TARGETING IMMUNOSUPPRESSIVE MACROPHAGES AND TREGS BY REPURPOSING METABOLIC DRUGS

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Background Accumulating evidence demonstrates that the immunosuppressive tumor microenvironment (TME) contributes to tumor progression and invasion, and hampers response to cancer therapies. Among the immune suppressive cells and mediators in the TME, regulatory T cells (Tregs) and M2-like tumor-associated macrophages are known to suppress tumorspecific CD8+ T cells activity and contribute to the development of an immunosuppressive TME. The differentiation/function of Tregs and the phenotype/activity of macrophages are related to their metabolism. Thus, we hypothesized that metabolic drugs could be repurposed to target these immune suppressive cells.

Methods Clinically relevant metabolic drugs were selected to target different metabolic pathways (glutaminolysis, fatty acid oxidation, and mitochondrial respiration) of human peripheral blood mononuclear cells (PBMCs)-derived Tregs/macrophages and murine bone-marrow-derived macrophages. The effect of the drugs on the differentiation and polarization of Tregs/macrophages was determined by flow cytometric analysis. And the cytotoxic activity of re-polarized macrophages was measured by co-culturing with tumor cells.

Results It was demonstrated that targeting fatty acid oxidation or mitochondria of M2-like macrophages, resulted in M2-to-M1 polarization with strong tumor-cytotoxic activity. Moreover, targeting mitochondria or glutaminolysis inhibited the differentiation of T cells to Tregs, reduced the number of the differentiated Tregs, and decreased the expression of the immunosuppressive marker without affecting the proliferation and activation of CD4+ and CD8+ conventional T cells.

Conclusions These results demonstrate that targeting the metabolism of Tregs and tumor-associated macrophages could reverse the immune suppressive tumor microenvironment into an environment that could support cancer immunotherapies. This study opens a new avenue to repurpose clinically available metabolic drugs for metabolic reprogramming of the tumor microenvironment.