Comprehensive Identification of Tumor-reactive TCRs and Cognate Targets for Novel TCR T-cell Cancer Therapies

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Abstract

TCR-engineered T-cell therapy is one of the most promising approaches to cancer therapy but is currently limited by a lack of diverse targets and by an inability to comprehensively identify off-target interactions. These limitations are addressed by "TScan," a genome-wide screen that enables the unbiased identification of the natural targets of T cell receptors. Here, we demonstrate the application of the TScan technology to therapeutic development in two ways. First, TScan was used to identify two previously unknown off-targets of a MAZE-A3-specific TCR, neither of which were obvious based on sequence similarity. Second, TScan was used to discover a novel TCR target using TILs from a colo-rectal cancer patient. Based on these results, a high-throughput discovery platform was developed to identify tumor-reactive TCRs that recognize novel shared antigen targets from patient TILs. Using this platform, we identified several novel targets that are currently being evaluated for further development. Collectively, this platform enables construction of a repository of therapeutic TCRs with diverse targets and HLA restrictions, providing a way to develop multiplexed TCR therapy tailored for each patient.

Learning from patients that are winning their fight against cancer ...to treat those that are not

As proof-of-concept, the TScan screen was used to identify all the targets of a MAZE-A3-specific TCR. (A) In addition to the known target, the screen identified three ‘off-targets’ MAGE-A6, PLCL and FAT2. (B) All four targets were subsequently verified. (C) The peptide sequences of PLCL and FAT2 share HLA sequence similarity with MAZE-A3, demonstrating the value of using an experimental approach to identify off-target interactions, rather than bioinformatics.

Multiplexed screening

Identification of new targets for TCR T-cell therapy

TCR targets and antigens of TILs

High-throughput discovery

Screening TILs for new TCR/target pairs

Multiplexed therapy

A therapeutic strategy to address tumor heterogeneity

Because solid tumors are heterogeneous, successful TCR therapy will rely on a cocktail of TCRs. Our goal is to provide customized, off-the-shelf, multiplexed therapy by building a repository of safe and effective TCRs that recognize a broad range of targets and HLAs.

Conclusion

Safe and effective TCR therapy requires tools to identify the natural targets of anti-cancer TCRs and to ensure they do not exhibit problematic off-target effects. Here, we showed that a genome-wide screening technology, TScan, can identify the known target of a TCR and identify previously unknown off-targets. Based on these results, a high-throughput discovery platform was developed to identify tumor-reactive TCRs from patient TILs. This platform enables the discovery of several novel tumor targets and is currently being used to build a repository of therapeutic TCRs for multiplexed TCR T-cell therapy.