DETERMINING THE HISTOCOMPATIBILITY BARRIERS BETWEEN UNIVERSAL CAR T (UCART) CELLS AND NK CELLS

Kimberly Apodaca*, Chong Xu, Kelsey Stanton, Beatriz Carreno, Gerald Linette. University of Pennsylvania, Philadelphia, PA, USA

Background Chimeric antigen receptor (CAR) T cell adoptive therapies have proven efficacy in the treatment of hematological malignancies. However, there are challenges to the current CAR T cell manufacturing process, one being manufacturing failure due to dysfunctional, patient-derived T cells. A proposed solution to overcoming this limitation is the development of universal CAR T (UCART) cells engineered from healthy, normal donor-derived T cells. Histocompatibility barriers must be addressed when creating the UCART cell. Ablation of the alpha/beta T cell receptor surface expression will prevent graft-versus-host disease while host-versus-graft responses will be mitigated by ablating the surface expression of the major histocompatibility complex (MHC) class I and II molecules. These triple knockout (TKO) T cells could serve as universal recipients for development of the UCART cell. Importantly, a consequence of MHC class I ablation is NK cell activation due to the “missing-self” response. HLA-E, a non-classical MHC class I molecule, is known to interact with the NK cell inhibitory receptor NKG2A and we propose its overexpression on UCART cells will mitigate NK cell activation.

Methods Because the HLA-E/NKG2A interaction is dependent upon the peptide presented by HLA-E, 10 HLA-E single-chain trimer (SCT) constructs expressing various peptide sequences were created to determine which HLA-E/peptide complex would result in significant NK cell inhibition. K562 cells transduced to express these HLA-E/peptide complexes were used as a model for UCART cells in preliminary experiments.

Results An HLA-E SCT presenting an HLA-C leader peptide (HLA-E/C) resulted in significant inhibition of NK cells as determined by flow cytometry-based NK cell degranulation (CD107a) assays. Decreased lysis of K562 HLA-E/C-expressing target cells in 51Cr release assays further validated the inhibitory effect of HLA-E/C complexes on NK cell activation. Finally, HLA-E/C complex expression on TKO T cells lead to protection against NK lytic activity.

Conclusions Altogether these data demonstrate the effectiveness of selected HLA-E/peptide complexes to inhibit NK cell activation due to the “missing-self” response. Modifications such as the one described here may prevent UCART cell clearance due to host recognition (NK cell activation) and may ultimately lead to a more potent, safe, and long-term persistent UCART cell therapy.

REFERENCES
