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Protein and Molecular Alterations in EMT Pathways of Lung Cancer: A Comparative Analysis between NSCLCs

Topic: Proteins in Lung Cancer and Proteomics

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Background: The adoption of next-generation sequencing (NGS) may help to identify single nucleotide variants (SNVs), small insertions—deletions (indels), and larger structural variations including chromosomal rearrangements. Many molecular alterations have protein-level associations that can be questioned using immunohistochemistry (IHC). The goal of our work was investigated molecular patterns of predictive biomarkers and new genes involved as potential therapeutic targets with an emphasis on protein IHC and their translational promise.

Methods: We studied 212 formalin fixed and paraffin embedded tissues: 8 high-grade and 20 low-grade neuroendocrine carcinomas(NEC), 102 adenocarcinomas(ADC), 65 squamous cell carcinomas (SCC) and 17 large cell carcinomas(LCC), placed in tissue microarrays(TMAs). EGFR,P53,KRAS,ALK,ERBB2,PTEN,-BRAF,VEGF,CD24 and CD44 were examined using IHC and Aperio system. DNA extracted(QIAmp) from a subset was used to analyze several variants including *EGFR*, *ERBB2*, *PIK3CA*, *MMP2*, *SNAI*, *VGFA*, *VIM*, *ZEB1*, *AXL*, *CD44*, *CD276*, and *CDH1*, using the TruSeq Custom Amplicon assay on the Illumina MiSeq System, resulting data set for 80 LC were analyzed using the Variant-Studio software and correlated them with the clinocopathological data.

Results: The median age of the patients was 64 yrs (minimum-maximum, 24-88yrs). The population included 98(44.5%) women; 32(14,5%) never smokers and 100(45,5%) former smokers; only 2(1%) Asians. Our image analysis showed that the median IHC protein expressions were similar between low and high-grade NEC, but those were different compared to others ($P<0.05$). Indeed, EGFR, EBB2, P53 and BRAF IHC expression were significantly lower in NEC group compared to other subtypes ($P<0.05$). Overall, LCC have lower protein expression than ADC and SCC, specially P53 and VEFG. We detected several drivers mutation including EGFR 22%(19/80), ERBB2 2%(5/80), immune regulated genes CD276 6.8%(17/80) and CTLA 15.4%(39/80). We observed also EMT gene mutations as CD44 30.7%(78/80), MMP2 2.8%(7/80), VGFA 2%(5/80), CDH1 2.4%(6/80), SNAI 2.8%(7/80), VIM 1.2%(3/80), and ZEB1 4%(12/80). Interestingly, a significant higher AXL and CD44 gene expression was found in ADC and SCC specimens compared to NEC($P=0.001$ and $P=0.04$,respectively) Similar to the protein expression in overall low gene expressions was also observed in LCC compared to others.

Conclusion: We detected different patterns of protein and gene alteration in LC with predominant low expression in NEC. Furthermore, the high expression of EMT genes as *AXL* and *CD44* observed among ADC and SCC can be a evidence that those genes might be a distinctive RTK in these tumor than in NEC tumor suggesting that targeting these genes will be benefit as anticancer treatment.

Keywords: Immunohistochemistry, next generation sequencing, epithelial—mesenchymal transition, non-small cell lung cancer

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Identification of a Novel Oncogenic Ubiquitin Ligase from a Lung Cancer Epigenome-Wide Association Study (EWAS)

Topic: Proteins in Lung Cancer and Proteomics

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