expression and Activity of PRPS Isozymes

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Cancer cells are addicted to supra-physiological nucleotide levels to sustain unabated proliferation, a feature that renders them vulnerable to many chemotherapeutic agents. But the use of these agents lead to serious side effects and secondary ailments. Thus, there is a need to understand the mechanistic basis for such an addiction. Phosphoribosyl pyrophosphate synthetase isoforms (PRPS1 and PRPS2) are key rate limiting enzymes catalyzing the conversion of ribose-5-phosphate to phosphoribosyl pyrophosphate (PRPP). In normal cells, optimum rate of nucleotide production is maintained by regulating PRPS1 enzyme activity via end-product feedback inhibition and low expression of feedback-refractory PRPS2. Mutations in PRPS1 imbue developmental disorders and drive resistance to chemotherapy in relapsed B-ALL, while c-Myc mediated PRPS2 upregulation drives enhanced nucleotide production in Myc-transformed cells. Myc-overexpression increases PRPS2 translation via a unique eIF4E-dependent cis-acting regulatory element called PRTE (pyrimidine-rich translational element), located within the PRPS2 5'UTR (untranslated region). Analysis of publicly available ribosome profiling data revealed a strong isolated peak of ribosome footprint density within PRPS1 5'UTR. The sequence is conserved evolutionarily across 20 mammals, suggesting the relevance of a potential PRPS1 5'uORF (upstream open reading frame). This project, thereby, aims to explore whether PRPS1 and PRPS2 5'UTR elements co-evolved to acquire different structural and biochemical properties. Additionally, we aim to investigate whether the isozymes exist as a heterodimeric complex as evinced from a preliminary PRPS1-PRPS2 co-immunoprecipitation data. Thus, an understanding of the dichotomy in the expression and activity of the two isozymes will not only help us in understanding how stoichiometric changes influence nucleotide production but also lead us towards a safer and precision based anti-cancer therapy.

POSTERS

17.

Combined Targeting of Estrogen Receptor Alpha and XPO1 Prevent Akt Activation, Remodel Metabolic Pathways and Induce Autophagy to Overcome Tamoxifen Resistance

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Majority of breast cancer specific deaths in women with ER α (+) tumor occur due to metastases that are resistant to endocrine therapy. There is a critical need for novel therapeutic approaches to resensitize recurrent ER α (+) tumors to endocrine therapies. The objective of this study was to elucidate mechanisms of improved effectiveness of combined targeting of ER α and XPO1, a nuclear transport protein in overcoming endocrine resistance. Selinexor (SXR), an XPO1 antagonist, has been evaluated in multiple later stage clinical trials in patients with relapsed and /or refractory hematological and solid tumor malignancies. Using human phosphokinase array to profile kinase signaling pathways, we found that 4-OH Tamoxifen, SXR or their combination induced differential Akt phosphorylation profiles, changing the phosphorylation status and activity of the kinase. Also, our RNA sequencing data indicated that 4-OH Tamoxifen+SXR combination treatment causes gene expression changes distinct from 4-OH Tamoxifen and SXR treatments alone in tamoxifen-resistant cell lines. Since we observed dramatic changes in Akt activity and we saw a differential gene expression pattern with individual and combined 4-OH Tamoxifen and SXR treatments, we hypothesized that metabolic profile of breast cancer cells would change in the presence of 4-OH Tamoxifen and SXR. We showed that ER α -XPO1 targeting changes metabolic phenotype of breast cancer cells from an energetic to quiescent profile, demonstrating that combined targeting of XPO1 and ER α rewires metabolic pathways and shuts down both glycolytic and mitochondrial pathways that would eventually lead to autophagy. Remodeling metabolic pathways to regenerate new vulnerabilities in endocrine resistant breast tumors is novel, and given the need for better strategies for improving therapy response of relapsed ER α (+) tumors, our findings show great promise for uncovering the role of ER α -XPO1 crosstalk plays in reducing cancer recurrences.

POSTERS

18.

GREB1 Modulates Signaling Through the PI3K/Akt/mTOR Pathway to Regulate Proliferation of Breast Cancer Cell Lines

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Over 70% of breast cancers express the estrogen receptor (ER) and depend on ER activity for survival and proliferation. Patients diagnosed with ER-positive breast cancer are treated with hormone therapies that target receptor activity. However, tumors invariably develop resistance highlighting the need for new and innovative therapies. While the mechanism by which ER regulates proliferation is poorly understood, one gene target of ER, growth regulation by estrogen in breast cancer 1 (GREB1), has been implicated in this process. Despite the relationship between GREB1 and estrogen-induced proliferation of breast cancer cells, the mechanism by which GREB1 regulates proliferation has been largely uncharacterized. We show that knock-down of GREB1 results in growth arrest and that exogenous GREB1 expression halts proliferation and induces senescence, suggesting an optimal level of GREB1 expression necessary for proliferation of breast cancer cell lines. Under both of these conditions, GREB1 is able to regulate signaling through the PI3K/Akt/mTOR pathway, which has been implicated in the survival and proliferation of many different types of malignant cells, including breast cancer. Exogenous expression of GREB1 results in the hyperactivation of the PI3K/Akt/mTOR pathway. Conversely, GREB1 knock-down reduces activation of the PI3K/Akt/mTOR pathway in breast cancer cells, indicating GREB1-driven activation of this pathway is necessary for proliferation. Expression of constitutively activated Akt rescues these cells from growth arrest. Together, these data suggest a novel mechanism by which GREB1 regulates signaling through the PI3K/Akt/mTOR signaling cascade to modulate proliferation of breast cancer. These findings are critical to better understanding how ER-target genes lead to proliferation of breast cancer cells and identifying new therapeutic targets downstream of ER-signaling.

POSTERS

19.

Evaluating the Role of BRUCE in Liver Disease Progression

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Liver disease describes several liver damaging conditions and is a leading cause of death in the US, yet little is known about pathways which regulate progression of these disorders. Chronic injury and inflammation are often associated with hepatocellular carcinoma (HCC) pathogenesis as they often promote the activation of the DNA damage response and repair network of pathways regulated by major kinases, such as the ATM (ataxia-telangiectasia mutated) and ATR (ataxia-telangiectasia and Rad3-related protein). Our lab has evaluated the impact of BRUCE in ATM and ATR DNA repair activity. Our preliminary data shows that BRUCE heterozygous mice develop spontaneous HCC after 10 months of age and that over 50% of human chronic liver disease patient samples have decreased BRUCE expression. To gain insight on the influence of BRUCE loss on liver disease progression, we have generated a BRUCE liver-specific knockout (BRUCE Alb-KO) mouse model. Increased nuclear γ H2AX staining in the BRUCE Alb-KO hepatocytes suggests that upon drug-induced liver injury with the DNA damaging environmental carcinogen diethylnitrosamine (DEN), BRUCE deficiency contributes to increased DNA damage in the liver. Additionally, DEN-induced HCC data observations show that BRUCE Alb-KO mice develop tumors at an 100% incidence as compared to the 80% incidence observed in the wild-type (WT) mice. Yet the influence of BRUCE in HCC pathogenesis remains unclear. Interestingly, BRUCE Alb-KO mice also have increased cell proliferation, as well as nuclear β -catenin localization in tumor and non-tumor tissue. We hypothesize that upon liver injury, BRUCE promotes efficient DDR contributing to the regulation of DNA repair and appropriate activation of the β -catenin pathway. This data suggests that upon liver injury, BRUCE plays a protective role against liver disease and HCC progression.

