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A PD-L2-based immune marker signature helps to predict survival in resected pancreatic ductal adenocarcinoma

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Background: Programmed cell death protein 1 (PD-1) is a key immune checkpoint that regulates peripheral tolerance and protects against autoimmunity. Programmed death ligand-2 (PD-L2) is a less studied ligand to PD-1 and has yet to be fully explored, especially in pancreatic ductal adenocarcinoma (PDAC).

Methods: In this study, we performed immunohistochemistry to detect the PD-L2, CD3, CD8, transforming growth factor-β2 (TGF-β2) and FOXP3 levels in paraffin sections from 305 patients with resected PDAC as a training set. Expression levels of intratumoral and stromal immune markers were compared in relation to survival using Kaplan-Meier curves, random survival forest model and survival tree analysis. A multivariable Cox proportional-hazards model of associated markers was used to calculate the risk scores.

Results: PD-L2 was expressed in 71.5% of PDAC samples and showed strong correlations with CD3+, CD8+ T cells and FOXP3+ regulatory T cell densities. High levels of intratumoral PD-L2 and FOXP3 were related to poor survival; only stromal FOXP3 overexpression was associated with worse prognosis. Four patterns generated from survival tree analysis demonstrated that PD-L2lowstromalFOXP3low patients had the longest survival, while PD-L2highintratumoralCD3low patients had the shortest survival ($P < 0.001$). The area under the curve was 0.631(95% confidence interval (CI): 0.447-0.826) for the immune marker-based signature and 0.549 (95% CI: 0.323-0.829; $P < 0.001$) for the clinical parameter-based signature, which was consistent with the results in the validation set including 150 patients ($P < 0.001$). A higher risk score indicated shorter survival and could serve as an independent prognostic factor. PD-L2 was also showed associated with TGF-β2 and other immune molecules based on bioinformatics analysis.

Conclusions: Our work highlighted PD-L2 as a promising immunotherapeutic target with prognostic value combined with complex tumor infiltrating cells in PDAC.

Biography

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