IL1RAP blockade mediates anti-fibrotic effects in pancreatic cancer-associated fibroblasts

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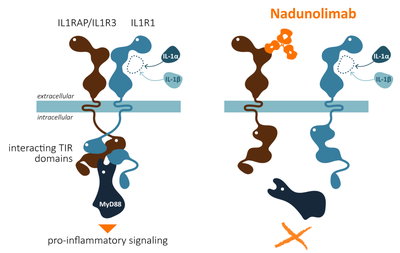
BACKGROUND

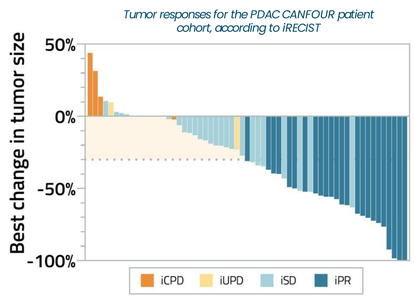
Pancreatic ductal adenocarcinoma (PDAC) patients have poor prognosis partly due to excessive activity of cancer-associated fibroblasts (CAFs). CAFs drive the fibrosis that causes excessive type III collagen and extracellular matrix deposition that in turn reduces drug response resulting in poor survival.

High levels of the type III collagen serum biomarker PRO-C3 correlates with poor survival in PDAC. While TGF-β is thought to be one of the main drivers of PRO-C3 and tumor fibrosis, cytokines such as Interleukin 1 (IL-1) play a key role in the pancreatic tumor microenvironment and may play a significant role in also tumor fibrosis.

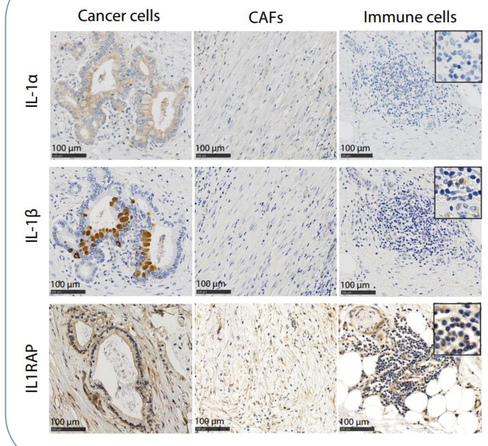
In this study, we first investigated the potential of IL-1 in activating fibroblasts to drive fibrosis and produce PRO-C3. Subsequently, we established a co-culture of pancreatic cancer cells and pancreatic CAFs to investigate the anti-fibrotic properties of nadunolimab, a fully humanized ADCC-enhanced monoclonal IgG1 antibody that targets IL1RAP and disrupts both IL-1α and IL-1β signaling.

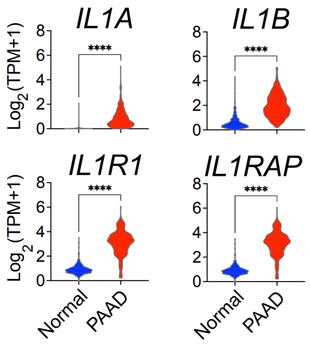
Nadunolimab is currently in phase I/IIa clinical development for treatment of pancreatic cancer in combination with gemcitabine and nab-paclitaxel (CANFOUR, NCT03267316). Interim phase IIa data show stronger OS and iPFS compared to reported values for gemcitabine and nab-paclitaxel alone with a median overall survival in the 73 CANFOUR PDAC patients of 13.2 months.





IL-1 AND IL1RAP IN PANCREATIC CANCER





IL-1α, IL-1β, and IL1RAP are all expressed in PDAC tumors, on cancer cells (left images), CAFs (middle images), and immune cells (right images).

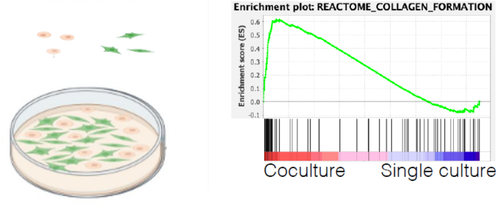
Gene expression data from GTEx and TCGA public datasets show increased levels of IL-1 and its receptors in Pancreatic adenocarcinoma (PAAD) tumors (n=178) compared to normal pancreatic tissue (n=171).

METHODS

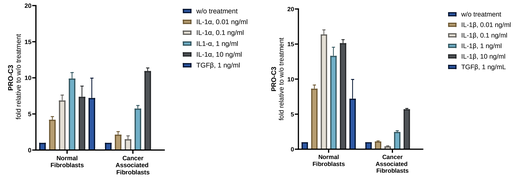
1. Pancreatic cancer cells (BxPc3) and pancreatic CAFs were cultured either alone or in a co-culture. Nadunolimab or isotype control were added at start of the cultures and supernatants were collected at day 3.
2. Human primary pancreatic cancer-associated fibroblasts (CAFs) and normal fibroblasts (NF) were cultured in Ficoll-media (Scar-in-a-jar, SiaJ) supplemented with TGF-β, IL-1α or IL-1β for 12 days.
3. The fibrotic activity of the fibroblasts was investigated by measuring the formation of type III collagen (PRO-C3)

RESULTS

Coculturing fibroblasts with BxPc3 cancer cells induced collagen formation

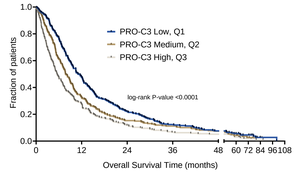


Fibroblast monoculture: IL-1 induced collagen type III formation :



PRO-C3 is prognostic in PDAC

BIOPAC (NCT03311776)	Study population (n = 810)
Age, (years), Median (min, max)	66 (37-89)
Gender, n (% Female)	377 (47%)
BMI, Median (min, max)	23 (14-39)
Metastatic sites, ≠1 site, n (%)	434 (54%)
Stage 1+2	138 (17%)
Stage 3	237 (29%)
Stage 4	431 (53%)
Performance status, ≠2, n (%)	94 (12%)



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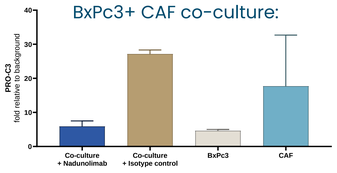
Nadunolimab blocked the induction of type III collagen formation in co-culture



CONCLUSIONS

1. Co-cultures of pancreatic tumor cells and CAFs induced formation, including collagen type III formation, and nadunolimab inhibited the collagen type III formation, suggesting anti-fibrotic properties.
2. Activated fibroblasts had induced type III collagen formation (PRO-C3) suggesting that IL-1 is a driver of tumor fibrosis in PDAC.
3. Nadunolimab, which is currently in clinical development for treatment of pancreatic cancer, has the potential to counteract the detrimental, fibrotic progression in tumors by targeting IL1RAP and blocking both IL-1α and IL-1β signaling
4. PRO-C3 could potentially be used for prognostic/predictive enrichment and as a pharmacodynamic marker in future studies evaluating anti-IL-1 modalities in PDAC.

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