Session 1: Metabolic pathways in cancer
July 14th, 2021

AGENDA

11:00am et/8:00am pt
Welcome & opening remarks
Dan Gallahan, Ph.D.
Director, Division of Cancer Biology, National Cancer Institute

11:35am et/8:35am pt
Keynote address
Matt Vander Heiden, M.D., Ph.D.
Director, Koch Institute for Integrative Cancer Research at MIT

Title: Influence of diet on tumor nutrient availability
Abstract: Many cancer patients seek dietary advice, and more guidance is needed on how dietary choices affect outcomes. There is extensive evidence linking obesity and whole-body metabolism to the risk of getting some cancers. There is also a growing appreciation that dietary factors can impact tumor growth and the response to some therapies, but evidence is limited for which dietary choices are best for specific patients. We have found that diet composition can affect which nutrients are available to cancer cells in tumors. By comparing the effects of different diets on tumor nutrient availability, and those track with diet-induced changes in cancer phenotypes, we have uncovered novel mechanisms by which low glycemic diets can impact tumor growth. More generally, we find that dietary interventions must be considered in the context where they are used to realize their benefit.

12:20pm et/9:20am pt
Christian Metallo, Ph.D.
Professor, The Salk Institute

Title: Tracing mechanistic drivers in dietary cancer therapy
Abstract: Serine, glycine and other nonessential amino acids are critical for tumor progression, and strategies to limit their availability are emerging as potential therapies for cancer. However, the molecular mechanisms driving this response remain unclear and the effects on lipid metabolism are relatively unexplored. Serine palmitoyltransferase (SPT) catalyses the de novo biosynthesis of sphingolipids but also produces noncanonical 1-deoxysphingolipids when using alanine as a substrate—or in conditions of low serine availability—to drive neuropathy. We have recently described how altered amino acid metabolism can drive accumulation of deoxysphingolipids to slow tumor progression. Here I will summarize these findings and share additional results that shed light on tissue-specific and cell-specific metabolic alterations in response to serine restriction. These findings highlight an underappreciated role for amino acids in impacting membrane lipid metabolism and functionality which may be actionable in the context of cancer therapy.

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12:40pm et/9:40am pt
Jon Coloff, Ph.D.
Assistant Professor of Physiology & Biophysics, University of Illinois at Chicago

Title: Targeting Serine Auxotrophy in Luminal Breast Cancer
Abstract: A major challenge of targeting metabolism for cancer therapy is pathway redundancy, where in many cases nutrients that are essential for tumor growth can either be synthesized de novo or acquired through the diet. As a result, starving cancer cells of critical nutrients can be challenging. We have taken the approach of analyzing human tumor gene expression data to identify scenarios where pathway redundancy is limited due to lineage-dependent gene expression, thereby creating potential vulnerabilities. Using this approach, we have discovered that luminal breast tumors—the largest subtype of breast tumors—are auxotrophic for the non-essential amino acid serine due to lineage-specific epigenetic silencing of the serine biosynthesis gene PSAT1. Low PSAT1 prevents de novo serine biosynthesis and sensitizes luminal breast cancer cells to serine and glycine starvation both in vitro and in vivo. This work demonstrates how a lineage-specific metabolic phenotype can potentially be exploited through a targeted dietary intervention

1:00pm et/10:00am pt BREAK

2:00pm et/11:00am pt
Heather Christofk, Ph.D.
Professor of Biological Chemistry, UCLA David Geffen School of Medicine

Title: Targeting Cancer Asparagine Dependence
Abstract: My lab studies how nutrients impact cancer. Here I will present data showing that asparagine is a critical nutrient for cancer anabolism and growth. Tumors acquire asparagine through consumption from the microenvironment and *de novo* synthesis by asparagine synthetase. Targeting these two main routes of tumor asparagine acquisition reduces tumor growth in mouse models of lung, breast, and pancreatic cancer. I will also present evidence that asparagine is an important output of mitochondrial respiration for signaling to the kinase mTORC1 and the transcription factor ATF4, suggesting that asparagine synthesis is a fundamental purpose of tumor mitochondrial respiration. Lastly, I will discuss how we can harness these findings for therapeutic benefit to cancer patients.

2:20pm et/11:20am pt
Jason Locasale, Ph.D.
Associate Professor of Pharmacology and Cancer Biology, Duke University School of Medicine

Title: Dietary methionine in cancer
Abstract: This presentation will focus on methionine metabolism in health and cancer. I will first discuss methionine content in human food and dietary patterns. I will next focus on how changes to dietary methionine can produce defined consequences on cellular metabolism. I will then discuss work on dietary influences on the activity of the pathway and its relation to the regulation of one carbon metabolism in cancer. How methionine restricted diets may allow for interventions in cancer treatment and relevant mechanisms will be discussed including how changes to dietary methionine can influence interventions that target one carbon metabolism involving radiation and antimetabolite chemotherapies such as 5-fluorouracil. The link between nutritional methionine status and chromatin biology and epigenetics will also be introduced in this talk.

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2:40pm et/11:40am pt
Kathryn Wellen, Ph.D.
Associate Professor, Department of Cancer Biology, University of Pennsylvania Perelman School of Medicine

Title: Diet, metabolites, and regulation of the epigenome
Abstract: An exciting frontier in cancer metabolism research is the impact of diet on tumor progression and therapeutic responses. Metabolites serve important functions as modulators of the epigenome, but the impact of diet on metabolic signaling in the context of cancer biology remains poorly understood. Additionally, metabolism is highly compartmentalized and nuclear metabolite abundance may not be reflected by whole cell measurements. In this presentation, I will discuss recent efforts to understand the impact of nutrient availability on compartmentalized metabolite availability and insights into to regulation of the epigenome.

