Mutations in KRAS are among the most frequent RAS alterations in human cancers and the prevalent driver event in lung adenocarcinoma (LUAD). There are still no effective targeted therapies for KRAS-driven LUAD, although specific KRAS G12C inhibitors are showing very promising results in clinical trials. Small-molecule inhibitors of the MAPK pathway, one of the prominent downstream KRAS mediators, showed minimal clinical activity either as single agents or in combination with chemotherapy. We observed that loss of wild-type KRAS enhances tumor fitness in KRAS mutant cancer cells while concomitantly increasing sensitivity to MEK inhibition. Given the challenges of reanalyzing prior clinical trials, future clinical studies of targeted inhibitors should evaluate and/or stratify patients based on the relative expression of wild-type and mutant KRAS alleles to determine their correlation with treatment outcome. We also showed that dimerization/oligomerization between KRAS proteins is a key regulator for lung adenocarcinoma biology and determinant of treatment response. We generated an inducible system to force either wild-type/mutant or mutant/mutant KRAS dimerization, which showed that forced dimerization between wild-type/mutant KRAS resulted in impaired cell growth as compared to forced mutant/mutant KRAS dimerization. Summary: Loss of wild-type KRAS enhances tumor fitness in KRAS mutant cancer cells while concomitantly increasing sensitivity to MEK inhibition. Dimerization of wild-type KRAS with mutant KRAS results in growth inhibition and changes the therapeutic index for MEK inhibitors. Mutant-mutant KRAS dimerization is critical for the full oncogenic properties of mutant KRAS. Collectively these observations suggest that strategies designed to interfere with KRAS dimerization should be evaluated as a therapeutic approach in KRAS mutant cancers.
frequencies of mutation and copy number alterations, mutation signatures, intratumor heterogeneity, pathway alterations, and histology as well as overall survival were performed. We found that deleterious mutation burden was significantly greater in invasive ADC. Intratumor heterogeneity occurs as early as in AIS. More copy number loss was observed in AIS/MIA. Twenty-one significantly mutated genes were shared among three groups. Mutation signature profiling had no significant difference among three groups, although APOBEC signature was associated with ADC subgroup and poor survival. Mutations of KRAS, TP53, and NFI were found at an increasing frequency from AIS/MIA to ADC. A cancer progression model revealed selective early and late drivers. Subclonal KRAS mutations and a gene signature consisting of PIK3CG, ATM, EPPK1, EP300, or KMT2C mutations were associated with poor survival. Our results demonstrate several sequences of genetic driver events, gene clonality, and mutated gene signatures associated with outcome in early lung ADC with potential future implications in the management of early ADC.

IA07
Plasma Proteomic, Glycomic, and Autoantibody Biomarkers for Lung Cancer Early Detection
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Lung cancer is the leading cause of cancer deaths worldwide, with >159,000 deaths annually in the US alone. Making matters worse, five-year survival rates remain a dismal ~18%, since most lung cancer cases are identified at an advanced stage, which confers a poor prognosis. The National Lung Screening Trial (NLST) employed low-dose computed tomography (CT) imaging to screen for lung cancer in a high-risk population (smokers aged 55-74) and demonstrated a 20% reduction in mortality. These and other results led the US Preventative Services Task Force (USPSTF) to recommend CT screening for 55- to 80-year-old, 30-pack-year smokers. Unfortunately, screening uptake has been poor and pulmonary nodules are relatively common in this group compared to the incidence of cancer, leading to potentially avoidable radiation exposure, morbidity, and mortality effects. Also, CT performs best for detection of lung adenocarcinoma (LUAD) and less well for other subtypes. In line with several other groups, we propose that plasma biomarkers could help sort which nodules are malignant. Our approach combines proteomic, glycomic, and autoantibody plasma measures along with CT semantic and radiomic features to evaluate nodules particularly of the indeterminate size range (6-30 mm). Furthermore, we have found specific markers that predict or detect squamous cell carcinoma (LUSQ) and small cell lung cancer (SCLC)—subtypes that are less frequently found via CT. We have combined two novel approaches to improve risk stratification for subjects with pulmonary nodules. The first is based on a large-format antibody array we created containing >3,200 different antibodies to interrogate prediagnostic plasma sample sets for cancer early detection biomarkers. We utilize the same antibody array platform for proteomic, glycomic, and autoantibody-antigen interrogation by implementing three