CANCER

Combination of metabolic intervention and T cell therapy enhances solid tumor immunotherapy

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Treatment of solid tumors with T cell therapy has yielded limited therapeutic benefits to date. Although T cell therapy in combination with proinflammatory cytokines or immune checkpoints inhibitors has demonstrated preclinical and clinical successes in a subset of solid tumors, unsatisfactory results and severe toxicities necessitate the development of effective and safe combinatorial strategies. Here, the liposomal avasimibe (a metabolism-modulating drug) was clicked onto the T cell surface by lipid insertion without disturbing the physiological functions of the T cell. Avasimibe could be restrained on the T cell surface during circulation and extravasation and locally released to increase the concentration of cholesterol in the T cell membrane, which induced rapid T cell receptor clustering and sustained T cell activation. Treatment with surface anchor-engineered T cells, including mouse T cell receptor transgenic CD8$^+$ T cells or human chimeric antigen receptor T cells, resulted in superior antitumor efficacy in mouse models of melanoma and glioblastoma. Glioblastoma was completely eradicated in three of the five mice receiving surface anchor-engineered chimeric antigen receptor T cells, whereas mice in other treatment groups survived no more than 64 days. Moreover, the administration of engineered T cells showed no obvious systemic side effects. These cell-surface anchor-engineered T cells hold translational potential because of their simple generation and their safety profile.

INTRODUCTION

T cell therapy has demonstrated great clinical and preclinical successes in treatment of hematological malignancies (*1*, *2*). Despite these encouraging results, treatment of solid tumors with T cells yields limited therapeutic benefits (*3*). Most studies have focused on the coadministration of proinflammatory cytokines or immune checkpoint inhibitors with T cells to boost efficacy (*4*–*8*). However, unsatisfactory results and severe side effects observed in some patients necessitate the development of effective and safe combination therapies (*9*, *10*). Previous studies have demonstrated that the suppressive metabolic state of the oxygen- and nutrient-deprived tumor microenvironment impedes T cell infiltration, survival, and effector function, which likely compromises the therapeutic benefit of solid tumor T cell therapy (*11*, *12*). T cell metabolism involves multiple diverse pathways, offering a breadth of potential intervention targets (*12*). For example, T cell function is dependent on the amount of cholesterol on cell membrane to cluster T cell receptors (TCRs) and form an immunological synapse (*13*–*15*). Therefore, modulation of cholesterol metabolism in combination with T cell therapy holds potential for improving solid tumor immunotherapy.

Avasimibe (Ava), an inhibitor of the cholesterol-esterification enzyme acetyl-CoA acetyltransferase 1 (ACAT1), elevates plasma membrane cholesterol concentrations, which, in turn, promote TCR clustering and thus improve effector function of T cells (*16*). We therefore hypothesized that combining Ava with T cell therapy would boost solid tumor immunotherapy. However, the pharmacokinetics and biodistribution of Ava are different from those of T cells, which imposes a challenge on optimizing the two as a combination therapy (*17*–*20*). Thus, there is a need to develop promising combinatorial technologies that maximize both individual therapies.

Genetically engineered T cells can serve as a living factory to produce designed protein drugs (*21*–*23*). However, heterogeneous expression of engineered proteins, combined with potential for toxicity, reduces the efficacy of this strategy (*24*, *25*). In addition, small molecular drugs cannot be manipulated in this genetic manner. An alternative to genetic engineering can be accomplished by backpacking nanoparticulated drugs onto the T cell surface via chemical conjugation or ligand-receptor biorecognition. This strategy has been shown to augment T cell function and widen the therapeutic window of combined drugs (*26*–*28*). Of note, backpacking strategies may impair the physiological functions of T cells. These effects can be due to long-term occupation of the functional biomolecules on the T cell membrane or due to changes to the glycometabolism of the T cell (*27*–*31*). Thus, technology to backpack nanoparticulated drugs onto the T cell surface can be further improved to reduce the impact of backpacking on the function of T cells.

Here, inspired by glycosylphosphatidylinositol-anchored proteins on the plasma membrane and click chemistry (*32*–*34*), we developed an alternative strategy to backpack drugs on the T cell surface by T cell–surface anchor-engineering technology. Specifically, we introduced functional tetrazine (Tre) groups onto the T cell surface via lipid insertion in the cell membrane. Next, liposomal Ava containing bicyclo [6.1.0] nonyne (BCN) groups was clicked onto the cell surface without disturbing the physiological functions of engineered T cells. We show that the liposomal Ava was retained on the T cell surface during circulation as well as extravasation and locally released to increase cholesterol in the T cell membrane. The increased cholesterol promoted rapid TCR clustering and sustained T cell activation. Last, we found that engineering TCR transgenic CD8$^+$ T cells and chimeric antigen receptor T cells (CAR T cells) to carry liposomal Ava showed superior antitumor efficacy in mouse models of melanoma and glioblastoma.

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