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 reinforce the notion that molecular profiles based on nucleic acids are incomplete and are critically complemented by analyses of proteins and their post-translational modifications (PTMs). We present the first 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 described including one suggesting an alternative mechanism of oncogenicity in KRAS mutant tumors. Highlighted important outliers seen only in the phosphoproteomic data, were defined. 120 proteins including CLDN18, ANK1 and PTPRCAP had 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 down-regulation 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.