Non-small cell lung cancer (NSCLC) is a histologically, genetically, and metabolically heterogeneous disease. The mitochondria are essential regulators of cellular energy and metabolism, and they play a critical role in sustaining growth and survival of lung tumor cells. However, our understanding of mitochondrial metabolism in cancer at an in vivo level has been limited, thus leaving a large gap in our knowledge of how mitochondrial bioenergetics support tumor growth. To better study mitochondrial bioenergetics in lung tumors, we recently developed and validated a voltage-sensitive, positron emission tomography (PET) tracer known as 4-\([18F]\)fluorobenzyl triphenylphosphonium (4F-BnTP) that we used to profile mitochondrial bioenergetics in autochthonous K-Ras driven mouse models of lung cancer. The use of 4F-BnTP PET imaging enabled us to functionally profile mitochondrial bioenergetics in live tumors and discover distinct functional mitochondrial heterogeneity conserved across different NSCLC tumor subtypes. In order to study mitochondria at the level of ultrastructure, we coupled 4F-BnTP PET with 3D serial block-face scanning electron microscopy (3D SBEM). By coupling these two techniques, we are able to image and quantify mitochondrial heterogeneity from whole tumors down to the ultrastructures of individual mitochondria within tumor cells. Our study reveals distinct organization of mitochondrial structure and function as lung tumors adapt during tumorigenesis. We anticipate that coupling 3D SBEM with 3D SEM will have dynamic applications beyond that of lung cancer and enrich our understanding of how mitochondria impact human disease.

Identification of New Therapeutic Targets in Non-Small Cell Lung Cancer

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Our laboratory is focused on understanding the mechanisms that contribute to tumor initiation, progression, and metastasis. Using unbiased forward genetic screens, we have identified novel genes that promote transformation of human bronchial epithelial cells (HBECs) and contribute to lung cancer pathogenesis. This approach enabled our discovery of novel oncopgenic cell surface receptors in non-small cell lung cancer that may represent new therapeutic targets. For example, we recently identified the Transmembrane Serine Protease TMPRSS11B as a gene that promotes transformation of immortalized HBECs. TMPRSS11B is upregulated in human lung squamous cell cancers (LSCC), and high expression is associated with poor survival of non-small cell lung cancer patients. TMPRSS11B inhibition in human LSCCs reduced transformation and tumor growth. Given that TMPRSS11B harbors an extracellular protease domain, we hypothesized that catalysis of a membrane-bound substrate accelerates tumor progression. Interrogation of a set of soluble receptors revealed that TMPRSS11B promotes solubilization of Basigin, an obligate chaperone of the lactate monocarboxylate transporter MCT4. Basigin release mediated by TMPRSS11B enhanced lactate export and glycolytic metabolism, thereby promoting tumorigenesis. These findings established an oncogenic role for TMPRSS11B and provided support for the development of therapies that target this enzyme at the surface of cancer cells. Our latest results related to TMPRSS11B and other cell surface proteins in lung cancer will be presented. Together, these studies illustrate the power of unbiased forward genetic screening approaches to identify new oncogenic pathways and potential therapeutic targets in human malignancies.

Role of the Tumor Microenvironment in Sensitivity and Resistance to Immunostimulatory Therapies in NSCLC

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Effective anticancer immunostimulatory therapies can overcome dominant immune regulatory signals, restore tumor recognition, and achieve clinically meaningful/sustained tumor-cell killing. In most solid malignancies, the tumor microenvironment contains multiple and sometimes overlapping tolerogenic signals that suppress immune function and favor tumor progression. Understanding the immune composition and dominant tolerogenic pathways in lung cancer can support the identification of predictive biomarkers and guide the design of novel therapeutic modalities. This presentation will address current knowledge about the composition, molecular context, and functional tumor-immune interactions in human lung carcinomas. The presentation also includes discussion of novel approaches to analyze the tumor microenvironment using high multiplexed/spatially resolved methods and machine learning strategies.