NEOANTINGENS, T AND B CELLS IN SQUAMOUS ESOPHAGEAL CANCER

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Abstract

Esophageal cancer (EC) is one of the ten most incident and lethal neoplasms worldwide. The chemotherapy of choice still involves taxane and platinum-based regimens, without any molecular targets. Therefore, it is of utmost importance to better characterize these tumors in order to develop biomarkers and new therapeutical strategies. Esophageal squamous cell carcinoma (ESCA) exhibits high intratumoral molecular heterogeneity that might favor immunotherapy, such as the immune checkpoints blockade. Nonetheless, the success of such therapies depends on the immune-based microenvironment characteristics of the tumor. RNA-seq analysis from 14 tumor and adjacent normal tissue samples from ESCA patients without previous treatment (INCA - CEP 116/11) was performed using Illumina Hi-Seq 2000. Mutations were detected following GATK best practices protocol. Differential gene expression was calculated by RSEM followed by DESeq R package. Class I and II HLA alleles and expression were defined by Optitype and Seq2HLA. ANNOVAR and VEP were used for annotation and gene to protein conversion. NetMHCpan v4.0 was applied to in silico of HLA affinity. Peptides with binding values higher than 500 nM were considered neoantigens. TCR and BCR repertoire were evaluated by MiXCR and tcR R package. Deconvolution analysis of immune subpopulations were performed by CIBERSORT and xCell. TCGA-ESCA samples (n=75) were used as an independent cohort of patients. R software was used for graphic and statistical analysis along with in-house perl scripts. A high number of mutation derived neoantigens and tumor aberrant antigens (TAA) number varied across tumor samples. Although not detected by RNA-seq, four proteins were expressed by the tumor and surrounding areas. All tumors are enriched with immune checkpoint and activators genes compared to normal counterparts, but their expression varied between patients explaining partially why immune checkpoint blockade therapy are not effective against this tumor. Our analysis evidenced a complex immune landscape in ESCA with major macrophages and T cells infiltration. The high number of B cell clones (mostly IgG) infiltrating the tumors and the high active B cell meta-signatures found suggest B cells may play a role in ESCA progression. Also, B cells are significantly correlated with better overall survival and were found in tertiary lymphoid-like structures within the tumor.

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