Synergistic Anti-Tumor Immune Response to Combination Immunotherapy Consisting of Anti-Tumor Antibodies, Extended Half-Life Interleukin-2, and Other Immunomodulatory Agents

Technical Summary

Cancer immunotherapies under development have generally focused on either stimulating T-cell immunity or driving antibody-directed effector functions of the innate immune system such as antibody-dependent cell-mediated cytotoxicity (ADCC). However, as our understanding of anti-tumor immune responses grows, it has become increasingly apparent that single agent therapies may be insufficient to effectively stimulate all aspects of a complex robust anti-tumor response in a large proportion of patients. Thus, rational combination of single agent immunotherapies has become an area of increasing interest.

In this work, we find that a combination of an anti-tumor antigen antibody and an untargeted IL-2 fusion protein with delayed systemic clearance induces significant tumor control in aggressive isogenic tumor models via a concerted innate and adaptive response. We find that this therapy induces the infiltration of various immune effectors such as neutrophils, eosinophils, NK cells, and CD8+ T-cells that appear to direct cytolytic activity against tumor cells. In particular, the presence of neutrophils is a signature of the synergistic response as these effectors only play an anti-tumor role in the setting of combination therapy. We also identified cross-talk between NK cells and macrophages producing MIP-2 to induce intratumoral recruitment of neutrophils but with the requisite presence of anti-tumor antibodies and IL-2 simultaneously. This combination therapy also induces an intratumoral “cytokine storm,” potentially re-polarizing the tumor microenvironment into one that is immunologically anti-tumor.

We further enhanced the efficacy of this two-component therapy with the addition of a potent amphiphile-based anti-tumor peptide vaccine in combination with checkpoint blockade of anti-PD-1 and anti-CTLA-4. This multi-component therapy was tested in a setting of a low-mutational burden GEM lung cancer model with a single known and targetable antigen: human carcinoembryonic antigen (CEA). We find that in the subcutaneous setting and autochthonous setting, both components of checkpoint blockade are necessary for full efficacy. While a 5-component therapy is admittedly unwieldy for clinical translation, understanding the complementary yet non-overlapping contributions of each agent may inform improved development of additional immunotherapy agents and their combinations in the clinic.