PD-1+ polyfunctional T cells dominate the periphery after tumor-infiltrating lymphocyte therapy for cancer

Infusion of highly heterogeneous populations of autologous tumor-infiltrating lymphocytes (TILs) can result in tumor regression of exceptional duration. Initial tumor regression has been associated with persistence of tumor-specific TILs one month after infusion, but mechanisms leading to long-lived memory responses are currently unknown. Here we studied the dynamics of bulk tumor-reactive CD8+ T cell populations in patients with metastatic melanoma following treatment with TILs. Experimental Design: We analyzed the function and phenotype of tumor-reactive CD8+ T cells contained in serial blood samples of sixteen patients treated with TILs. Results: Polyfunctional tumor-reactive CD8+ T cells accumulated over time in the peripheral lymphocyte pool. Combinatorial analysis of multiple surface markers (CD57, CD27, CD45RO, PD-1 and LAG-3) showed a unique differentiation pattern of polyfunctional tumor-reactive CD8+ T cells, with highly specific PD-1 upregulation early after infusion. The differentiation and functional status appeared largely stable for up to 1 year post-infusion. Despite some degree of clonal diversification occurring in vivo within the bulk tumor-reactive CD8+ T cells, further analyses showed that CD8+ T cells specific for defined tumor-antigens had similar differentiation status. Conclusions: We demonstrated that tumor-reactive CD8+ T cell subsets which persist after TIL therapy are mostly polyfunctional, display a stable partially differentiated phenotype and express high levels of PD-1. These partially differentiated PD-1+ polyfunctional TILs have a high capacity for persistence and may be susceptible to PD-L1/PD-L2-mediated inhibition.