DISCOVERY OF MUTANT IDH1 REACTIVE T CELL RECEPTORS FOR TRANSGENIC T CELL THERAPY


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Background The discovery of exploitable tumor-specific antigens is central to the development of clinically relevant immunotherapeutic strategies for cancer. Mutations in the gene encoding isocitrate dehydrogenase 1 (IDH1) present an ideal therapeutic target due to their high prevalence across various cancer entities, including glioma, chondrosarcoma, cholangiocarcinoma, and acute myeloid leukemia, as well as the early occurrence in oncogenesis and the uniform expression in tumor cells. Previously we have not only successfully demonstrated the immunogenicity of a peptide vaccine encoding one of these IDH1 mutations (IDH1R132H) in pre-clinical studies and a Phase-1 clinical trial (NOA-16; NCT02454634), but also successfully identified a T-cell receptor (TCR) which specifically targets that mutation. This raises the question of whether other IDH1 mutations are capable of eliciting immunogenicity, thus potentially expanding the repertoire of therapeutic targets for a broader range of patients.

Methods To evaluate immunogenicity and identify TCRs specific to mutated IDH1 (mIDH1), we immunized MHC-humanized A2.DR1 mice, enabling effective antigen presentation of mIDH1 via MHC class II, with peptides encoding the four most abundant IDH1 mutations after R132H, including R132G, R132C, R132L, and R132S. T cells from these mice were isolated for subsequent subjection to single-cell RNA and VDJ sequencing, and immunogenicity was evaluated by Interferon-gamma Enzyme Linked Immuno Spot Assay (ELISpot). Furthermore, to facilitate future adoptive cell therapy testing, tumor cell lines were established with the corresponding overexpression of the respective IDH1 mutations.

Results We were able to demonstrate a significant T-cell-mediated immune response specific to the mutations tested, indicating that the immunogenicity of IDH1 mutations remains evident irrespective of the specific amino acid substitution. Utilizing single-cell TCR sequencing we observed a remarkable clonality in the TCR repertoire post-vaccination. We successfully employed a safe and innovative S/MAR-based gene therapy vector to deliver the expanded candidate TCRs, which were then validated using the NFAT luciferase-based T cell activation assay designed for assessing TCR activity against antigens presented on MHC class II complexes. This approach ultimately enabled us to successfully identify mIDH1-reactive TCRs, which have the potential to serve as targets for T-cell-based cancer immunotherapy across all the tested IDH1 mutations.

Conclusions In summary, our findings highlight the robust immunogenicity exhibited by the entire spectrum of IDH1 mutations. These results provide a foundation for future investigations in adoptive cell therapy, specifically targeting MHC class II-restricted antigens, by employing mIDH1-reactive TCRs as a potential therapeutic strategy for patients affected by these mutations to advance targeted immunotherapy in IDH1-mutated cancers.

Ethics Approval The animal work has been approved under government law by german authorities. The official approval document number is: TVA256–18

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