Laidlaw Scholars Undergraduate Leadership and Research Programme

Research Report

Can Helminths be Modelled as 'Old Friends' to the Human Immune System and Metabolism?

A Literature Review

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Abstract

This research project assesses the future of the relationship between humans and parasitic worms. Helminths are found in our soils, freshwater and livestock and have lived with and threatened humans for millions of years. The 'Old Friends' hypothesis proposes that our immune system may have evolved dependence on worm exposure. The hypothesis is that to survive in their human host longer, helminths suppress the immune system, which protects the host from allergic, autoimmune and inflammatory diseases caused by a hypersensitive immune response. This is important because the increased cleanliness and sterilisation in wealthy urbanised societies has seen a loss of helminth exposure alongside a concomitant increase in these types of diseases. This literature review investigates evidence of the 'Old Friends' hypothesis in experimental mouse models and clinical trials in humans. Research found that while the immunosuppressive effect of helminth infection is temporary, and lost upon clearance of infection, there is immense therapeutic potential for helminths and their secreted products in treating immune-mediated and metabolic diseases. It concluded that helminths are both friend and foe: they can cause malnutrition and anaemia but may also suppress inflammation and susceptibility to metabolic diseases such as obesity and diabetes. Looking ahead, the chemical messengers that helminths secrete to suppress the immune system show promise in treating non-communicable autoimmune and metabolic pathology.

Abbreviations (In Alphabetical Order)

Abbreviation	Definition
BCG	Bacillus Calmette–Guérin vaccine against Tuberculosis
CD	Crohn's Disease
HFD	High Fat Diet
IBD	Inflammatory Bowel Disease
IL	Interleukin
ILC-2	Type 2 Innate Lymphoid Cell
IFN	Interferon
PAMPs	Pathogen Associated Molecular Patterns
STH	Soil-Transmitted Helminths
Th	T helper cell
Treg	Regulatory T cell
T2DM	Type 2 Diabetes Mellitus
TSO	Trichuris Suis Ova
UC	Ulcerative Colitis
UCP1	Uncoupling Protein 1
WAT	White Adipose Tissue

Introduction

Helminths are parasitic worms that have co-evolved with their human hosts over hundreds of millions of years. Their footprint on human civilisation is evidenced in historical records dating back as far as 3000 BC in the societies of Ancient Egypt and China (1). Through our varied diets, migration patterns and diverse habitats, humans may be the most parasitised animal of all (2). In tropical and subtropical areas, where sanitation and hygiene are poor, soil-transmitted helminths (STH) are highly prevalent. Helminth infections are associated with nutritional deficiencies, impaired cognitive development, and amplification of poverty. Hence, helminths have long been considered a deleterious foe to be eradicated (3). Most developed countries have successfully eradicated human helminth infection, and many developing countries have implemented mass deworming drug administration programmes. However, epidemiological studies have correlated helminth eradication with an increased prevalence of autoimmune and allergic diseases (4). Researchers have proposed that exposure to microorganisms and pathogens, including helminths, shaped the evolution of the mammalian immune system and promote immunological tolerance, protecting humans against inflammatory disease. This is a concept known as the 'Old Friends' hypothesis (5).

Helminth Life Cycles

Helminths are complex organisms with multi-stage life cycles including an egg, multiple immature larval stages and the sexually mature adult worm. They are broadly categorised into STH that settle and reproduce in the intestinal lumen, and tissue-dwelling helminths that require intermediate hosts such as snails (e.g. *schistosoma spp*.) or pigs (e.g. cestodes/tapeworms) to complete their life cycle. Humans become infected by ingestion of eggs or larvae, by direct contact with skin-invading larvae, and by direct cutaneous inoculation during insect bites (6). Larval development within the human host often involves invasive transit through multiple internal organs. For example, the soil-transmitted hookworm *Ancylostoma duodenale* penetrates skin, enters the circulation, exits in the lungs, and gains access to the gastrointestinal tract by ascending the airways to the throat where it is swallowed (Figure 1) (7). By contrast, trematodes such as *Schistosoma spp.* mature and reproduce within the circulatory system and it is their eggs that drive tissue pathology as they accumulate in the liver, or migrate through the intestinal or bladder wall (8).