distinct probing strategies. Using prediagnostic lung cancer case and control specimens from the Cardiovascular Health Study (CHS), we found 68 proteins were upregulated in cases (p<0.02). Ten of these were also upregulated (p<0.05) in a validation set of malignant and benign nodules collected at the FHCRC Lung Cancer Early Detection and Prevention Clinic (LCEDPC). For glycomic analysis, of 9 and 8 proteins with higher sialyl-Lewis A (i.e., CA19-9) and sialyl-Lewis X levels that met stringent selection criteria, 2 and 2 proteins, respectively, were validated in the LCEDPC samples. For antibody-antigen analysis, of 81 and 44 proteins bound to IgG and IgM, 25 and 4 antigens, respectively, were validated in the LCEDPC samples. Differentiating non-small cell lung cancer (NSCLC) samples into LUAD or squamous cell carcinoma (LUSQ) generated a 4-marker LUAD-specific panel with an AUC of 0.82 in CHS and 0.87 in LCEDP and a LUSQ-specific panel had an AUC of 0.94 in CHS and 0.91 in LCEDPC. The second approach is to analyze both semantic and radiomic CT features and combine them with the plasma biomarkers. Using Lasso regression analysis to choose features from the validated set of plasma markers, we found 5 semantic, 2 radiomic, and 8 plasma markers yielded an AUC>0.95 in LCEDPC samples from people with indeterminate (6-30 mm) nodules that are now testing in an additional cohort. Since CT screening approaches capable of early detection for NSCLC have not proved effective for SCLC, we examined autoantibody-antigen levels that can distinguish case from control and found them >2x higher in SCLC compared to other cancer types, including NSCLC, colon, breast, and pancreas cancer. Using high-density antibody arrays, we discovered and twice validated 9 IgG and 12 IgM highly specific autoantibodies for SCLC in cohorts from the CHS, Vanderbilt, and the LCEDPC (total N=240). Using optimized logistic regression, we identified 4 autoantibody-antigen complexes with fixed coefficients (average AUC, 0.86) that performed well in each study. 4/4 panel autoantibodies were similarly effective when the plasma was drawn up to 1 year prior to diagnosis, at limited-stage or extensive-stage diagnosis and 2/4 were upregulated when the plasma was drawn up to 2 years prior to diagnosis. We have evidence that each panel autoantibody is specific for SCLC as none are upregulated in NSCLC (N=59) samples or in other comorbidities examined, including COPD (N=31) and autoimmunity (N=15). Our vision is that using blood drawn at the time of lung cancer screening, one could more definitively assign indeterminate nodules to different treatment paths (e.g., none, repeat CT, biopsy) and indicate when further imaging workup might be appropriate for potential cases of LUSQ or SCLC.

IA06
Intercepting Lung Cancer by Understanding Premalignant Changes in the Airway Field
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Lung cancer is the leading cause of cancer death. In order to decrease mortality, we need innovative strategies to intercept cancer development by diagnosing the disease at its earliest and potentially most curable stage. Development of lung cancer risk biomarkers and interception strategies requires a detailed understanding of the earliest molecular alterations involved in lung carcinogenesis that occur in the respiratory epithelium. Exposure to cigarette smoke creates a field of injury throughout the entire respiratory tract by inducing a variety of genomic alterations that can lead to an at-risk airway where lung squamous premalignant lesions develop. Lung squamous cell carcinoma arises in the epithelial layer of the bronchial airways and is often preceded by the development of premalignant lesions through a stepwise histologic progression from normal epithelium to hyperplasia, squamous metaplasia, dysplasia (mild, moderate, and severe), carcinoma in situ, and finally to invasive cancer. The presence of high-grade persistent or progressive dysplasia is a marker of increased lung cancer risk, although many lesions have varied outcomes. Recent molecular profiling of endobronchial biopsies representing a range of histologic scores revealed an upregulation of cell cycle, proliferation, and DNA repair pathways and downregulation of inflammation and immune-associated pathways in high-grade progressive/persistent lesions. This work provided a foundation with which to further our understanding of the mechanisms that drive these early alterations and to develop robust biomarkers to detect their presence and future behavior. Recent projects that build upon this work to elucidate the pathways responsible for histologic progression will be presented. These projects will be put into the context of the collaborative effort to create a lung pre-cancer atlas that will include large-scale genomic, immunogenomic, and clinical multidimensional data. This larger effort will serve to both validate existing observations and biomarkers and further enhance lung cancer interception efforts.