Gene Modified T Cell Therapies for Hematological Malignancies

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KEYWORDS

• Gene therapy • Gene editing • Adoptive immunotherapy • T cell receptor • Chimeric antigen receptor • Lentiviral vectors • Leukemia • Lymphoma

KEY POINTS

- T cells engineered with chimeric antigen receptors mediate high levels of leukemic remission.
- Emerging gene editing techniques are now being incorporated.
- Challenges for dissemination to a larger number of patients are being addressed.

INTRODUCTION

Harnessing the immune system to actively seek and specifically eradicate tumor cells is attractive as an anticancer therapy and provides a valuable addition to existing strategies based on chemotherapy and radiotherapy. Genetic engineering of T cells for use against hematological malignancies has delivered some of the most compelling evidence to date that such approaches can be effective. This article reviews recent developments in this area, considers the potential of emerging therapies, and discusses the challenges in delivering such products.

GENETIC REDIRECTION OF T CELLS AGAINST TUMOR ANTIGENS

T cells express heterodimeric antigen-specific $\alpha\beta$ receptors (TCRs) that recognize antigenic peptides, including certain tumor-associated antigens, expressed by

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cell-surface MHC molecules. In general, helper T cells with CD4 expression interact with peptides expressed by MHC class II, and cytotoxic CD8 T cells interact with MHC class I:peptide complexes. Expression of recombinant TCRs with defined MHC:peptide specificity can redirect immunity and result in targeted killing of malignant cells. This approach is restricted to intracellular peptides derived from tumor antigens and requires MHC loading and surface presentation to allow immune synapse formation. Efforts to confer durable, high-level T cell modification have largely relied on genetic transfer of TCR genes by integrating γ-retroviral or lentiviral vectors. Early examples included retroviral transfer of genes encoding TCR αβ chains against melanoma antigen MART1, where melanoma regression was reported in 2 of 15 initial subjects treated,[1] and subsequent studies where NY-ESO-1 was targeted in patients with melanoma and synovial cell sarcoma.[2] Mindful of the risks of aberrant cross-pairing between recombinant TCR chains and their endogenous counterparts, additional disulphide bridges or murine constant chain domains have been used to mitigate against the risk of generating novel autoreactive TCRs. Further improvements include modification of TCR complementarity determining regions (CDRs) with enhanced-avidity TCRs and predictive strategies to determine on-target and off-target adverse effects. Alternatively, cross-pairing can be excluded by knocking out the endogenous TCR chains using designer nucleases such as zinc-finger nucleases[3,4] and transcription activator-like effector nucleases (TALENs).[5] An example of unpredicted effects caused by off-target antigen cross-recognition was encountered when an HLA-A01 restricted affinity-enhanced MAGE-A3 TCR-mediated unexpected cardiac toxicity through detection of the peptide antigen, titin.[6,7] Unanticipated neural complications have arisen because of MAGE expression in the central nervous system, where TCR-engineered cells mediated on-target recognition.[8]

In the context of hematological malignancies, suitable target antigens that discriminate between malignant and nonmalignant cells have proven elusive. Clinical trials targeting Wilms tumor antigen 1 (WT1) on acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) are underway in the United Kingdom[9,10] and the United States.[11–15] A similar approach is being developed to target certain viral infections, with programs for the application of cytomegalovirus, Epstein Barr virus and hepatitis B-related disease.[16]

A key limitation of TCR-based cellular therapy is the need to generate receptor combinations for multiple HLA/peptide populations. Chimeric antigen specific receptors (CARs) have the advantage of not being HLA restricted and independent of antigen processing and presentation. CAR epitopes include surface expressed proteins such as cluster of differentiation (CD) molecules but also lipid antigens. CARs comprise an extracellular antigen-binding domain (usually a single-chain antigen-recognition domain) with a transmembrane anchor (eg, derived from immunoglobulin G [IgG] or CD8), and intracellular signaling motifs from CD3 molecules linked to costimulatory domains from CD28, 4-1BB, OX40, and other elements.[17]

Costimulatory configurations based on 4-1BB-CD3ζ signaling have reported some remarkable results in trials where lentiviral delivery of CAR receptors specific for the B cell antigen, CD19, have produced significant leukemic remissions.[18–20] Cell infusions following lymphodepleting conditioning using chemotherapy (combinations of cyclophosphamide, bendamustine, pentostatin, and etoposide) in subjects with CLL and ALL may be critical in supporting expansion and persistence of incoming effector populations. Anti-CD19 CARs with alternative CD28-CD3ζ activation domains in T cells transduced by gamma-retroviral vectors have been investigated at National Cancer Institute (NCI)-mediated clinical responses in 6 of 8 patients with CLL and follicular lymphoma[21,22] and have also been applied in trials of allogeneic donor CAR T cells