POSTERS

20.

Commensal Bacteria Calibrate Host Defense by Enhancing Retinoic Acid Signaling

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Interactions between the intestinal microbiota and the mammalian host are essential for effective defense against pathogenic infection. However, despite critical associations between commensal bacteria and infection, the underlying mechanisms by which protective microbial cues are integrated by host cells remain unclear. Here, we find that the intestinal epithelial cell (IEC)-associated commensal bacteria, Segmented Filamentous Bacteria (SFB), enable early protection against *Citrobacter rodentium* that did not require CD4⁺ T cells. Our recent work revealed that expression of epigenetic modifiers in IECs enable microbiota to protect against *C. rodentium* infection, provoking the hypothesis that beneficial commensal bacteria may prime defense by directing critical epigenetic modifications in IECs. Consistent with this hypothesis, we found that SFB colonization induced enrichment of the enhancer-associated histone modification, H3K27Ac, within regulatory regions of thousands of genes in IECs. SFB-induced H3K27Ac sites were significantly enriched for RAR/RXR receptor motifs, suggesting that SFB may alter retinoic acid receptor-mediated signaling in IECs. Interestingly, we found that SFB-colonized mice exhibited elevated retinoic acid levels in the intestine compared to germ-free mice, and increased IEC expression of RAR targets. Further, administration of retinoic acid to SFB-deficient mice decreased *C. rodentium* infection, whereas inhibiting RAR signaling in SFB-colonized mice increased pathogenic burden. Collectively, these data suggest that enhanced or primed retinoic acid receptor activation in IECs may represent a novel mechanism by which the microbiota calibrates host defense.

POSTERS

21.

Fanconi Anemia Defects Disrupt the Structure and Function of Human Skin

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Squamous cell carcinoma (SCC) is a common cancer with global public health burden that arises from the malignant transformation of epidermal stem and progenitor cells (ESPCs) in the skin and mucosa, the basal keratinocytes that give rise to the squamous epithelium. To elucidate how genetic risk factors lay the foundation for SCC and develop effective prevention strategies, it is critical to understand ESPC biology. Extreme predisposition to SCC is a hallmark of Fanconi anemia (FA). Studying FA pathogenesis in the epidermis has been challenging since mouse models do not recapitulate human phenotypes spontaneously. Therefore, we generated the first personalized model of the FA epidermis using induced pluripotent stem cells that harbor a conditional FA pathway (cFA-iPSCs). These served as the source of ESPCs to identify developmental origins responsible for increased SCC predisposition in FA.

Somatic cells from FA patients in the complementation group A were transduced with a doxycycline-inducible FANCA expression vector and then reprogrammed into iPSCs. The resulting FA-iPSC lines were differentiated into ESPCs and engineered into 3D epidermis. We demonstrate that cFA-iPSCs can give rise to ESPCs and engineered epidermis, which appear morphologically normal based on histological analyses. However, FA pathway-deficient engineered epidermis harbored decreased numbers of cellular junctions and increased proliferation in the basal ESPC compartment. Adhesion abnormalities were validated in the skin of individuals with FA compared to controls, and these pathologies translated into strikingly accelerated blistering following mechanically-induced stress. Thus, we identify a new role for the FA pathway in skin integrity and propose a model whereby epidermal pathologies leave the FA epidermis vulnerable to mechanical insults and potential environmental exposures, thus further compounding the existing genome instability to promote SCC.

POSTERS

22.

Localized GTP Biosynthesis Fuels Renal Cell Carcinoma Migration and Metastasis

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Background and Purpose: Renal cell carcinoma (RCC) is the 8th most common cancer diagnosed in the United States. Over 40% of all RCC patients will be diagnosed with stage IV (metastatic) disease and the five-year survival of stage IV patients is less than 10% despite recent advances in therapeutics. There remains a clear need to develop more effective therapeutics and preventative measures for mRCC and to understand the mechanisms behind RCC metastasis. Methods: Utilizing cell-based immunohistochemistry, immunofluorescence, and wound healing assays in cells genetically or pharmacologically manipulated, we show GTP metabolism plays a role in RCC migration. Results: Using IHC analysis on RCC patient tumor samples, we discovered high expression of the key enzyme for GTP biosynthesis, inosine 5'-monophosphate dehydrogenase II (IMPDH2), is significantly correlated with distal metastases. In wound healing assays, we found that RCC migration is inhibited by both CRISPR-mediated knockout of IMPDH and pharmacological inhibition. Furthermore, we found both IMPDH and the downstream biosynthetic enzymes guanosine 5'-monophosphate synthase (GMPS) and nucleoside diphosphate kinase A (NDPK-A) localize to the leading edge of RCC cells during migration. Nuclear sequestration of IMPDH2 decreases cell migration in wound healing and transwell migration assays, suggesting the possibility that localization of GTP-metabolic enzymes to the leading edge promotes concentrated GTP production for activation of Rho GTPases. Conclusion: Together, our data implicates a connection between metabolism and cell migration in invasive tumors and unveils a potential therapeutic intervention for the prevention of RCC metastasis

POSTERS

23.

Role of FAK in the Maintenance of Tumor Cell Survival in MMTV-Wnt1 Driven Basal-like Mammary Tumors

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Breast cancer is a heterogeneous disease. Stratification of patients based on the subtype of breast cancer is a key to successful treatment of breast cancer. Focal Adhesion Kinase (FAK), a cytoplasmic tyrosine kinase is highly activated across several breast cancer subtypes including the basal subtype which has a very poor prognosis. To address whether inhibition of FAK would be beneficial in basal-like mammary tumors, we generated mice with conditional deletion of FAK in MMTV-WNT1 driven mammary tumors, classified as basal-like breast tumors. We found that loss of FAK decreased tumor growth and metastasis of WNT1 driven mammary tumors. Interestingly loss of FAK activity in WNT1 tumors resulted in accumulation of cleaved caspase 3, suggesting that loss of FAK activity compromised tumor cell survival. Next, we compared the transcriptomic profile of Wnt tumor cells with and without FAK and found that mTOR signaling pathway and Ribosome gene signature were affected. These could be a result of reduced AKT activation that we found upon loss of FAK. We further analyzed survival of the FAK deficient cells under a number of stress conditions and found that upon perturbation of calcium homeostasis via the use of SERCA inhibitors such as Thapsigargin, the survival of FAK deficient WNT1 tumor cells were severely compromised. However, we found that the increased sensitivity of FAK deficient cells to SERCA inhibitors is not related to their effects on ER stress. Lastly, we found that FAK deficient cells have a lower basal level of intracellular calcium, which is disrupted upon treatment with Thapsigargin, suggesting that FAK might be required for survival of the tumor cells under high calcium concentration. In summary, our studies show that in a basal-like mammary tumor model, FAK is required for survival of the tumor cells. Additionally, inhibition of FAK in combination with SERCA inhibitors could potentially be an effective therapeutic strategy for basal-like tumor cells.

