60P - Deciphering CD8+ T-cell-related gene signatures in the tumor microenvironment to predict the immunotherapy response and prognosis of ovarian cancer patients

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Background

The survival of patients with ovarian cancer (OC) is correlated with the presence of infiltrating CD8+ T lymphocytes in the tumor microenvironment, but the underlying regulatory mechanisms and therapeutic significance of CD8+ T cells are still not clearly known.

Methods

We retrieved 13 immune cell line-associated datasets, RNA-sequencing data and clinical information were downloaded from the Gene Expression Omnibus, The Cancer Genome Atlas, and the International Cancer Genome Consortium in an effort to find biomarkers to improve the treatment of OC. CD8+ T-cell-associated genes were identified with weighted correlation network analysis. Survival and nomogram analyses were performed. Model effects were also validated using the immunotherapy dataset IMvigor210. Quantitative real-time PCR (qRT-PCR) and immunohistochemistry (IHC) staining were used to evaluate the expression of the signature genes in OC.

Results

We identified 520 CD8+ T-cell-associated genes that were significantly enriched in immune function-related pathways, as well as 3 OC molecular subtypes (immune cluster 1 [IC1], IC2, IC3). The IC1 and IC2 subtypes have a worse prognosis than IC3 (Figure 1). IC3 has higher IFNγ scores, immune T-cell lytic activity, immune cell infiltration, and high expression of immune checkpoint-related genes (Figure 2), which indicates that the IC3 subtype was more sensitive to immune checkpoint inhibitors. A 10-gene signature comprising SEMA4F, CX3CR1, STX7, PASK, AKIRIN2, HEMGN, GBP5, NSG1, CXorf65, and TXK was constructed.

Multivariate Cox regression analysis showed that the gene signature-based risk model was significantly associated with OS ($p<1e-5$). A nomogram incorporating signature and age was constructed, and calibration plots and DCA confirmed its stable prognostic power (Figure 3). The accuracy of gene signatures in OC patient tissue samples was confirmed by IHC and qRT-PCR results (Figure 4), which were consistent with the bioinformatics analysis. The risk model's potency as a predictor was demonstrated using the Imvigor210 immunotherapy dataset.

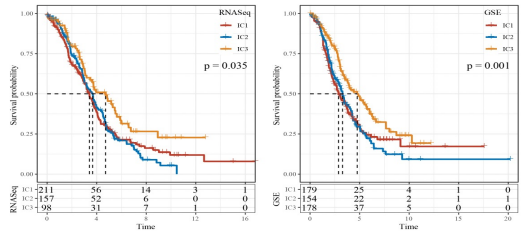

Figure 1. Survival curves for the molecular subtypes in the RNASeq dataset and the GSE-OV dataset cohort.

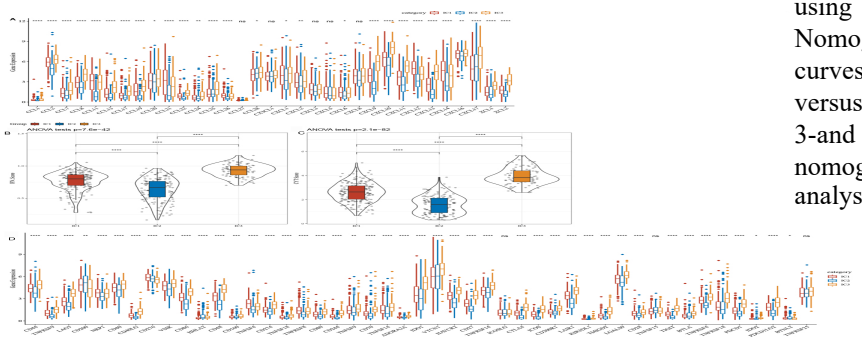

Figure 2. Differences in the expression of immune molecules and function between molecular subtypes in the RNASeq cohort for (A) immune cell infiltration, (B) IFNγ, (C) immune T-cell lysis activity, and (D) immune checkpoint genes.

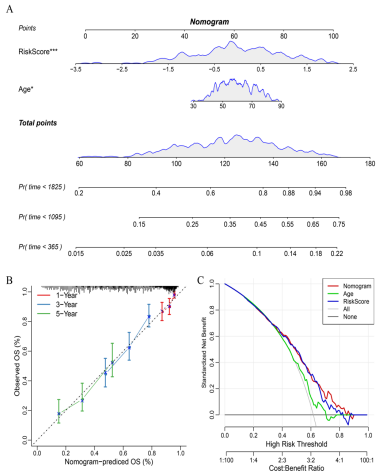

Figure 3. Nomogram and forest plot constructed with the RiskScore and clinical features using the TCGA dataset. (A) Nomogram. (B) Calibration curves showed the observed OS versus predicted probability of 1-, 3-and 5-year survival of the nomogram. (C) Decision curve analysis plot.

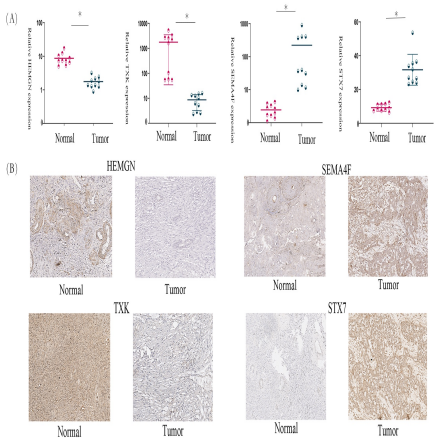

Figure 4. The qPCR (A) and IHC (B) results showed that HEMGN and TXK expression was low and that SEMA4F and STX7 expression was high in OC tissues.

Conclusion

We established a novel CD8+ T-cell-associated gene signature that can help assess prognostic risk and immunotherapy response in patients with OC.

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