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
CTLA-4 and PD-1 axis has changed treatment and prognosis of diverse cancers. In addition, these developments have prompted the need to understand the immunobiology of tumors and design the optimal current and future therapies combining immune and non-immune mechanisms. This progress is also accompanied with new challenges. Possibly, two of the most critical questions in the field include: i) the establishment and refinement of strong predictive biomarkers and ii) the identification of additional non-redundant immune inhibitory targets to treat patients with the so-called “non-inflamed” tumors lacking prominent pre-existing tumor immune infiltration.

Blockade of the PD-1/PD-L1 axis induces prominent and lasting clinical responses in ~20% of patients with non-small cell lung cancer (NSCLC). Recent studies have shown also an adequate safety profile and significant clinical advantage of these therapies over more traditional chemotherapy agents. The success of these therapies uncovered the power of blocking immune inhibitory signals that are enriched in the tumor microenvironment. Because of the prominent but numerically low proportion of patients showing objective benefit form PD-1 blockade, development of predictive biomarkers is needed to reduce overtreatment and costs associated with these compounds. Diverse studies have found that expression of PD-L1 by immunohistochemistry (IHC) and pre-existence of tumor infiltrating lymphocytes (TILs) are associated with benefit to these therapies, supporting the notion that a pre-existing anti tumor immune response is required for immune re-invigoration using PD-1 axis blockers. However the predictive value of IHC assays is limited and there are different PD-L1 test available that have not been standardized or tested for equivalence. To date, only one PD-L1 IHC assay (22C3) has been approved as companion biomarker for PD-1 blockade in NSCLC. Recently, it was reported that the total mutational burden or predicted neo-antigen load detected by whole exome sequencing analysis has the potential to inform about the likelihood of response to the anti PD-1 compound pembrolizumab in advanced NSCLC. However, this test requires validation as a biomarker, standardization and the use of sophisticated sequencing and bioinformatics resources that are not available in most non-academic institutions. Inflammation, interferon-gamma (IFN-γ) related mRNA-based signatures and T-cell receptor sequencing have also recently been suggested to have association with response to PD-1 blockade. However, their predictive value has not been demonstrated in lung cancer and their systematic measurement represents a technical challenge. Integration and refinement of available immunotherapy biomarkers could provide optimal use of immunostimulatory therapies in lung cancer.

**Impact of co-mutations on the immune microenvironment of KRAS-mutant lung adenocarcinoma**

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Activating mutations in KRAS account for the most prevalent molecularly defined subset of lung adenocarcinoma (LUAC), yet therapeutic strategies aimed at targeting KRAS-mutant lung tumors have achieved limited clinical success. Breaking immune tolerance with inhibitors of immune checkpoints, particularly those involving the PD-1/PD-L1 axis, has emerged as a novel paradigm in the treatment of NSCLC, leading to the recent FDA approval of nivolumab and pembrolizumab. It has been postulated that KRAS-mutant LUAC may be particularly amenable to immunotherapy; however, heterogeneous clinical responses have been observed in clinical trials. We have recently identified co-occurring genetic events as major determinants of the molecular diversity of KRAS-mutant LUAC. Specifically, KRAS-mutant lung cancers can be segregated into three major subgroups that are dominated, respectively, by co-occurring genetic alterations in STK11/LKB1 (KL), TP53 (KP) and CDKN2A/B, the latter coupled with low expression of the TTF1 transcription factor (KC). Co-mutation defined subsets exhibit distinct biological behavior, variable phenotypic characteristics and unique therapeutic vulnerabilities.

Importantly, KRAS co-mutations can also impact the tumor immune micro-environment and may thus promote mechanisms of immune evasion that are specific to the tumor oncogenotype. We have identified that inactivation of the LKB1 serine/threonine kinase, a master regulator or cellular bio-energetics and polarity, is associated with a “cold” immune micro-environment across several datasets of both chemotherapy-naïve and platinum-refractory LUAC. This is characterized by low densities of intra-tumoral CD3+ and CD8+ lymphocyte sub-populations and low expression of PD-L1-positive tumor and non-tumor cells. The mechanistic basis of this finding as well as its implications for therapy with