POSTERS

24.

Mechanisms of HER3 Activation and Regulation Upon Inhibition of HER2

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HER2 is amplified in about 25% of breast cancers. HER3 plays a critical role in HER2 mediated tumorigenesis. We wished to investigate the effect of the pan HER inhibitor neratinib on HER2+ breast cancer cells. We examined the effect of neratinib on BT474 and SKBR3 HER2+ breast cancer lines on proliferation via crystal violet staining using 8 nM to 1000 nM neratinib and 1 μ M lapatinib as a control. Proliferation assays showed the inhibitory effect of neratinib on cell growth. We determined the effect of neratinib on HER2/HER3 signaling by immunoblots using antibodies against P-HER3, P-HER2, HER2, P-AKT, AKT, P-ERK, ERK, and actin as a loading control. There was a reduction in P-HER2, HER2, P-HER3, HER3 P-AKT, AKT and P-ERK1/2 in both cell lines as assessed by immunoblots. We next sought to identify HER3 binding protein partners that could phosphorylate HER3 upon pharmacological inhibition of HER2. We have immunoaffinity-purified HER3 from BT474 and SKBR3 cells treated \pm neratinib. Following immunoprecipitation and washing of cross-linked complexes on beads coated with a HER3 antibody, binding partners were released by incubation with DTT and RIPA buffer. We have identified protein bands that are present upon inhibition of HER2 with neratinib and absent under DMSO control treatment from HER3 immunoprecipitates. Currently, mass spectrometry experiments are underway to determine the identity of proteins that bind HER3 upon neratinib treatment. In conclusion, these studies seek to mechanistically determine regulation of HER3 in the context of inhibition of HER2 in HER2+ breast cancers.

POSTERS

25.

In Utero BPA Exposure Alters the Extracellular Matrix to Increase Mammary Gland Density

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Mice exposed in utero to BPA have increased susceptibility to mammary gland tumors later in life. However, it is unclear which alterations to the mammary gland increase the potential of carcinogenic transformation in adulthood and promote tumor growth. Herein, we performed RNA-seq analysis on enriched fibroblast, luminal epithelial, and basal epithelial cell populations from adult mice treated in utero with BPA or control to identify molecular alterations that may promote cancer initiation and growth. While few transcriptional changes were observed in the luminal cell population most likely to eventually become cancer, we found a large number of genes altered in the fibroblast population. Interestingly, during fetal development, ER alpha is expressed strictly in the mouse mesenchyme and thus may be the molecular target of BPA action in utero. Genes altered in the fibroblast population were associated with changes to the extracellular matrix. We further characterized the extracellular matrix changes by showing increased collagen in the BPA exposed mammary glands. Using a novel fluidics system, we demonstrate that primary fibroblasts from BPA exposed mice remodel collagen to increase the density of the extracellular matrix. As extracellular matrix density has been shown to increase tumor susceptibility, these data suggest at least one target of BPA action is through stromal remodeling of the mammary gland.

POSTERS

26.

Ron Receptor Signaling Promotes Resistance to Androgen Ablation Therapy in Prostate Cancer

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Prostate cancer (PCa) is the second leading cause of cancer related deaths in men. Several deaths result from resistance to androgen ablation therapy, defined as Castration Resistant PCa (CRPC), where median survival is only 19 months. CRPC often develops by reactivation of the Androgen Receptor (AR). We have strong data suggesting that the Ron tyrosine kinase activates AR in PCa to promote resistance to androgen ablation therapy. Prior studies established that Ron is highly expressed and plays a functional role in promoting PCa. To address Ron's role in CRPC, human tissues were analyzed and Ron was observed to be highly expressed in all CRPC samples. Overexpression of Ron in androgen sensitive PCa cell lines used in murine models of CRPC show that Ron overexpression is sufficient to drive CRPC in vivo. Ron overexpressing prostate tumors have elevated AR activation and require AR for growth under androgen deprivation. Enhanced macrophage recruitment was observed in Ron overexpressing tumors and castration resistant growth of Ron overexpressing cells was inhibited in vivo when macrophages were depleted in combination with castration therapy, suggesting a non-cell autonomous role for macrophages in promoting Ron mediated CRPC. Further studies focused on the role of Ron in CRPC may provide the scientific underpinnings for targeting Ron signaling to combat resistance to androgen ablation therapy.

POSTERS

27.

Targeting Breast Cancer Metastasis by Novel RNA Aptamers

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Metastatic breast cancer (MBC) is the leading cause of cancer-related death in women worldwide. Approximately 75% of breast cancer cases are estrogen receptor positive (ER+) and both experimental and clinical evidence support a key role for ER signaling in metastasis. MED1 is the ER-interacting subunit of the Mediator transcriptional coactivator complex bridging ER to RNA Polymerase II and allows for ER-target gene transcription. MED1 interacts with ER directly through its two classical LxxLL motifs and our recent research has demonstrated that when these motifs are mutated in mice, they are grossly normal other than defects in pubertal mammary gland development. We have further crossed these MED1 LXXLL-mutant mice with mammary tumor-prone MMTV-PyVT mice and observed significant loss in tumor growth and metastasis. In this study, we have isolated novel RNA aptamers to target these MED1 LxxLL motifs and disrupt its function. RNA aptamers are an emerging class of diagnostics and therapeutic agents with the ability to bind specifically to a desired target, rivaling antibodies and small molecules. In particular, they are highly stable in vivo, capable of carrying a number of functional moieties like siRNAs, and do not elicit unwanted immune response. Currently, we have 8 aptamers candidates that can specifically bind to the MED1 LxxLL motifs and disrupt the ER-MED1 interaction. Importantly, we have found at least one such aptamer (aptamer "SP") that cannot only significantly inhibit ER-target gene expression, tumor growth, migration and invasion in vitro, but also block tumor growth in an orthotopic xenograft mouse model.

POSTERS

28.

ATAC Sequencing Uncovers Estradiol-Induced Global Changes in Chromatin Accessibility Linked to Gene Repression

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Significant efforts have been paid to identify gene targets of estrogen signaling that drive estrogen receptor-positive breast cancer. However, estrogen-induced chromatin remodeling, which sets the basis for gene induction or repression, remains unclear. More in depth analysis of open chromatin versus closed chromatin will provide greater mechanistic insight into gene regulation in breast cancer.

