ENHANCING TCR-T RESPONSES AND OVERCOMING THE TUMOR MICROENVIRONMENT BY COMBINATION WITH A TGF-β-SPECIFIC CAR

Background
Overcoming the suppressive tumor microenvironment (TME) remains an important unmet challenge for chimeric antigen receptor (CAR) T cell therapies. A key suppressive factor, transforming growth factor β (TGF-β), is a primary driver of T cell suppression reducing T cell receptor (TCR)-mediated cytotoxicity and driving the differentiation of immunosuppressive regulatory T cells (Tregs) in the TME.

Methods
To overcome TGF-β-specific immunosuppression, we employed a TGF-β-targeting CAR co-expressed in T cells with a human papillomavirus type 16 (HPV16) E711–19-specific, HLA-A*02:01-restricted TCR (E7 TCR).

Results
In comparison to T cells expressing E7 TCR alone or E7 TCR with an irrelevant CD19-targeting CAR, T cells co-transduced with E7 TCR and TGF-β CAR showed enhanced proliferation and cytokine production, while maintained cytotoxicity throughout repeat antigen challenge assays with HPV16+ Ca Ski tumor cells. The inclusion of TGF-β CAR also reduced PD1+ expression and Treg differentiation after repeat antigen challenges. Transcriptional analysis further confirmed reduced FOXP3 expression as well as enhanced proinflammatory genes such as TNF and IFNG.

Conclusions
In combination, these data clearly show that a TGF-β CAR can enhance TCR function and limit Treg differentiation and is therefore likely to improve the function and persistence of TCR therapies in the TME.

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