Helminths target macrophage epigenetics and metabolism to evade immunity

Everts, B.

CellPress

Trends in Parasitology

Spotlight

Helminths target macrophage epigenetics and metabolism to evade immunity

Bart Everts [1,*]

Parasitic helminths are well known master regulators of host immune responses. Yet, the underlying molecular principles remain largely enigmatic. Recent work from Bohnacker *et al*. reveals that glutamate dehydrogenase (GDH), a metabolic enzyme secreted by *Heligmosomoides polygyrus*, can suppress type 2 immunity by multimodal regulation of macrophage metabolism and epigenetics.

More than 2 billion people worldwide are infected with – or are at risk of becoming infected with – parasitic worms. These infections are often chronic in nature due to the elaborate mechanisms that worms have developed throughout millions of years of coevolution to modulate host immunity and prevent their expulsion. This often involves suppression of antihelminth type 2 immune responses and/or promotion of the regulatory arms of the immune system to indirectly dampen type 2 immunity. Understanding the underlying molecular mechanisms through which helminths subvert host immune responses may not only inform design of novel treatments against the parasites themselves but may also identify new approaches to dampen unwanted overzealous immune responses that are at the root of many inflammatory diseases ranging from allergies to autoimmune disorders. A number of studies on the secretome of parasitic worms and their various life-cycle stages have revealed immunomodulatory effects on a wide range of immune cells [1]. However, we are only starting to scratch the surface when it comes to identifying the individual molecules and their mechanism of action through which these parasites are able to evade host immunity.

Esser-von Bieren and colleagues recently identified a metabolic enzyme, GDH, secreted by *H. polygyrus*, a rodent nematode parasite commonly studied as a model for human hookworm infection, with potent ability to suppress type 2 immunity [2]. Using these findings as a starting point, the current work from Bohnacker *et al.* [3] dissects the underlying molecular mechanisms through which GDH suppresses type 2 immunity. First, they show that antibody-based neutralization of GDH during infection increases worm expulsion rates, demonstrating the physiological importance of this single enzyme in suppressing host immunity. To probe the underlying mechanisms, they focused on macrophages given their importance in mediating antiparasite immunity. Additionally, macrophages are likely to be readily exposed to GDH *in situ* as they closely interact with these parasites in the gut. Indeed, recombinant helminth (he)GDH was able to induce an immunosuppressive phenotype in human monocyte-derived macrophages, characterized by, on the one hand, high expression of regulatory factors IDO, IL-10, and prostaglandin family members, and on the other hand, reduced expression of type 2-inducing mediators such as cysteinyl leukotrienes (cysLTs). Through alignment of ChIP-seq and RNA-seq data of these genes, they found an important role for altered histone acetylation (H3K27ac) downstream of histone-acetyl transferase p300 in the GDH-driven alterations in macrophage phenotype (Figure 1). Next, the authors explored the contribution of the enzymatic activity of GDH to macrophage modulation. Interestingly, using a kinase dead mutant they found suppression of cysLTs to be dependent on its enzymatic activity, while induction of other regulatory features by the macrophages, such as IL-10 and PGE2, was not. Instead, through crystallography, they identified the N-terminal tail, which is unique to heGDH, to be required for that (Figure 1).

It is now well established that macrophage biology and functions are intricately linked to their metabolic state. Having established the importance of the enzymatic activity of GDH in underpinning some of its immunomodulatory functions, the authors wondered whether GDH may induce metabolic reprogramming of macrophages. Mammalian GDH catalyzes the conversion of glutamate into α-ketoglutarate (a-KG), a metabolic intermediate of the tricarboxylic acid (TCA) cycle. Consistent with the enzymatic activity of the mammalian counterpart, treatment with heGDH resulted in reduced glutamine and glutamate levels, and increased levels of 2-hydroxyglutarate (2-HG), a downstream product of a-KG. Importantly, 2-HG suppressed cysLT production by macrophages, thereby tying enzyme activity-dependent metabolic reprogramming by heGDH to reduced leukotriene synthesis. In parallel, heGDH promoted glycolysis and suppressed oxidative phosphorylation which was dependent on p300 activity (Figure 1). Yet, the functional consequences of this metabolic shift were not assessed.

