



Perona-Wright, G. and McSorley, H. J. (2022) Lessons from helminths: what worms have taught us about mucosal immunology. *Mucosal Immunology*, 15(6), pp. 1049-1051. (doi: [10.1038/s41385-022-00560-5](https://doi.org/10.1038/s41385-022-00560-5))

There may be differences between this version and the published version. You are advised to consult the published version if you wish to cite from it.

<http://eprints.gla.ac.uk/277545/>

Deposited on 24 August 2022

Enlighten – Research publications by members of the University of Glasgow
<http://eprints.gla.ac.uk>

Lessons from helminths: What worms have taught us about mucosal immunology

Georgia Perona-Wright¹ and Henry J McSorley²

Author Information:

Affiliations

1. School of Infection & Immunity, University of Glasgow, Glasgow, UK.
2. Division of Cell Signalling and Immunology, School of Life Sciences, University of Dundee, Dundee, UK.

Contributions

GPW and HJM wrote and edited the manuscript.

Correspondence

Georgia.Perona-Wright@glasgow.ac.uk and HMcsorley001@dundee.ac.uk

Competing interests

The authors declare no competing interests

Parasitic helminths are unique pathogens, being the largest, most chronic, and yet often the least pathogenic infectious agents that we encounter. They travel across and persist in many mucosal sites, and their impact, experimentally and clinically, has supported many of our current models of mucosal immunity. Here, we present a special collection of recent *Mucosal Immunology* articles highlighting key advances made possible through the study of helminth infections, from the discovery of new immuno-epithelial cells to the cross-kingdom interactions that govern intestinal immunity and the therapeutic promise of helminth-mediated immune suppression. Together these articles are a celebration of the power of the worm to provide new insight into the mechanisms of mucosal immunity, and we hope you enjoy reading the collection.

Lessons from helminths began very early in history. Parasitic helminths are visible to the naked eye and were the first pathogens to be described, with the earliest known medical text, the Ebers papyrus (~1500 BC), describing human tapeworm, roundworm, schistosome, hookworm and guinea worm infections¹. Helminths have long been associated with type 2 immune responses, many aspects of which were uncovered using experimental infections (Fig 1). The first to be identified were eosinophils and mast cells, discovered in the late 1800s by Paul Ehrlich² and later shown to be associated with parasitic worm infections^{3,4} (Fig 1-1). Likewise, early helminth infection studies led Bridget Ogilvie and her team to describe “Reginin-like antibodies” (later renamed “IgE”) in 1964¹ (Fig 1-2). When Mosmann and Coffman originally proposed the Th1/Th2 paradigm, this was supported by the identification of Th2-phenotype cells in helminth-infected mice⁵ (Fig 1-3), while the impact of the Th2 signature cytokines was demonstrated in helminth infections of early IL-4 and IL-13 knockout animals^{6,7,8}. Initially, IL-4 and IL-13 were thought to fulfil redundant roles in the immune response, until helminth infection studies revealed the dominant role of IL-13 in whipworm expulsion⁹. IL-13 was later shown to be a critical cytokine at mucosal surfaces, activating the “epithelial escalator” (increased epithelial turnover)¹⁰ and a key part of the “weep and sweep” response (coordinated increases in epithelial permeability, mucus production and intestinal motility) that clears intestinal parasites¹¹ (Fig 1-6). The first experimental data supporting the mucus layer as a key part of mucosal immunity was also provided by experimental helminth infections, in the early 1980s¹². More recently, the first studies on the alternative activation of macrophages¹³ (Fig 1-5), and the concept of wound healing as an immune outcome¹⁴, were also built on helminth infection experiments. Such infections have also shown that tissue macrophages proliferate in situ¹⁵ (Fig 1-8) and that T follicular helper cells are functionally polarised^{16,17}. Finally, the identification and characterisation of 2 of the critical initiators and regulators of type 2 immunity - type 2 innate lymphoid cells (ILC2s)¹⁸ (Fig 1-7) and tuft cells¹⁹ (Fig 1-10) - both depended on the use of helminth infections.

Today, the contribution of helminths to fundamental understanding of mucosal immunology continues at pace. Two research articles in this collection describe the dialogue between tuft cells and ILC2s: first showing that the cytokine MIF is required for tuft cell and ILC2 activation, critical for rapid expulsion of intestinal helminths²⁰, and second that the SOCS-family member CISH regulates that tuft cell-ILC2 circuit, controlling the thresholds of epithelial and immune cell interaction²¹. In a review article in this issue, De’Broski Herbert and colleagues discuss current understanding of cell-cell interactions in the infected mucosa, highlighting the function of non-traditional immune cells such as epithelial cells, neurons and fibroblasts, and arguing that communication between haematopoietic, stromal and neural cells is essential not only for the initiation of mucosal immunity, but also for its amplification, regulation and repair²².

