JOURNAL ARTICLE

Tumor gene signatures that correlate with release of extracellular vesicles shape the immune landscape in head and neck squamous cell carcinoma

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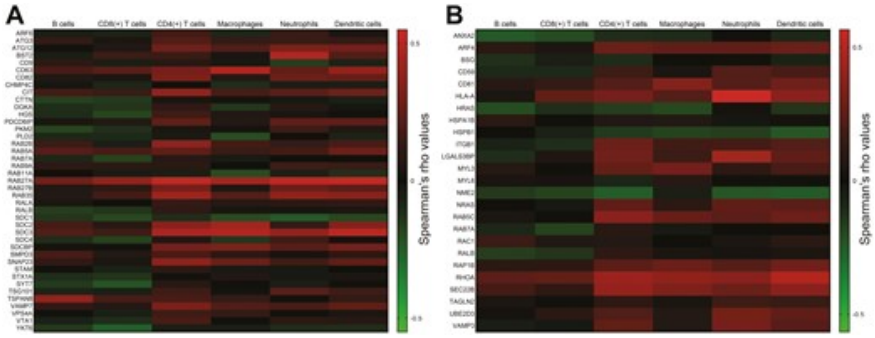
Abstract

Head and neck squamous cell carcinomas (HNSCCs) evade immune responses through multiple resistance mechanisms. Extracellular vesicles (EVs) released by the tumor and interacting with immune cells induce immune dysfunction and contribute to tumor progression. This study evaluates the clinical relevance and impact on anti-tumor immune responses of gene signatures expressed in HNSCC and associated with EV production/release. Expression levels of two recently described gene sets were determined in The Cancer Genome Atlas Head and Neck Cancer cohort (n = 522) and validated in the GSE65858 dataset (n = 250) as well as a recently published single-cell RNA sequencing dataset (n = 18). Clustering into HPV(+) and HPV(−) patients was performed in all cohorts for further analysis. Potential associations between gene expression levels, immune cell infiltration, and patient overall survival were analyzed using GEPIA2, TISIDB, TIMER, and the UCSC Xena browser. Compared to normal control tissues, vesiculation-related genes were upregulated in HNSCC cells. Elevated gene expression levels positively correlated (P < 0.01) with increased abundance of CD4(+) T cells, macrophages, neutrophils, and dendritic cells infiltrating tumor tissues but were negatively associated (P < 0.01) with the presence of B cells

and CD8(+) T cells in the tumor. Expression levels of immunosuppressive factors *NT5E* and *TGFB1* correlated with the vesiculation-related genes and might explain the alterations of the anti-tumor immune response. Enhanced expression levels of vesiculation-related genes in tumor tissues associates with the immunosuppressive tumor milieu and the reduced infiltration of B cells and CD8(+) T cells into the tumor.

Graphical Abstract



Keywords: extracellular vesicles, exosomes, HNSCC, tumor-infiltrating immune cells, tumor microenvironment

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