Abstract

The clinical application of gene-modified T cell therapy has revolutionized the treatment of hematologic malignancy, as highlighted by the FDA approval of CD19-specific chimeric antigen receptor (CAR) T cell therapy for acute lymphoblastic leukemia; however this success is not readily translated to the solid tumor setting where additional barriers of immunosuppression and limited penetrance may exist. Still, it is clear that T cells play a central role in the control of a wide range of solid tumors, as evidenced by the correlation between T cell infiltration in tumors and favorable prognosis. Further supporting this notion is the finding that in select tumor, such as melanoma, the adoptive transfer of autologous tumor infiltrating lymphocytes (TILs) can mediate dramatic and durable tumor regression in treatment refractory patients. Findings from these studies highlighted the importance of antigen specificity, differentiation status and patient pre-conditioning for effective treatment of solid tumor. To broaden this therapy for other cancers, we and others have genetically modified T cells to endow them with tumor reactivity using a T cell receptor (TCR) with HLA-restricted tumor antigen specificity, sometimes derived from TILs that have mediated objective clinical responses in patients. T cells engineered to express TCRs specific for shared tumor associated antigen have demonstrated the reproducible capacity to mediate solid tumor regression, and in some cases, toxicity against normal tissue expressing the target antigen, emphasizing the importance of antigen selection. Unlike TCR engineered T cells, CAR T cells recognize surface tumor antigens in an HLA-independent manner, thereby potentially providing a universal approach to solid cancer treatment. While clinical trials are ongoing, the earliest reports of CAR T cell therapy for solid tumor have shown limited clinical responses, yet with the risk for on-target toxicity. To improve the efficacy and safety of CAR T cell therapy for solid tumor, we and others have identified safer tissue-specific target antigens and developed novel approaches to enhance tumor penetrance, reduce immunosuppression and address the challenge of tumor antigen heterogeneity, whilst instilling CAR T cells with synthetic system that permit orthogonal control of T cell activity. These novel approaches represent the cutting edge of gene-engineered T cells and the next wave of synthetically engineered T cells for solid tumor.