Developing Next-Generation Cell Therapy Approaches for AML

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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+ acute lymphoblastic leukemia (ALL), patients with relapsed/refractory acute myeloid leukemia (AML) have not benefitted from this innovative treatment strategy yet. Antigen selection, antigen heterogeneity and a highly immunosuppressive tumor microenvironment (TME) have emerged as important obstacles when trying to devise AML-CAR strategies.

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. We have discovered that Intracellular Glucose-regulated-protein 78 (GRP78), a member of the unfolded protein response (UPR) is 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. GRP78 is a key regulator of the UPR, 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.[1]

To successfully target AML blasts with heterogeneous antigen expression, it is key to devise multi-antigen targeting strategies. We have thus developed a tandem CAR approach, linking a short peptide antigen recognition domain (GRP78) to an scFv (CD123). We have tested a variety of linkers with varying length and rigidity and performed extensive functional characterization in vitro and in vivo. Structural prediction of the peptide-scFv antigen recognition domains allowed us to validate and reconcile our findings. We have demonstrated that peptide-scFv-CAR T cells successfully recognized more than one cell surface antigen on AML blasts and is an effective strategy to circumvent antigen heterogeneity.[2]

AML also boasts a highly immunosuppressive tumor microenvironment. Current preclinical xenograft models provide extremely useful information regarding antitumor activity. However, given that they lack an intact immune system, information on the impact of the TME on AML-CAR T cells is limited. We have developed a novel immunocompetent AML-CAR system that allows us to gain insight into factors that contribute to the immunosuppressive TME and devise strategies to bypass it.

In conclusion, targeting high risk malignancies using CAR T cell therapies still faces many challenges but ongoing strategies to surmount these barriers hold promise of providing further insights and warrant further exploration.

References

1. 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).
2. Zoine, J.T., *et al.* Peptide-scFv antigen recognition domains effectively confer CAR T cell multiantigen specificity. *Cell Rep Med* **5**, 101422 (2024).