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.

Adenocarcinoma indolence and progression: Biological basis

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Lung adenocarcinoma can progress from an indolent in situ carcinoma to an invasive, aggressive, metastatic tumor. The WHO/IASLC/ATS Lung adenocarcinoma classification emphasizes the distinction of adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma from their invasive counterparts. Molecular biomarkers of invasion can distinguish invasive from non-invasive tumors, a distinction that is typically difficult to make in small biopsies and cytology specimens and is becoming increasingly important as the recognition of early stage adenocarcinoma increases with the widespread implementation of lung cancer screening programs in the United States.

The early stage in tumor progression to a state of invasiveness and metastasis is characterized by epithelial dysregulation and instability that drives loss of cellular adhesion and increased cell mobility and proliferation. In many cases, signaling pathways important in lung development are critical for mediating these processes. The biological processes required for this progression include alterations in the TGF-Beta signaling pathway, and genomic copy number alterations of CDK4 and MDM2, and mutations in key oncogenic regulators. Equally important in mediating adenocarcinoma progression is the contribution by the tumor microenvironment. The microenvironment is a complex system comprised of stromal fibroblasts, macrophages, lymphocytes, other bone marrow-derived cells (BMDCs), and extracellular matrix (ECM) that in a reciprocal fashion, can contribute to tumor regression or progression. Key regulators of the tumor microenvironment regulation of tumor progression include the TGF-Beta signaling pathway, thrombospondin-1 (Tsp-1), and the composition of the tumor immune contexture.

Taken together, these advances in the understanding of tumor mediated and microenvironment mediated processes that regulate adenocarcinoma progression and metastasis will drive advances in translational approaches to improve diagnosis and treatment of lung cancer.

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