Fibroblast derived type III collagen pro-peptides (PRO-C3) in plasma are associated with outcome for patients with NSCLC treated with anti-PD1 plus chemotherapy

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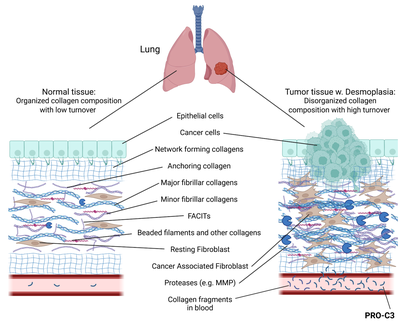
BACKGROUND

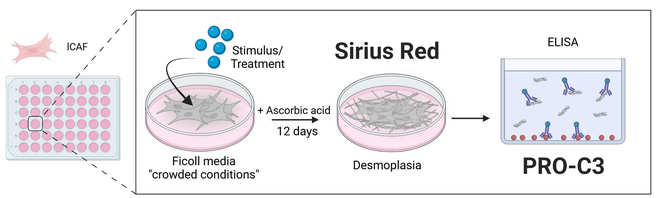
- Tumor fibrosis is essential for defining outcome of patients with various solid tumors including lung cancer
- The cancer associated fibroblast (CAF) activation and increased deposition of type III collagen leads to immune exclusion and high interstitial pressure in the tumor microenvironment
- Recently, FDA issued a Letter-of-Support to encourage use of the non-invasive tumor fibrosis biomarker PRO-C3 (type III collagen pro-peptides) in patients with solid tumors
- Here we investigate PRO-C3 as a prognostic biomarker in patients with non-small cell lung cancer (NSCLC) treated with anti-PD1 + chemotherapy



METHODS

In vitro, Lung Cancer Associated Fibroblast:

- PRO-C3 (ELISA) and total collagen deposition (Sirius red staining) was measured in primary lung CAFs activated with TGF-beta:



Clinical samples, NSCLC:

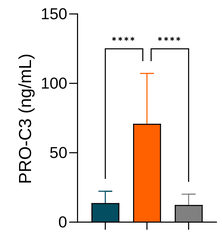
- PRO-C3 was measured in pre-treatment plasma samples from 40 patients with stage IIIa to IVb NSCLC treated with Pembrolizumab (anti-PD1) plus platinum-doublet therapy (carboplatin, cisplatin, pemetrexed, or paclitaxel)
- PRO-C3 was correlated to overall survival outcome (OS) by Kaplan Meier analysis and Cox regression analysis after allocating patients into PRO-C3 subgroups (below/above median of 51.5 ng/mL)

RESULTS

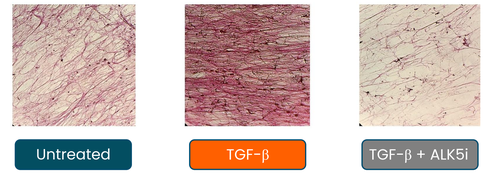
In vitro, Lung Cancer Associated Fibroblast:

- PRO-C3 is produced by lung CAFs after activation with TGF-beta and correlate to increased net-collagen deposition:

PRO-C3 levels in supernatant from lung CAF:

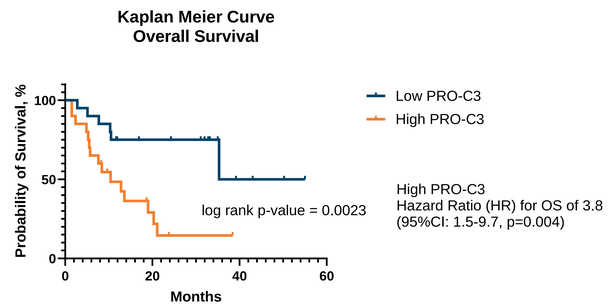


Sirius red stainings for total collagen:



Clinical samples, NSCLC:

- NSCLC patients with high PRO-C3 at baseline had ~3-fold shorter mOS and ~4-fold increased risk of dying as compared patients with low PRO-C3:



CONCLUSION

- Type III collagen pro-peptides (PRO-C3) is produced by activated lung CAFs and is a surrogate of fibrogenesis.
- High PRO-C3 levels in pre-treatment plasma associate with poor outcome for patients with NSCLC treated with anti-PD1 plus chemotherapy.
- These data suggest that quantifying tumor fibrosis is important for prognostication of patients with lung cancer

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