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STAT3 signaling mediates FAK inhibitor response and resistance in pancreatic cancer

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Pancreatic cancer is not responsive to targeted therapy. This may be due to the presence of a uniquely fibrotic and immunosuppressive tumor microenvironment present in pancreatic ductal adenocarcinoma (PDAC). Critical obstacles to targeted therapy in PDAC tumors include the dense desmoplastic stroma that acts as a physical barrier to drug delivery and the high numbers of tumor-associated immunosuppressive cells. In our previous study, we identified hyperactivated focal adhesion kinase (FAK) activity in neoplastic PDAC cells as a significant regulator of the fibrotic and immunosuppressive tumor microenvironment (TME). FAK inhibition (VS-4718) significantly limited tumor progression, and prolonged mice survival. Herein, we observed that STAT3 signaling was constantly activated in non-responsive and recurrent tumors, suggesting STAT3 signaling pathway regulates FAK inhibitor (FAKi) response and resistance. Furthermore, gene enrichment analysis showed that TGF- β signaling was significantly downregulated upon FAK inhibition, suggesting a negative feed back regulation of STAT3 by TGF- β signaling. We proposed that overcoming STAT3 reactivation upon FAK inhibition would enhance pancreatic cancer sensitive to FAK inhibitor. Accordingly, we found that combined STAT3 inhibition (Stattic) with FAK inhibition significantly prolonged the survival in the *p48-Cre/LSL-Kras^{G12D}/p53^{Flox}/Flox* (KPPC) mouse model of human PDAC. This alteration in tumor progression was associated with dramatically reduced tumor fibrosis, decreased numbers of immunosuppressive myeloid cells and increased tumor cell death. Together, our data indicate that STAT3 inhibition sensitizes PADC to FAKi and overcomes FAKi resistance.

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