The theme of resolution and repair is continued in a study showing that the phosphatase PTPN2 is a critical signalling step in the alternative activation of macrophages, and its absence correlates

with excessive lung damage in a model of pulmonary helminth infection²³. Type 2 immunity (including macrophage alternative activation) is associated with distinct metabolic requirements, favouring oxidative phosphorylation over aerobic glycolysis and these metabolic changes can have both dietary and immunological determinants (Fig 1-9). Our collection includes an intriguing new study of ILC activation in the intestine that demonstrates that a neuropeptide elicited by food consumption, VIP, synergises with cytokine alarmins to potently activate ILC2s and ILC3s in the intestinal tissue²⁴. A new review in this issue by Christoph Wilhelm and his team focuses on cutting-edge ILC2 biology and particularly the metabolic pressures that govern ILC activity and consequent immune decisions (Michla & Wilhelm, 2022, *Mucosal Immunology*).

One of the features of mucosal sites is constant interaction with external stimuli, such as food, dust, and commensal microorganisms. Mucosal infections take place in the context of this background stimulation, and helminth infections have provided fascinating new insight into the interactions that take place. A recent paper in our collection shows that the bacterial microbiota also influences helminth expulsion by regulating intestinal contractility²⁵. Cross-regulation also occurs via the immune system, and two new papers highlight the impact of interaction between opposing cytokine responses. Both describe an underlying IFN γ response present during helminth infection that limits the Th2 response critical for parasite expulsion^{26, 27}, and IL-10 is shown to be critical for keeping that IFN γ in check²⁷.

The immune regulation revealed by helminth infection is concentrated at the site of infection, but these infections have also revealed long-range immune modulation, driving our understanding of communication between distant immune locations. Helminths played a key role in describing the gut-lung axis, including the early demonstration that intestinal infection can alter pulmonary disease. Connections between other distal sites are now being established and an exciting new paper in our collection reveals profound changes in immune populations in the skin during strictly enteric helminth infection²⁸. Both the tissue specificity of immune responses and the connections between distant locations are explored in a new review by Graham Le Gros and colleagues in this issue²⁹, highlighting the long reach of helminth infections.

The mechanisms of immune regulation revealed by helminth infections have also been powerful drivers of therapeutic strategies, aiming to suppress and moderate pathological immune responses in a variety of tissue sites. Soon after the discovery of regulatory T cells³⁰, parasites were found to induce regulatory responses and suppress type 2 immunity, through the release of immunomodulatory products³¹ (Fig 1-4). P'ng Loke and colleagues review the latest information on the human immune response to parasitic helminths, how recent technological developments such as human challenge studies, single cell sequencing and organoid culture systems have aided these investigations. Recent insight is enabling new approaches to vaccine design and harnessing of parasite-mediated immune suppression to treat inflammatory disease³².

Parasitic helminths will continue to be a unique and physiologically relevant testbed for new concepts in mucosal immunology. Better understanding of immunity to helminths is urgently needed. Almost one quarter of the world's population is at risk of infection with parasitic helminths, causing significant morbidity and mortality, and yet we currently do not have any effective vaccines. But as this collection of reviews and current research papers illustrates, understanding the biology of helminth infections, their regulation and their tissue context is also answering key questions in immunobiology, mucosal immunity, and immunotherapy. Only by using human and animal model helminth infection experiments, can these fundamental questions be answered.

