Stroma-derived βigH3 (TGFBI) is the local mediator of pathological TGF-β activity in pancreatic fibroblasts and a target to treat in cancer patients with high fibrotic activity

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BACKGROUND & AIM

The pro-peptide of type III collagen (PRO-C3) is a circulating prognostic biomarker that can identify cancer patients with active fibrosis. Consequently, modifiers of PRO-C3 expression are potential anti-fibrotic targets for cancer.

The aim was to identify genetic variants associated with circulating PRO-C3 levels and explore the relevance as pharmacological targets for treatment of fibrotic cancers.

METHODS

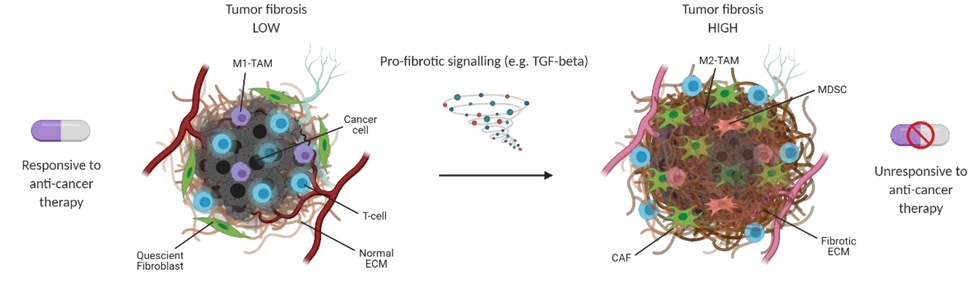
The Prospective-Epidemiology Risk Factors (PERF) cohort study (n=4968, PMID: 27789666) was used to investigate genetic variants (SNP's) associated with PRO-C3.

PRO-C3 was correlated to the identified protein in 178 patients with advanced (stage III+IV) pancreatic ductal adenocarcinoma (PDAC) (NCT03311776).

Pancreatic fibroblasts cultured for 10 days was used to explore whether the protein was also an inducer of PRO-C3, with or without the presence of transforming growth factor receptor β (TGF-β) and function blocking antibody (αBIGH3).

The cellular source of BIGH3 was evaluated in vitro by culturing macrophages and fibroblasts with or without the presence of TGF-β, as well as by single cell RNAseq data from PDAC and benign pancreas tissue (from Peng et al,. Cell Res 29, 725–738 (2019).

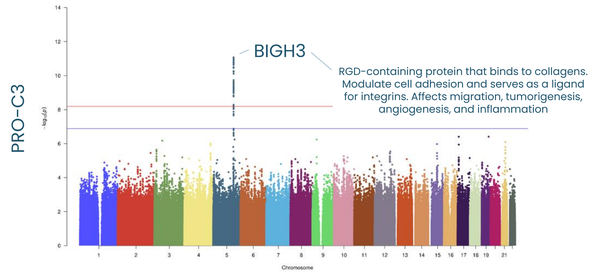
PRO-C3



Of note, PRO-C3 was recently awarded an US FDA "letter of support" as the first serological tumor fibrosis biomarker to be used for prognostic enrichment strategies in clinical trials of patients with solid tumors

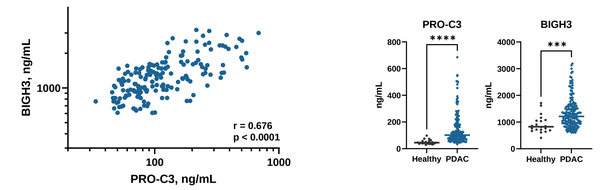
RESULTS

Only SNP's in *BIGH3* associate with serum PRO-C3 levels



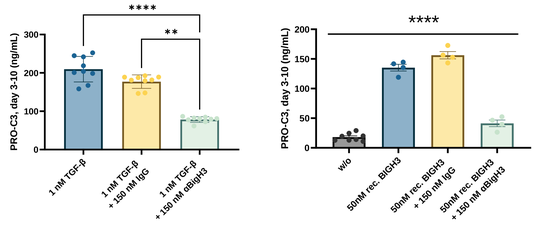
Manhattan plot of log2(PRO-C3) genome-wide association screen (GWAS) in the PERF cohort.

Serum PRO-C3 levels are correlated to serum BigH3 levels in pancreatic cancer



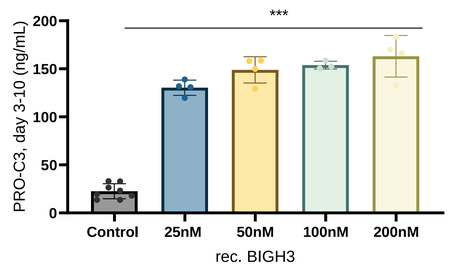
Left: correlation (Spearman) for pre-treatment serum levels of BIGH3 and PRO-C3 in 178 patients with PDAC.
Right: comparing pre-treatment BIGH3 and PRO-C3 levels in patients with PDAC with healthy controls.

Anti-BigH3 antibody (αBIGH3) blocks BigH3 and TGF-β induced fibrosis in vitro



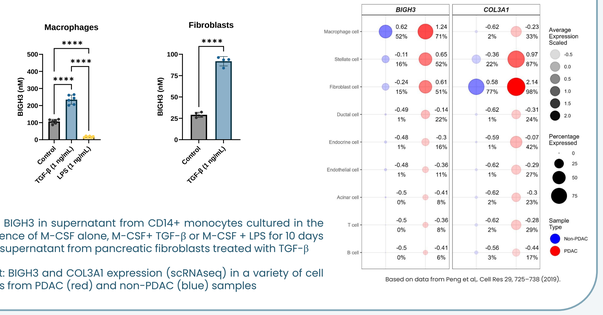
Left : PRO-C3 in supernatant from pancreatic fibroblasts treated with TGF-β +/- αBIGH3 or isotype control IgG.
Right: PRO-C3 lin supernatant from pancreatic fibroblasts treated with recombinant BIGH3 +/- αBIGH3 or IgG.

BIGH3 is an inducer of PRO-C3 in vitro



PRO-C3 in supernatant from pancreatic fibroblasts treated with recombinant BIGH3

BIGH3 is synthesized by fibroblasts and macrophages



Left : BIGH3 in supernatant from CD14+ monocytes cultured in the presence of M-CSF alone, M-CSF+ TGF-β or M-CSF + LPS for 10 days and supernatant from pancreatic fibroblasts treated with TGF-β

Right: BIGH3 and COL3A1 expression (scRNAseq) in a variety of cell types from PDAC (red) and non-PDAC (blue) samples

Based on data from Peng et al, Cell Res 29, 725–738 (2019).

CONCLUSION

An association between BigH3 and PRO-C3 was found by GWAS, *in vitro*, and in patients with PDAC:

TGF-β induce BigH3, which subsequently activate fibroblasts to become fibrotic, resulting in elevated levels of PRO-C3, which in turn can be modulated by an anti-BigH3 antibody.

This highlights the potential for treatment of tumor fibrosis by inhibiting BIGH3 in cancer patients with elevated PRO-C3 levels

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