CLUES FROM THE MATRIX – PERIPHERAL COLLAGEN FRAGMENTS ORIGINATING FROM ACTIVITY OF LYMPHOID CELLS, MYELOID CELLS, AND FIBROBLASTS MAY HAVE BIOMARKER POTENTIAL FOR CANCER IMMUNOTHERAPY

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Background Solid tumors have a high tissue turnover due to increased recruitment and activity of cells related to the fibro-inflammatory axis. The high tissue turnover generates small extracellular matrix (ECM) fragments, primarily from collagens, that are released into circulation. By mapping and quantifying collagen fragments with neo-epitopes that are generated by proteases from specific cell types, it is possible to develop peripheral biomarkers that reflect the activity of lymphoid cells, myeloid cells, and fibroblasts in the tumor microenvironment. Here we investigated the distribution of such biomarkers across 11 different cancer indications.

Methods ECM or collagen fragments related to activity of T-cells (C4G: Collagen-4 degraded by Granzyme B), Neutrophils (CPA9-HNE: Calprotectin degraded by neutrophil elastase), Macrophages (reC1M: Collagen-1 degraded by MMPs) and Cancer Associated Fibroblasts (PRO-C11: pro-peptide from Collagen-11) were measured by ELISA/ECLIA in pre-treatment serum from patients with various solid tumor types (n=220) including stage 1–4 bladder-, breast-, colorectal-, head and neck-, kidney-, lung-, ovarian-, pancreatic, stomach-, prostate-, and melanoma and compared to age-matched healthy controls (n=33) by ANOVA and AUROC.

Results As shown in figure 1, biomarkers of neutrophil and fibroblast activity were significantly increased in all solid tumor types (p<0.001–0.0001) and with an overall AUROC of 0.99 (p<0.0001) and 0.96 (p<0.0001), respectively. The macrophage activity marker was significantly elevated in most types of cancer and with an AUROC of 0.88 (p<0.0001). The T-cell activity marker was only slightly elevated in a few indications (p<0.05–0.01) and with an AUROC of 0.69 (p=0.0006). All biomarker levels were independent of age and disease stage (not shown).

Conclusions ECM fragments in serum that are derived from proteolytic activity of myeloid cells and fibroblasts, and to lesser extent lymphoid cells, are altered in serum from patients with cancer. If validated, such tools may increase the understanding of response and resistance mechanism associated to the fibro-inflammatory axis and serve as predictive and pharmacodynamic biomarkers in clinical trials investigating cancer immunotherapy.

Ethics Approval Sample collection was approved by an Institutional Review Board or Independent Ethical Committee and patients gave their informed consent: Russian Oncological Research Centre n.a. Blokhin RAMS (PG-ONC 2003/1) and Western Institutional Review Board, Inc. (WIRB® Protocol #20161665).

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