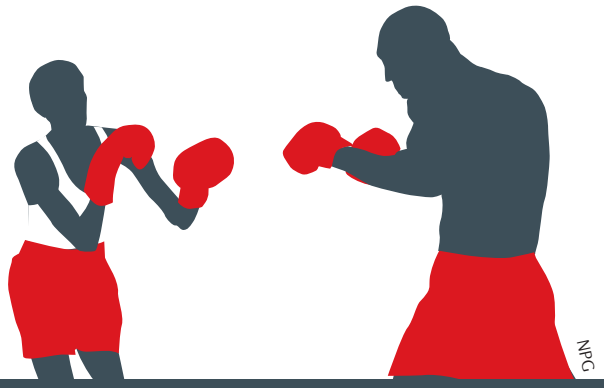

REGULATORY T CELLS

# $T_{Reg}$ cells separate the weak from the strong

Regulatory T ($T_{Reg}$) cells are known for their role in peripheral tolerance and are essential for preventing autoimmunity. But do they play a part during active immune responses to foreign antigens? In a new study, Amigorena and colleagues demonstrate that $T_{Reg}$ cells enhance the avidity of $CD8^+$ T cell responses to foreign antigens and thereby improve T cell memory.

In initial experiments in mice, the authors showed that $T_{Reg}$ cell depletion during the priming stage of a $CD8^+$ T cell response to an injected foreign antigen markedly increased the numbers of antigen-specific $CD8^+$ T cells in the spleen. Interestingly, however, the vast majority of these T cells recognized the antigen with only low avidity, and thus the overall avidity of the response was reduced in the absence of $T_{Reg}$ cells. By contrast, the depletion of $T_{Reg}$ cells at later time points affected only the proportion of antigen-specific T cells and not their avidity. This implies that $T_{Reg}$ cells might function during the priming of $CD8^+$ T cells to suppress low-avidity responses to foreign antigens.

> this mechanism could ... explain how $T_{Reg}$ cells seemingly distinguish between autoimmune and foreign-antigen-specific responses

But how do $T_{Reg}$ cells exert these effects? Intravital imaging of naive T cell receptor (TCR)-transgenic $CD8^+$ T cells interacting with antigen-loaded dendritic cells (DCs) in lymph nodes showed that the long-lasting interactions induced by a high-affinity antigen were unaltered by $T_{Reg}$ cell depletion. By contrast, the shorter duration T cell–DC contacts induced by a low-affinity antigen were extended in the absence of $T_{Reg}$ cells. This effect could be reversed by the addition of blocking antibodies specific for CC-chemokine ligand 3 (CCL3), CCL4 and CCL5, suggesting that $T_{Reg}$ cells inhibit the production of chemokines that stabilize low-affinity T cell–DC interactions.

These findings were corroborated in an *in vivo* infection model using ovalbumin-expressing *Listeria monocytogenes*. Again, a lack of $T_{Reg}$ cells at the priming stage decreased the avidity of the ovalbumin-specific $CD8^+$ T cell response. This was associated with a reduction in T cell interferon-γ production and a rise in the production of CCL2, CCL3 and CCL4 in the spleen. Although no impact on the clearance of the primary infection was observed in this model, the depletion of $T_{Reg}$ cells prior to the primary infection resulted in higher bacterial burdens during a secondary infection. In addition, there were corresponding decreases in the number and relative affinities of ovalbumin-specific $CD8^+$ T cells during the secondary response. This suggests that the presence of $T_{Reg}$ cells during naive T cell priming promotes the subsequent generation of functionally effective high-avidity memory $CD8^+$ T cell responses.

So, this study reveals an intriguing new role for $T_{Reg}$ cells in the suppression of low-avidity $CD8^+$ T cell responses to foreign antigens. As most autoreactive T cells in the periphery have only low affinities for self antigens, the authors propose that this mechanism could also underlie the $T_{Reg}$ cell-mediated suppression of these cells and may thus explain how $T_{Reg}$ cells seemingly distinguish between autoimmune and foreign-antigen-specific responses.

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**ORIGINAL RESEARCH PAPER** Pace, L. *et al.* Regulatory T cells increase the avidity of primary $CD8^+$ T cell responses and promote memory. *Science* **338**, 532–536 (2012)