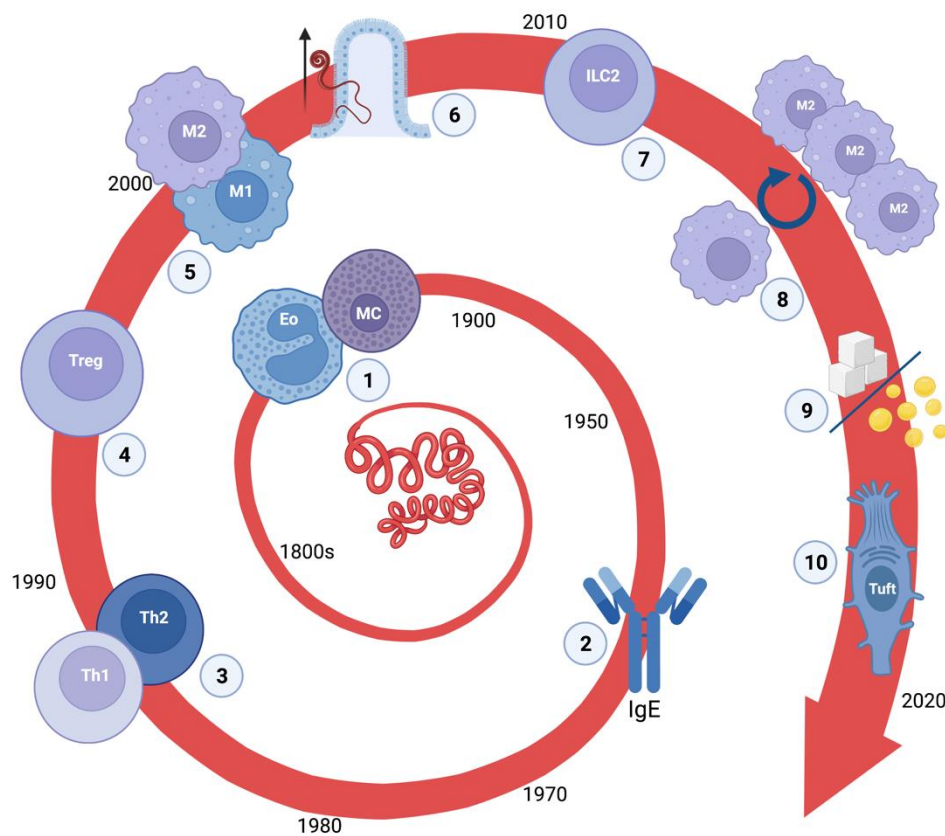


Figure 1: Landmark discoveries from helminth immunology.

- 1.1 Mast cell and eosinophil identification (late 1800s).
- 1.2 IgE (“Reagin-like antibodies”) induced in parasite infection (1964).
- 1.3 Th1/Th2 paradigm: Th1 in bacterial and Th2 in parasitic infections (1989).
- 1.4 Discovery of regulatory T cells (1995).
- 1.5 M1/M2 paradigm, M2 (“alternatively-activated”) macrophages in parasite infections (2000).
- 1.6 “Epithelial escalator” as part of the response to intestinal helminths (2005).
- 1.7 Characterisation of the anti-parasite role of type 2 innate lymphoid cells (ILC2) (2010)
- 1.8 In situ proliferation of M2 macrophages (2011)
- 1.9 Metabolic shift during type 2 immunity from glycolysis to lipid metabolism (2016)
- 1.10 Identification of tuft cells as a critical epithelial cell type in initiation of anti-parasite immunity (2016)

Created with BioRender.com

References:

1. Ogilvie, B.M. Reagin-Like Antibodies in Animals Immune to Helminth Parasites. *Nature* **204**, 91-92 (1964).
2. Kay, A.B. The early history of the eosinophil. *Clin Exp Allergy* **45**, 575-582 (2015).
3. Basten, A., Boyer, M.H. & Beeson, P.B. Mechanism of eosinophilia. I. Factors affecting the eosinophil response of rats to *Trichinella spiralis*. *J Exp Med* **131**, 1271-1287 (1970).
4. Kelly, J.D. & Ogilvie, B.M. Intestinal mast cell and eosinophil numbers during worm expulsion in nulliparous and lactating rats infected with *Nippostrongylus brasiliensis*. *Int Arch Allergy Appl Immunol* **43**, 497-509 (1972).
5. Mosmann, T.R. & Coffman, R.L. TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annu Rev Immunol* **7**, 145-173 (1989).
6. Finkelman, F.D. *et al.* Interleukin-4- and interleukin-13-mediated host protection against intestinal nematode parasites. *Immunol Rev* **201**, 139-155 (2004).
7. Kuhn, R., Rajewsky, K. & Muller, W. Generation and analysis of interleukin-4 deficient mice. *Science* **254**, 707-710 (1991).
8. Noben-Trauth, N. *et al.* An interleukin 4 (IL-4)-independent pathway for CD4+ T cell IL-4 production is revealed in IL-4 receptor-deficient mice. *Proc Natl Acad Sci U S A* **94**, 10838-10843 (1997).
9. Bancroft, A.J., McKenzie, A.N. & Grencis, R.K. A critical role for IL-13 in resistance to intestinal nematode infection. *J Immunol* **160**, 3453-3461 (1998).
10. Cliffe, L.J. *et al.* Accelerated intestinal epithelial cell turnover: a new mechanism of parasite expulsion. *Science* **308**, 1463-1465 (2005).
11. Anthony, R.M., Rutitzky, L.I., Urban, J.F., Jr., Stadecker, M.J. & Gause, W.C. Protective immune mechanisms in helminth infection. *Nat Rev Immunol* **7**, 975-987 (2007).
12. Miller, H.R., Huntley, J.F. & Wallace, G.R. Immune exclusion and mucus trapping during the rapid expulsion of *Nippostrongylus brasiliensis* from primed rats. *Immunology* **44**, 419-429 (1981).
13. Loke, P., MacDonald, A.S., Robb, A., Maizels, R.M. & Allen, J.E. Alternatively activated macrophages induced by nematode infection inhibit proliferation via cell-to-cell contact. *Eur J Immunol* **30**, 2669-2678 (2000).
14. Allen, J.E. & Wynn, T.A. Evolution of Th2 immunity: a rapid repair response to tissue destructive pathogens. *PLoS Pathog* **7**, e1002003 (2011).
15. Jenkins, S.J. *et al.* Local macrophage proliferation, rather than recruitment from the blood, is a signature of TH2 inflammation. *Science* **332**, 1284-1288 (2011).

