STAT3 in cancer-associated fibroblasts promotes an immunosuppressive tumor microenvironment

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BACKGROUND

Pancreatic adenocarcinoma (PDAC) is a highly lethal malignancy and is projected to become the second leading cause of cancer deaths by 2030.

- Contributing to its recalcitrance is the presence of an inhospitable dense and immunosuppressive stroma consisting of several distinct cell types, including cancer associated fibroblasts (CAFs).
- Stroma-targeting studies have revealed a dichotomous role in which the stroma can exert both tumor-suppressive and promoting properties.

Previous work from our group has found that loss of PTEN in pancreatic CAFs can result in increased tumor growth and increase in macrophage infiltration in the tumor microenvironment (TME).

- Initial investigations into PTEN KO CAFs revealed STAT3, a transcription factor involved in many cell activities, including immune activation, was upregulated.

- Hypothesis: STAT3 signaling in pancreatic CAFs promotes an immunosuppressive TME in PDAC

METHODS

Determine the effect of stromal STAT3 activity on the immune cell populations of the PDAC tumor microenvironment using fibroblast-specific Cre (Fsp-Cre) to knockout STAT3 in the KPF mouse (a genetically engineered mouse model of PDAC developed by our lab).

RESULTS

- Loss of PTEN in pancreatic CAFs results in activation of STAT3
- STAT3 signaling in pancreatic CAFs decreases survival and tumorigenesis in the KPF model of PDAC
- Fibroblast STAT3 signaling may play a role in increased ECM deposition
- Fibroblast STAT3 decreases CD8+ T cell and increases Foxp3+ Treg infiltration in the tumor microenvironment (TME)
- Fibroblast STAT3 increases M2 macrophage infiltration in the TME
- Fibroblast STAT3 promotes M2 macrophage polarization through CXCL1

Future Directions:

- Mechanism by which PTEN and STAT3 interact in CAFs
- Further characterize immune microenvironment by flow cytometry
- CXCL1 inhibitor studies

REFERENCES


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CONCLUSIONS AND FUTURE DIRECTIONS