The IL1RAP-blocking antibody nadunolimab disrupts pancreatic cancer cell and fibroblast crosstalk, reduces recruitment of myeloid cells and inhibits tumor growth.

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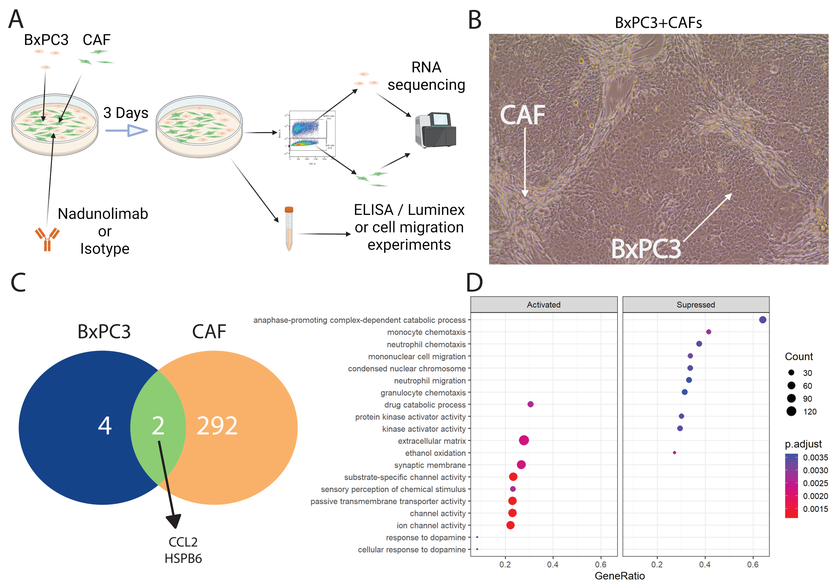
Introduction

IL1RAP is expressed by tumor and stromal cells in pancreatic ductal adenocarcinoma (PDAC). Signaling by IL1 through the IL1R1/IL1RAP complex promotes cancer progression and contributes to the immune suppressive microenvironment in PDAC.[1] The IL1RAP-blocking antibody nadunolimab blocks the signaling of both IL1a and IL1b and is currently evaluated in a phase I/IIa clinical study for PDAC (NCT03267316). Cancer-associated fibroblasts (CAFs) are a primary constituent of the PDAC stroma and has previously been shown to be regulated by IL1.[2] The aim of this study was to explore the functional consequences of nadunolimab treatment on the crosstalk between tumor cells and CAFs.

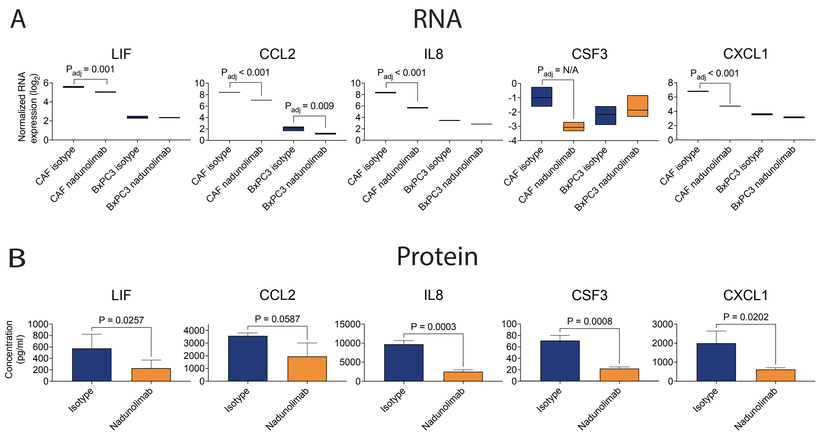
References: 1. Tjomsland et.al. Neoplasia (2011). 2. Biffi et.al. Cancer Discovery (2019).

Nadunolimab induces changes in gene expression of CAFs cocultured with PDAC cells



