

Targeting tumors with genetically enhanced T lymphocytes

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Abstract

Our ability to simply and rapidly transduce human cells offers novel prospects for the targeting and functional enhancement of tumor-reactive T lymphocytes. Recognition of self tumor antigens is indeed constrained by mechanisms of immune tolerance. Furthermore, tumors exploit a number of mechanisms to elude or derail immunity, including the down-regulation of antigen and/or MHC expression and the inactivation of effector T cells through mechanisms such as anergy, apoptosis and suppression. The advent of effective methods for gene transfer in T cells provides a new means for generating tumor-specific T cells endowed with the ability to overcome barriers to their full activation within the tumor microenvironment.

We recently reported a novel strategy to offset the costimulatory deficit that characterizes the tumor microenvironment. We hypothesized that tumor antigen-specific T lymphocytes that constitutively express costimulatory ligands could themselves serve to deliver activating costimulatory signals. We have now shown that the constitutive expression of CD80 and 4-1BBL in human T lymphocytes fully substitutes for the lack of these ligands on APCs, including tumor cells. CD80 and 4-1BBL co-transduction confers upon T cells the ability to expand and amplify effector functions following repeated exposure to antigen, in both cytomegalovirus (CMV)-specific T cells activated through their endogenous TCR or in polyclonal T cells transduced with a chimeric antigen receptor. Primary T cells that are genetically targeted to prostate specific membrane antigen (PSMA), a model target antigen investigated in prostate cancer immunotherapy, and co-express CD80 and 4-1BBL thus display robust tumor antigen-dependent proliferation and reject large tumor burdens in mice bearing systemic prostate tumors in the lungs, lymph nodes, and bone marrow. Altogether, our studies establish the occurrence of both *auto*- and *trans*-costimulation in T cells expressing costimulatory ligands, and support the broad applicability of this novel paradigm for enhancing the efficacy of adoptive T cell therapy.