**Leveraging Novel Body Composition Indices and Immuno-Metabolomic Biomarkers to Disentangle the Obesity Paradox in Epithelial Ovarian Cancer**

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A fundamental conundrum regarding our understanding of how obesity impacts immunity and cancer outcomes currently exists. Pre-clinical evidence indicates obesity leads to immunosuppression and tumor progression in ovarian tumor models. Yet, the impact of body composition on epithelial ovarian cancer (EOC) outcomes remains poorly understood, with recent data suggesting there is either no association or an obesity paradox. However, we recently reported that high-adiposity and low-muscle ‘risk’ body composition profiles before chemotherapy are associated with up to two-fold increases in EOC mortality in comparison to patients with optimal body composition (high muscle/low adiposity), but whether body composition is associated with immunity in EOC patients remains unknown. Herein, we sought to define the association of immuno-metabolomic biomarkers with body composition profiles.

Leveraging CT-based body composition data and biospecimens from 500 patients in the Body Composition and Epithelial Ovarian Cancer Survival Study (PI: Cannioto), muscle and adiposity cross-sectional area was dichotomized as high/low adiposity and normal/low skeletal muscle index. Treatment-naïve serum samples from 200 patients were assayed using Biocrates MxP Quant 500 for targeted metabolomics and Luminex kits for adipokines and Th1/Th2 cytokines. Limma moderated T-tests were used to identify differentially abundant markers.

Risk profiles were associated with increased abundance of over 150 circulating immuno-metabolomic biomarkers for which many have been linked with immune suppression or tumor progression in the literature (e.g., triacylglycerides, diacylglycerides, lactic acid, phosphatidylcholines, long-chain acylcarnitines, cholesteryl esters, methionine, leptin). Conversely, optimal body composition was associated with increased abundance of biomarkers linked with tumor suppression (e.g., lauric acid, IL-1β, adiponectin, IL-2).

These data suggest clinically relevant body composition profiles previously reported by our group are also associated with distinct circulating immuno-metabolomic milieus. As circulating biomarkers may not represent the tumor immune microenvironment (TiME), the most relevant site for prognosis, additional work to profile the TiME according to body composition phenotypes is ongoing. If distinct immune profiles are confirmed in the TiME, dietary and exercise interventions ancillary to standard-of-care therapies could be a potential strategy for improving tumor immunity and outcomes in the most fatal gynecological malignancy with no well-established modifiable lifestyle prognostic factors previously established in the extant literature.