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T CELL RESPONSES

Antiviral immunity ticks both T-boxes

During chronic viral infections, such as with hepatitis C virus (HCV), antigen-specific T cells are persistently exposed to viral antigens, resulting in increased T cell turnover and the depletion of long-lived T cell populations. This can lead to the eventual 'collapse' of the adaptive immune response. This study identifies separate populations of progenitor and terminally differentiated virus-specific $CD8^+$ T cells that are present in chronic infection and must be balanced to maintain a durable response. These populations could be distinguished by differential expression of the T-box transcription factors T-bet and eomesodermin (EOMES).

In mice chronically infected with lymphocytic choriomeningitis virus (LCMV), T-bet and EOMES were reciprocally expressed by LCMV-specific $CD8^+$ T cells. The $EOMES^{hi}$ T cells had higher levels of expression of inhibitory receptors such as PD1 and produced lower levels of pro-inflammatory cytokines than $T\text{-}bet^{hi}$ T cells, but had greater cytotoxicity. The $EOMES^{hi}$ T cells outnumbered $T\text{-}bet^{hi}$ T cells by a factor of ~20 overall. Furthermore, the $EOMES^{hi}$ T cells showed evidence of recent extensive proliferation but were not currently dividing. Genetic deletion of *Tbx21* (which encodes T-bet) resulted in increased EOMES and PD1 expression by $CD8^+$ T cells and increased proliferation, whereas deficiency of EOMES led to increased T-bet expression and cytokine production, decreased PD1 expression and decreased proliferation. Thus, T-bet and EOMES mark distinct but related populations of $CD8^+$ T cells during chronic infection, with different regenerative and antiviral capacities.

The authors then used adoptive-transfer experiments to examine the lineage relationship between these two populations. LCMV-specific $PD1^{hi}EOMES^{hi}$ $CD8^+$ T cells divided only modestly and retained high expression levels of PD1 after transfer to LCMV-infected hosts, whereas transferred $PD1^{int}T\text{-}bet^{hi}$ T cells underwent extensive proliferation *in vivo*, which was associated with their conversion to $PD1^{hi}$ cells. The conditional deletion of *Tbx21* from LCMV-specific $CD8^+$ T cells before transfer to infected hosts increased conversion to $PD1^{hi}$ cells, suggesting that T-bet has a crucial role in maintaining the $PD1^{int}T\text{-}bet^{hi}$ progenitor population. By contrast, conditional deletion of *Eomes* decreased the size of the $PD1^{hi}$ cell population, which suggests that EOMES is crucial for the generation of $PD1^{hi}$ progeny.

In the absence of either T-bet or EOMES, virus-specific $CD8^+$ T cells were unable to sustain an effective antiviral response. However, in mixed chimaeras, the combination of $Eomes^{-/-}$ $T\text{-}bet^{hi}$ and $Tbx21^{-/-}$ $EOMES^{hi}$ T cells did not improve viral control over either population alone. It therefore seems that it is the progenitor–progeny relationship between $T\text{-}bet^{hi}$ and $EOMES^{hi}$ $CD8^+$ T cells that is the crucial factor in maintaining a virus-specific response, rather than some form of cooperation between distinct functions of the two populations.

Persistent antigen exposure was required for the proliferation of $T\text{-}bet^{hi}$ T cells and their conversion to $EOMES^{hi}$ T cells, but EOMES expression was retained after antigen removal, which indicates that the $EOMES^{hi}$ progeny are terminally differentiated. So the authors suggest that if chronic antigen exposure induces $T\text{-}bet^{hi}$ precursors to continually proliferate and give rise to $EOMES^{hi}$ terminally differentiated progeny, then chronic infection could eventually deplete the $T\text{-}bet^{hi}$ population. Indeed, in patients infected with HCV, there was a marked accumulation of $EOMES^{hi}$ HCV-specific $CD8^+$ T cells and a depletion of $T\text{-}bet^{hi}$ cells in the liver during chronic infection (as compared with cell numbers following the resolution of infection).

In summary, the findings suggest that a crucial balance between $T\text{-}bet^{hi}$ $CD8^+$ T cell precursors with regenerative capacity and $EOMES^{hi}$ progeny with cytotoxic activity must be maintained during chronic infection to support the antiviral T cell response.

Kirsty Minton

> "it is the progenitor–progeny relationship between $T\text{-}bet^{hi}$ and $EOMES^{hi}$ $CD8^+$ T cells that is the crucial factor in maintaining a virus-specific response"

ORIGINAL RESEARCH PAPER Paley, M. A. *et al.* Progenitor and terminal subsets of $CD8^+$ T cells cooperate to contain chronic viral infection. *Science* **338**, 1220–1225 (2012)