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IMMUNE REGULATION

Balancing act

Many microbial infections, such as tuberculosis and malaria, are never eliminated completely by our immune system, even though we can be immune to a second attack. Now, a study in *Nature* shows that regulatory T (T_{Reg}) cells at the site of chronic infection might be crucial for parasite persistence and long-lasting immunity.

Infection of C57BL/6 mice with *Leishmania major* results in a skin lesion that heals after 8–10 weeks, leaving the mouse with long-lasting immunity to the parasite. But, a small number of viable parasites persist. Belkaid and colleagues found that a large number of $CD4^+$ T cells are present at the chronically infected site, of which 40–50% are $CD25^+$.

The lesion-derived $CD4^+CD25^+$ T cells did not respond to mitogenic stimuli *in vitro* and, similar to the naturally occurring $CD4^+CD25^+$ T_{Reg} cells that have been described in autoimmune settings, they could suppress proliferation and the secretion of effector cytokines (such as interferon- γ , IFN- γ) by $CD4^+CD25^-$ effector T cells.

When stimulated with *L. major*-infected dendritic cells (DCs) *in vitro*, $CD4^+CD25^+$ T cells from the chronic lesion produced large amounts of interleukin-10 (IL-10), but little IFN- γ or T helper 2 (T_H2) cytokines, such as IL-4 or IL-5. This seems to be an antigen-specific response, as DCs that were infected with other parasites or activated with CD40 failed to induce the secretion of IL-10.

To test the function of these putative T_{Reg} cells *in vivo*, lesion-derived T-cell subsets were transferred into lymphopaenic (*Rag^{-/-}*) mice, which were then infected with *L. major*. Mice that received $CD4^+CD25^-$ T cells were highly resistant to infection, whereas those that received $CD4^+CD25^+$ T cells developed severe disease. Mice that received a 1 to 10 ratio of $CD25^+$ to $CD25^-$ T cells developed a healing lesion with persistent parasites, similar to the response of wild-type mice. This shows clearly that $CD4^+CD25^+$ lesion-derived T cells can suppress *L. major* immunity. Additional adoptive-transfer experiments indicated that these regulatory cells originate from the naturally occurring $CD4^+CD25^+$ regulatory T-cell pool.

This study shows that a fine balance between regulatory and effector T cells might be essential for parasite

persistence. But, it seems that this phenomenon is not just of benefit to the parasite. IL-10-deficient mice clear infection completely, but, unlike wild-type mice, they do not have long-lived immunity. So, by allowing the persistence of parasites, IL-10-secreting T_{Reg} cells might benefit the host by maintaining protective immunity.

Jennifer Bell

References and links

ORIGINAL RESEARCH PAPER Belkaid, Y. *et al.* $CD4^+CD25^+$ regulatory T cells control *Leishmania major* persistence and immunity. *Nature* **420**, 502–507 (2002)

FURTHER READING Shevach, E. M. $CD4^+CD25^+$ suppressor T cells: more questions than answers. *Nature Rev. Immunol.* **2**, 389–400 (2002) | Sacks, D. & Noben-Trauth, N. The immunology of susceptibility and resistance to *Leishmania major* in mice. *Nature Rev. Immunol.* **2**, 845–858 (2002)

WEB SITES

Ethan Shevach's lab:

<http://www.niaid.nih.gov/dir/labs/li/shevach.htm>

David Sacks' lab:

<http://www.niaid.nih.gov/dir/labs/lpd/sacks.htm>