CAR T cell therapy for high risk leukemias

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Learning Objectives

- Describe adoptive cell therapy strategies to target leukemias
- Recognize the complexity of antigen target selection
- Understand factors that influence the effectiveness of adoptive cell therapies

Abstract

The adoptive transfer of chimeric antigen receptor (CAR) modified T-cells has evolved as a promising treatment for patients with hematological malignancies. Despite successes using CD19-CAR T-cells for pediatric patients with relapsed/refractory CD19+ ALL, patients with relapsed/refractory AML and T-ALL have not benefitted from this innovative treatment strategy yet. Antigen selection has emerged as one of the main obstacles when trying to devise strategies for AML and T-ALL.

Finding the ideal immunotherapy target for AML has proven challenging and is limited by overlapping expression of antigens on hematopoietic progenitor cells (HPCs) and AML blasts. CD123 is an attractive immunotherapy target due to its high expression on AML blasts and LSCs. We have generated a CD123-specific second-generation lentiviral vector that also encodes for full-length CD20 as a safety switch and are currently testing it in our institutional clinical trial (NCT04318678).[1] In addition, we have proposed that members of the unfolded protein response (UPR) are a good candidate target since the UPR regulates hallmarks of cancer including the ability of cancer cells to resist cell death, sustain proliferation, and metastasize. Intracellular Glucose-regulated-protein 78 (GRP78) is a key UPR regulator, which normally resides in the endoplasmic reticulum (ER). GRP78 is overexpressed and translocated to the cell surface in a broad range of solid tumors and hematological malignancies in response to elevated ER stress, making it an attractive target for immune-based therapies with T cells expressing chimeric antigen receptors (CARs). We have generated a peptide-based second generation GRP78-CAR and have proven that it has robust antitumor activity against AML.[2] We have shown that we can further potentiate this antitumor activity by manufacturing GRP78-CAR T cells in the presence of dasatinib and are exploring further applications of this strategy.

To target T-ALL, we have focused on targeting CD7. CD7 is overexpressed in a large proportion of T-ALL (>90%) and some AML subtypes (~30%). However, it is also expressed on normal T and NK cells. Several groups have utilized gene or base editing or protein retention strategies to bypass fratricide. We harnessed a population of naturally occurring CD7 negative T cells and expressed. We have shown that CD7- T cells have potent antitumor activity when expressing CD7-CARs to target T-ALL. This antitumor activity is robust and longstanding. In addition, CD7 negative T cells expressing a CD19-CAR effectively targeted B-ALL.[3] Moreover, by analyzing transcriptomic data obtained from our institutional CD19-CAR T cell therapy trial (NCT03573700) we were able to determine that CD7- T cells expressing CD19 CARs are present in pre- and post-infusion clinical samples. In addition, patients that responded to CD19-CAR T cell therapy had a higher proportion of CD4+CD7- T cells[3].

In conclusion, targeting high risk malignancies using CAR T cell therapies still faces many challenges, including selecting the best antigen to target. Currently ongoing strategies to surmount this obstacle hold promise of providing further insights and warrant further exploration.

References:

1. Riberdy, J.M.*, et al.* The Art and Science of Selecting a CD123-Specific Chimeric Antigen Receptor for Clinical Testing. *Mol Ther Methods Clin Dev* **18**, 571-581 (2020).
2. Hebbar, N.*, et al.* CAR T cells redirected to cell surface GRP78 display robust anti-acute myeloid leukemia activity and do not target hematopoietic progenitor cells. *Nat Commun* **13**, 587 (2022).
3. Freiwan, A.*, et al.* Engineering Naturally Occurring CD7 Negative T Cells for the Immunotherapy of Hematological Malignancies. *Blood* (2022).