The composition of the tumor immune microenvironment dictates responsiveness to cancer immunotherapies, though discrete biomarkers to predict responsiveness are yet to be defined. Much of the focus of the field of biomarker research has been on the spatial distribution and activation status of CD8 T cells when defining whether a tumor is "inflamed" and potentially responsive to immunotherapy. However, the majority of the leukocyte composition of most tumors, including non-small cell lung cancer (NSCLC), is of myeloid, not lymphoid, origin, and these cells appear to play a role in dictating therapeutic efficacy. Through single-cell analysis at the proteomic and transcriptomic level we can define the resident myeloid populations within the tumor, to determine the role these subsets play in developing an immunosuppressive tumor microenvironment, and identify potential therapeutic targets. Through mass cytometry our group has demonstrated selective depletion of resident alveolar macrophages, with enrichment of a distinct tumor-associated macrophage (TAM) population within the tumor. Single-cell RNA sequencing confirms the disparate transcriptome of these TAMs contrasted with resident lung macrophages, and direct concordance between a defined monocyte-derived TAM and T regulatory cell enrichment, as well as T effector cell dysfunction. These inhibitory myeloid subsets present a potential therapeutic target to further potentiate current immunotherapy approaches. We have identified multiple chemokine and cytokine pathways that may be integral to recruitment and maintenance of this immunosuppressive milieu, and validated dependence on these pathways in preclinical studies. To investigate the role of two of these myeloid-recruitment pathways in vivo in humans, we have designed a neoadjuvant "window-of-opportunity" trial that will evaluate the synergy of PD-1 blockade with disruption of the CCR2/5 or interleukin-8 mediated myeloid recruitment and retention within early-stage NSCLC lesions.

Targeting Myeloid Cells that Define the Tumor Immune Microenvironment in NSCLC

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Decoding Critical Targets of LKB1/STK11 in NSCLC

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Inactivating mutations in the LKB1 (STK11) tumor suppressor are the third most frequent genetic alteration in non-small cell lung cancer (NSCLC). LKB1 encodes a serine/threonine kinase that directly phosphorylates and activates 14 members of the AMP-activated protein kinase family. The function of many of the AMPK-related kinases (AMPK Rs) remains obscure, and which are most critical to the tumor-suppressive function of LKB1 remains unknown. Recently we have combined CRISPR and genetic analysis of the AMPK family in NSCLC cell lines and mouse models, revealing multiple surprises. First, despite an unwavering role in inhibiting mTOR progrowth signaling, loss of AMPK at initiation in Kras GEMMs results in a block in tumor progression, which we could connect to a loss of lysosome and metabolic adaptive capability. Moreover, we found a surprising critical role for the SIK subfamily. Conditional genetic loss of SIK1 revealed increased tumor growth in mouse models of Kras-dependent lung cancer, which was further enhanced by loss of the related kinase SIK3. As most known direct substrates of SIK1 and SIK3 control transcription, gene-expression analysis was performed, revealing specific transcriptional programs that contribute to LKB1-dependent tumorigenesis. Additional pathways by which one might therapeutically target these tumors based on the signaling and metabolic pathways dysregulated from LKB1-deficiency will be discussed.

A New Generation of Anti-Myc Mini-Proteins as Potential Therapy for NSCLC


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MYC is one of the most wanted targets for therapeutic intervention in cancer, having a key role in driving and maintaining most, if not all, human tumors, including lung cancer. Despite this indisputable therapeutic opportunity, MYC has long been perceived as "undruggable" for its intrinsically disordered nature and fear of catastrophic side effects.