Transcriptomics and Immunoinformatics Analyses Reveal Midkine as a Promising Therapeutic Target in Pancreatic Ductal Adenocarcinoma

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Introduction: Pancreatic ductal adenocarcinoma (PDA) remains one of the deadliest malignancies due to late diagnosis, extensive metastasis, and limited treatment options. A multifunctional growth factor, midkine (MK) is significantly upregulated in PDA and has been implicated in various oncogenic signaling pathways. This study aims to delineate MK's mechanistic roles in PDA tumor microenvironment (TME) and evaluates its potential as a target for cancer vaccine development. Methods: Transcriptomics analyses were performed in RStudio on single-cell RNA sequencing and spatial transcriptomics datasets. Data preprocessing and analysis were carried out according to the Seurat package workflows, and MK-mediated intercellular and intracellular signaling mechanisms were identified with CellChat and NicheNet. The MK vaccine was designed with reverse vaccinology epitope prediction, structural modeling, and in silico immune and molecular docking simulations. Results: MK was secreted by mucinous epithelial cells and cancer-associated fibroblasts and exerted effect through autocrine and paracrine signaling. Through activating the NF-kB, MAPK/ERK, JAK/STAT, Notch, and PI3K-Akt pathways, MK promoted immune evasion by facilitating CD8 T-cell and B cell exhaustion while inducing regulatory T cells and tumor-associated macrophages differentiation. Computational vaccine design indicated a structurally stable, antigenic, non-allergenic, and non-toxic MK vaccine, which elicited strong Th1-dominant immune response with high binding affinity to immune cell receptors. Conclusion: This study is the first to demonstrate MK as a driver of PDA immune evasion. The MK vaccine represents a promising novel immunotherapeutic strategy that should be synergistically tested with current PDA therapies.

Awards Won: