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ORIGINAL ARTICLE

Whole-exome sequencing and immune profiling of early-stage lung adenocarcinoma with fully annotated clinical follow-up

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Background: Lung adenocarcinomas (LUADs) lead to the majority of deaths attributable to lung cancer. We performed whole-exome sequencing (WES) and immune profiling analyses of a unique set of clinically annotated early-stage LUADs to better understand the pathogenesis of this disease and identify clinically relevant molecular markers.

Methods: We performed WES of 108 paired stage I-III LUADs and normal lung tissues using the Illumina HiSeq 2000 platform. Ten immune markers (PD-L1, PD-1, CD3, CD4, CD8, CD45ro, CD57, CD68, FOXP3 and Granzyme B) were profiled by imaging-based immunohistochemistry (IHC) in a subset of LUADs ($n = 92$). Associations among mutations, immune markers and clinicopathological variables were analyzed using ANOVA and Fisher's exact test. Cox proportional hazards regression models were used for multivariate analysis of clinical outcome.

Results: LUADs in this cohort exhibited an average of 243 coding mutations. We identified 28 genes with significant enrichment for mutation. *SETD2*-mutated LUADs exhibited relatively poor recurrence- free survival (RFS) and mutations in *STK11* and *ATM* were associated with poor RFS among *KRAS*-mutant tumors. *EGFR, KEAP1* and *PIK3CA* mutations were predictive of poor response to adjuvant therapy. Immune marker analysis revealed that LUADs in smokers and with relatively high mutation burdens exhibited increased levels of immune markers. Analysis of immunophenotypes revealed that LUADs with *STK11* mutations exhibited relatively low levels of infiltrating CD4+/CD8+ T-cells indicative of a muted immune response. Tumoral PD-L1 was significantly elevated in *TP53* mutant LUADs whereas *PIK3CA* mutant LUADs exhibited markedly down-regulated PD-L1 expression. LUADs with *TP53* or *KEAP1* mutations displayed relatively increased CD57 and Granzyme B levels indicative of augmented natural killer (NK) cell infiltration.

Conclusion(s): Our study highlights molecular and immune phenotypes that warrant further analysis for their roles in clinical outcomes and personalized immune-based therapy of LUAD.

Key words: lung adenocarcinoma, whole-exome sequencing, immune profiles