A persistent central deficiency in our knowledge of cancer concerns how genomic changes drive the proteome and phosphoproteome to execute phenotypic characteristics. Furthermore, increasing evidence implicating epigenetic and post-translational changes in cancer biology reinforces the notion that molecular probes of this sort are gaining increasing importance. Here, we present an integrated proteogenomic study on a prospectively collected lung adenocarcinoma (LUAD) cohort, and provide new insights including on molecular taxonomy, novel mutations and fusions, protein and PTM associations with canonical driver mutations, metabolic dependencies and the immune milieu. The National Cancer Institute’s Clinical Proteomics Tumor Analysis Consortium (CPTAC) collected 110 LUAD tumors and 101 paired normal adjacent tissues using rigorous standard protocols to minimize ischemic time and other pre-analytical variability. Approximately equal numbers of Eastern (China, Vietnam) and Western patients were enrolled and the population included ~ 40% never-smokers. Comprehensive genomic and proteomic characterization provided whole exome, whole genome, copy number, RNAseq, microRNA, long non-coding RNA, methylation, global proteome, phosphoproteome, and acetylene data. The distribution of top driver mutations paralleled that of large genomics studies; both novel structural variants in established driver genes and novel ALK fusion partners were defined. 120 proteins including CLDN18, ANK1 and PTPRCAP had evidence of regulation by DNA methylation. Association analyses highlighted important outliers seen only in the phosphoproteomic data, including potential therapeutic targets such as SOS1 in KRAS mutant and PTPN11 (Shp2) in EGFR mutant tumors. Novel KEAP1 mutants including potential therapeutic targets such as SOS1 in KRAS mutant tumors and PTPN11 (Shp2) in EGFR mutant tumors. Novel KEAP1 mutants including potential therapeutic targets such as SOS1 in KRAS mutant tumors. Further work is under way to provide new insights into LUAD biology and facilitate testable therapeutic hypotheses, including for the development of targeted chemotherapeutics and immuno-therapies.

A02 Proteogenomic Characterization Reveals Therapeutic Vulnerabilities in Lung Adenocarcinoma

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A03 Lung Adenocarcinoma Resident Microbiome May Contribute to Cancer Hypomethylation Status

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Lung cancer is a devastating disease, and is responsible for the greatest fraction of cancer-associated deaths worldwide. Human lungs were long thought to be sterile, but as a barrier organ, are colonized by numerous bacterial communities. Here, we sought to characterize the lung adenocarcinoma (LUAD) microbiome and determine if it plays a role in tumor behavior. After patient consent, paired LUAD tumors and adjacent non-malignant tissues (NM, n=77) were obtained. Extracted DNA was sequenced (16S rRNA V4 regions) using MiSeq. Methylstatus of tumor tissue was determined by DNA bisulfite conversion and hybridization to the Illumina Human Methylation 27 array after tissue microdissection and DNA extraction. Methylation data was normalized, and average Beta values were compared by paired T-test. Validation of bacterial abundances was performed on publicly available whole RNA sequencing data depleted of reads aligning to the human genome (TCGA, 484 tumors and 58 NM). The potential functionality of the bacterial metagenome was assessed using the PICRUSt2 platform. When LUAD tumors are compared to NM tissue, we observe an increase in alphaproteobacteria, specifically Bradyrhizobium (p-adjusted=0.02). Conversely, a significantly lower abundance of gammaproteobacteria (Acinetobacter) is observed in the tumors, and an enrichment of this family is observed in NM samples (p-adjusted=0.03, Figure 1). Interestingly, we also observed a significant increase in Deinococcus in tumors (p=0.04; previously reported in LUSC). Using functional metagenome prediction, we observed a significant decrease in S-adenosyl-L-methionine synthesis (SAM; a global methyl donor) when tumors were compared to NM samples. In assessing the global patterns of DNA methylation in corresponding tissues, we observed hypomethylation of tumors compared to NM tissue genome-wide (p<0.001). To delineate the association of bacterial profiles with observed methylation patterns, we assessed tumor methylation data in the context of predicted SAM involvement. Indeed, tumors with high predicted SAM biogenesis in their microbiome had significantly more methylated regions than those with low involvement (high/low quartiles, p=0.002). Here, we assess the microbiome profile of LUAD and NM tissue, and find that LUAD is enriched in alphaproteobacteria and deficient in gammaproteobacteria. In tumors, we find that downregulation of SAM biogenesis in the bacterial population, potentially as a result of intratumoral selection pressure, is associated with patterns of global hypomethylation in lung cancer.

A04 Lung-Resident Microbial Signature Precedes Signs of Lung Malignancy

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Shifts in the microbial populations that colonize human tissues have been shown to affect host biologic pathways. In fact, changes in the lung-epithelial-resident microbiota have been associated with various lung diseases. In cancers in general, specific bacteria have been shown to confer increased risk of disease (e.g., H. pylori in gastric cancer). In