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Summary

ATM-DEFICIENT TUMOR EPITHELIA RESHAPE PANCREATIC CANCER-ASSOCIATED FIBROBLASTS TO FOSTER CANCER AGGRESSIVENESS VIA A DRUGGABLE TGF B SIGNALING AXIS

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ATM deficiency in pancreatic ductal adenocarcinoma drives TGFβ-mediated myofibroblastic cancer-associated fibroblast reprogramming that promotes chemoresistance and tumor invasion, reversible with TGFβ receptor inhibition.

KEY POINTS

- ATM-deficient PDAC tumors exhibit enrichment of myofibroblastic cancer-associated fibroblasts (myCAFs) with an imbalanced myCAF/iCAF ratio, driven by greater TGFβ release from ATM-deficient tumor cells and downstream canonical TGFβ signaling activation in fibroblasts.
- The ATM loss-mediated cancer-associated fibroblast rewiring correlates with chemoresistance and invasive tumor features, which are reversed upon TGFβ interference.
- Combinatorial therapy with a TGFβ receptor I inhibitor reverses cancer-promoting tumor microenvironment remodeling and enhances FOLFIRINOX cytotoxic effects in ATM-deficient homologous recombination deficient PDAC in multiple ex vivo and in vivo models.
- The study uses murine ATM and P53 knockout models, 21 clinically annotated human ATM and/or TP53-mutated PDACs, and transcriptomic, proteomic, and secretome analyses to characterize genotype-specific tumor-stroma interactions.
- This work is relevant to researchers and clinicians interested in genotype-directed therapeutic strategies targeting tumor-stroma interactions in pancreatic cancer with homologous recombination deficiency.

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