Project Title: Defining the immune footprint in tumor microenvironment following high salt induced breast cancer progression

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Summary:

Chronic inflammatory milieu and compromised T-cell immune-surveillance in the tumor microenvironment is suggested to play a decisive role in cancer progression and metastasis. Although various immune effector cells are recruited to the tumor site, their anti-tumor function is down-regulated in response to signals derived from the tumor microenvironment. However, the precise molecular signals for this mechanism remain poorly characterized. Our preliminary studies have demonstrated that stimulation of naive human CD4+T cells and monocytes with high NaCl concentrations (0.2 M) resulted in a temporal-dependent bimodal effect on IL-17 secretion, with an initial increase (1-3 days), followed by a decrease in IL-17 secretion (5-7 days), and an increase in anti- inflammatory IL-10 secretion. This later phase decrease in IL-17 after exposure to high salt is accompanied by enhanced activation of immune-suppressive Tregs(CD4+Foxp3+) and MΦ2-like macrophages, along with up-regulation of immune exhaustion markers (CTLA4, PD1, Tim3, LAG3) in CD4+T cells. Thus, we hypothesize that high-salt concentration in the tumor microenvironment is linked to modulation of IL-17, resulting in tumor growth with immune-exhaustion and immune-suppression responses. These events lead to a dysfunctional late phase effector immune-elimination, culminating to enhance cancer progression and metastasis. Using murine breast cancer models where mice are fed a diet with varying salt content, we will utilize advanced sodium(Na23)-MRI and immunological techniques to test this hypothesis with the following two specific aims: (1) Define and characterize the temporal effect on the functional changes in infiltrating Treg (CD4+FoxP3+IL-10+T cells), Th17(CD4+IL-17+T cells), and macrophages (MΦ1/MΦ2 switch) leading to breast cancer progression; (2) Define the role of immune check-point inhibitors, CTLA4 and PD1 mAb, in high salt-mediated tumor progression compared to checkpoint inhibitor therapy combined with a low-salt diet in two mouse models of breast cancer. We envision that the outcomes of this study will help delineate the molecular mechanisms involved in high salt-mediated dysfunction of immune responses in the tumor microenvironment with a potential clinical translational relevance of lowering salt tissue levels in patients undergoing treatment with immune-check point inhibitors.