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Effect of NT-I7 treatment on CD8 T cell differentiation during chronic LCMV

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Chronic viral infections and cancers affect millions of people worldwide. Many of those remain uncurable. The failure of the immune system to respond effectively is largely attributed to T cell exhaustion. Using PD-1 pathway blockade, the gold standard immunotherapy for checkpoint inhibition, some of the effector CD8 T cell functions are restored. Unfortunately, PD-1 therapy is effective only in certain types of cancer and benefits only a subset of patients. Thus, it is necessary to find strategies to improve efficacy of PD-1 blockade therapy. A promising approach is to use combination therapies that can significantly boost the number of T cells capable of responding to PD-1 therapy. The exhausted CD8 T cell pool is heterogeneous; stem-like CD8 T cells differentiate in the terminally differentiated (TD) ones. The stem-like cells have self-renewal capacity whereas the TD have more effector functions. IL-7 is a homeostatic cytokine critical to the survival and proliferation of T cells. In a chronic LCMV murine model, we showed that treatment with a long-acting recombinant human IL-7, NT-I7 (efineptakin alfa), preferentially expanded stem-like CD8 T cells compared to the TD. Interestingly, NT-I7 treatment induced these stem-like CD8 T cells to exit the spleen and circulate to other tissues. In addition, scRNAseq revealed that NT-I7 treatment generated a distinct CD8 T cell subset that maintained many features of stem-like CD8 T cells. These results highlight the promising potential of NT-I7 as an immunotherapy and its combination with PD-1 therapy to improve treatment efficiency.