

BACKGROUND

KRAS mutations drive NSCLC, but responses to KRAS-targeted therapy are often heterogeneous and transient pointing beyond tumor-intrinsic mutations alone.

Myfibroblastic cancer-associated fibroblasts (myCAFs) are critical players for progression and resistance, within KRAS mutated tumors by promoting collagen deposition to build a fibrotic niche.

Collagen remodeling can be tracked noninvasively through circulating collagen-derived peptide biomarkers.

This study profiles NSCLC CAF subtypes and collagen landscape to find novel liquid biomarkers linked to KRAS signaling and inhibitor efficacy.

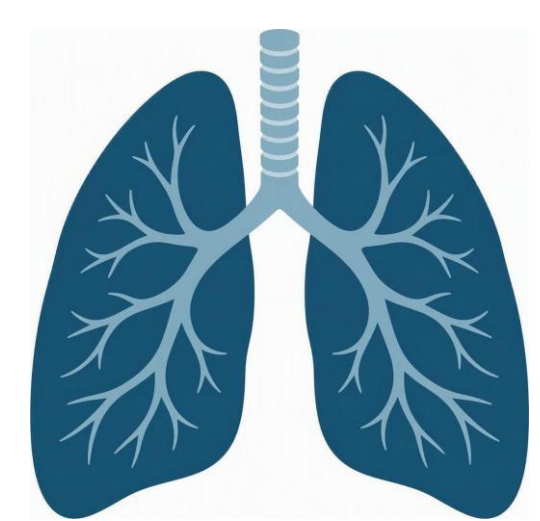
METHODS

KRAS-mutated NSCLC (n=74, TCGA); KRAS and TGF- β signaling correlated with collagen expression.

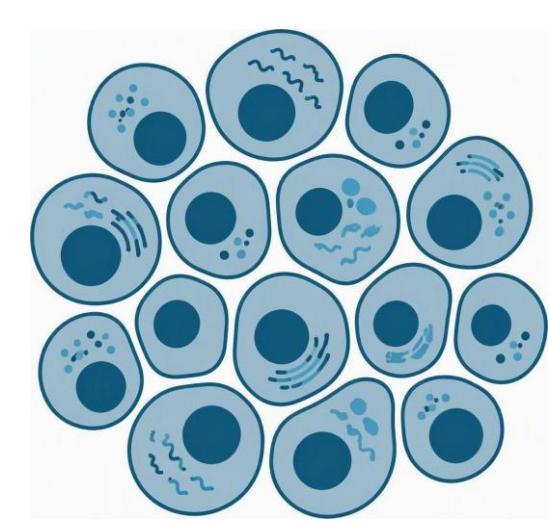
CAF subtypes and collagen expression were derived from public NSCLC single-cell RNA-Seq (scRNAseq; PMID: 36973297).

scRNAseq from KPPC mice treated with KRAS inhibitor MRTX1133 – CAF subtypes and collagen expression compared between treated and untreated mice.

Collagen biomarkers PRO-C3 (COL3A1), PRO-C5 (COL5A2), PRO-C8 (COL8A1), PRO-C11 (COL11A1), and PRO-C12 (COL12A1) were quantified by ELISA in serum from patients with NSCLC (n=20) and age-matched healthy subjects (n=31)