To investigate the effects of estradiol (E2) signaling on chromatin architecture, we employed Assay for Transposase-Accessible Chromatin using sequencing (ATAC-seq), a high-throughput method to map chromatin accessibility via a hyperactive transposase that inserts sequencing tags into open regions. ATAC-seq was performed on MCF-7 cells, an estrogen receptor-positive breast cancer cell line, treated with E2 or vehicle control for 1 or 3 hours. Results from the ATAC-seq were compared to RNA-seq data of 3-hours E2-treated MCF-7 cells to determine which regions of E2-regulated open or closed chromatin coincide gene transcription or repression. We observed greater chromatin accessibility changes in genes that are repressed by E2 compared to genes that are induced by E2.

To mechanistically dissect this unexpected finding, we performed motif enrichment analysis of chromatin regions affected by E2. This analysis showed expected enrichment of estrogen response element (ERE), and pioneer factor FOXA1 and GATA3 response elements in E2-inducible genes with enhanced chromatin accessibility after E2-treatment. Surprisingly, genes with chromatin accessibility changes but repressed by E2 were enriched for pioneer factors FOXA2, FOXA3, bMYB and TEAD. Thus, it appears that FOXA family members have distinct roles in E2-inducible and E2-repressed genes. This work demonstrates novel findings regarding E2-induced chromatin remodeling and provides grounds for future work to study fundamental relationships between E2 regulated chromatin accessibility and gene expression in breast cancer.

POSTERS

29.

Macrophage-specific Ron Signaling Supports Breast Cancer Stem Cell Maintenance

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Current treatment against breast cancer (BC) targets rapidly-proliferating cells. However, tumor recurrence and therapeutic resistance persist, highlighting their lack of effectiveness. A small population within breast tumors, named Breast Cancer Stem Cells (BCSCs), has been shown to be essential for tumor development, recurrence, and metastasis due to their increased self-renewal, survival, migration, and therapeutic resistance. BCSC properties are stimulated by intrinsic regulatory mechanisms and extrinsic mechanisms induced by cells in the tumor microenvironment (TME), such as macrophages. The Ron receptor tyrosine kinase is primarily expressed in macrophages and epithelial cells and is found overexpressed in human BCs, being associated with increased metastasis and poor prognosis. Recently, we demonstrated that Ron drives BCSC maintenance by intrinsically regulating their self-renewal and tumorigenic potential as well as by regulating the TME. However, it is unknown whether Ron signaling in macrophages affects BCSC phenotypes and tumor growth. Tumor kinetics, flow cytometry analyses for BCSC markers, and mammosphere formation assays for tumors from mice with or without a conditional deletion of Ron in macrophages show that Ron loss in macrophages diminishes tumor growth, BCSC numbers, and their self-renewal ability. Further mammosphere formation analyses also demonstrate that macrophage-specific Ron signaling enhances BCSC self-renewal through the production of a soluble factor. Overall, our data provides the first evidence showing that Ron expression in macrophages stimulates BC growth and BCSC maintenance through the production of a secreted factor. These studies suggest Ron as potential therapeutic target to effectively eradicate BCSCs and improve the outcome of BC patients.

POSTERS

30.

Dissecting the genomic inception of tumorigenicity via the immortalization of primary breast epithelial cells

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Background: Immortalization overcomes the limited replicative potential of primary cells and is the earliest step in tumorigenesis. Due to a lack of sufficient primary cells, the genomic events associated with progression from immortalization to transformation have been studied extensively but not those leading to immortalization. Identifying immortalization-associated events is critical to develop early biomarkers of tumorigenesis.

Methods: Breast epithelial cells from core biopsies of seven healthy women were cultured then immortalized by overexpression of human telomerase reverse transcriptase. RNA sequencing was performed on the matched primary and immortalized cells and EdgeR was used to perform differential expression analysis. To account for differences in differentiation status, genes previously known to be differentially expressed in progenitor and differentiated cells were excluded. Subsequent genes were analyzed via Ingenuity pathway analysis (IPA).

Results: Over 1500 unique genes were differentially expressed between primary and immortalized cells, 700 of which were upregulated in the latter. Many overlapped with pathways meaningful to tumorigenicity including cellular growth, proliferation, death and survival as well as DNA replication and repair. Of particular interest, FACT complex components SSRP1 and SUPT16H, BRCA1 associated BARD1, BRCA1 interactor TONSL were all upregulated. Several of these upregulated genes have previously been found to be essential to cell viability.

Conclusion: With the unique resource of primary breast cells from healthy women, the genomic event associated with immortalization and its link with tumorigenicity has been further explored. Based on the upregulation of FACT complex components in immortalized cells, we propose that alterations in transcription-associated DNA damage response are the earliest event in immortalization, and these alterations could serve as tumor initiation biomarkers.

POSTERS

31.

Regulatory Function of Beta-Actin In Phosphatidylserine-Mediated Proliferation of Pancreatic Cancer Cells

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Deciphering the molecular mechanisms regulating proliferation in PDAC will lead to the discovery of new therapeutic targets for treatment. Phosphatidylserine (PS) externalization activates ADAM17, a protein known to facilitate proliferation in cancer cells. Although PS expression is elevated on the surface of pancreatic tumors compared to normal tissue, the mechanism by which PS is externalized in pancreatic cancer cells and its potential role in promoting cancer progression has not been elucidated. The objective of our study was to identify the mechanism by which PS is externalized in pancreatic cancer cells and to study its function in promoting cell proliferation. It is known that increased actin polymerization in cells regulates intracellular calcium by promoting ER calcium release. Furthermore, increased intracellular calcium regulates PS externalization in cancer cells. Thus, we hypothesized that PS externalization would be associated with increased actin polymerization and proliferation in pancreatic cancer cells. For the purpose of our studies, experiments were conducted in a PDAC metastasis-derived cell line (CFPAC-1) and a healthy pancreatic epithelial cell line (HPDE). We measured: 1) actin protein expression 2) F: G actin ratio 3) effects of drug-induced actin polymerization on surface PS expression 4) ADAM17 activity and 5) proliferation. Our studies demonstrate that: 1) PS externalization is associated with increased beta-actin expression, specifically. 2) PS externalization is associated with increased F:G actin ratio. 3) Induction of actin polymerization promotes PS externalization. 4) PS externalization is associated with increased ADAM17 activity and proliferation. From this data, we propose that beta-actin overexpression mediates proliferation in pancreatic cancer by inducing actin polymerization and PS externalization.

POSTERS

32.

mTOR Kinase Inhibition Reduces Tissue Factor Expression and Growth of Pancreatic Neuroendocrine Tumors

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Background: Full-length tissue factor (flTF) and alternatively spliced TF (asTF) contribute to growth and spread of pancreatic ductal adenocarcinoma. It is unknown, however, whether flTF and/or asTF contribute to pathobiology of pancreatic neuroendocrine tumors (pNET).

Objective: To assess TF expression and the effects of mTOR complex 1/2 (mTORC1/2) inhibition in pNET.

