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Sox2 cooperates with Lkb1 loss to promote squamous cell lung cancer

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Squamous cell carcinoma (SCC) of the lung is the second most common subtype of lung cancer with limited treatment options and a poor survival rate. Until recently, mouse models of SCC have been limited. Using lentiviral delivery of Sox2 to the mouse lung, we tested the ability of Sox2 to promote tumorigenesis in multiple tumor suppressor backgrounds. Expression of Sox2 specifically cooperates with loss of Lkb1 to promote squamous lung tumors. Importantly, Sox2 expression and mTOR pathway activation frequently co-occur in human squamous tumors. Mouse squamous tumors exhibit characteristic histopathology and biomarker expression similar to human SCC. Murine SCCs also mimic human SCCs by activation of therapeutically relevant pathways including STAT and mTOR. We show that Sox2 expression is sufficient to induce phosphorylated Stat3 in vitro (Mukhopadhyay et al, Cell Reports, 2014). An inducible genetic model of Sox2 expression and Lkb1 have been generated and are being used to interrogate the cell of origin for squamous cell lung cancer. In addition, Sox2-driven tumors exhibit innate and adaptive immune cell infiltration, similar to the recent PTENfl/flLkb1fl/fl model of SCC. These models may be useful to study immunotherapies and their mechanism of action, and to test the contribution of additional driver alterations in SCC.

Proximalization therapy for KRas mutant adenocarcinoma

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KRAS activating mutations are common in lung adenocarcinoma and are currently not able to be directly targeted. These are most likely early mutations in the adenoma-adenocarcinoma sequence and may be present in phenotypically normal lung. Thus, targeted therapy would be useful in early stage and/or screened patients. In order to begin to develop agents targeting these early lesions, we have used cell lineage specific CreER mouse models to analyze cell-of-origin in the mouse lung. When KrasG12D is induced in various cells throughout the respiratory epithelium, Type II cells are the primary cell-of-origin of lung adenocarcinoma. To delve into mechanism, using gain and loss of function genetic models, we discovered that low Sox2 expression with resulting active Notch signaling dictate the ability of Type II cells to proliferate and progress into adenocarcinoma upon KrasG12D activation. Because low Sox2 and high Notch expression characterize a distal lung epithelial progenitor state, we hypothesized that Kras activation leads to dedifferentiation of Type II cells. We demonstrated that Kras activation in Type II cells leads to Spc+Rage+ bipotent progenitor-like cells that also express specific the lung embryonic development markers Sox9 and Ezh2. Next, we use a mouse genetic approach to show that this dedifferentiation requires Notch signaling. Additionally, Sox2 upregulation genetically and chemically profound inhibit KrasG12D-induced...
lung tumor formation in Type II cells. Finally, using an in vitro 3D tumor sphere culture system derived from Kras activated Type II cells, we discovered small molecules that specifically inhibit KrasG12D driven tumor sphere formation by differentiation of Type II cells to Kras-resistant proximal cells. Our findings could provide new therapeutic strategies to target Kras-activated lung cancer by either blocking Type II cell dedifferentiation or promoting Type II cell proximalization.

Identification and targeting of long-term tumor-propagating cells in small cell lung cancer

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Small cell lung cancer (SCLC) is a neuroendocrine subtype of lung cancer characterized by fast growth, early dissemination, and rapid chemotherapy resistance. We identified a population of long-term, tumor-propagating cells (TPCs) in a genetically engineered mouse model of SCLC. This population, marked by high levels of the EpCAM and CD24 cell surface proteins, is also prevalent in human primary SCLC tumors derived from circulating tumor cells (CTCs). SCLC TPCs are numerous and highly proliferative but not intrinsically chemoresistant, indicating that not all the clinical features of SCLC tumors can be linked to TPCs. SCLC TPCs possess a distinct transcriptional compared to non-TPCs, including increased neuroendocrine features and elevated MYC activity. Importantly, genetic and pharmacological inhibition of MYC in mouse and human SCLC cells to non-TPC levels inhibits long-term propagation but not short-term growth. These studies identify a highly tumorigenic population of SCLC cells in mouse models, cell lines and patient CTCs. In addition, this work provides a rationale for therapeutic strategies aimed to reduce the activity of MYC and other possible oncogenic drivers to eradicate SCLC TPCs, thus specifically preventing the maintenance and the spread of this aggressive disease while minimizing harmful effects on the rest of the organism.

Predictive biomarkers for immunotherapy in lung cancer: Opportunities and challenges

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The success achieved with the use of novel immunostimulatory therapies targeting the inhibitory checkpoints...