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Identification of Functional T Cell Receptors Reactive to Tumor Antigens from the T Cell Repertoire of Healthy Donors

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Abstract : Tumor-reactive T cell receptors (TCRs) are being subject of intense investigation since they offer great potential in adoptive cell therapies against cancer. However, the identification of tumor-specific TCRs has proven challenging, for instance, due to the limited expansion capacity of tumor-infiltrating T cells (TILs) and the extremely low frequencies of tumor-reactive T cells in the repertoire of patients and healthy donors. We have developed an approach for rapid identification and characterization of neoepitope-reactive TCRs from the T cell repertoire of healthy donors. CD8 T cells isolated from multiple donors are subjected to a first sorting step after staining with HLA multimers carrying the peptide of interest. The isolated cells are expanded for two weeks, after which a second sorting is performed using the same peptide-HLA multimers. The cells isolated in this way are then processed for single-cell sequencing of their TCR alpha and beta chains. Newly identified TCRs are cloned in appropriate expression vectors for functional analysis on Jurkat, NK92, and primary CD8 T cells and tumor cells expressing the appropriate antigen. We have identified TCRs specifically binding HLA-A2 presenting epitopes of tumor antigens, which are capable of inducing TCR-mediated cell activation and cytotoxicity in target cancer cell lines. This method allows the identification of tumor-reactive TCRs in about two to three weeks, starting from peripheral blood samples of readily available healthy donors.

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