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MUCOSAL IMMUNOLOGY

What memories are made of

This article is a tribute to Dr Leo Lefrançois, Professor and Chairman of the Department of Immunology and Director of the Center for Integrated Immunology and Vaccine Research, University of Connecticut Health Center, Connecticut, USA. The editors of Nature Reviews Immunology *are deeply saddened to hear of his unexpected passing and extend our condolences to his family and colleagues. His contribution to the field of immunology, in particular to our understanding of memory T cell responses, has been extensive and will be long remembered; this most recent study is testament to that.*

> “mouse γδ T cells that can form a stable memory population and that can provide protection in the intestinal mucosa”

γδ T cells — best known for their innate-like characteristics — are not generally considered to be the first choice cells for a memory recall response. However, recent studies, including this paper by Leo Lefrançois and colleagues, suggests that γδ T cells in the intestinal tissues can in fact provide long-lasting memory responses, similarly to conventional αβ T cells.

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Research investigating the role of γδ T cell responses in protection against *Listeria* spp. infection has been hampered by the absence of a mouse model that mimics natural infection. So the authors used a modified strain of *Listeria monocytogenes* that efficiently invades the mouse intestinal epithelium and that establishes a true enteric infection following oral inoculation. After oral infection, a large population of $CD27^{-}CD44^{hi}$ γδ T cells appeared in the mesenteric lymph nodes (MLNs) and was still detectable there 5 months later. Following secondary challenge with oral *L. monocytogenes*, this γδ T cell population rapidly expanded in the MLNs, blood and intestinal lamina propria, but not in the intestinal epithelium or peripheral lymph nodes (PLNs), which suggests that these cells are activated in the MLNs and that they migrate via the blood to the lamina propria.

Analysis of the specificity of this recall response showed that only the $CD27^{-}CD44^{hi}$ γδ T cell subset, and not other γδ T cell subsets, responded to *L. monocytogenes*; the $CD27^{-}CD44^{hi}$ γδ T cell subset only expanded following oral infection not following intravenous infection and they did not respond to oral infection with another intestinal bacterial pathogen. In addition, the kinetics of the γδ T cell secondary response were comparable to those of the antigen-specific αβ T cell memory response. These observations support the idea that the γδ T cell response is a context-dependent, pathogen-specific, bone fide memory response.

Further analysis confirmed that the $CD27^{-}CD44^{hi}$ γδ T cell population that expands in the MLNs following infection with *L. monocytogenes* was distinct to the γδ T cell subsets in the PLNs. In particular, the MLN γδ T cell population was unique in its ability to simultaneously produce high levels of both interferon-γ (IFNγ) and interleukin-17A (IL-17A). The small subset of MLN memory γδ T cells expressed either IFNγ or IL-17A 3 months after infection, and during the secondary response the mucosal MLN γδ T cell subset upregulated both cytokines and became the main source of IL-17A.

So, does this γδ T cell memory subset have a protective role in *L. monocytogenes* infection? Treatment of the mice with a monoclonal antibody specific for the γδ T cell receptor (TCR), which causes TCR internalization and which hinders the ability of the γδ T cells to respond to antigens, did not affect protection against *L. monocytogenes*. Furthermore, depletion of both $CD4^{+}$ and $CD8^{+}$ T cells only resulted in a minimal loss of protection. However, when $CD4^{+}$ and $CD8^{+}$ T cell depletion was combined with γδ TCR internalization, the mice suffered a much greater loss of protection in *L. monocytogenes* infection.

So, the authors have identified mouse γδ T cells that can form a stable memory population and that can provide protection in the intestinal mucosa in collaboration with αβ T cell memory.

Lucy Bird

ORIGINAL RESEARCH PAPER Sheridan, B. S. *et al.* γδ T cells exhibit multifunctional and protective memory in intestinal tissues. *Immunity* **39**, 184–195 (2013)

FURTHER READING Vantourout, P. & Hayday, A. Six-of-the-best: unique contributions of γδ T cells to immunology. *Nature Rev. Immunol.* **13**, 88–100 (2013)

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