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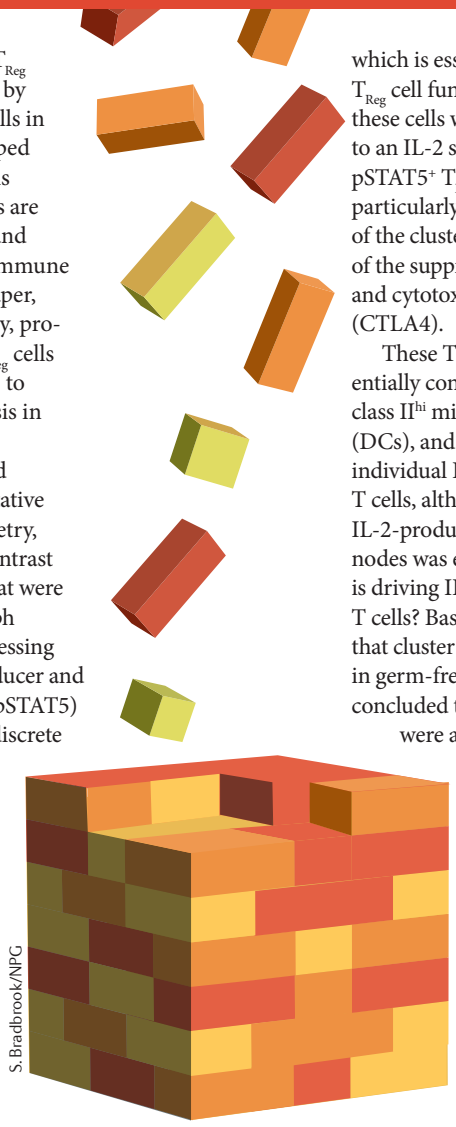
REGULATORY T CELLS

Peripheral positioning

FOXP3$^+$ regulatory T cells (T_{Reg} cells) prevent autoimmunity by controlling self-reactive T cells in the periphery that have escaped negative selection. But little is known about where T_{Reg} cells are positioned in lymph nodes and how exactly they maintain immune homeostasis. This *Nature* paper, from the Germain laboratory, provides a new view on how T_{Reg} cells suppress self-reactive T cells to mediate immune homeostasis in peripheral tissues.

Using a recently described method of multiplex, quantitative imaging, termed histocytometry, Liu *et al.* observed that, in contrast to other FOXP3$^+$ T_{Reg} cells that were distributed through the lymph node, FOXP3$^+$ T_{Reg} cells expressing phosphorylated signal transducer and activator of transcription 5 (pSTAT5) primarily localized in a few discrete aggregates in the outer paracortical T cell region of lymph nodes of healthy mice. pSTAT5 is induced by interleukin-2 (IL-2), which is essential for maintaining T_{Reg} cell function, suggesting that these cells were actively responding to an IL-2 signal. Indeed, most of the pSTAT5$^+$ T_{Reg} cells in these clusters, particularly those towards the centre of the cluster, expressed high levels of the suppressive molecules CD73 and cytotoxic T lymphocyte antigen 4 (CTLA4).



S. Bradbrook/NPG

These T_{Reg} cell clusters preferentially contained CD11b$^+$MHC class II^{hi} migratory dendritic cells (DCs), and some of them contained individual IL-2-producing CD4$^+$ T cells, although the frequency of IL-2-producing cells in the lymph nodes was extremely low. So, what is driving IL-2 production by these T cells? Based on the observation that cluster formation was unaffected in germ-free mice, the authors concluded that these CD4$^+$ T cells were activated by self-antigens, possibly presented by the migratory DCs. These data suggest that even in the presence of T_{Reg} cells, a small fraction of T cells can be sufficiently activated by self-antigen in the steady state to become IL-2-producing 'proto-effector' T cells.

In addition to IL-2, TCR signals are necessary for T_{Reg} cell function in the periphery. Conditional deletion of TCRα in T_{Reg} cells resulted in a disrupted spatial distribution of T_{Reg} cells, with fewer T_{Reg} cells forming discrete clusters. Furthermore, CD73 and CTLA4 expression levels were reduced, particularly at the centre of the clusters.

Finally, blocking IL-2 function in the steady state resulted in an increase in the frequency and total number of IL-2-producing CD4$^+$ T cells in the spleen and lymph nodes. Further studies confirmed that T_{Reg} cell-sensing of IL-2 produced by proto-effector T cells is essential for T_{Reg} cell-mediated suppression of self-antigen-induced T cell activation and maintenance of self-tolerance.

So, this study suggests that TCR signals help T_{Reg} cells to localize in clusters with self-reactive T cells in the steady state where they sense IL-2 to prevent autoimmune responses.

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