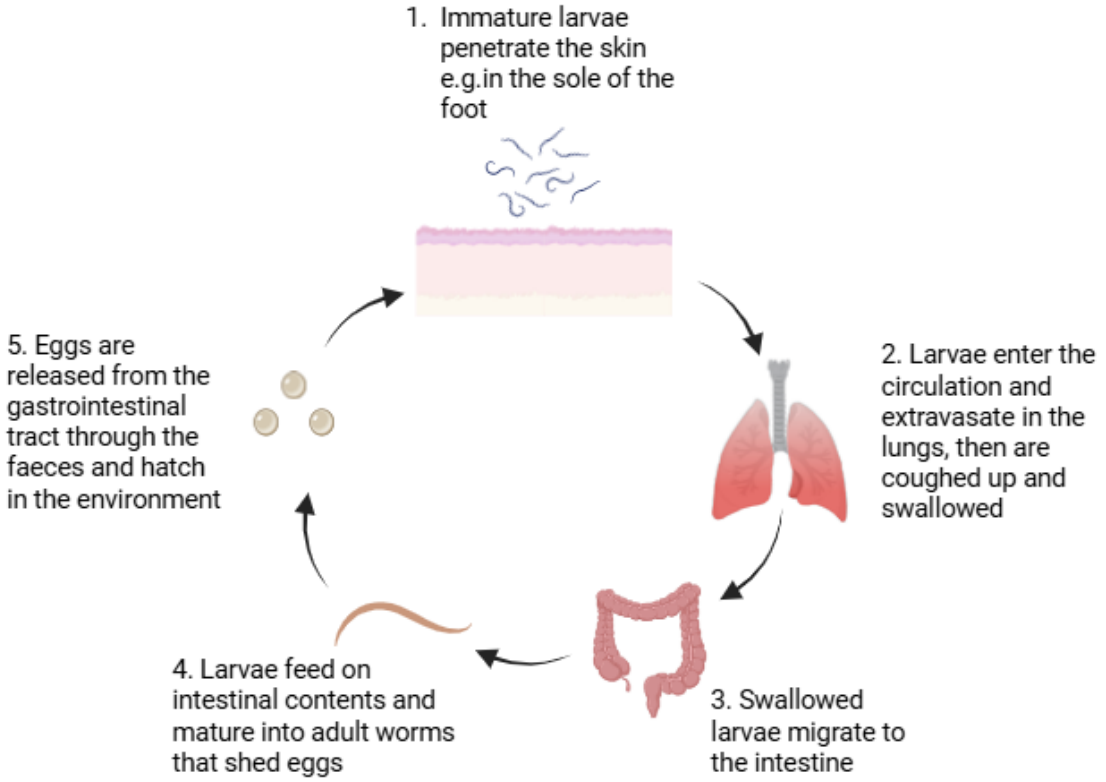

Figure 1. The Life Cycle of *Ancylostoma duodenale* (9)

Left untreated, a helminth infection lasts as long as the life span of an adult worm, which can be several years (6). Despite continuous exposure, sterilising immunity does not occur, which reflects how helminths have evolved mechanisms to evade immune detection. A state of homeostasis is established within their human host, preserving its fitness to prevent symptoms and support prolonged infection. However, helminths have a challenge – they are large, invasive, and unable to hide within host cells like viruses. To survive, they suppress the immune system to hide in plain sight, and exploit its pathways to ensure timely repair of tissue destruction associated with invasive stages of its life cycle (6).

