A Good Day for Helminths

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A Good Day for Helminths: how parasite-derived GDH suppresses inflammatory responses

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Parasitic helminths are often associated with immunoregulation, which allows them to survive in their hosts in the face of type 2 immune responses. They achieve this feat through the secretion of multiple immunomodulatory factors. In this issue of *EMBO Reports*, Prodjinotho *et al* show that the parasitic cestode *Taenia solium* induces regulatory T-cell responses in mice and humans through the release of the metabolic enzyme Glutamate dehydrogenase (GDH), which may be a conserved pathway of immunoregulation in many helminths (Prodjinotho *et al*, 2022).

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See also: **UF Prodjinotho *et al***

Helminths can be divided into cestodes, nematodes or trematodes, an evolutionary diverse group of organisms. Many helminth parasites form chronic infections despite the presence of parasite-toxic immune effector responses. These responses are suppressed by the helminths through the release of sophisticated immunomodulatory factors, allowing them to evade the host immune system and survive in the host, while preventing damaging inflammation. Indeed, when an inflammatory response is raised against a chronic parasitic infection, this can often lead to debilitating or fatal pathology, for instance, elephantiasis in lymphatic filarial infections, cachexia in acute schistosomiasis and neurocysticercosis in tapeworm infection (McSorley & Maizels, 2012). Gaining further understanding of how the presence of helminths modulates and controls the host immune system, and what happens when this control fails, may be instrumental in the design of new treatments for helminth infections, and could garner better understanding of how to control inflammatory diseases.

Recent work has identified and characterised a range of immunomodulatory proteins secreted by helminth parasites. These include proteins capable of antagonising cytokines or their receptors (e.g. HpARI, HpBARI, and p43), interfering with cell signalling (ES-62) or suppressing dendritic cell maturation (ω-1) (Lothstein & Gause, 2021). However, a common and important shared pathway of immunomodulation is the induction of regulatory T cells, by either acting directly on T cells or via induction of tolerogenic antigen presenting cells (e.g. HpTGM, AIP-2 and GDH) (Lothstein & Gause, 2021).

In the study published in this issue of *EMBO Reports*, the authors described modulation of the host immune system via secretory products of the cestode tapeworm *Taenia solium* (Prodjinotho *et al*, 2022). During a *T. solium* infection, the parasite forms cysts in the brain, leading to neurocysticercosis (NCC), an inflammatory disease of the central nervous system (CNS). NCC can lead to epileptic seizures, and affects between 2.5 and 8 million people worldwide, particularly in Central and South America, Africa and Asia (Badur *et al*, 2018). Previously, it was unclear how viable cysts in the brain remain hidden to the host immune system, while inflammation only appears to occur when cysts die and break down. Recently, it has begun to be understood that the asymptomatic stages of NCC are associated with elevated levels of regulatory T cells (Tregs—an immunosuppressive subset of T cells), while cyst death leads to decreased Treg levels, activation of inflammation and symptomatic NCC (Badur *et al*, 2018; Prodjinotho *et al*, 2022).

Products released from either viable (CLys and CSN) or dead (CVF) cysts were collected and applied to human and mouse antigen-presenting cells (APCs) to assess the resulting effect on the immune response (Prodjinotho *et al*, 2022). Interestingly, the authors found that while CVF products strongly induced the release of the inflammatory cytokines TNF-α and IL-6, CLys and CSN instead induced the immunosuppressive cytokines TGF-β and IL-10. Furthermore, the presence of CLys/CSN leads to a tolerogenic phenotype of APCs due to a lack of upregulation of APC maturation markers. Strikingly, CLys- or CSN-treated APCs were capable of stimulating Treg differentiation and expansion, which further expressed surface markers known to drive T-cell trafficking to the CNS and lymphoid tissues (Prodjinotho *et al*, 2022). This APC-T-cell tolerogenic axis was maintained whether they used peripheral APCs, or microglia, the resident macrophage population in the brain.

