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 (18F-BnTP) that we used to profile mitochondrial bioenergetics in autotransplanted K-Ras driven mouse models of lung cancer. The use of 18F-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 18F-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 our approach will enable new 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 oncogenic 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 Basp1, an obligate chaperone of the lactate monocarboxylate transporter MCT4. Basp1 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 therapeutically targets in human malignancies.