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"Long-chain Fatty Acid Sensing by GPR132 Regulates $CD8^+$ T Cell Responses to Infection"

By

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Cancer Center, G1196

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ABSTRACT

$CD8^+$ T cells undergo robust expansion upon priming to control pathogen replication and provide host immunity; however, T cell function must be tightly regulated to ensure effective immunosurveillance without immunopathology. G protein coupled receptors sense environmental signals and are essential for modulating T cell function, and the lipid sensing receptor GPR132 is rapidly upregulated by T cells upon activation and maintained after infection is resolved. Ligands for this receptor include oxidized long-chain fatty acids derived from dietary linoleic acid, and these are increased under proinflammatory conditions. Additionally, mimics of these ligands are synthesized by commensal and pathogenic microorganisms. GPR132-deficient (KO) mice develop an autoimmune syndrome accompanied by expansion of the T cell compartment, suggesting GPR132 as a key target for T cell regulation. We examined the cell-intrinsic role of GPR132 in $CD8^+$ T cell responses during infection and found that KO T cells displayed significantly enhanced expansion over wild-type (WT) cells. However, WT and KO T cells had similar proliferation and gene expression profiles upon TCR-engagement *in vitro*. There were also no GPR132-dependent changes in T cell expansion observed during lymphopenia-driven proliferation *in vivo*, or when GPR132KO mice were aged in a SPF facility, indicating GPR132 inhibits T cell expansion specifically in the context of inflammation. An in-depth inquiry into the mechanism of action revealed that GPR132 limits T cell proliferation at peak of infection, while subsequently escalating cell death during contraction. Moreover, when T cells lacked GPR132 signaling, we observed an increase in the maintenance of $CX3CR1^+$ effectors. Transcriptomic analysis of splenic WT and KO antigen-specific $CD8^+$ T cells supported this finding, as GPR132 deficiency results in enlarged frequencies of cytotoxic effector cells at the expense of the memory compartment after infection. Additionally, formation of tissue-resident memory pools was diminished. GPR132 also regulated effector function, as granzyme production was reduced while cytokine production was increased in KO T cells. Lastly, despite increased numbers of KO memory T cells, they displayed similar expansion potential as WT memory cells, yet retained enhanced proinflammatory cytokine production during rechallenge. Altogether, these studies reveal a role for GPR132 in detecting self and commensal lipids to regulate T cell responses against pathogens and indicate that GPR132 can be targeted to modulate T cell number and function without induction of autoimmunity.