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T CELLS

The T cell collective

> establishes T cell quorum regulation as an additional layer of regulation

Upon infection, T cell populations expand and then contract before establishing a stable memory population. It is unclear whether this behaviour is solely controlled by signals derived from other cell types or whether T cells themselves contribute to regulating their population dynamics. Now a study published in *Immunity* shows that, by clustering together, $CD8^+$ T cells create communication hubs that enable collective regulation of T cell proliferation versus death according to cell density.

Following antigen encounter, T cells form clusters around dendritic cells (DCs) mediated by interactions between T cell-expressed leukocyte function-associated molecule 1 (LFA1) and DC-expressed intercellular adhesion molecule 1 (ICAM1). Zenke et al. noted that activated T cells also upregulate ICAM1 expression, suggesting that they adhere to each other. Indeed, in a DC-free system, $CD8^+$ T cells incubated with cognate antigen still clustered and proliferated. This clustering was abrogated by blockade of the ICAM1–LFA1 interaction.

Credit: Andy Rouse/Getty

Within bacterial communities, individual cells sense each other and adjust their behaviour accordingly — a process known as quorum regulation. To understand how clustered T cells might communicate with each other, the authors used a bioinformatics approach to screen a library of possible receptor–ligand pairs. Of the multiple candidates identified, they focused on CD80 and CD86 and their shared receptors CD28 and cytotoxic T lymphocyte antigen 4 (CTLA4), which provide costimulatory and inhibitory signals, respectively.

Although half of all naive $CD8^+$ T cells express CD86, CD80 was only expressed following T cell activation. The authors showed that clustered T cells require stimulation by CD28 for population expansion and that this could be provided by neighbouring T cells. Co-culturing of wild-type and *Cd80*$^{-/-}$*Cd86*$^{-/-}$ T cells in a transwell system revealed the involvement of a soluble mediator in promoting population expansion. *Cd80*$^{-/-}$*Cd86*$^{-/-}$ T cells produced less interleukin-2 (IL-2) than wild-type T cells and CD28 stimulation increased IL-2 concentrations. So, CD80 and CD86 expression enabled T cells to support T cell population expansion via CD28-driven IL-2 production.

Next, Zenke et al. observed that CD28 and IL-2 increase T cell expression of the anti-apoptotic proteins BCL-X_L and BCL-2, respectively, and inhibit cell death. Accordingly, proliferation of *Cd80*$^{-/-}$ *Cd86*$^{-/-}$ and wild-type T cells was similar but *Cd80*$^{-/-}$*Cd86*$^{-/-}$ T cells showed reduced accumulation after 3 days, suggesting that they had poorer survival. By culturing cells in u-bottomed plates (that enforce close proximity) or flat-bottomed plates, the authors showed that cell density correlated with IL-2 concentration, which is consistent with quorum regulation.

Thus, CD28-driven IL-2 promotes cluster growth, which drives further IL-2 and CD80 expression, establishing a positive-feedback circuit. So what keeps the system in check and allows T cell population contraction? CD28 and IL-2 not only promote T cell population expansion but also drive T cell expression of CTLA4, which competes with CD28 for binding to CD80 and CD86 and inhibits IL-2 production, resulting in T cell apoptosis. CTLA4 expression correlated with cell density, thereby providing an antagonistic feedback loop linked to cell density.

Mathematical modelling confirmed that antagonistic feedback loops operating via CD28, IL-2 receptor and CTLA4 explain T cell population dynamics and supported the notion that signalling between T cells enables them to promote and inhibit their own population expansion (depending on the relative expression of CD28 and CTLA4).

Finally, they investigated whether mutual regulation of T cells occurred in vivo. Infection-induced expansion of adoptively transferred *Icam1*$^{-/-}$ T cells was half that of control cells, suggesting that reduced cluster formation limited their survival. Moreover, adoptive transfer of *Icam1*-transgenic or *Il2*-transgenic $CD8^+$ T cells supported the expansion of endogenous $CD8^+$ T cells whereas transfer of *Ctla4*-transgenic $CD8^+$ T cells suppressed expansion. This indicates that $CD8^+$ T cells coordinate their behaviour in vivo and establishes T cell quorum regulation as an additional layer of regulation beyond the effects mediated by DCs and regulatory T cells.

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ORIGINAL ARTICLE Zenke, S. et al. Quorum regulation via nested antagonistic feedback circuits mediated by the receptors CD28 and CTLA-4 confers robustness to T cell population dynamics. *Immunity* **52**, 313–327 (2020)