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Heterogeneity of Specific CD4+ and CD8+ T Cells Stimulated by CMV pp65 and IE1 Antigens

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Abstract

Characterization of human cytomegalovirus-specific T cells (CMV-T) is of critical importance for their potential use in adoptive immunotherapy after allogeneic hematopoietic stem cell transplantation. Background frequencies of CMV-T in peripheral blood mononuclear cells (PBMCs) of CMV-seropositive healthy subjects are usually very low, hence the requirement for prolonged culture time and multiple stimulations to expand them. The evaluation of the end-culture specificity and composition has sometimes been neglected or difficult to assess in these settings. We explored the identity and the functionality of pp65-specific and IE1-specific T cells, enriched in short-term cultures from PBMCs. Antigen-specific T cells were further isolated by IFN- γ capture system and/or CD154 microbeads. Frequency of IE1-specific cytotoxic T cells in PBMCs secreting IFN- γ was higher compared with the pp65-specific one, whereas the latter cell types showed a higher median CD107a degranulation. Cell viability, rate of CMV-T increase, and multicytokine secretion profile after epitope-specific short-term cultures were heterogenous. T cells were mainly of late effector stages but they significantly dropped off upon CMV rechallenge with peptide pools. In parallel, CMV-T expansion was accompanied by a significant increase of cytotoxic naive/memory stem cells (CTLs), whereas the CD4 counterpart significantly increased only upon stimulation with IE1. Outcome was variable and showed donor and epitope dependency. Differences in human leukocyte antigen and epitope dominance and variability in the relative number of CD3 effector cells and IFN- γ /CD154 expression among healthy donors could reflect the observed individual CMV-specific cellular immunity. This heterogeneity raises points to be considered when approaching adoptive immunotherapy.