Self-renewal capacity of semi-differentiated CD8$^+$ T cells sustains long-term protective responses in chronic persistent infection

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CD8$^+$ T lymphocytes have a major role in the elimination of target cells infected by intracellular pathogens, and transformed cells expressing oncoantigens. This happens when host nucleated cells are able to present proteasome-derived antigens or indirectly cross-presented peptide antigens in association with major histocompatibility complex (MHC) class I molecules (1). Upon recognition of the MHC-peptide complexes by CD8$^+$ T cells via their antigen receptors (TCR), cytotoxic lymphocytes release granules containing perforins and granzymes that cause direct damage to target cells, as well as expressed factors such as the Fas ligand and tumor necrosis factor-alpha (TNF-α) that induce apoptosis, thus preventing the spread of infection or tumor growth (2). It is noteworthy that the function of CD8$^+$ T lymphocytes is not limited to eliminating target cells, these cells also participate in other mechanisms of host defense, mainly through the production of interferon-gamma (IFN-γ). IFN-γ has the ability to directly inhibit viral replication, activate macrophages by increasing its cytotoxic and antigen presenting capacity, and may further induce the synthesis of class I MHC molecules as well as other proteins involved in antigen processing and presentation (2).

The persistence of long-lived CD8$^+$ T cells is crucial to ensure protective immunity against pathogen infections as well as effective protection against tumor. These cells are part of the host memory lymphocyte repertoire able to respond to a specific invader or transformed cells and prompt eliminate them. They are able to persist for the host's lifetime, and can be re-activated for a faster response to an invader similarly to the one they fought in the past thus granting lifelong immunity to the host (1,2). Memory CD8$^+$ T cells are subdivided into central memory (T_{CM}), effector memory (T_{EM}), tissue-resident memory (T_{RM}) based on the expression of surface markers, tissue-residence, and their ability to produce cytokines and proliferate (1). Recent studies in a murine model of *Toxoplasma gondii*-infection have characterized an intermediate population of memory CD8$^+$ T cells that gives rise to terminally differentiated effector CD8$^+$ T cells during infection (3). This differentiation commitment occurs during blastogenesis of quiescent memory CXCR3$^+$ KLRG1$^+$ CD8$^+$ T cells and results in a robust increase of the antigen-specific effector CXCR3$^-$ KLRG1$^+$ CD8$^+$ T cell population which plays a major role in acquired immunity (3). These findings shed light into the dynamics of the lineage differentiation commitment of CD8$^+$ T cells and should improve our understanding how to regulate the destiny of responding CD8$^+$ T cells in immunotherapies and approaches to vaccine development.

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Footnote

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