1210 THE POTENTIAL OF MEMBRANE-TETHERED IL-2 AGONISTS IN OVERCOMING CAR T CELL EXHAUSTION

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Background Chimeric antigen receptor (CAR) T cell therapy has demonstrated marked success in the control of hematological malignancies. However, CAR T cell therapy has been less successful when applied to solid tumors. This has been attributed to multiple factors including tumor infiltration, antigen heterogenicity, and the immunosuppressive tumor microenvironment. The hostile milieu and chronic exposure to antigen that CAR T cells face in the tumor microenvironment induces T cell exhaustion. Characterized by an increased expression of inhibitory receptors, reduced proliferation, and a loss of cytotoxic function, T cell exhaustion is associated with an overall loss of therapeutic efficacy.

Methods Strategies for overcoming T cell exhaustion are being developed to improve CAR T cell efficacy in the treatment of solid tumors. One strategy focuses on incorporating the expression of survival-promoting proteins, such as cytokines, in CAR T cells to produce a local immune supportive environment. Interleukin-2 (IL-2) is a cytokine that acts as a potent growth factor in T cells; however, therapeutic application of systemic IL-2 has been associated with severe toxicities and T cell exhaustion. To address this, IL-2 partial agonists have been developed and shown to have reduced STAT5 signaling and has been shown to promote the maintenance of a stem-like phenotype in effector T cells.[1] We have bound IL-2 and IL-2 partial agonists to the cell surface membrane of CAR T cells with a variety of tethers. As IL-2 is a secreted protein that has known cis and trans signaling capabilities, tethering the cytokines to the surface of the CAR T cells has the potential to maximize autocrine signaling and prevent side-effects.

Results Here, we evaluate the influence of partial agonist and tether composition on the proliferation, exhaustion state, and cytotoxic function of CAR T cells. CAR T cells expressing the membrane tethered IL-2 and IL-2 partial agonists had reduced reliance on exogenously delivered IL-2 and CAR T cells expressing the membrane tethered IL-2 partial agonist demonstrated improved cytotoxic function.

Conclusions Exhaustion of antigen-specific T cells is a challenge in multiple cancer immunotherapy modalities, and the proposed membrane tethered IL2 partial agonists have the potential to revolutionize immunotherapy for solid tumors as an effective and widely applicable solution.

REFERENCE

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