Update on Lung Adenocarcinoma Classification: Histology and Genomics

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The extent of the invasive component seen in lung adenocarcinoma is associated with histological subtype and with clinical outcomes. Similar to malignancies in other organs, such as breast and cervix, tumors are defined as non-invasive (in-situ carcinoma), micro-invasive (microscopic invasion) or as invasive carcinomas. The World Health Organization has subclassified adenocarcinoma based upon predominant cell morphology and growth pattern such as bronchioloalveolar carcinoma (BAC), adenocarcinoma with mixed subtypes (AC-mixed), and homogenously invasive tumors with a variety of histological patterns. The clinical importance of lung adenocarcinoma invasion is supported by several recent studies indicating that the risk of death in non-mucinous BAC is significantly lower than that of pure invasive tumors and in tumors with greater than 0.6 cm of fibrosis or linear invasion. These features have been incorporated into a proposed revision of lung adenocarcinoma classification scheme (Journal of Thoracic Oncology, in Press). Together, these studies suggest that non-invasive tumors are biologically indolent with five-year survival after resection approaching 100%, and that following the paradigm of other adenocarcinoma cancers, some *in situ* tumors may acquire molecular alterations that promote invasion and thus the risk of metastatic disease and death.

To identify molecular pathways important for distinguishing adenocarcinoma subclasses and for mediating the acquisition of invasion, we and others performed *microarray gene expression profiling of lung adenocarcinoma to identify signatures associated with histology and invasion. The results of unsupervised analyses show lung adenocarcinomas segregate into three major branches comprised predominantly of BAC, AC-Mixed subtype, and pure invasive tumors and provide biological plausibility to support the notion that these adenocarcinoma subtypes are distinct entities.* Among the genes differentially expressed in the progression from BAC to invasive tumors was the transforming growth factor-ß (TGF-ß) type II receptor (*TβRII)*, that was less highly expressed by AC-Mixed and solid invasive tumors compared with BAC. This finding suggests that TβRII repression is important for lung adenocarcinoma progression from BAC to invasive adenocarcinom and is supported by *in vitro* studies showing that loss of TGFBRII in lung cancer cells increases tumor cell invasion and by constitutive genetic models of *TBRII* targeted deletion in other organ systems. To determine the direct role of *TβRII* repression on adenocarcinoma invasion *in vivo*, we generated a genetic model of murine lung adenocarcinoma with targeted deletion of TBRII. In this model, instillation of Ad.Cre led to both activation of a mutated Kras gene and loss of the TBRII gene in the same epithelial cells. We demonstrate that this murine model recapitulates both the histological and genomic changes that accompany invasion and metastasis in human lung adenocarcinoma tumors.