Variations in fibrotic activity of cancer-associated fibroblasts from different tissues measured using noninvasive, clinically validated biomarkers

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BACKGROUND

Cancer-associated fibroblasts (CAFs) are pivotal orchestrators of tumor progression through their modulation of the extracellular matrix (ECM), particularly via the deposition of collagens. Different stimuli (e.g. TGF-β, PDGF-AB, IL-1α) can activate fibroblasts and induce phenotypic alterations in CAFs, promoting a pro-tumorigenic microenvironment characterized by enhanced ECM synthesis and remodeling. Consequently, targeting CAFs and their related pathways presents a promising therapeutic strategy for cancer treatment. However, numerous studies have revealed that CAFs exhibit heterogeneity both within and between individual tissues. Despite this, the specific patterns of collagen deposition by different CAFs remain insufficiently characterized.

In this study, we investigated the fibrotic activity of CAFs from various cancer tissues by measuring the production of three specific collagen peptides in vitro using non-invasive, clinically validated biomarkers.

METHODS

Primary human CAFs from pancreas (pCAF), breast (bCAF), colon (cCAF) and lung (lCAF) were cultured over a 12-day period in ficoll-based media under both untreated conditions and TGF-β (10 ng/ml) or PDGF-AB (100 ng/ml) stimulation. Additionally, cells were subjected to treatment with the ALK5/TGF-β1 receptor kinase inhibitor (ALK5i, 1.9 μM). The assessment of type I collagen (PRO-C1), type III collagen (PRO-C3), and type VI collagen (PRO-C6) formation was conducted in the cell supernatant from day 3, 6, 9 and 12 using competitive ELISA.
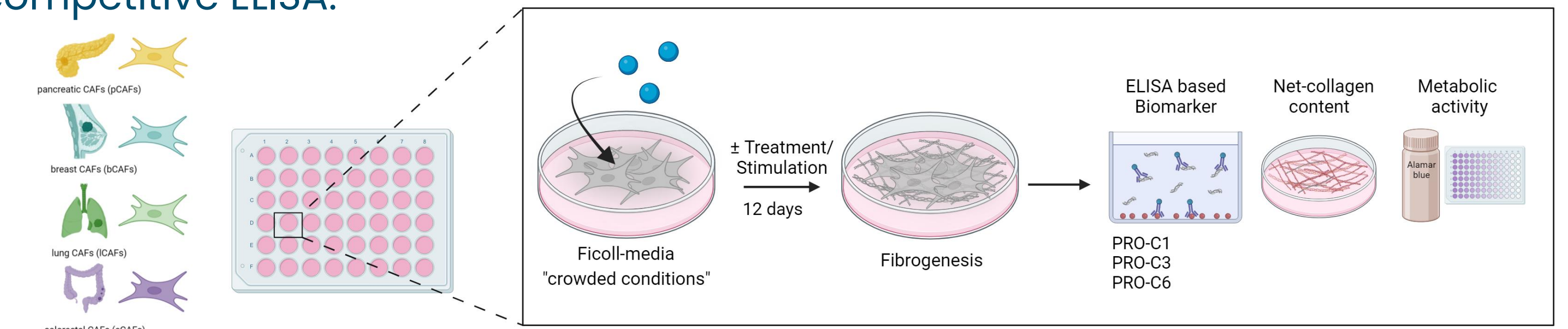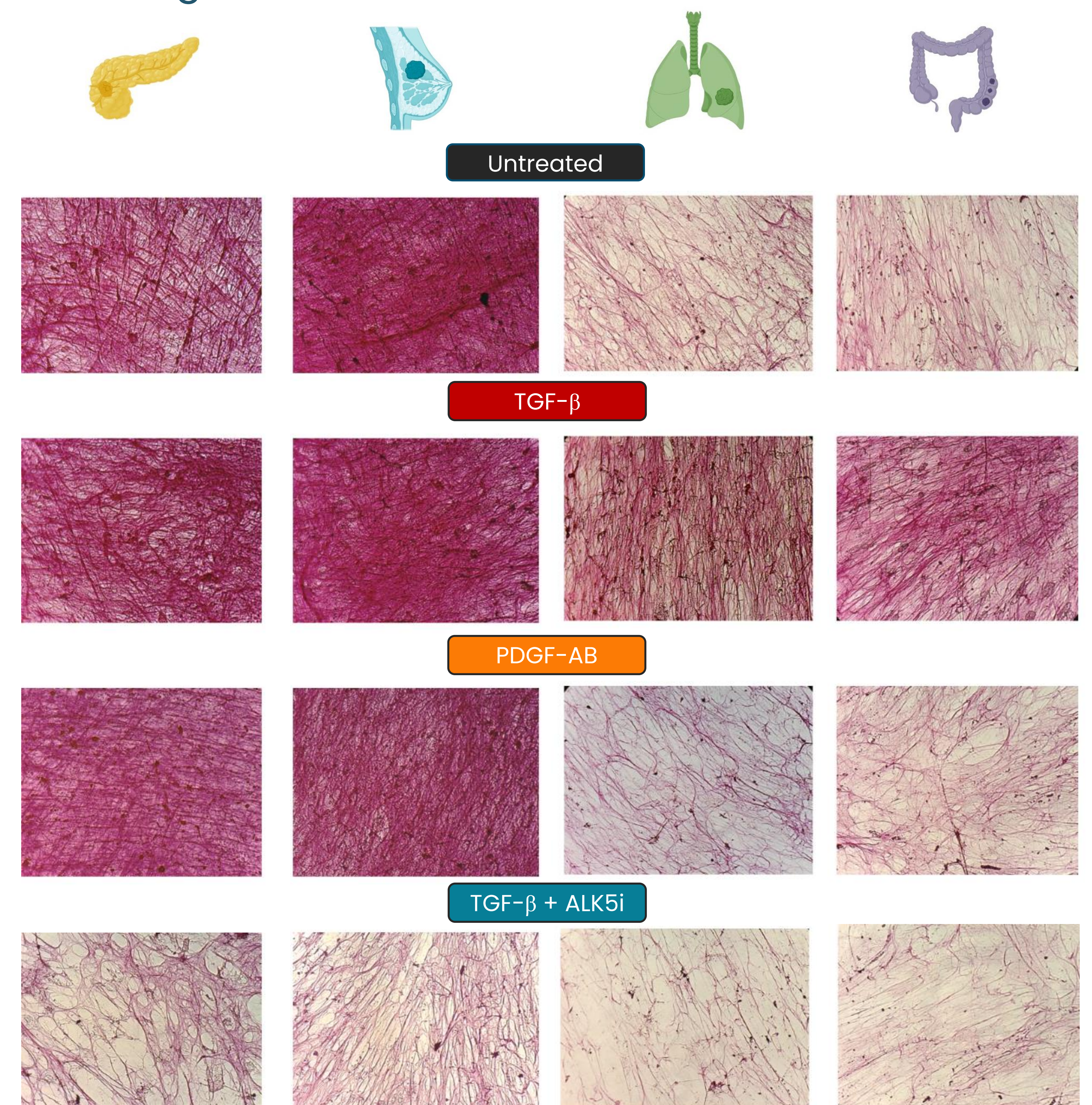

