

Conference Abstracts

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BCMA Trogocytosis Drives CAR T-Cell Exhaustion and Functional Decline

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Abstract

Background

BCMA-directed CAR T-cell therapy induces deep responses in relapsed/refractory multiple myeloma; however, loss of CAR T-cell persistence and functional fitness contributes to treatment failure and relapse. Increasing target antigen density represents one strategy to enhance CAR T-cell activity, and γ -secretase inhibitors (GSIs) increase surface BCMA by limiting its proteolytic shedding. However, greater BCMA availability may have unintended consequences by enhancing trogocytosis, whereby CAR T cells acquire BCMA from tumor cells. While our previous findings demonstrated that GSI-enhanced BCMA density augments trogocytosis. Here, we investigated the phenotypic, functional, and transcriptional consequences of BCMA trogocytosis, with particular emphasis on exhaustion and differential responses of CD4⁺ and CD8⁺ CAR T-cell subsets.

Methods

Healthy donor T cells expressing a fully human BCMA-specific 4-1BB/CD3 ζ CAR were co-

cultured with myeloma cells following GSI exposure. Trogocytosis was quantified by flow cytometry. Trogo⁺ and Trogo⁻ CAR T cells were evaluated for proliferation, tumor rechallenge cytotoxicity, fratricide, differentiation, and activation/exhaustion phenotypes. Single-cell RNA sequencing with paired T-cell receptor sequencing characterized transcriptional programs associated with trogocytosis.

Results

GSI-mediated enhancement of BCMA density significantly increased trogocytosis, with CD4⁺ CAR T cells acquiring more BCMA than CD8⁺ cells at 10 minutes (P=0.01), 2 hours (P=0.01), and 6 hours (P=0.004). Trogocytosis was actin-dependent and inhibited by latrunculin A. Trogo⁺ CAR T cells demonstrated reduced proliferation (P=0.002), impaired cytotoxicity upon tumor rechallenge (P=0.01), and susceptibility to CAR T-cell fratricide. CD4⁺ Trogo⁺ cells exhibited increased effector differentiation and higher frequencies of PD-1⁺LAG-3⁺ (P=0.007), PD-1⁺TIM-3⁺ (P<0.0001), and TOX⁺TIM-3⁺ (P=0.006) cells, demonstrating prominent exhaustion-associated remodeling. Single-cell

analysis identified distinct subset-specific transcriptional states. CD4⁺ Trog⁺ cells preferentially upregulated inflammatory cytokines and chemokines, including CCL22, CCL1, LTA, and CSF2, with enrichment of TNF α /NF- κ B, inflammatory response, IL-6/JAK/STAT3, and IL-2/STAT5 signaling. Conversely, CD8⁺ Trog⁺ cells preferentially expressed activation/cytotoxicity-associated genes including TNFRSF9, CRTAM, and TNFSF4, accompanied by enrichment of MYC, mTORC1, oxidative phosphorylation, and fatty-acid metabolism pathways.

Conclusion

BCMA trogocytosis promotes exhaustion-associated remodeling and functional decline, characterized by reduced expansion, impaired secondary tumor killing, and fratricide. CD4⁺ CAR T cells are particularly susceptible to this process. These findings identify trogocytosis as a potential mechanism limiting CAR T-cell fitness and therapeutic durability. Ongoing studies are evaluating strategies to enhance CAR T-cell expansion and generate functionally fitter cells capable of overcoming trogocytosis-associated dysfunction and improving therapeutic durability.

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