ABSTRACT

HARNESSING METABOLIC MODULATION TO PROMOTE T CELL MEMORY FORMATION FOR CANCER IMMUNOTHERAPY

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Adaptive immunity mediated by antigen-specific T cells is critical to protection from microbial pathogens and tumors. Tumor antigen specific CD8 T cells can control tumors but are often rendered functionally inactive in the tumor microenvironment by a multitude of suppressive factors. A prominent mechanism of blunting anti-tumor CD8 T cell activity is differentiation into exhausted T cells by chronic antigen-mediated stimulation. Exhausted CD8 T cells in the tumor microenvironment are heterogenous and two major subsets have been distinghished. Progenitor exhausted T cells (Tpex) and terminally exhausted T cells (Tex). The former share functional properties of memory T cells and the size of the Tpex subset correlates with good prognosis and sensitivity to immune checkpoint blockade therapy. Both conventional memory T cells (Tm) and Tpex share metabolic pathways including a reliance on oxidative phosphorylation (Oxphos) and fatty acid oxidation (FAO). In contrast, Tex cells exhibit features of metabolic impairment including reduced glycolyis and mitochondrial dysfunction. Mounting evidence supports a central role of memory T cells in sustaining anti-tumor immunity and in endowing adoptively transferred T cells with potent anti-tumor activity and clinical response. We and others have uncovered numerous points of metabolic modulation of activated T cells steering their differentiation towards memory type T cells. In this talk, I discuss the role of inhibitors of mTORC, mitochondrial pyruvate carrier and isocitrate dehydrogense 2 in tilting differentiation of recently activated T cells toward memory type T cells. Inclusion of such inhibitors for a limited period of time during the ex vivo expansion of T-cells for adoptive transfer therapy enhances their ability to control tumors in in vivo experimental models. These observations have important implications in both understanding the immune metabolic pathways underlying T cell differentiation and designing optimized culture protocols for the generation of potent T cell products for therapy of cancer.

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