The authors hypothesised that bioactive lipid mediators were important in this immunosuppressive pathway. They carried out lipidomics on supernatants from cyst product-treated APCs, finding that viable cyst products lead to the release of the arachidonic acid metabolites prostaglandin D_2 (PGD_2) and PGE_2 (Prodjinotho *et al*, 2022). Interestingly, Treg induction was

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attenuated when PGE_2 receptors or PGE_2 production was blocked, particularly in combination with IL-10 blockade, while stimulation of cells using a PGE_2 analogue significantly increased Treg induction. *T. solium* viable cysts, therefore, release factors capable of inducing tolerogenic T-cell phenotypes via APC-derived PGE_2 and IL-10.

To address exactly how *T. solium* products drove this immunoregulatory pathway, proteomic analysis of *T. solium* products was carried out, comparing the immunoregulatory CLys/CSN viable parasite products to the inflammatory CVF non-viable parasite products, finding that two proteins were particularly enriched in CLys/CVN; glutamate dehydrogenase (GDH) and isocitrate dehydrogenase (IDH) (Prodjinotho *et al*, 2022). GDH and IDH are metabolic enzymes in mammalian cells, producing α-ketoglutarate from glutamate or isocitrate respectively. Recently, it was suggested that GDH and IDH are involved in the production of various lipid mediators in mammalian cells (Badur *et al*, 2018). GDH and IDH are widely conserved among free-living and parasitic helminths, including in the murine intestinal nematode *Heligmosomoides polygyrus*, in which GDH was first shown to have an immunoregulatory role. In this context, *H. polygyrus* GDH acted on macrophages to induce PGE_2 and IL-10 release, subsequently modulating and suppressing type 2 immune responses in the context of a model of allergic asthma (de Los Reyes Jiménez *et al*, 2020).

Similarly, Prodjinotho *et al* (2022) showed that inhibition of GDH and/or IDH activity in CLys/CVN abrogated promotes PGE_2 and IL-10 release from APC, and subsequent Treg expansion. This PGE_2, IL-10 and Treg induction could be partially rescued by the addition of recombinant *T. solium* GDH. Intriguingly, despite the fairly high levels of conservation of GDH between different species, human GDH could not mediate this activity. Therefore, GDH from parasitic helminths appears to have developed a new function; to modulate the host immune response (Fig 1).

The finding that the immunoregulatory activity of GDH is shared by the cestode *T. solium* and the nematode *H. polygyrus* is an intriguing one. Many of the helminth-