16. Glatman Zaretsky, A. *et al.* T follicular helper cells differentiate from Th2 cells in response to helminth antigens. *J Exp Med* **206**, 991-999 (2009).
17. King, I.L. & Mohrs, M. IL-4-producing CD4+ T cells in reactive lymph nodes during helminth infection are T follicular helper cells. *J Exp Med* **206**, 1001-1007 (2009).
18. Neill, D.R. *et al.* Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. *Nature* **464**, 1367-1370 (2010).
19. Gerbe, F. *et al.* Intestinal epithelial tuft cells initiate type 2 mucosal immunity to helminth parasites. *Nature* **529**, 226-230 (2016).
20. Varyani, F. *et al.* The IL-25-dependent tuft cell circuit driven by intestinal helminths requires macrophage migration inhibitory factor (MIF). *Mucosal Immunol* (2022).
21. Kotas, M.E. *et al.* CISH constrains the tuft-ILC2 circuit to set epithelial and immune tone. *Mucosal Immunol* **14**, 1295-1305 (2021).
22. Inclan-Rico, J.M., Rossi, H.L. & Herbert, D.R. "Every cell is an immune cell; contributions of non-hematopoietic cells to anti-helminth immunity". *Mucosal Immunol* (2022).
23. Spalinger, M.R. *et al.* Loss of protein tyrosine phosphatase non-receptor type 2 reduces IL-4-driven alternative macrophage activation. *Mucosal Immunol* **15**, 74-83 (2022).
24. Pascal, M. *et al.* The neuropeptide VIP potentiates intestinal innate type 2 and type 3 immunity in response to feeding. *Mucosal Immunol* (2022).
25. Moyat, M. *et al.* Microbial regulation of intestinal motility provides resistance against helminth infection. *Mucosal Immunol* (2022).
26. Kapse, B. *et al.* Age-dependent rise in IFN-gamma competence undermines effective type 2 responses to nematode infection. *Mucosal Immunol* (2022).
27. Webster, H.C. *et al.* Tissue-based IL-10 signalling in helminth infection limits IFN-gamma expression and promotes the intestinal Th2 response. *Mucosal Immunol* (2022).
28. Classon, C.H. *et al.* Intestinal helminth infection transforms the CD4(+) T cell composition of the skin. *Mucosal Immunol* **15**, 257-267 (2022).
29. Vacca, F. & Le Gros, G. Tissue-specific immunity in helminth infections. *Mucosal Immunol* (2022).
30. Sakaguchi, S., Sakaguchi, N., Asano, M., Itoh, M. & Toda, M. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. *J Immunol* **155**, 1151-1164 (1995).

31. Maizels, R.M. & Yazdanbakhsh, M. Immune regulation by helminth parasites: cellular and molecular mechanisms. *Nat Rev Immunol* **3**, 733-744 (2003).
32. Loke, P., Lee, S.C. & Oyesola, O.O. Effects of helminths on the human immune response and the microbiome. *Mucosal Immunol* (2022).