Methods: Human pNET specimens were immunostained for flTF and asTF. Human pNET cell lines QGP1 and BON were evaluated for TF expression and responsiveness to mTOR inhibition. shRNA were utilized to knock down TF expression in BON. TF cofactor activity was assessed via two-step FXa generation assay. TF promoter activity was assessed via transient transfection of human TF promoter-driven reporter constructs. Mice bearing orthotopic BON tumors were treated with mTORC1/2 ATP-site competitive inhibitor sapanisertib / MLN0128 (3 mg/kg, oral gavage) for 34 days.

Results: Immunostaining of pNET tissue revealed positivity for flTF and asTF. BON and QGP1 expressed both TF isoforms, with BON exhibiting significantly higher levels. shRNA directed against TF suppressed BON proliferation. Treatment of BON with sapanisertib inhibited mTOR signaling and markedly suppressed TF promoter activity, the levels of flTF and asTF mRNA and protein, and TF cofactor activity. BON tumors grown in mice treated with sapanisertib had significantly less TF protein and co-factor activity, and were smaller compared to tumors grown in vehicle treated mice.

Conclusions: TF isoforms are expressed in pNET. Sapanisertib suppresses TF mRNA and protein expression as well as TF co-factor activity in vitro and in vivo. Thus, further studies are warranted to evaluate the clinical utility of TF-suppressing mTORC1/2 inhibitor sapanisertib in pNET management.

POSTERS

33.

FOXM1 Inhibitor RCM-1 Attenuates Carcinogenesis by Inhibiting Nuclear Beta-Catenin

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The oncogenic transcription factor FOXM1 has been previously shown to play a critical role in carcinogenesis by inducing cellular proliferation in multiple cancer types. RCM-1, A small molecule compound, has been recently identified from high throughput screening as an inhibitor of FOXM1 in vitro and in mouse model of allergen-mediated lung inflammation. In the present study, we examined anti-tumor activities of RCM-1 using tumor models. Treatment with RCM-1 inhibited tumor cell proliferation as evidenced by increased cell cycle duration. Confocal imaging of RCM-1-treated tumor cells indicated that delay in cellular proliferation was concordant with inhibition of FOXM1 nuclear localization in these cells. RCM-1 reduced the incidence and growth of tumor cell colonies in the colony formation assay. In animal models, RCM-1 treatment inhibited growth of mouse rhabdomyosarcoma Rd76-9, melanoma B16-F10 and human H2122 lung adenocarcinoma tumors. RCM-1 decreased FOXM1 protein in the tumors, reduced tumor cell proliferation and increased tumor cell apoptosis. RCM-1 decreased protein levels and nuclear localization of beta-catenin, and inhibited protein-protein interaction between beta-catenin and FOXM1 in cultured tumor cells and in vivo. Altogether, our study provides important evidence of antitumor potential of the small molecule compound RCM-1, suggesting that RCM-1 can be a promising candidate for anti-cancer therapy.

POSTERS

34.

mTORC1-dependent Tumors have Innate Vulnerability to Autophagic Cell Death by HDAC Inhibitors

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mTORC1 plays a significant role in the development and progression of many different types of cancers. Although mTORC1 inhibitors, such as Rapamycin, have anti-tumor effects on some specific cancers, their efficacy is still largely limited to anti-proliferative effects. Histone deacetylase (HDAC) inhibitors have been proven to be effective in cancer treatment including some solid cancers. We have previously established a vascular tumor cell line, Tsc1 Δ EC, which was derived from Tsc1 deletion in mouse endothelial cells leading to constitutive activation of mTORC1. Here, we found that a pan-HDAC inhibitor, SAHA, caused Tsc1 Δ EC cell death and growth arrest in vitro and in vivo. Our data showed that a selective Class I HDAC inhibitor CI994 treatment also caused Tsc1 Δ EC cell death. Unlike mTORC1 inhibitors, the anti-tumor activity of SAHA was dependent on mTORC1 activation but it had little effect on mTORC1 activity in mTORC1 activated tumor cells. We found that Z-VAD-FMK, a pan-caspase inhibitor, had no inhibitory effect on SAHA treatment. Cell death pathway array analysis revealed that SAHA treatment in Tsc1 Δ EC upregulated obviously autophagy-related genes. Further experiments revealed that both autophagy gene Fip200 deletion and autophagy inhibition by spautin-1 in Tsc1 Δ EC impaired tumor cell death by SAHA treatment. We further found that SAHA could play a role by increasing reactive oxygen species (ROS) via autophagy. Fip200 deletion caused Nrf2 activation through p62 accumulation, which can lead to antioxidant effect through p62-Keap1-Nrf2 pathway. We showed that inhibition of p62 expression re-sensitized Fip200 deleted Tsc1 Δ EC to SAHA treatment. Taken together, HDAC inhibitors treatment provides an alternative promising therapeutic strategy for mTORC1-dependent cancers.

POSTERS

35.

Warping Developmental Space-Time: A Perspective from Single-cell RNA-seq of Mammary Tumors

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Intra-tumoral heterogeneity is a major cause for therapy resistance in breast cancer. Studies from breast cancer stem cells (BCSCs) have illuminated the importance of accounting for cells with less-differentiated states. However, there may be limitations to the over-simplified binary concept of universal BCSCs co-existing with bulk tumor cells. Through single-cell RNA-sequencing, we found that 4T1, BRCA1-null, PyMT and Neu mammary tumors each occupied a spectrum of minimally overlapping cell differentiation states [4T1: fetal MaSCs, BRCA1-null: basal cells, PyMT: luminal progenitor cells, Neu: alveolar progenitor and differentiated cells]. By understanding the hierarchy of cell states within the tumors, we were able to identify CD14 as a putative BCSC marker in the Neu tumor. Additionally, breast cancer subtype assignment at the single-cell level revealed the presence of subtype heterogeneity within the tumors. Altogether, our findings provide a revised framework for BCSCs with distinct stem/progenitor populations as putative BCSCs in each of the models examined.

POSTERS

36.

Patient-derived HER3 Mutations Activates ER+ and HER2+ Breast Cancer Cells via MAPK Pathway

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We sought to investigate the role of patient-derived HER3 mutations in HER2+ and ER+ breast cancer cells using ectopic expression of HER3 mutants. We aim to identify mechanism(s) by which HER3 mutants enhance HER2-mediated or hormone-driven transformation and if HER3 mutations confer resistance to HER2 or ER inhibitors.