Finally, the authors explored the *in vivo* relevance of these findings by injecting heGDH into mice during *H. polygyrus* infection. Corroborating their initial findings showing that neutralization of natural GDH during infection increased resistance, its supplementation had the opposite effect. This was accompanied by increased PGE2 levels and reduced Th2 cell accumulation in the intestine. Consistent with this, helminth antigen-driven Th2 responses in human peripheral blood mononuclear cell cultures were suppressed by heGDH in a partially PGE2-dependent

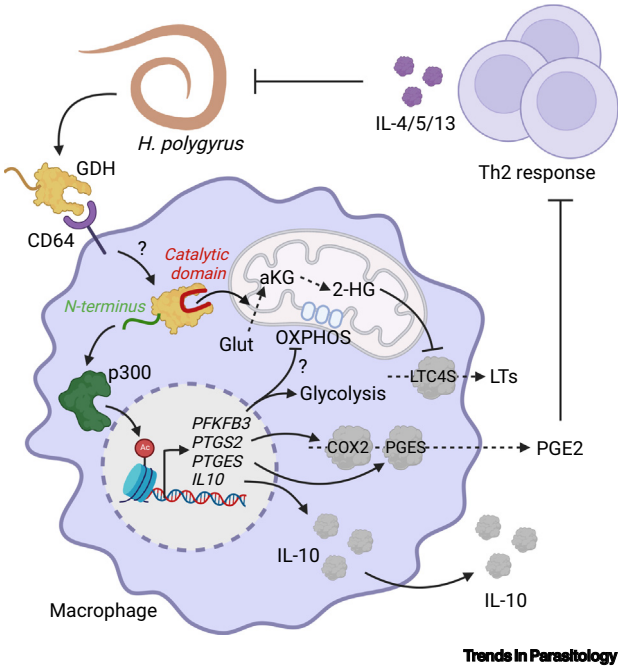

Figure 1. Proposed mechanism through which helminth-derived glutamate dehydrogenase (GDH) modulates macrophages to subvert immunity. *Heligmosomoides polygyrus*-derived GDH becomes internalized by macrophages via CD64. Through its N-terminal domain, it can then alter histone acetylation in a p300-dependent manner and promote expression of genes encoding glycolytic enzyme PFKFB3, prostaglandin E2 (PGE2)-synthesizing enzymes cyclo-oxygenase 2 (COX2) and prostaglandin E synthase (PGES), and interleukin 10 (IL-10). In parallel, through its enzymatic activity, GDH can promote synthesis of α-ketoglutarate (aKG) and 2-hydroxyglutarate (2-HG) from glutamate (Glut), which can suppress the activity of leukotriene C4 synthase (LTC4S) and thereby leukotriene synthesis. Subsequently, enhanced PGE2 production by macrophages can suppress Th2 responses to limit antihelminth immunity. Abbreviations: LTs, leukotrienes; OXPHOS, oxidative phosphorylation. Figure created using BioRender.

manner, possibly indicating that heGDH promotes helminth chronicity by suppressing Th2 responses through macrophage-derived PGE2 (Figure 1).

This elegant study provides novel insights into the intricate ways through which parasitic worms interact with the host to modulate host immune responses to their own benefit as well as the host by preventing excessive potentially tissue damaging inflammatory responses. There is a growing body of literature reporting that pathogens can modulate and exploit host (immune) cell metabolism to increase survival and replication rates [4]. This is one of the first studies showing that multicellular parasites have developed mechanisms to do so as well, as well as showing how they do it.