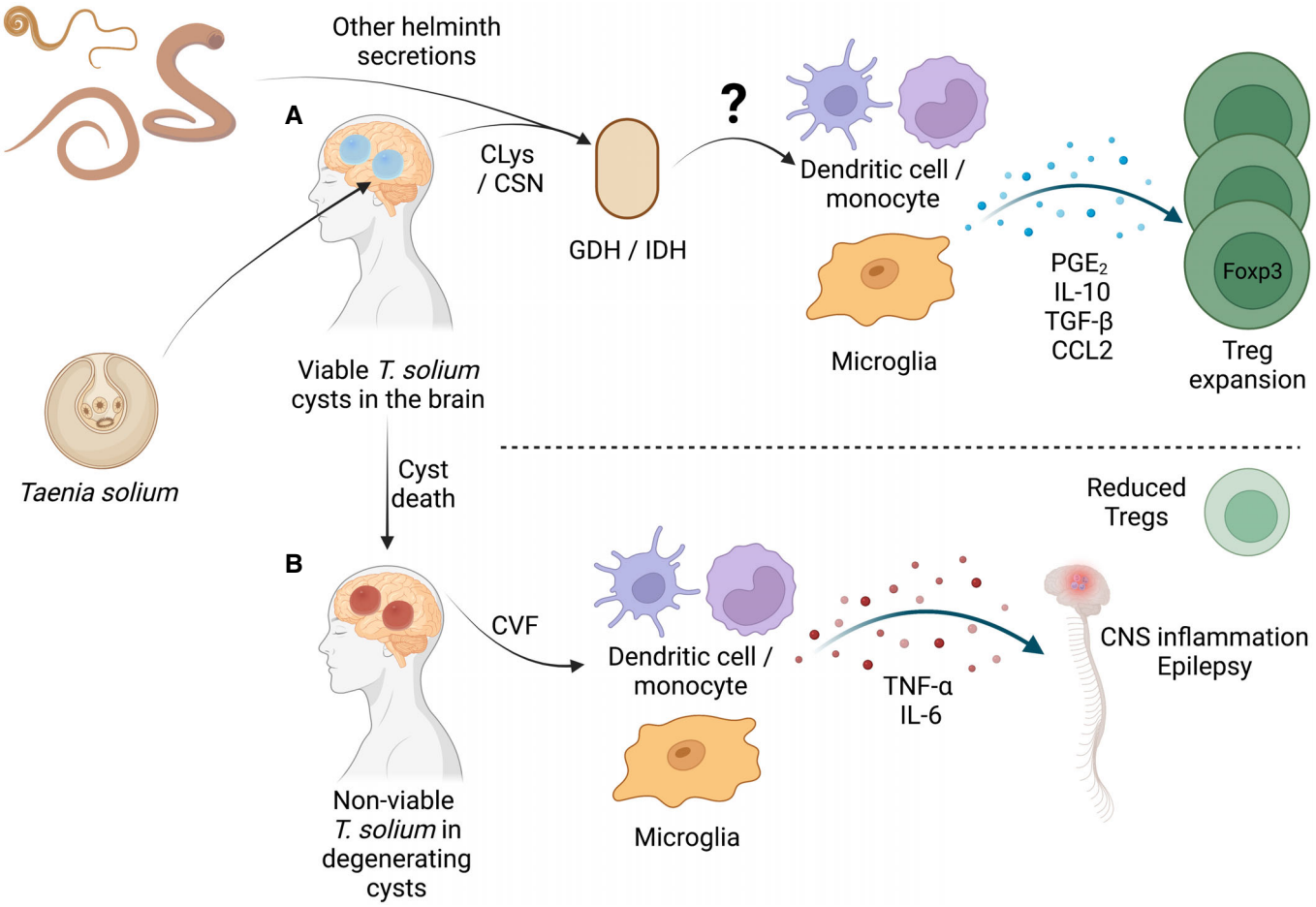

Figure 1. Schematic of the effect of *Taenia solium* cyst products on host immune cell populations.

(A) *T. solium* helminths form cysts in the brain. Viable cyst products, CLys and CSN, promote PGE_2, IL-10, TGF-β and CCL2 release by antigen presenting cells (APC). They achieve this through the action of glutamate dehydrogenase (GDH) and isocitrate dehydrogenase (IDH) (enzymes also encoded by other helminths), which lead to differentiation of $Foxp3^+$ regulatory T cells (Treg) and a tolerogenic environment. (B) Non-viable cyst product CVF conversely promotes TNF-α and IL-6 release by APCs, with limited Treg differentiation and increased tissue inflammation. This inflammation in the brain leads to a range of symptoms including epileptic seizures. This figure was created with BioRender.com.

derived immunomodulatory proteins so far described appear unique to one helminth (e.g. HpTGM, HpARI and HpBARI from *H. polygyrus*), or to a small family of closely related parasites (e.g. p43 from *Trichuris* spp., ω-1 by *Schistosoma* spp.). The discovery of an immunomodulatory protein conserved across the range of helminth parasites could have interesting implications for control of a range of parasite infections, and the prevention of immune-mediated diseases such as asthma.

This study raises several questions: does this activity of helminth GDH depend on its known enzymatic and metabolic activity, or has it developed a novel function? How widely is the immunomodulatory activity of GDH shared among the helminth family? GDH is present in free-living nematodes such as *Caenorhabditis elegans*, do these species share this activity or was it an adaptation to parasitism? Parasitism has arisen independently several times in the helminth family (International Helminth Genomes Consortium, 2019), therefore GDH's immunomodulatory function may also have evolved several times. Finally, how much of the immunoregulatory activity of helminths can be pinned on GDH, and can its activity be replicated in immunoregulatory treatments for human disease?

Development of symptomatic disease in NCC is often associated with administration of the common anthelmintics praziquantel and albendazole, resulting in death of the encysted parasite and resulting inflammation. Therefore, understanding how this inflammation is controlled by the parasite could lead to better treatments for this debilitating and dangerous disease.

Disclosure and competing interests statement

The authors declare that they have no conflict of interest.

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