RESULTS

Different collagen profiles can be detected in CAFs from various cancer indications
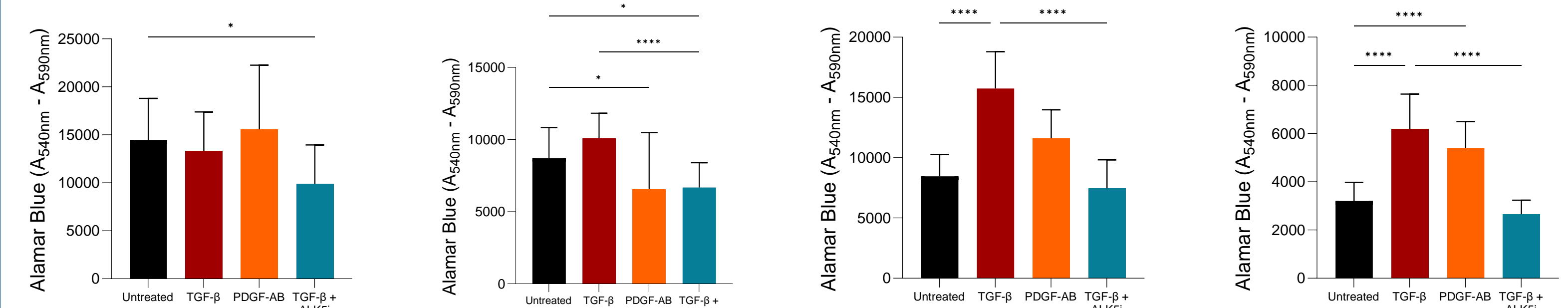