NSCLC cohort
TCGA, n=74



CAF single-cell RNA-seq
Public NSCLC data



KRAS-inhibitor mouse model
KPPC + MRTX1133



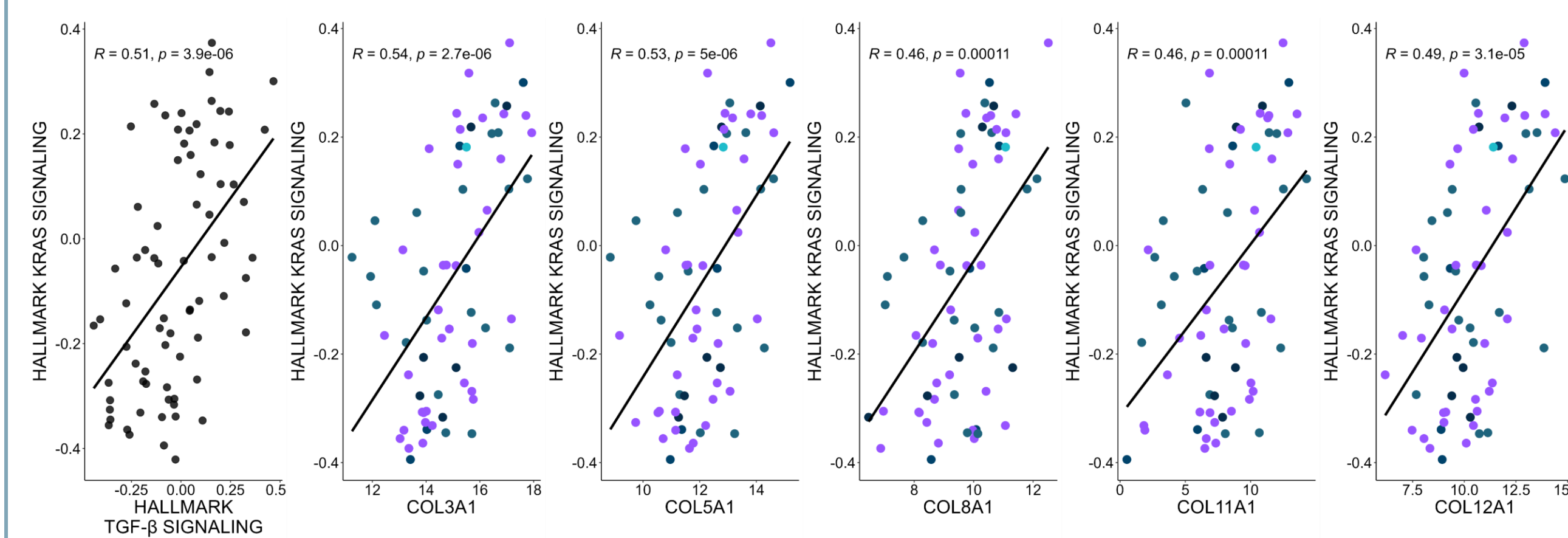
Serum collagen biomarkers
ELISA: NSCLC (n=20) vs healthy (n=31)

CONCLUSIONS

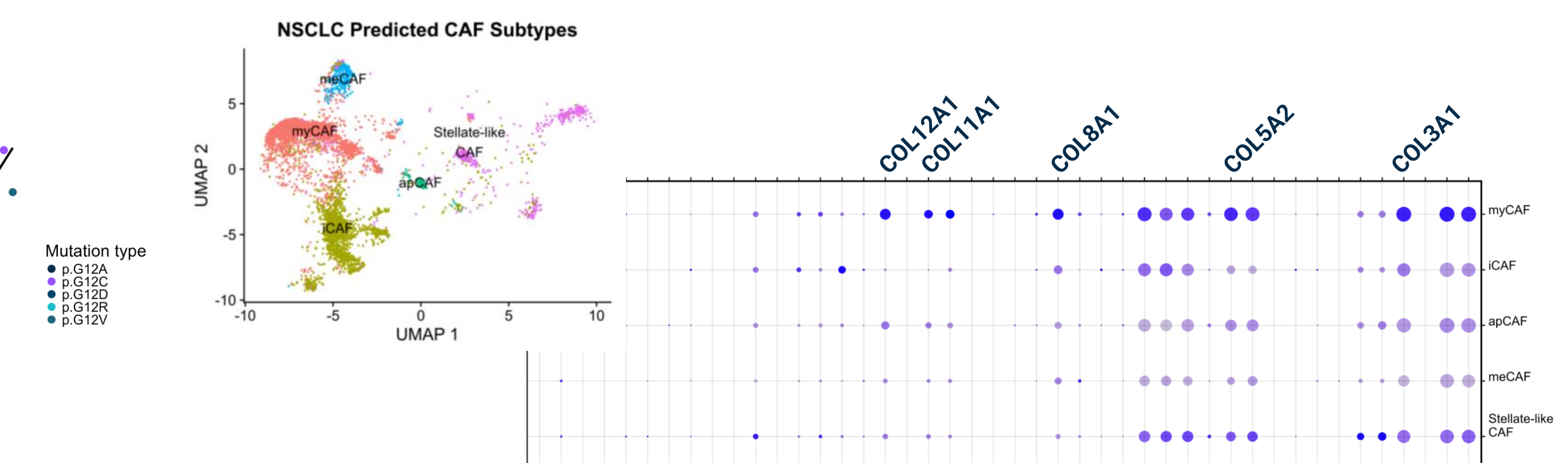
KRAS mutated NSCLC have high myCAF activity characterized by a specific collagen expression pattern, which is altered by KRAS inhibitor treatment. Non-invasive collagen biomarkers that quantify these myCAF collagens were elevated in patients with NSCLC. Integrating KRAS mutation status with myCAF-derived collagen biomarkers provides a more comprehensive framework to understand tumor-stroma interactions in NSCLC. This combined approach has the potential to improve patient stratification, identify mechanisms of resistance to KRAS-targeted therapies, and guide the development of combination strategies targeting both tumor cells and the fibrotic microenvironment.