HER3 mutations (F94L, G284R, D297Y, D313H, K329T, T355I, L792V and E1261A) were introduced and stable cell lines were generated in MCF10AHER2 and ER+ MCF-7 and T47D cells. HER3T355I mutant had increased p-HER3/p-ERK1/2 expression compared to controls. Receptor tyrosine kinase array results indicated that T47D and MCF-7 expressing HER3T355I had increased p-HER4 and p-HER1 levels, respectively. Cells expressing HER3T355I were subjected to lapatinib in the presence or absence of the ER inhibitor fulvestrant and specific ERK1/2 inhibitor, SCH772984. The data indicated that the induced proliferating activity of HER3T355I is via HER4/MAPK in T47D and HER1/MAPK signaling in MCF-7 cells. Immunoblotting data indicated that cyclin D1 and p-ERK1/2 expression were altered in response to combined treatment of lapatinib with or without fulvestrant and SCH772984 indicating that cyclinD1 mediated signaling downstream of the MAPK pathway. HER3T355I and HER3WT demonstrated reduced cell proliferation and matrigel colony formation in presence of lapatinib and fulvestrant/SCH772984. We noted crosstalk between ER α and HER3 in T47D cells. Based on structural modelling, HER3 T355I likely disrupts the interactions between domain III and the hinge region pocket that stabilizes the tethered conformation of HER3T355I, potentially making the hinge more flexible, shifting the equilibrium from the tethered to the untethered state.

Several HER3 mutants acquired gain-of-function phenotype and were resistant to lapatinib and partially resistant to neratinib in MCF10AHER2 cells. These mutants also increased HER2-HER3 hetero-dimerization.

POSTERS

37.

Retinoid X Receptor is a Positive Regulator of Normal Hematopoietic Stem Cell Activity Through Cell-autonomous and Non Cell-autonomous Signaling

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Retinoid X receptors (RXRs) are central members of superfamily of nuclear receptors. They play essential roles in multiple biological processes, such as development, organogenesis and fatty acids homeostasis. However, the function of RXR signaling in hematopoiesis is not clear. Activation of RXRs is ligand-dependent. Out of the three RXRs (α , β and γ), only RXR α and RXR β are expressed in hematopoietic cells. To study the RXR signaling in the bone marrow (BM) hematopoietic stem cells (HSC), first we systemically activated RXRs by treating C57BL/6 mice with vehicle control or bexarotene (Bex), an FDA-approved agonist of RXR, currently in phase II clinical trials in acute myelogenous leukemia (AML) therapy. After 2 weeks of treatment, the mice treated with Bex had an expansion (1.7 fold) of the BM content of immunophenotypically and functionally-defined HSCs. To dissect out the cell-autonomous from a non-cell autonomous effect of RXR signaling in hematopoiesis, we generated full hematopoietic chimeras by transplanting whole BM cells from Tie2-CreTg^{-/-}; RXR α flox/flox;RXR β flox/flox (RXR KO mice) or Tie2-Cre^{-/-}; RXR α flox/floxRXR β flox/flox mice into lethally irradiated congenic mice. After 8 weeks engraftment, the full chimera mice were treated with a vehicle control or Bex (60 mg/kg/day) p.o. for 2 weeks followed by quantification of HSC activity in a competitive repopulation assay in vivo. As expected, the deletion of RXR α and RXR β in hematopoietic cells blunted the effect of Bex on the HSC repopulating ability. Interestingly, Bex rescued the competitive repopulation ability of HSC by 50% from RXR KO chimeric mice. Together, this data indicates that Bex can induce non cell-autonomous RXR signaling with effect on the BM HSC activity.

In summary, we found that, opposite to AML, RXR is a positive regulator of normal BM HSC function, through cell-autonomous and non cell-autonomous signaling relevant for HSC transplantation and gene therapy approaches.

POSTERS

38.

Investigating the TAM-S6K1 Axis as a New Therapeutic Strategy for Glioblastoma

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Glioblastoma (GBM), the most lethal type of malignant brain cancer in adults, sustains frequent mutations and/or deletions in the tumor suppressor gene PTEN (phosphatase and tensin homolog), resulting in the activation of the downstream kinase S6K1. The TAM receptor tyrosine kinases TYRO-3, AXL, and MERTK are overexpressed in GBM, and correlate with therapeutic resistance. In our present study, we are investigating the coordinated targeting of S6Ks and TAMs in GBM. LY2584702, an S6K inhibitor and BMS777607, a TAM inhibitor, were ineffective against PTEN-deficient GBM as single agents, but were highly effective when used for combination treatment. We proposed experiments to test the hypothesis that PTEN and TAM kinases act through differential effects on S6K1 and S6K2. We have showed that CRISPR-targeted S6K1^{-/-} and S6K2^{-/-} LN229 cells exhibit reduced phosphorylation of ribosomal S6, a S6K1 substrate that regulates pyrimidine biosynthesis. Interestingly, TAM inactivation reduced substrate phosphorylation in S6K1^{-/-} LN229 cells, suggesting that S6K1 signaling operates in parallel to TAM signaling. In short, our data support unique features of S6K1 and S6K2 regulation by PTEN and TAM kinases, suggesting the importance of both kinases as clinical targets in GBM.

POSTERS

39.

Exploring the Role of Nucleus-localized FIP200 in Breast Cancer Cells

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FIP200 is a component of the ULK1/ATG13/FIP200/Atg101 complex essential for autophagy induction in mammalian cells, and our previous studies showed that Fip200 deletion suppressed BCa in MMTV-PyMT mouse model, which relied on its autophagy function. It has been well established that FIP200 is predominantly localized in cellular cytoplasm, while in other cases it is able to be diffused into nucleus. The purpose of this study is to evaluate the potential different functions of FIP200 by its spatial distribution. We found that FIP200 deletion by Crispr-Cas9 led to increased migration and partial EMT for BrCA cells with strong nucleic FIP200, while suppressed those functions for the cells with little nucleic FIP200. Similar results were found by using autophagy inhibitor and deleting ATG13 in cells with strong expression of nucleic FIP200. We further generated a FIP200 mutant construct, which disabled its nucleic localization and still maintain autophagy induction function, and rescued WT and mutant FIP200 expression in FIP200-KO cells originally with strong nucleic FIP200 distribution. Interestingly, WT FIP200 suppressed partial EMT and migration, while its mutant further enhanced those phenotypes. Those results raised the interesting possibility that FIP200 might own dual functions in terms of inducing partial EMT by its spatial distribution, cytoplasmic FIP200 contributing to EMT-like behavior through autophagy induction while nucleic fraction suppressing those functions.

POSTERS

40.

