SIREN: Schwann Cell–Derived TGF-β Drives Regulatory T Cell Enrichment and $CD8^+$ Exclusion in Pancreatic Ductal Adenocarcinoma

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❖ ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is one of oncology's most lethal malignancies, marked by persistent resistance to immunotherapy, targeted therapy, and surgery. The origin of its immunosuppressive tumor microenvironment remains unresolved, contributing to late detection, poor treatment outcomes, and rapid relapse after rare response. To address this, SIREN proposes a novel, testable hypothesis. Schwann cells, present in perineural invasion in over 80% of PDAC cases, may drive immunosuppressive tumor microenvironment (TME) formation through overexpression of TGF-β, forming a testable neuro-immune axis. Through a six-aim multi-omics approach combining transcriptomic, spatial, interaction, survival, temporal, and cross-cancer analysis, SIREN suggests PDAC as a neuro-immune disease, exposing a Schwann cell–TGF-β axis as a potential druggable origin point pending experimental and translational validation.

❖ INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most treatment-resistant malignancies in modern oncology, with a 10% five-year survival rate that has changed little in fifty years. PDAC's lethality is driven by late detection and a strongly immunosuppressive tumor microenvironment (TME), which limits the effectiveness of treatments such as immune checkpoint inhibitors (Leiphrakpam et al., 2025; Moyana & Merz, 2025). In many cases, the TME prevents $CD8^+$ T cells from functioning effectively while promoting regulatory T cells (Tregs) (Ju et al., 2024), however, the initiating mechanism of this immunosuppression remains unknown. Perineural invasion (PNI), observed in over 80% of PDAC cases, is another consistent but less explored feature (Wang et al., 2021). Its role in shaping the TME has not been clearly defined. This is notable because Schwann cells, which are involved in PNI, have been shown to undergo reprogramming (Ebrahim et al., 2025; Deborde et al., 2022). Some early transcriptomic evidence suggests that these cells may express immunosuppressive signals such as transforming growth factor beta (TGF-β) during early tumor development, including the PanIN stage (Carpenter et al., 2023), although this has not been directly confirmed. This study asks whether Schwann cell-derived TGF-β signaling drives immunosuppressive TME formation during early (PanIN stage) PDAC. To address this, SIREN integrates transcriptomic, spatial, interaction, survival, temporal, and cross-cancer analyses across six sequential aims to identify Schwann cells as a therapeutic target.

❖ LITERATURE REVIEW

PDAC's consistent resistance to treatment is not incidental, but architectural (Olaoba et al., 2024). Its TME, dominated by tumor-associated macrophages, cancer-associated fibroblasts, and a dense extracellular matrix, aggressively drives ICI response rates below 1% in unselected patients (Pan et al., 2025; Giurini et al., 2025). Lyman et al. (2025) also found that early PanIN lesions already carry immune microenvironments nearly identical to late-stage PDAC, suggesting immunosuppression established before diagnosis. However, it is still unclear whether this finding generalizes beyond their cohort. Evidence suggests something is building this environment early. While fibroblasts and myeloid cells are established contributors, PNI – present in over 80% of cases – has been minimally investigated as a direct TME driver, making it the most underexplored remaining candidate (Wang et al., 2021). Deborde et al. (2022) demonstrated that, during PNI, activated Schwann cells generate tumor-activated Schwann cell tracks, later linked by Ebrahim et al. (2025) to elevated TGF-β expression, known to suppress both adaptive and innate immunity (Tauriello et al., 2022). Together, these findings suggest early remodeling, which remains unconfirmed, a critical gap SIREN aims to bridge.

❖ METHODOLOGY

The methodology, designed to be fully executable on a laptop (minimum 8 GB RAM) with no ethical concerns, is organized into six sequential aims spanning transcriptomic profiling, spatial mapping, interaction, survival correlation, temporal dynamics, and cross-cancer analyses:

Aim 1 (Transcriptional Co-expression Analysis): The molecular basis of the axis is first examined by using WGCNA on VST-normalized TCGA-PAAD bulk RNA-seq data from 183 primary tumors, using soft-thresholding ($R^2 \geq 0.85$) to identify modules in which Schwann activation, defined by an S100B/SOX10/NGFR signature, correlates positively with Treg infiltration and inversely with $CD8^+$ abundance estimated through ssGSEA. Hub genes then undergo BH-corrected GO and Reactome enrichment using clusterProfiler, following Tan et al. (2021), and results will only be retained if enrichment is robust across ≥70% of iterations, forming a transcriptional scaffold for subsequent spatial mapping. **Aim 2 (Spatial Co-localization):** HTAN PDAC Visium sections are then SCTransform-normalized and cell-type scored within Seurat (Hao et al., 2021), with Moran's I and SPARK-X used to test whether Schwann–Treg co-localization reflects structured spatial organization rather than transcriptional coincidence, establishing a necessary tissue-level basis before signaling inference. **Aim 3 (Ligand-Receptor Modeling):** NicheNet and CellChat are run independently across a curated set of over 3,000 ligand–receptor pairs, retaining only interactions with ≥70% concordance between both tools and confirmed cell-type–resolved expression, reducing artifacts from ambient RNA and misannotation. Additional filtering requires ligand and receptor co-expression above the 75th percentile within their respective populations. TGF-β is prioritized as the primary axis, consistent with immune evasion pathways described by Tauriello et al. (2022), Deborde et al. (2022), and Ebrahim et al. (2025). **Aim 4 (Survival Analysis):** A LASSO-regularized STC index, derived from Schwann, Treg, and $CD8^+$ signatures with cross-validated λ selection, is strictly evaluated against overall survival using Kaplan–Meier analysis and multivariate Cox regression, adjusting for stage and treatment history, following prognostic approaches validated in PDAC by Huang et al. (2023). **Aim 5 (Pseudotemporal Trajectory Inference):** Monocle3 is used to order these populations along inferred pseudotime, with progressive immunosuppression defined as a monotonic increase in suppressive signature scores, interpreted as supportive rather than causal due to the inferential nature of pseudotime analysis. **Aim 6 (Cross-Cancer Validation):** The full pipeline is finally applied to TCGA-HNSC and TCGA-PRAD, adding over 1,000 additional tumor samples, comparing STC-associated hazard ratios using Fisher's z-transformation to assess whether this axis generalizes across PNI malignancies, consistent with broader PNI biology (Deborde et al., 2022).

Reproducibility: Analyses will be implemented in R and Python using reproducible pipelines on TCGA and HTAN datasets with fixed random seeds, with code open-sourced on GitHub.

❖ CONCLUSION

SIREN aims to determine whether PDAC immune failure originates in Schwann cell-derived TGF-β signaling operating long before diagnosis is possible. If confirmed, this axis would reframe PDAC pathogenesis and intervention strategies, though translating SIREN from paper to clinical procedure will require experimental validation, including Schwann-specific TGF-β perturbation, orthotopic PDAC models, and spatial multi-omics confirmation, followed by multi-center trials prioritizing future therapeutic targeting and early detection strategies. Despite limitations, with cross-cancer implications rooted in PNI biology, SIREN points toward a more precise, earlier intervention point for one of medicine's most treatment-resistant cancers.

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