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## COMPARISON OF THE CYTOKINE AND CHEMOKINE SECRETOME OF BENIGN AND MALIGNANT PERITONEAL FLUID IDENTIFIES FGF AND IL 1R ALPHA AS POTENTIAL DRIVERS OF TUMOR GROWTH

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**Background** Peritoneal fluid, in patients with carcinomatosis, constitutes a fluid phase tumor microenvironment that could contribute significantly to tumor progression in the peritoneal cavity. Little is known of the changes in cytokine or chemokine concentration (i.e., the secretome) along the spectrum from benign physiologic peritoneal fluid to fluid from patients with localized abdominal malignancy to those with frank carcinomatosis. In this study, we compare the peritoneal fluid secretome from participants in each of these categories to identify potential drivers of tumor growth and dissemination in the peritoneal fluid tumor microenvironment.

**Methods** In this pilot study, we compared the normal peritoneal secretome (n=5, derived from patients undergoing elective surgery for benign conditions) with that of abdominal cancer patients (colon, stomach, cholangial, liver, appendix, pancreas cancers), either with (n=29) or without (n=21) carcinomatosis. The peritoneal secretome of patients without carcinomatosis was also compared to that of their serum (n=22). The peritoneal fluid secretome was defined as quantitative assessment of cytokine and chemokine concentrations from fluid specimens, as determined using the Luminex 38plex panel plus IL-6Ralpha and TGF-beta.<sup>1</sup>

**Results** The secretomes of benign physiologic fluid and peritoneal fluid collected from patients with cancer but without carcinomatosis were indistinguishable, but differed from serum in having markedly upregulated FGF2 and IL1Ralpha concentrations. The secretome of peritoneal fluid from patients without carcinomatosis had higher FGF2(1983 pg/mL) than either serum (400-fold, p=0.000000) or malignant ascites (50-fold elevation, p=0.000002). However, the peritoneal fluid from patients with carcinomatosis had significantly elevated levels of GRO, EGF, EOTAXIN, TGFalpha, sCD40L, CCL22, CX3CL1, CXCL10, GM-CSF, TGFbeta, TNFalpha, VEGF, MCP3, MIP-1beta, IL-1beta, IL-6, IL-6Ralpha, IL-10 and IL-12.

**Conclusions** Physiologic peritoneal fluid contains markedly elevated levels of FGF2 and IL1Ralpha, which may contribute to tumor progression by driving the epithelial to mesenchymal transition or through down regulation of E-cadherin,<sup>2</sup> among other mechanisms. We identified characteristic secretome abnormalities of peritoneal fluid derived from patients with carcinomatosis, compared with physiologic fluid or patients with localized cancers. The secretome profile described here could find utility both in developing biomarkers of advanced disease status and in identifying potential targets for directed immunotherapeutic interventions in patients with peritoneal malignancy.

### REFERENCES

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**Ethics Approval** The study was approved by the Institutional Review Board of Allegheny Health Network (Protocol 2021-085). Informed consent was obtained from all study participants.

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