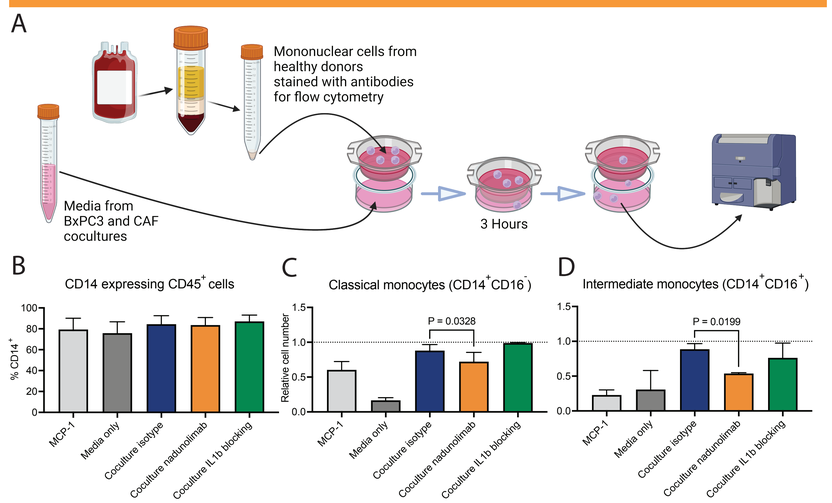
BxPC3 PDAC cells were cocultured with pancreatic CAFs with 20µg/ml nadunolimab or isotype antibody. (A) After 3 days the two cell populations were sorted based on EPCAM expression and RNA sequencing was performed . (B) Cocultured BxpC3 cells and CAFs form structures in the cell culture plate . (C) Nadunonlimab induced dysregulation of 294 genes in CAFs and 6 genes in BxPC3 (P_{adj}< 0.05). Interestingly CCL2 was significantly downregulated in both cell types. (D) Gene set enrichment analysis (GSEA) revealed that Nadunolimab suppressed several chemotaxis and leukocyte migratory gene expression signatures.

Nadunolimab reduces CAF secretion of cytokines recruiting myeloid immune cells.



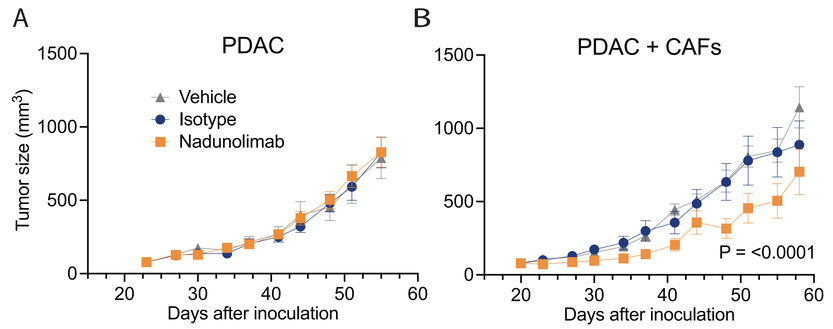
Addition of nadunolimab to BxPC3 + CAF cocultures reduced the secretion of several cytokines that are involved in recruitment of innate immune cells to tumors. Pairwise comparison of (A) RNA expression in CAF and BxPC3 cells sorted from cocultures and (B) cytokine concentration in the coculture media.

Nadunolimab reduces CAF induced monocyte migration



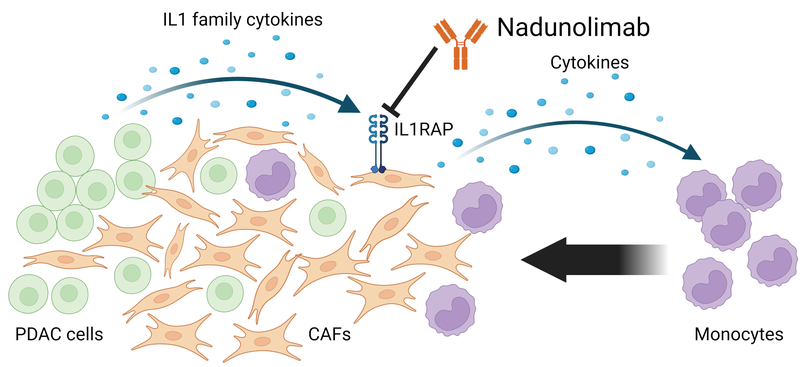
BxPC3 cells and CAFs were cocultured with nadunolimab or isotype. (A) The media from the cocultures were used in a transwell chemotaxis assay. (B) Among the CD45+ peripheral blood mononuclear cells migrating, the majority was CD14+. (C and D) The conditioned media from cultures with nadunolimab induced less migration of CD14+ monocytes measured as number of cells migrating, while blockage of only IL1B did not result in reduced migration.

Nadunolimab treatment reduces the growth of tumors with CAF and PDAC cells.



Nadunolimab treatment of Balb/c nude mice reduced the tumor size in mice inoculated with a mix of BxPC3 and CAF cells. (A) Mice receiving BxPC3 cells alone or (B) mixed with CAFs. Mice were divided into two groups with equal average tumor size (9 to 10 mice per group) three weeks after inoculation. Then treatment with isotype or nadunolimab antibodies were started (10mg/kg, ip, bi-weekly).

Conclusions



- Nadunolimab alters gene expression in CAFs cocultured with the PDAC cell line BxPC3.
- Nadunolimab decreases CAF secretion of cytokines recruiting myeloid cells .
- Nadunolimab reduces migration of monocytes.
- Nadunolimab treatment of mice reduces the size of tumors with BxPC3 PDAC cells and CAFs.

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