Collagens essential for embryogenesis reoccur in CAF subtypes:

Circulating collagen biomarkers may guide drug development of CAF-modulating therapies

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INTRODUCTION

- Collagen remodeling is an essential part of embryogenesis and defines tissue structure and function in adulthood.
- The abundant, major collagens serve a structural role, whereas the less abundant, minor collagens serve a more regulatory role.
- Fibroblasts are the primary source of collagens and different cancer-associated fibroblast (CAF) subtypes, have been attributed important roles in cancer and are the target of novel therapies.
- Minor collagens are aberrantly expressed in cancer and linked to specific fibroblast subtypes, suggesting biomarker potential.
- In this study, we sought to profile the expression of collagens at multiple levels with the goal of identifying actionable cancer biomarker to guide drug development of CAF-modulating therapies

METHODS

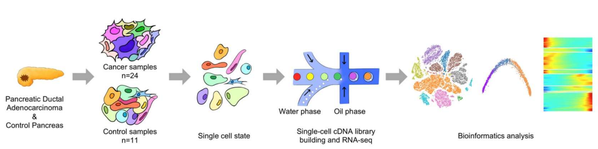
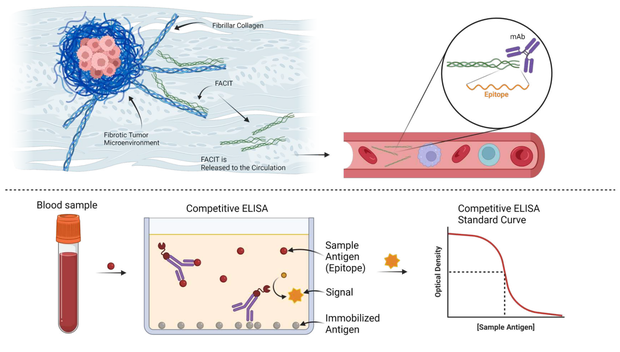


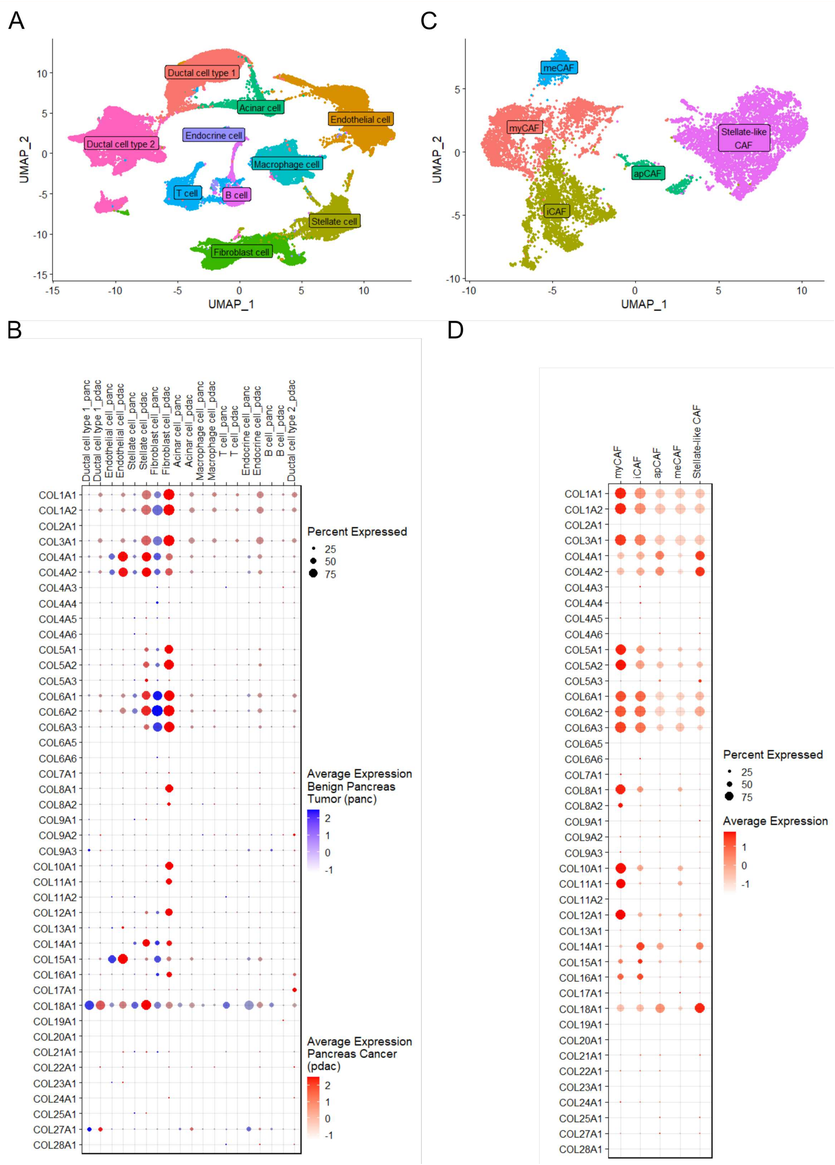
Figure from Peng et al doi: 10.1038/s41422-019-0195-y.