3:00pm et/12:00pm pt
Day 1 Summary
Kris Willis, Ph.D.
Division of Cancer Biology, National Cancer Institute

3:10pm et/12:10pm pt
Panel discussion, Day 1 speakers
co-chairs,
Kris Willis, Ph.D., Division of Cancer Biology, National Cancer Institute
Matt Vander Heiden, M.D., Ph.D., Koch Institute

4:00pm et/1:00pm pt
Close Day 1

Session 2: Cancer Metabolism Across Systems
July 15th, 2021

11:00am et/8:00am pt
Remarks
Ned Sharpless, M.D.
Director, National Cancer Institute

11:20am et/8:20am pt
Stacey Finley, Ph.D.
Associate Professor of Biomedical Engineering, University of Southern California

Title: Modeling tumor-stromal metabolic crosstalk in colorectal cancer
Abstract: Drug resistance is a key contributor to the high morbidity and mortality rates of colorectal cancer (CRC). The acquired resistance is strongly influence by tumor-stromal metabolic crosstalk in the tumor microenvironment. However, the way in which stromal cells, specifically cancer-associated fibroblasts (CAFs), affect the metabolism of tumor cells remains unknown. Here we take a data-driven approach to investigate metabolic interactions between CRC cells and CAFs, integrating constraint-based modeling and LC-MS metabolomics profiling. We construct a network model of central carbon metabolism in CRC cells and perform unsteady-state parsimonious flux balance analysis to infer flux distributions from metabolomics data and the effects of enzyme knockouts. Our work gives mechanistic insights into the metabolic interactions between CRC cells and CAFs and provides a framework for testing hypotheses towards CRC targeted therapies.

11:40am et/8:40am pt
Marcia Haigis, Ph.D.
Professor, Department of Cell Biology, Harvard Medical School

Title: The role of high fat diet on tumor and immune cell interactions
Abstract: Our society is in the midst of an epidemic of obesity and metabolic dysfunction. Although obesity is a major risk factor for cancer, we still do not fully appreciate the mechanistic drivers of why obesity increases cancer risk. Here, I discuss the role of mitochondria as dynamic organelles that provide cells with energy and metabolites needed for survival and growth even during dramatic changes in diet and stress. I will discuss our recent findings that changes in systemic metabolic state during high fat diet – induced obesity alters the metabolic interaction between tumor and immune cells to reduce anti-tumor immune functions.

12:00pm et/9:00am pt
Vishwa Deep Dixit, D.V.M., Ph.D.
Professor of Comparative Medicine and of Immunobiology, Yale School of Medicine

Title: Immunometabolic checkpoints of inflammation
Abstract: The active Nlrp3 inflammasome complex is formed upon sensing of damage, including metabolic danger signals to controls the secretion of bioactive IL-1β and IL-18 from myeloid cells. It is now established that inflammasome is a predominant player in instigating inflammaging and metabolic dysfunction. Interestingly, specific metabolic substrates, such as ketone metabolites can deactivate the inflammasome in neutrophils and macrophages to lower inflammatory diseases. These studies suggest that NLRP3 inflammasome is a major driver of age-related inflammation and therefore dietary or pharmacological approaches to lower NLRP3 holds promise in reducing multiple chronic diseases. This presentation will how address tissue resident macrophages control inflammation in aging? How immune-metabolic interactions can reveal targets that may be harnessed to enhance the healthspan?

Session 2: Cancer Metabolism Across Systems
July 15th, 2021

12:20pm et/9:20am pt
Omer Yilmaz, M.D., Ph.D.
Associate Professor of Biology, Koch Institute for Integrative Cancer Research at MIT

Title: Dietary control of stem cells in physiology and disease
Abstract: Organismal diet has a profound impact on tissue homeostasis and health in mammals. Adult stem cells mediate many aspects of tissue adaptation by balancing self-renewal and differentiation divisions to alter tissue composition in response to the environment. Because somatic stem cells may respond to organismal physiology to orchestrate tissue remodeling and some cancers are understood to arise from transformed stem cells, these findings raise the possibility that organismal diet, stem cell function, and cancer initiation are interconnected. Here I will present work from my group that describes our emerging view of how diet, metabolites and nutrient-sensing pathways instruct mammalian intestinal stem cell fate in homeostasis, adaptation to diet and diseases such as cancer.

12:40pm et/9:40am pt
Marcus Da Silva Goncalves, M.D., Ph.D.
Assistant Professor of Biochemistry and Medicine, Weill Cornell Medical College

Title: Diet as Both Cause and Intervention for Cancer
Abstract: Dietary factors account for more than 50% of deaths worldwide, and about 10% of global cancer-related deaths. Diets with high glycemic load (GL), those rich in refined carbohydrates and simple sugars, are particularly harmful. These diets are characterized by fast glucose absorption, with a consequent rise in insulin levels. Several large prospective studies support a link between GL, sugar, insulin, and different cancers including endometrial and colorectal cancer. This presentation will use these two examples to highlight how dietary factors can promote or inhibit tumorigenesis.

1:00pm et/10:00am pt BREAK

2:00pm et/11:00am pt
Day 2 Summary
Phil Daschner
Division of Cancer Biology, National Cancer Institute

2:10pm et/11:10am pt
Panel discussion, Day 2 speakers
co-chairs,
Natalia Mercer, Ph.D., Division of Cancer Biology, National Cancer Institute
Matt Vander Heiden, M.D., Ph.D., Koch Institute

3:00pm et/12:00pm pt
Overall summary

3:30pm et/12:30pm pt
Close