Molecular antagonization of myeloid cell-associated SRA/CD204 to enhance cancer immunotherapy

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Lay Abstract

Myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) are major tumor stroma cells, which have been implicated in tumor progression or invasion. These myeloid cells in the tumor microenvironment have been shown to dampen the strength of antitumor immune responses following cancer immunotherapy, and enables tumors to evade immune recognition or escape immune destruction. These tumor-associated myeloid cells also promote tumor resistance to conventional cancer treatment modalities, i.e., radiotherapy, and chemotherapy. Defining molecules that regulate the activities of these myeloid cells and developing novel molecular-targeted strategies are expected to provide enhanced therapeutic benefits to cancer patients.

CD204, also called scavenger receptor A (SRA), is a molecule primarily expressed on myeloid cells (e.g., macrophages, MDSCs, dendritic cells,) and tumor infiltration by SRA/CD204-expressing myeloid cells correlates with human cancer aggressiveness and poor outcome. Our previous work has revealed a novel function of SRA/CD204 in suppressing antitumor immunity generated by therapeutic cancer vaccines. The effect of SRA/CD204 in these contexts has, at least in part, been attributed to the reduced immunostimulatory capacity of antigen-presenting cells. Recently, we made new observations that tumors could induce significant upregulation of SRA/CD204 on myeloid cells, and more strikingly, soluble SRA/CD204 that is capable of inhibiting T cell functions also exists in tumor-bearing hosts. This suggests that SRA/CD204 may be directly involved in tumor-mediated immunosuppressive mechanism and consequently contributes to the immune evasion.

This collaborative project involves the integrative efforts of a team of researchers with expertise in cancer immunology and medicinal chemistry. We will characterize the mode of direct SRA/CD204 interaction with tumor-reactive immune effectors (i.e., T cells), and develop assays for testing the biological activity of SRA/CD204 inhibitors. Our preliminary studies recently identified a natural product, Sennoside B, as a novel inhibitor for SRA/CD204. A series of new derivatives will be designed and synthesized based on the structure skeleton of this natural product, and will be tested for their inhibitory activities against SRA/CD204 using *in vitro* and *in vivo* models. Upon completion of this project, these studies are expected to provide a better understanding of tumor-associated immunosuppressive mechanisms involving SRA/CD204-T cell interactions. Furthermore, development of selective SRA/CD204 inhibitors may potentially lead to novel therapeutics that counteract SRA/CD204-mediated immune suppression, and restore the functions of tumor-reactive T cells in cancer patients.