We investigated collagen expression in pancreatic cells and CAF subtypes in a publicly available single-cell RNA-Seq dataset (GSA: CRA001160, Peng et al doi: 10.1038/s41422-019-0195-y). 24 samples were from patients with pancreatic ductal adenocarcinoma (PDAC) and 11 samples were from pancreatic cysts, bile duct- or duodenal-tumors.



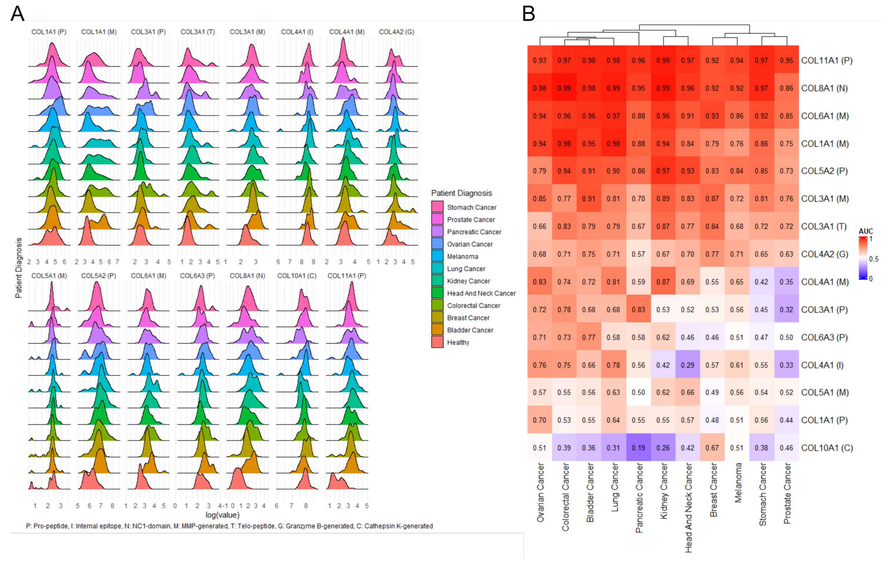
We generated a collagen turnover profile using a panel of immunoassays to measure specific collagen fragments in the serum of 220 patients with various solid tumor types and 33 healthy controls. The included immunoassays measured collagen epitopes associated with either formation, degradation, or other modifications of collagens.

MINOR COLLAGENS ARE SPECIFIC TO CAFs



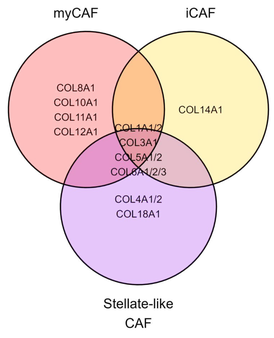
Major collagens, including COL1A1, COL3A1, COL4A1, and COL6A1, were highly expressed in both healthy fibroblasts and PDAC CAFs, whereas minor collagens such as COL8A1, COL10A1, COL11A1, and COL12A1 were exclusively expressed in CAFs. Major collagens were expressed in all CAF subtypes. In contrast, the minor collagens were exclusively expressed in the myCAFs.

MINOR COLLAGENS ARE ELEVATED IN SERUM

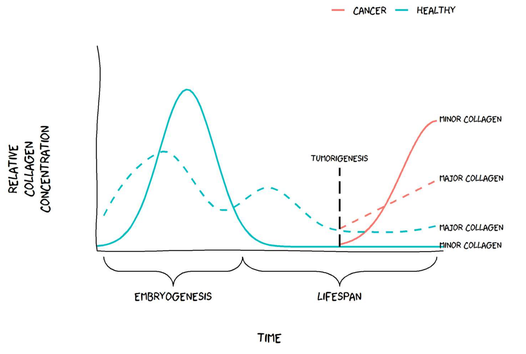


When measuring these collagens in serum, the minor collagens were elevated across all cancer types when compared to healthy control serum. Contrastingly, the major collagens were not elevated in any cancers or only elevated in a few cancer types.

MINOR COLLAGENS AS BIOMARKERS OF CAFs



Venn diagram summarizing how collagen subtypes are associated with CAF subtypes.



Minor collagens are typically expressed during embryogenesis or tissue development. In cancer, these specialized collagens are expressed again.

CONCLUSION

Collagens in general are highly expressed in cancer. However, minor collagens may be more cancer-specific than major collagens. Our findings also suggest that minor collagens may be specific to certain subtypes of CAFs. These collagens can be quantified in blood, making them promising actionable biomarkers that may guide drug development aimed at targeting CAFs.

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