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**Anti-tumor Efficacy of Wnt-modulated CD8+ T Cells**

Metastatic melanoma is one of the most aggressive human cancers and is a leading cause of cancer deaths in developed countries. Currently, the administration of *ex vivo*-activated and -expanded autologous tumor-specific T cells, known as adoptive cell therapy (ACT), is the most effective treatment for patients with this form of cancer; half of patients with previously refractory tumor demonstrate an objective or complete response following ACT. Patient response rate is highly correlative with persistence of the infused T cells *in vivo*, and the proliferative potential of the infused cells is thought to be the key determinant in persistence.

Although treatment with low-dose IL-2, a  $\gamma$ -chain cytokine, has previously been shown to support persistence of adoptively transferred T cells *in vivo*, high-doses of IL-2 have historically been required to obtain the quantity of cells required for ACT. *In vivo* administration of IL-2 can induce activation-induced cell death, as well as promote the development of regulatory T cells, actions that potentially counteract the anti-tumor response of ACT in the patient. Furthermore, high-dose IL-2 administration induces rapid T cell differentiation and exhaustion.

Increasing evidence suggests that differentiation of CD8+ T cells decreases their ability to induce tumor regression upon adoptive transfer, and modulation that can suppress differentiation may actually enhance CD8+ T cells for ACT. Indeed, IL-21, a  $\gamma$ -chain cytokine, suppresses the differentiation of murine naïve CD8 T cells into cytolytic T cells following stimulation, and when used for ACT, these cells exhibit augmented anti-tumor activity compared to cells alternatively expanded in the presence of IL-2<sup>1</sup>. Exposure to IL-21 during priming promotes expression of Tcf7 and Lef1, gene targets of the Wnt/ $\beta$ -catenin-dependent signaling pathway<sup>1</sup>. Tcf7 and Lef1 expression are also induced upon activation of the Wnt/ $\beta$ -catenin-dependent signaling pathway during priming<sup>2</sup>. Wnt/ $\beta$ -catenin-dependent signaling, like IL-21 signaling, suppresses differentiation of murine CD8+ T cells following stimulation *in vitro*; cells acquire central memory characteristics such as enhanced *in vivo* persistence, expression of lymph node homing receptors and rapid recall response to antigen<sup>2</sup>, all of which enhance ACT efficacy.

With human CD8+ T cells, IL-21 exposure during stimulation promotes the expansion of antigen-specific CD8+ T cells characterized by an early effector/central memory-like phenotype predicted to be useful for ACT; acquisition of this phenotype is unique to IL-21, and is not observed when cells are stimulated in the presence of other  $\gamma$ -chain cytokines IL-2, IL-7 or IL-15<sup>2</sup>. Although the effects of direct modulation of the Wnt/ $\beta$ -catenin-dependent signaling pathway in human CD8+ T cells have yet to be defined, it is possible that Wnt/ $\beta$ -catenin-dependent signaling in human CD8+ T cells will mimic its characteristics in murine T cells and will mediate antigen-specific differentiation arrest.

Our project is focused on modulation of the Wnt/ $\beta$ -catenin-dependent signaling pathway and the IL-21 signaling pathway to identify factors contributing to both proliferation and differentiation arrest of melanoma-specific CD8+ T cells; we hope to develop strategies to manipulate T cell differentiation to generate CD8+ T cells with characteristics useful for ACT.

References

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