Canonical Autophagy Facilitates Tumor Promotion in PyMT Tumors Through Up-regulation of Adipogenesis Related Genes

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Autophagy genes have been reported to have either tumor promoting or inhibition functions in various cancers, but it is convoluting because of autophagy-independent functions of the respective autophagy genes. We previously reported that suppression of Fip200, one of autophagy related genes, inhibited tumor growth in PyMT tumor mice model. To clarify whether it is by autophagy-dependent function, we recently established Fip200 Knock-in PyMT tumor mice with MMTV-Cre (cKI), allowing for conditional inhibition of autophagy in mammary glands. Compared to wild type (WT) tumors, tumor initiation, growth and metastasis were significantly suppressed in both cKI tumors and conditional Fip200 deleted tumors (cKO). The staining of cleaved-Caspase3 showed that loss of autophagy increased apoptosis rate in PyMT tumors compared to WT tumors. This increase of apoptosis was also detected in vitro using isogenic PyMT deficient cells under starvation condition. Microarray analysis (GSEA) showed that adipogenesis related genes were significantly enriched in WT tumors compared to cKO tumors. The mRNA expression of Pparg, which is also one of master genes related adipogenesis, were significantly increased with autophagy induction under starvation condition compared to Fip200 KO and KI cells. Many genes regulated by Pparg transcriptionally were down-regulated in autophagy deficient tumors. Then we established Pparg overexpressed PyMT isogenic cells. The re-expression of Pparg in autophagy deficient cells decreased apoptosis rate under starvation condition. In conclusion, our results indicate that tumor promotion of PyMT driven tumors was dependent on canonical autophagy. Our future studies will provide the more detailed mechanism of autophagy dependent tumor growth through the modification of Pparg expression.

POSTERS

41.

MED1 Promotes ER-positive Breast Cancer Cell Invasion and Metastasis through Regulating MMP9

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MED1 (Mediator subunit 1), as an Estrogen Receptor (ER) coactivator, plays a crucial role in the growth of breast cancer cells and is associated with the resistance of endocrine therapy and poor outcome of breast cancer patients; however, its effect on the process of invasion and metastasis of breast carcinoma remains unclear. Here, we first establish the relationship between MED1 and the aggressiveness of ER-positive breast cancer cells. Using Tet-inducible MED1 knockdown MCF7 and BT474 cells, we show that silencing MED1 efficiently blocks cell migration and invasion in vitro, as well as the metastasis of breast carcinoma in vivo using xenograft models in nude mice. Meanwhile, the expression of matrix metalloproteinase-9 (MMP9) is decreased after silencing MED1, whereas, over-expression of MED1 significantly increases MMP9 expression, enhancing the migration and invasion of MCF7 and BT474 cells. Promoter reporter and ChIP assays indicate that MED1 localizes to the proximal AP-1 binding site and regulates the recruitment of AP-1, transcriptional corepressor HDAC1, and coactivator CBP on endogenous MMP9 promoter. Taken together, our results reveal that MED1 plays a key role in invasion and metastasis of ER-positive breast carcinoma through transcriptional regulation of MMP9. Inhibition of MED1 expression or function may provide a new therapeutic strategy to prevent breast cancer metastasis.

POSTERS

42.

Establishment IROA Methodology for Comparative Profiling of ccRCC-kidney Pairs Metabolome Using In Vivo Produced Heavy Isotope Labeled Standards

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LC-MS based metabolomics is the current state technology revolutionizing the field of cancer metabolism. However, data analysis is a significant bottle neck in most metabolomics work-flows where interpretation of features is confounded by instrumental disturbances, background ions, sample prep variation and chromatographic anomalies. These challenges can be even more pronounced in samples derived from humans due to increased biological variability. Isotope Ratio Outlier Analysis (IROA) has the potential to overcome these technical limitations using both isotope labeled internal standards and software. Here, we develop growth conditions suitable for extending the IROA methodology to the analysis of solid tissues exemplified by clear cell renal cell carcinoma (ccRCC) orthotopic xenografts and adjacent mouse kidney tissue. Which has been further applied to tissues derived from human patient including ccRCC tumors and Kidneys.

POSTERS

43.

KDM6B Histone Demethylase Promotes Acquired Resistance to FASNi in Mutant KRAS NSCLC Cells

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KRAS mutations (KM) are the most frequent genetic aberrations found in lung cancer (LC). However, no effective therapies for KMLC have been developed yet. Our group demonstrated that inhibition of Fatty acid synthase with TVB-3664 (FASNi) leads to promising results in KMLC preclinical models and early phase clinical trials in KMLC patients. Clinical experience demonstrates that chemotherapy and targeted therapies, including agents targeting metabolism, are often hampered by the emergence of acquired drug resistance. To gain insight into the mechanisms that underlie acquired FASNi-resistance and to establish the rationale for future combination therapy trials, we developed a preclinical model of acquired FASNi-resistance using KMLC cell lines. To this end, we treated KMLC cell lines with increasing concentrations of FASNi for 2 months. We confirmed by HPLC and ¹³C-labeled acetate flux analysis that FASNi was intracellularly retained and actively inhibited palmitate synthesis. As expected, FASNi-resistant cells were not affected by *de novo* lipogenesis ablation. Notably, FASNi-resistant cells display EMT and cancer stem cell (CSC) markers, such as high CD133 expression and ALDH enzymatic activity. Interestingly, the drug resistance phenotype was reverted when resistant KMLC cell lines were cultured in the absence of FASNi for 2 months. Such reversible reprogramming suggests that acquired FASNi-resistance is likely due to epigenetic changes rather than to genetic mutations. Our previous studies reported that expression of JumonjiC (JmjC) demethylases is often deregulated in multidrug-resistant NSCLC cells altering drug sensitivity. Thus, we tested whether JmjC proteins might mediate acquired resistance to FASNi. Indeed, we found that KDM6B is the only JmjC demethylase upregulated in FASNi-resistant KMLC cell lines with respect to parental cells. Accordingly, FASNi-resistant cells, but not the parental sensitive cells, showed a significant sensitivity to GSK-J4, a KDM6B selective inhibitor. Moreover, GSK-J4 treatment re-sensitized resistant cells to FASNi, leading to synergistic drug response. On the other hand, treatment with either inactive enantiomers or inhibitors of other JmjC family members did not elicit any significant change on cell viability, ruling out the possibility of off-target effects. To confirm our findings *in vivo*, experiments on KMLC mouse models are ongoing. Our findings indicate so far that KDM6B demethylase accounts for FASNi-acquired resistance of KMLC and that its inhibition might open a therapeutic opportunity for FASNi refractory patients.

POSTERS

44.

FASN as a Novel Therapeutic Target in Mutant KRAS Lung Cancer.

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Mutant KRAS (KM), the most commonly mutated oncogene in lung adenocarcinoma (LC), and is required for the maintenance of KMLC. KM has been widely associated with cancer-driven metabolic reprogramming. For instance, we determined that KM upregulates Fatty acid synthase (FASN) and that KMLC depends on the FA Acyl-transferase ACSL3 for survival. Thus, we tested the functional role of FA metabolism in KMLC.

We applied a mass spectrometry high-resolution lipidomic approach to microdissected lung specimens of transgenic mice, and coupled it with MALDI-imaging analysis (MSI). This unique approach allowed us to characterize KMLC cell-associated lipid profile and to accurately visualize the major lipid species within the KMLC in vivo.

