Abstract

Patient T cell responses to cancer cells can induce dramatic clinical responses when enhanced by immunotherapy, such as checkpoint inhibition. However, most patients eventually relapse.
By contrast, T cells from human leukocyte antigen (HLA)-matched donors can cure leukemia. Donor T-cell repertoires are unbiased by thymic central tolerance, and by the immunosuppressive environment of the tumor and are easily accessible. We have demonstrated that naïve T cells from healthy individuals are able to respond to neoantigens that are ignored by the T cells of melanoma patients in vivo. T-cells re-directed with T-cell receptors identified from such donor T cells are capable of mediating killing of patient tumor cells harbouring the relevant mutation. This approach was recently utilized to generate a T-cell receptor that targets a recurrent mutation in leukemia. The data provide a rationale for the use of “outsourced” T-cell receptors in cancer immunotherapy. Non-synonymous mutations are highly attractive therapeutic targets as they are tumor-specific. Most neoantigens are, however, private, and therapeutic application of T-cell receptor-mediated targeting therefore requires identification of T-cell receptors for every patient. A major hurdle for widespread therapeutic application is thus lack of cost-efficient and rapid methods for gene transfer. In contrast, targeting of shared antigens has the obvious advantage that a single immune receptor can be used in many patients, as for CAR19. A major limitation for extension of the success of CAR therapy to other cancers than B-cell leukemia is the scarcity of suitable cell-type restricted cell surface targets. T-cell receptors have the advantage over CARs and therapeutic antibodies that they can recognize antigens from any cellular protein. T-cells that recognize self-antigens in context of self-HLA with high affinity are, however, depleted during negative selection in the thymus. We have demonstrated that donor T cells can provide a source of T-cell receptors that specifically and efficiently recognize shared cell-type specific peptides in the context of mismatched HLA. I will discuss the possibility that donor-derived T-cell receptor repertoires can overcome some of the limitations of host T-cells in cancer immunotherapy and potential therapeutic contexts for such T-cell receptors.