Nonetheless, some questions remain to be addressed. For instance, the functional relevance of the metabolic shift towards glycolysis remains unanswered but would be interesting to address given that immunosuppressive macrophages are commonly characterized and supported by increased oxidative phosphorylation [5]. At the immunological level, the data presented in this study suggest an inhibitory role for macrophage-derived PGE2 on Th2 responses. How this can be reconciled with other studies – which have shown that, in the context of helminth infections, PGE2 can also promote Th2 responses when produced by dendritic cells [6] – needs further investigation to better understand the pleiotropic nature of this fatty acid in the context of type 2 immunity.

In addition, this work opens new avenues for exploration. For instance, it raises the exciting possibility that GDH, by its ability to alter the epigenetic landscape of macrophages, may exert long-lasting effects on type 2 immune responses, thereby impacting susceptibility to other inflammatory diseases and/or immunity to subsequent infections. This would align with, and further support, recent findings pointing towards an important role for induction of innate immune memory by helminth-derived factors to protect against inflammatory diseases [7]. Finally, although this work is centered around functional characterization of a product derived from a rodent parasite, immunomodulatory homologs of this enzyme have been found in human parasites as well, including protozoa [8], cestodes [9], and nematodes [10], thereby identifying this as a potentially highly conserved host–parasite interaction also relevant to human parasitic diseases. In this light, this study offers the rationale and the exciting future prospect of exploring the therapeutic potential of harnessing this crosstalk to treat inflammatory and infectious diseases.

Acknowledgments

B.E. is supported by NWO (VIDI grant #91719349).

Declaration of interests

The author declares no competing interests.

[1]Leiden University Center for Infectious Diseases (LUCID), Leiden University Medical Center (LUMC), Albinusdreef 2, 2333ZA Leiden, The Netherlands

*Correspondence:
b.everts@lumc.nl (B. Everts).

https://doi.org/10.1016/j.pt.2025.01.012

References

1. Maizels, R.M. *et al.* (2018) Modulation of host immunity by helminths: the expanding repertoire of parasite effector molecules. *Immunity* 49, 801–818
2. de Los Reyes Jimenez, M. *et al.* (2020) An anti-inflammatory eicosanoid switch mediates the suppression of type-2 inflammation by helminth larval products. *Sci. Transl. Med.* 12, eaay0605
3. Bohnacker, S. *et al.* (2024) A helminth enzyme subverts macrophage-mediated immunity by epigenetic targeting of prostaglandin synthesis. *Sci. Immunol.* 9, eadl1467
4. Olive, A.J. and Sassetti, C.M. (2016) Metabolic crosstalk between host and pathogen: sensing, adapting and competing. *Nat. Rev. Microbiol.* 14, 221–234
5. Wang, Y. *et al.* (2021) Mitochondrial metabolism regulates macrophage biology. *J. Biol. Chem.* 297, 100904
6. Kaisar, M.M.M. *et al.* (2018) Dectin-1/2-induced autocrine PGE2 signaling licenses dendritic cells to prime Th2 responses. *PLoS Biol.* 16, e2005504

7. Cunningham, K.T. *et al.* (2021) Helminth imprinting of hematopoietic stem cells sustains anti-inflammatory trained innate immunity that attenuates autoimmune disease. *J. Immunol.* 206, 1618–1630
8. Montes, C.L. *et al.* (2006) A *Trypanosoma cruzi* antigen signals CD11b+ cells to secrete cytokines that promote polyclonal B cell proliferation and differentiation into antibody-secreting cells. *Eur. J. Immunol.* 36, 1474–1485
9. Prodjinotho, U.F. *et al.* (2022) Helminthic dehydrogenase drives PGE(2) and IL-10 production in monocytes to potentiate Treg induction. *EMBO Rep.* 23, e54096
10. Cheng, Y.K. *et al.* (2024) Biological characteristics and functions of a novel glutamate dehydrogenase from *Trichinella spiralis*. *Parasite* 31, 65