Molecular basis of T cell exhaustion: Insights for immunotherapy
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T cell exhaustion is common during chronic infections and cancer and prevents optimal immunity. Exhausted CD8 T cells (Tex) are defined by the loss of ability to perform effector functions efficiently, low proliferative capacity and poor survival following antigen stimulation. Tex also co-express multiple inhibitory receptors that negatively regulate their function. Indeed, receptors such as PD-1 have become major targets of clinical immunotherapies in cancer and infectious disease aimed at re-invigorating Tex. Despite the clinical success of PD-1 based therapies in human melanoma and other cancers, the majority of patients do not have durable clinical benefit from anti-PD-1 monotherapy. A major challenge remains identifying which patients will respond to anti-PD-1 therapy and defining the underlying mechanisms for successful, durable response versus treatment failure.

Our previous studies in the LCMV model identified key transcription factors, including T-bet and Eomesodermin (Eomes) in controlling the sustainability and terminal differentiation of Tex populations. One key observation from these studies was that a key surrogate of reinvigoration of Tex is a population of Eomes$^{hi}$ PD-1$^{hi}$ Tex. We hypothesized that this population would facilitate tracking Tex responses to PD-1 blockade in humans. Indeed, Detailed immune profiling of peripheral blood from stage IV melanoma patients before and after pembrolizumab (pembro) identified reinvigoration in circulating Tex. These data indicated that nearly 80% of patients experienced a strong, on target immunological effect of PD-1 blockade. However, the objective clinical response rate in this cohort was less than 40% and reinvigoration of circulating Tex alone did not predict clinical outcomes. Rather, the magnitude of Tex re-invigoration in relation to pre-treatment tumor burden correlated with clinical response and predicted outcome. These results suggest that clinical failure of PD-1 blockade in many patients may not solely be due to an inability to induce immune re-invigoration but rather, an imbalance between T cell re-invigoration and tumor burden. Thus, by focused profiling of a mechanistically relevant circulating T cell subpopulation calibrated to pre-treatment disease burden, we identify a clinically accessible, on treatment, predictor of outcomes to PD-1 blockade. Interestingly, nearly all patients had a single peak of immune reinvigoration despite continued anti-PD-1 treatment. Indeed, it has been unclear whether blocking PD-1 can reprogram Tex into durable memory T cells (TMem). To address this question, we returned to the LCMV mouse model and found that re-invigoration of Tex by PD-1 pathway blockade caused minimal memory development. After blockade, re-invigorated Tex became re-exhausted if antigen remained high, and failed to become TMem upon antigen clearance. Tex acquired an epigenetic profile distinct from effector (Teff) and TMem cells and this epigenetic landscape was minimally remodeled following PD-1 pathway blockade. Nevertheless, PD-1 pathway blockade resulted in transcriptional rewiring and re-engagement of effector circuitry in the Tex epigenetic landscape. These data indicate that epigenetic fate inflexibility may limit current immunotherapies. Moreover, these findings provide a framework for dissecting distinct types of treatment failures in melanoma and have implications for stratifying patients into additional immunotherapeutic treatment approaches.