

Defining the role of stress-induced changes in the IgG-gut microbiome-neutrophil axis during breast cancer progression and metastasis

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Abstract: The immune system and gut microbiome both influence cancer progression and metastasis. We have shown that, at steady state, immunoglobulin G (IgG)-gut microbiome interactions control inflammation mediated through IL-17 and neutrophils, an axis further activated in response to stress, which also potentiates cancer progression. Our preliminary studies revealed that IgG deficiency accelerated tumor growth and metastasis in multiple models of cancer including breast cancer (BC). Critically, gut bacteria targeted by IgG promoted cancer progression in mice transplanted with these bacteria. Furthermore, we found that stress significantly increased IgG targeting of gut bacteria in BC-bearing mice. Since the gut microbiome also regulates physiological stress-induced inflammation, including neutrophil function, we hypothesize that chronic stress perturbs the IgG-gut microbiome-neutrophil axis. This in turn instigates neutrophil/myeloid-derived suppressive cell responses that promote tumor progression and metastasis. We will interrogate the role of IgG in regulating the gut microbiome and inflammation in response to stress and how stress disrupts the IgG-gut microbiome crosstalk to promote tumor progression and metastasis by identifying: 1) gut bacteria that bloom following stress in BC, 2) the role of IgG in controlling these bacteria and immune responses in BC, 3) IgG-interacting bacteria in BC patients to develop an immunization strategy to control pathogenic pro-tumorigenic gut bacteria. While complete loss of IgG is rare in humans, declines in humoral immunity are common during aging and treatment for autoimmune diseases. Therefore, using a novel IgG KO model to uncover previously unappreciated but crucial roles of IgG in cancer could offer opportunities for therapeutic interventions to mitigate the effect of IgG deficiency in the context of disease. Ultimately, our study will identify targetable gut bacteria and immune pathways to reverse the adverse effects of stress on BC progression and metastasis.