Targeting STAT3 Remodels the Tumor Microenvironment and Enhances Radiotherapy Response in Pancreatic Cancer

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Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies, characterized by a profoundly fibrotic and immunosuppressive tumor microenvironment (TME) that undermines the efficacy of systemic therapies and radiotherapy (RT). Cancer-associated fibroblasts (CAFs) are central mediators of stromal remodeling, immune exclusion, and therapeutic resistance, with STAT3 signaling emerging as a critical driver of CAF activation and pro-tumorigenic function. To dissect the role of fibroblast-intrinsic STAT3, we generated a fibroblast-specific STAT3 knockout model (*Col1a1;Stat3*$^{\Delta/\Delta}$) and established flank PDAC tumors. Ablation of STAT3 in fibroblasts significantly delayed tumor growth and improved overall survival compared to wild-type controls. Tumor analysis revealed substantial remodeling of the stroma, including reduced deposition of fibrotic markers such as αSMA, collagen type I, and PDGFRβ, alongside enhanced infiltration of effector $CD8^+$ T cells. Flow cytometry and immunofluorescence profiling confirmed an immune-permissive shift within the TME. Moreover, genetic deletion of STAT3 in combination with RT led to a synergistic delay in tumor progression compared to RT monotherapy, indicating that STAT3 activity contributes not only to immune suppression but also to intrinsic radioresistance. Collectively, these findings delineate a previously underappreciated role of fibroblast STAT3 signaling in orchestrating a fibrotic, immune-excluded, and radiation-refractory TME in PDAC. Therapeutically targeting of STAT3 in CAFs could significantly enhance the immunogenicity of PDAC tumors and improve responses to radiotherapy, supporting further translational investigation.