

BayPAT

The T-Cell-Therapy Success Code:

Signatures of recent T-cell activation allow isolation of highly functional tumor-specific T cell receptors

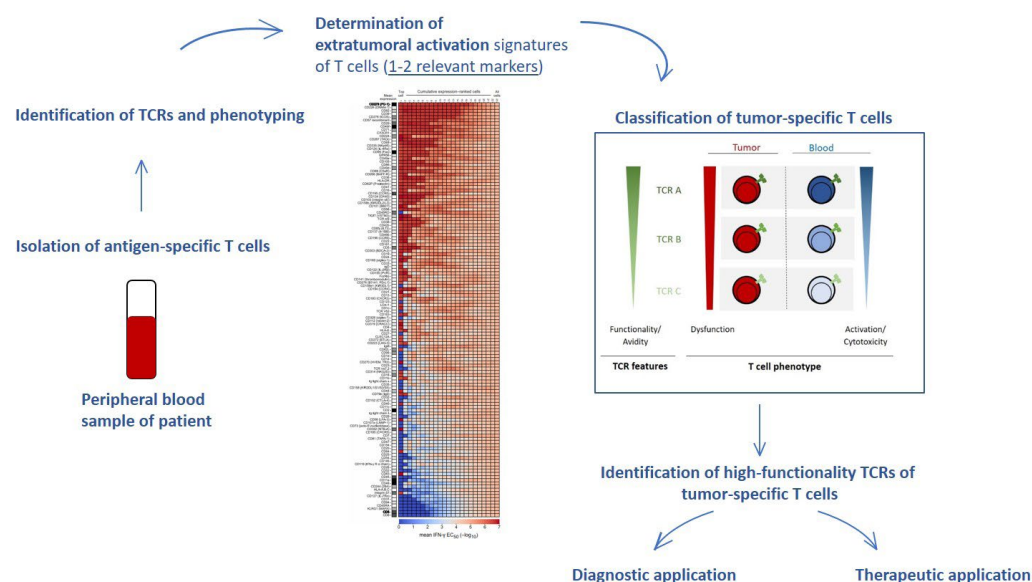
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CHALLENGE

Tumor antigen-specific T cells play a crucial role in the containment of cancer and are already used therapeutically in personalized medicine. In this context, it is known that the composition of the T cell receptor (TCR) repertoire changes both spatially and temporally in patients. In addition to TCR repertoire composition, TCR affinity is thought to be critical for the protective effects of tumor-specific T cells. Identification of highly functional tumor-specific T cell receptors is therefore very complex, but of high importance for therapeutic and diagnostic purposes.

INNOVATION

The invention describes an experimental system for investigating the TCR affinity-dependent signature of tumor-specific T cells in peripheral blood, an easily available examination sample in patients. With the help of this signature, it will be possible to pick out TCRs of certain quality and use them for therapeutic or diagnostic purposes in the future. Single-cell sequencing of neoantigen-specific T cells from two patients with melanoma—combined with transgenic reexpression of identified TCRs by CRISPR-Cas9-mediated orthotopic TCR replacement—revealed high-functionality TCRs to be enriched in T cells with RNA signatures of recent activation. Furthermore, of 130 surface protein candidates, PD-1 surface expression was most consistently enriched in functional TCRs. This validated findings from preclinical models, in which high PD-1 surface expression in peripheral blood also enriched for highly protective TCRs. The data thereby show that tumor-reactive TCRs with high protective capacity circulating in peripheral blood are characterized by a signature of recent activation.



COMMERCIAL OPPORTUNITIES

Easy and cost-efficient isolation of highly functional tumor-specific T cell receptors for T-cell therapy and diagnostic purposes.

DEVELOPMENT STATUS

Proof-of-Concept

REFERENCES:

1 Purcarea et al., Sci. Immunol. 7, eabm2077 (2022)



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