Polyfunctional T cells induced potent anti-tumor efficacy

Adoptive T cell therapy is a form of cancer immunotherapy using T cells to target cancer cells. In adoptive T cell therapy, white blood cells are collected from cancer patients, T cells (CD4+ and CD8+ cells) within the white blood cells are manipulated to create a strong immune response against a particular cancer antigen, and then re-infused into cancer patients. Clinical benefit has been demonstrated from adoptive T cell therapy using tumor infiltrated T cells in patients with advanced melanoma in 50% of patients. Efforts to enhance the anti-cancer effects of adoptive T cell therapy in order to make this therapy more broadly applicable have focused on the culture conditions of the T cells from white blood cells.

We postulated that exposing T cells to appropriate cytokine conditions in culture would improve the antitumor attributes of the T cells. Cytokines are small proteins that can regulate the activities of white blood cells and potentially affect the functioning of T cells. In a subtype of breast cancer defined by the presence of the surface protein HER2, we have previously found that the tumor specific T cells could be easily expanded in culture after HER2 vaccination. T cells cultured with specific cytokine combination (IL2/IL12) from HER2 vaccine-primed cells induced shrinkage of tumors in some of patients. Based on these results we questioned if other cytokine combinations would be more effective in improving the anti-tumor activity of HER2 specific T-cells. Using a mouse model of human HER2 expressing breast cancer, we first vaccinated mice with HER2, and then cultured the mouse spleen cells (equivalent to human white blood cells) with different cytokine conditions to determine how these combinations drove T cells into subtype differentiation and elicited antitumor effects.

Among the tested cytokine combinations, IL2 and IL21 (IL2/IL21) was associated with the greatest tumor shrinkage in HER2+ breast cancer mouse models. We investigated if the antitumor effects were the result of differences in CD4+ T cells, a particular type of T cell recognized to activate other immune cells through cytokine release. We demonstrated that in the IL2/IL21 culture, CD4+ cells differentiated into a polyfunctional population capable of producing a unique group of cytokines consisting of IFNgamma, TNFalpha, and IL17. Such polyfunctional T cells are known to be more effective than populations that secrete a single dominant cytokine. To better understand the role of these cytokines, we evaluated the antitumor effect of these T cells with blockade of these secreted cytokine individually. We found that the blockade of TNFalpha and IL17 significantly impaired the antitumor effects of the infused T cells resulting in increased tumor volumes. Our results demonstrated that TNFalpha and IL17 secreting T cells are required for the tumor inhibition.

Compared to other cytokine combinations, tumors treated with the IL2/IL21 cultured T cells also demonstrated a significant increase in tumor infiltrating CD8+ T cells, a particular type of T cells recognized to mediate cancer cell killing. Increasing CD8+ T cell influx into tumors has previously been a barrier to successful adoptive T cell therapy. Selective depletion of CD8+ cells eliminated the antitumor effects of the infused T cells.

In this study our goal was to determine the influence of cytokines on the function of CD4 T cells. Our studies demonstrate that the cytokine combination of IL2/IL21 can induce polyfunctional (Th1 and Th17) CD4 T cell population, and the infused polyfunctional CD4+ T cells promoted cytotoxic CD8+ T cells into tumors and enhanced anti-tumor efficacy. The potential to recapitulate these findings in human antigen-specific T cells provides the basis for the therapeutic infusion of Th1/Th17 tumor specific T cells in cancer patients.

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