Next, to test the hypothesis that KM lung cancer relies on FA homeostasis, we tested the effect of TVB-3664, a novel and selective inhibitor of FASN (FASNi), on a panel of non-small cell lung cancer (NSCLC) cell lines. FASNi preferentially inhibits cell proliferation of KMLC cells, inducing a block in the G2/M phase of the cell cycle. Notably, incubation of cells with palmitate completely rescues the deleterious effects of FASNi, ruling out possible FASNi off-target effects. On the contrary, LC cells harboring wild type KRAS (wtKRAS LC) are resistant to FASNi.

We verified by metabolic flux analysis that FASNi effectively inhibits palmitate synthesis and that wtKRAS LC cells neither excrete nor metabolically inactivate it. Interestingly, the introduction of KM in wtKRAS LC cells dramatically increases FASN protein level and triglyceride (TAG) production, sensitizing these cells to FASNi. These observations led us to conclude that KM triggers a dependency in LC on FASN. Accordingly, we tested FASNi in preclinical mouse models of KMLC. We verified that FASNi treatment (oral gavage/100 mg/kg/daily), significantly impairs the growth of KMLC lung cancer cells grown as xenograft in NOD/SCID mice. MS/MS analysis along with MSI confirmed that the drug localizes within the tumor and it is active, as shown by the significant decrease in TAG content and lipid raft disruption. Furthermore, FASNi

POSTERS

45.

S6K1 Protein Correlates with Treatment Efficacy in Breast Cancer

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S6K1 is amplified in about 12% of TCGA breast cancers, is a signaling mediator downstream of mTOR Complex 1. Because it can function both upstream and downstream of the estrogen receptor α (ER α), S6K1 amplification can contribute to oncogenic estrogen signaling in breast cancer. We hypothesize that S6K1 amplification enables breast cancer cells to sustain proliferation during hormone therapy. Data show that genetic knock down of S6K1 reduces the progression of breast cancer into S phase. For breast cancer patients who have failed on Estrogen ablation therapy, an approved second-line treatment is the mTORC1 inhibitor, Everolimus, in combination with an ER α antagonist. We found that ER α + cell lines revealed a wide range of S6K1 protein expression levels. We propose that patients with lower levels of S6K1, and therefore lower substrate phosphorylation, who complete a course of combination treatment will have better outcomes.

POSTERS

46.

Lung Metastases are Regulated by the Transcription Factor Forkhead Box F1 in Endothelial Cells

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Lung metastases occur when cancer cells from a local primary tumor site spread to the lung and are observed in 30-55% of all cancer patients. The most common cancers that metastasize to the lung are breast, colorectal, kidney, head and neck, testicular, bone, soft tissue sarcoma, melanoma, and thyroid cancer. Understanding the molecular and cellular mechanisms related to lung tumor cell attachment to endothelial cells (EC), extravasation, survival and colonization in the lung is important for diagnostic, prognostic, as well as therapeutic purposes. We have shown that the transcription factor Forkhead box f1 (Foxf1) is highly expressed in EC of the lung and is required for maintaining normal EC functions. Foxf1 is down-regulated in lung EC during spontaneous lung metastasis from primary breast adenocarcinoma. To study the role of Foxf1 in EC during lung metastases, we performed orthotopic inoculation of E0771 breast cancer cells in mice with an inducible EC-specific deletion of Foxf1 (endoFoxf1^{+/-}) to generate a novel lung metastasis model. The sizes of primary breast tumors were not affected by deletion of Foxf1 in lung ECs. However, the number and sizes of lung metastases in endoFoxf1^{+/-} mice were significantly increased. EndoFoxf1^{+/-} mice had increased cancer cell proliferation, decreased cancer cell death, and increased inflammatory cells in the lung. Our results indicated EC-Foxf1 is a suppressor of lung metastasis.

POSTERS

47.

Are Some Inflammatory Diseases Caused by a Cancer, by the Epstein-Barr Virus Transformed B Cell in Latency III?

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Explaining the genetics of many diseases is challenging because most genetic associations localize to incompletely understood regulatory regions. We show that transcription factors (TFs) occupy multiple loci of individual complex genetic disorders much more than expected by chance using novel computational methods. Application to 213 phenotypes and 1,544 TF binding datasets identifies 2,264 relationships between hundreds of TFs and 94 phenotypes, including AR in prostate cancer and GATA3 in breast cancer. Strikingly, nearly half of the European systemic lupus erythematosus (SLE) risk loci are occupied by the Epstein-Barr virus (EBV) Nuclear Antigen 2 (EBNA2) protein (OR=6, $P < 10E-24$ after Bonferroni correction), which co-clusters with a sub-set of 60 human TFs, revealing gene-environment interaction and identifying the EBV transformed B cell as a putative site for some of the genetic mechanisms altering disease risk. Analogous EBNA2-anchored associations exist in multiple sclerosis (MS), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), type 1 diabetes (T1D), juvenile idiopathic arthritis (JIA), and celiac disease (CeID). With SLE, these are the EBNA2-associated idiopathic inflammatory diseases (EBaIDs). Instances of allele-dependent DNA binding with downstream effects on gene expression at plausibly causal variants are consistent with EBNA2 dependent genetic mechanisms. Our results nominate mechanisms that operate across risk loci within disease phenotypes; they suggest new paradigms for disease origin and strongly support a role for Epstein-Barr virus in the generation of selected inflammatory diseases, apparently through the genomic mechanisms that operate in the EBV transformed B cell expressing the latency III program of EBV.

POSTERS

48.

BRUCE as a Regulator of Liver Cancer Progression Mediated by the Loss of the Tumor Suppressor PTEN

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Hepatocellular carcinoma (HCC) is the most common malignance of the liver and the third leading cause of cancer deaths worldwide, largely due to lack of understanding the pathogenesis. It is urgent to identify new pathogenic regulator and mechanism. BRUCE is a critical protein required for homologous recombination (HR) repair of DNA damage and for preservation of genome stability by recruitment of multiple critical HR proteins, including BRCA, RAD51, ATM and ATR at DNA damage sites. BRUCE-depleted cells are hypersensitive to radiation and chemotherapeutic drugs and accumulate genome instability. Although DNA damage is believed a major contributor to HCC genesis, the regulation of DNA damage in the liver against HCC is largely unclear. To investigate the role of BRUCE in the liver, we created a mouse model with liver-specific dual knockout (DKO) of BRUCE and the well-established liver tumor suppressor PTEN, mediated by Albumin-Cre recombinase. The DKO livers have markedly accelerated development of HCC compared to PTEN single KO mice which is attributable to exacerbated steatosis, inflammation, DNA damage accumulation and tumor-initiating/oval cell activation. Interestingly, the HCC developed in the DKO mice displays expanded population of cells positive for both CK19 and HNF4 α (cholangiocytes and hepatocytes markers respectively), suggesting that they are tumor-initiating cell origin and that BRUCE is required for suppression of their proliferation and expansion. This study reveals that BRUCE is a new HCC suppressor and its deficiency accelerates malignant transformation to HCC in PTEN deficient background. The study also advances the understanding of critical role of DNA damage repair mechanism in the suppression of HCC.

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