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Summary

SHP2 REGULATES CAF ACTIVITY AND ADAPTIVE STROMAL REMODELING DURING VERTICAL RAS PATHWAY INHIBITION IN PANCREATIC CANCER

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Combined SHP2 and MEK inhibition in PDAC induces dynamic cancer-associated fibroblast remodeling with transient inflammatory CAF expansion followed by myofibroblast re-establishment and adaptive resistance.

KEY POINTS

- SHP2 inhibition, in contrast to MEK or RAS inhibition alone, markedly reduced fibroblast viability and matrix-contractile function in vitro, accompanied by compensatory PI3K-AKT signaling activation.
- Dual SHP2/MEK inhibition in vivo induced transient expansion of inflammatory CAFs and alterations in extracellular matrix organization, followed by re-establishment of myofibroblastic CAF states under prolonged treatment and emerging adaptive treatment resistance.
- Vertical RAS pathway blockade and SHP2 inhibition affects tumor cell-intrinsic signaling and reshapes stromal architecture through CAF plasticity.
- Results support further evaluation of SHP2-based combination strategies to prevent stromal-mediated resistance and highlight the importance of targeting tumor-stroma crosstalk to enhance therapeutic efficacy of RAS inhibition strategies in PDAC.
- The study used murine and human primary fibroblasts, tumor-fibroblast co-cultures, autochthonous KPC and KPF tumor models, with in vitro assays, flow cytometry, multiplex immunohistochemistry, and single-cell RNA analysis.

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