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).

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 D₂ (PGD₂) and PGE₂ (Prodjinotho et al, 2022). Interestingly, Treg induction was...
attenuated when PGE2 receptors or PGE2 production was blocked, particularly in combination with IL-10 blockade, while stimulation of cells using a PGE2 analogue significantly increased Treg induction. *T. solium* viable cysts, therefore, release factors capable of inducing tolerogenic T-cell phenotypes via APC-derived PGE2 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 PGE2 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 PGE2 and IL-10 release from APC, and subsequent Treg expansion. This PGE2, 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-
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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