Background CD8+ T cells are critical components of the immune reaction against viral infections and cancer and have the potential to eliminate infected or malignant cells. However, when the antigen persists, CD8+ T cells enter an exhausted state. Chronic disease can lead to increased systemic noradrenaline (NA) levels, but it is currently still unclear how NA impacts the differentiation and function of exhausted CD8+ T cells. We here set out to characterize the effects of β adrenergic signaling on CD8+ T cells in chronic viral infection with LCMV-clone 13 and in murine cancer models.

Methods We used multiparameter flow cytometry, single cell RNA sequencing, immunofluorescence microscopy, a conditional genetic knockout model as well as pharmacological inhibition of adrenergic receptors with FDA-approved drugs to profile the effects of β adrenergic signaling on CD8+ T cells.

Results We observed that chronically infected mice had elevated systemic NA levels and CD8+ T cells expressed higher levels of the β1 adrenergic NA receptor, Adrb1. NA impaired T cell receptor signaling of ADRB1-expressing CD8+ T cells, and reduced T cell proliferation and function. Conversely, genetic ablation of ADRB1 prevented terminal CD8+ T cell differentiation in chronic viral infection and ADRB1-blockade enhanced T cell functionality in combination with immune checkpoint blockade (ICB) in an ICB-sensitive melanoma model. Expanding these observations to an ICB-resistant model of pancreatic cancer, we found that pharmacological blockade of adrenergic receptors synergized with ICB to genetically reprogram CD8+ T cells towards a tissue resident memory T cell-like state and improved T cell functionality, resulting in decreased tumor size.

Conclusions In summary, our data suggest that β adrenergic receptors represent a novel immune checkpoint that modulates CD8+ T cell differentiation and function in the context of chronic antigen exposure and that targeting adrenergic receptors may synergize with ICB in cancer patients.

Ethics Approval Animals were housed in specific-pathogen-free facilities at the Salk Institute and all experimental studies were approved and performed in accordance with guidelines and regulations implemented by the Salk Institute Animal Care and Use Committee (IACUC number 17–00032).

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