PRO-C1: Type I collagen formation

PRO-C3: Type III collagen formation

PRO-C6: Type VI collagen formation
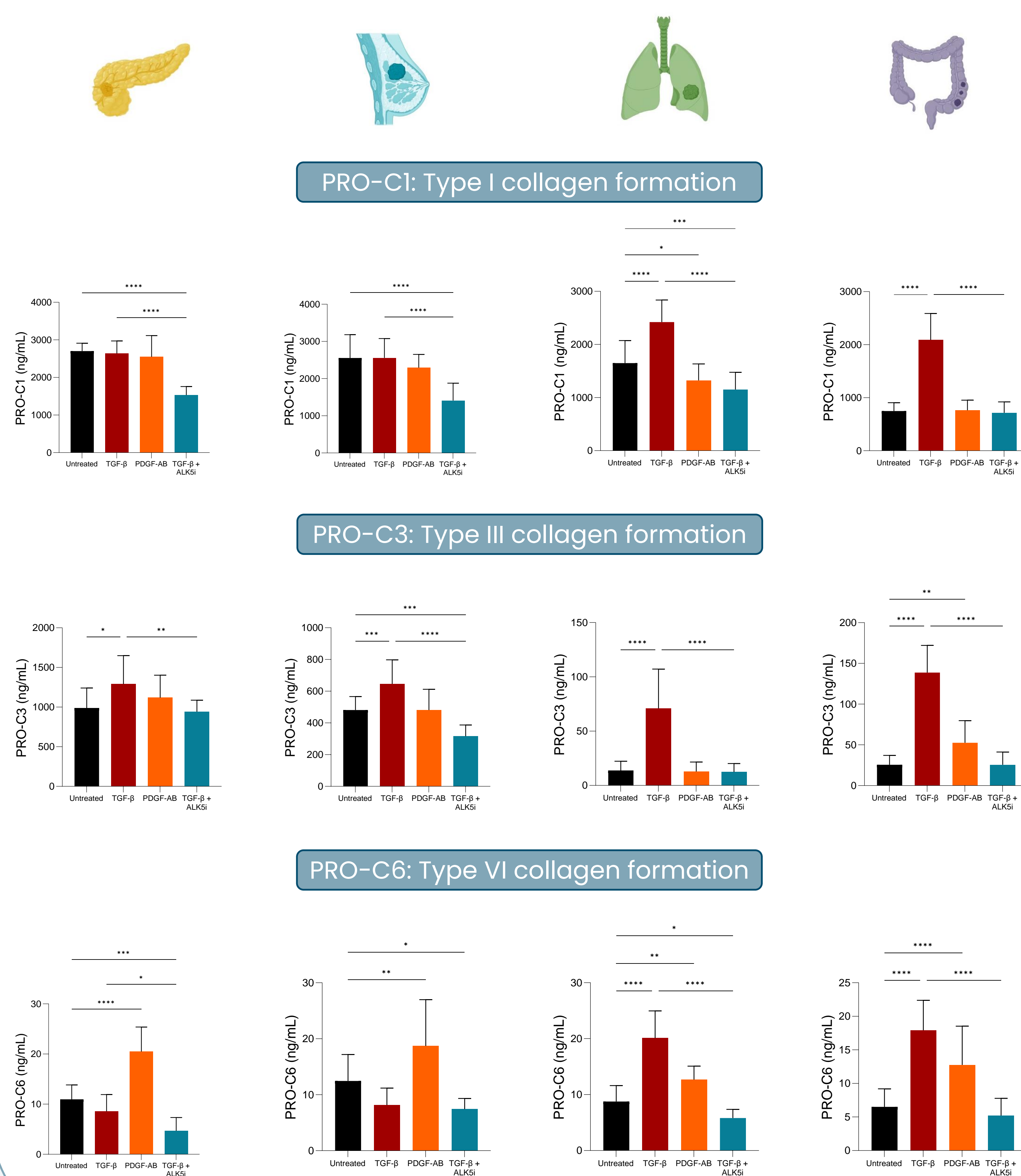
* p<0.05 ; ** p<0.01; *** p<0.001; **** p<0.0001

Net-collagen content reflects biomarker measurements

Untreated

TGF-β

PDGF-AB

TGF-β + ALK5i

Metabolic activity

NORDIC BIOSCIENCE
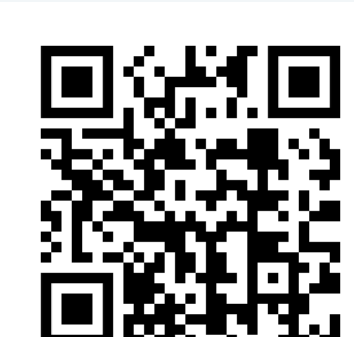
CONCLUSION

→ These findings underscore the heterogeneity in collagen production and fibrotic activity among CAFs from different indications, providing valuable insights into the ECM dynamics within distinct TMEs.

→ Collagen-based non-invasive biomarkers demonstrate the capability to differentiate between the fibrotic activity of CAFs isolated from different tissues.

→ This model proves to be a useful tool for anti-fibrotic drug screening.