RESULTS

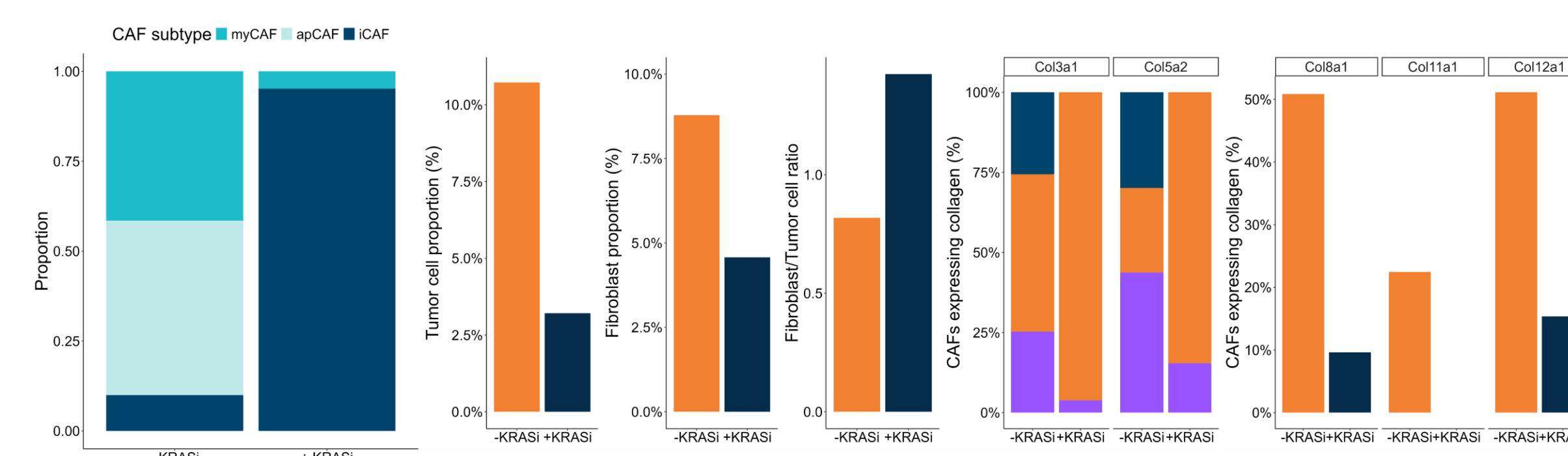
KRAS signaling was positively correlated to TGF- β signaling and expression of COL3A1, COL5A2, COL8A1, COL11A1, and COL12A1 across KRAS-mutated NSCLC patients.



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In vivo, KRAS inhibitor reduced expression of COL3A1, COL5A2, COL8A1, COL11A1, and COL12A1. In support, a change in myCAFs to iCAFs was observed.



Liquid biomarkers PRO-C3, PRO-C5, PRO-C8, PRO-C11 and PRO-C12 are elevated in serum from patients with NSCLC

