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Prehabilitation as a biologically active intervention reprograms pancreatic tumor-immune microenvironment to enhance anti-tumor immunity

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Background: Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy, and many patients are unable to undergo curative surgery due to frailty. Multimodal prehabilitation programs, incorporating exercise, nutritional support, and psychological optimization, improve functional readiness, but their biological impact on the PDAC tumor microenvironment (TME) remains largely unknown.
Methods: In this exploratory pilot analysis, we profiled resected PDAC tissues from prehabilitation-treated patients and matched controls using NanoString GeoMx Digital Spatial Profiling across immune ($CD45^+$), tumor ($PanCK^+$), and stromal cellular compartments. Transcriptomic signatures were evaluated through differential expression, GO/KEGG pathway enrichment, and MCP-counter deconvolution. Protein-level assessment was performed by multiplex immunofluorescence in an independent cohort (n = 8). Cell–cell communication dynamics were examined using ligand–receptor modeling. Prognostic relevance of key signatures was assessed using TCGA-PDAC (n = 178).
Results: Prehabilitation was associated with increased NK-cell cytotoxicity, interferon response, and chemokine recruitment in immune regions. MCP-counter analysis indicated higher neutrophil signatures ($p < 0.01$) and reduced fibroblast signatures ($p < 0.05$). Tumor compartments exhibited lower MAPK, PI3K/AKT, and Ras pathway activity, while stromal regions showed decreased TGF-β and Wnt/Hippo signaling and transcriptional patterns consistent with enhanced immune interaction. Multiplex immunofluorescence supported increased neutrophil infiltration and reduced fibroblast density. Ligand–receptor modeling suggested strengthened NK–tumor and stromal–immune communication. In TCGA, patients with neutrophil-high/fibroblast-low profiles had significantly longer survival (1,044.6 vs. 458.7 days, $p = 0.016$).
Conclusion: This exploratory pilot study suggests that multimodal prehabilitation may be associated with a more immune-active and less fibrotic TME in PDAC. These profiles resemble transcriptional states linked to improved survival, highlighting the need for prospective studies integrating biological and clinical endpoints to further evaluate prehabilitation as a biologically active adjunct to PDAC management.
strong text

Keywords

Multimodal prehabilitation; pancreatic tumor microenvironment; spatial profiling

Conflict of Interest & Ethical Approval

yes

Abstract submitters declaration

yes

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