<u>The Interaction of Helminths on the Mammalian Immune System</u>

The mammalian immune system is a complex network of cells and signalling molecules that protect the host from infectious challenge and maintain tissue homeostasis. Traditionally, the immune response to foreign invaders has been considered as two systems, innate and adaptive. Innate immunity provides a rapid inflammatory response to broadly conserved microbial patterns and markers of tissue disruption. It also primes adaptive immunity, which is a delayed but highly specific response that generates long-lasting protection against symptomatic re-infection (10). The key orchestrator of the adaptive response is the $CD4^+$ T helper (Th) cell, which supports the activation of

neighbouring immune cells through secretion of cytokines, chemical messengers (10). Upon activation, Th cells expand and differentiate into discreet lineages with effector functions that are tailored to fit a particular pathogen (11). The lineages can be broadly categorised into Th1, Th2 and Th17 (Figure 2) (11). Th1 cells drive cell-mediated immunity, secrete pro-inflammatory IFNγ, and are important in the response to intracellular infection. Th2 cells drive humoral immunity, secrete IL-4, IL-5 and IL-13, and are fundamental in the response to parasitic helminths (12). Th17 cells secrete IL-17 and IL-22 and target extracellular microbes, particularly bacteria. Regulatory T cells (Treg) are also $CD4^+$, secrete anti-inflammatory cytokines IL-10 and TGF-β and suppress neighbouring T cell activation (13).

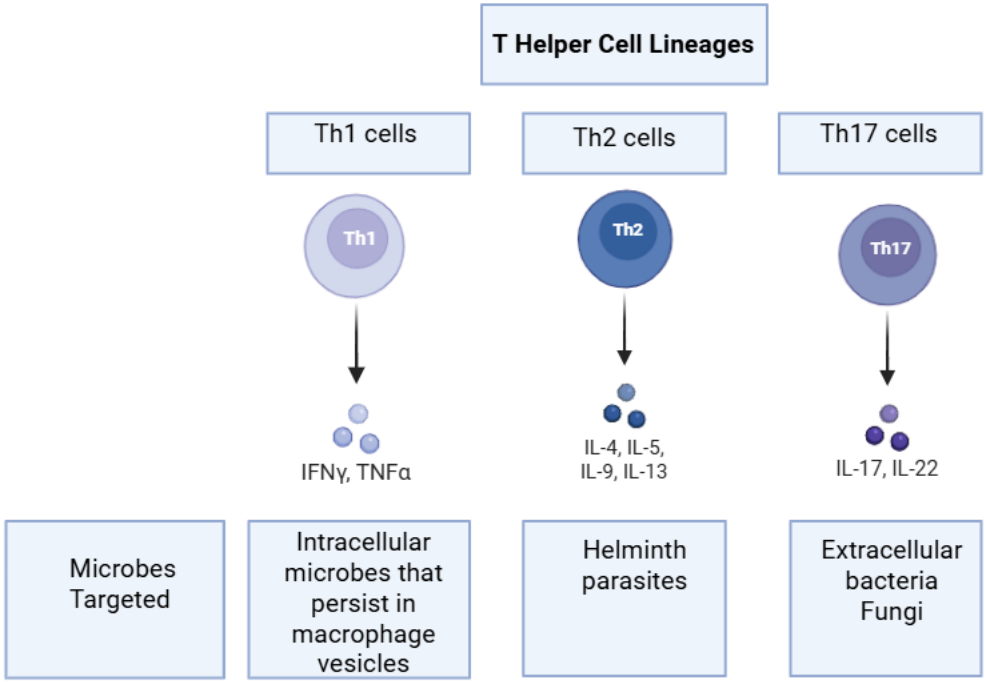

Figure 2. T Helper Cell Lineages (10)

The characteristic response to intestinal helminth infection involves an acute Th2 response and a regulatory response. Helminth-derived metabolites are detected by rare chemosensory tuft cells in the intestinal epithelium (14). Tuft cells secrete several alarmins, chemical messengers that signal danger (15). These alarmins activate type 2 innate lymphoid cells (ILC-2) to produce IL-5 and IL-13. IL-5 and IL-13 increase intestinal motility, increase goblet cell mucous production, and recruit innate immune cells called eosinophils that are loaded with helminth-toxic cytosolic granules (16). The early production of 'type 2' cytokines including IL-4, IL-5, and IL-13 drives Th cells to adopt a Th2 phenotype (17), which amplifies the circuit and re-enforces this 'weep and sweep' response (Figure 3) that prioritises intestinal parasite expulsion (18).

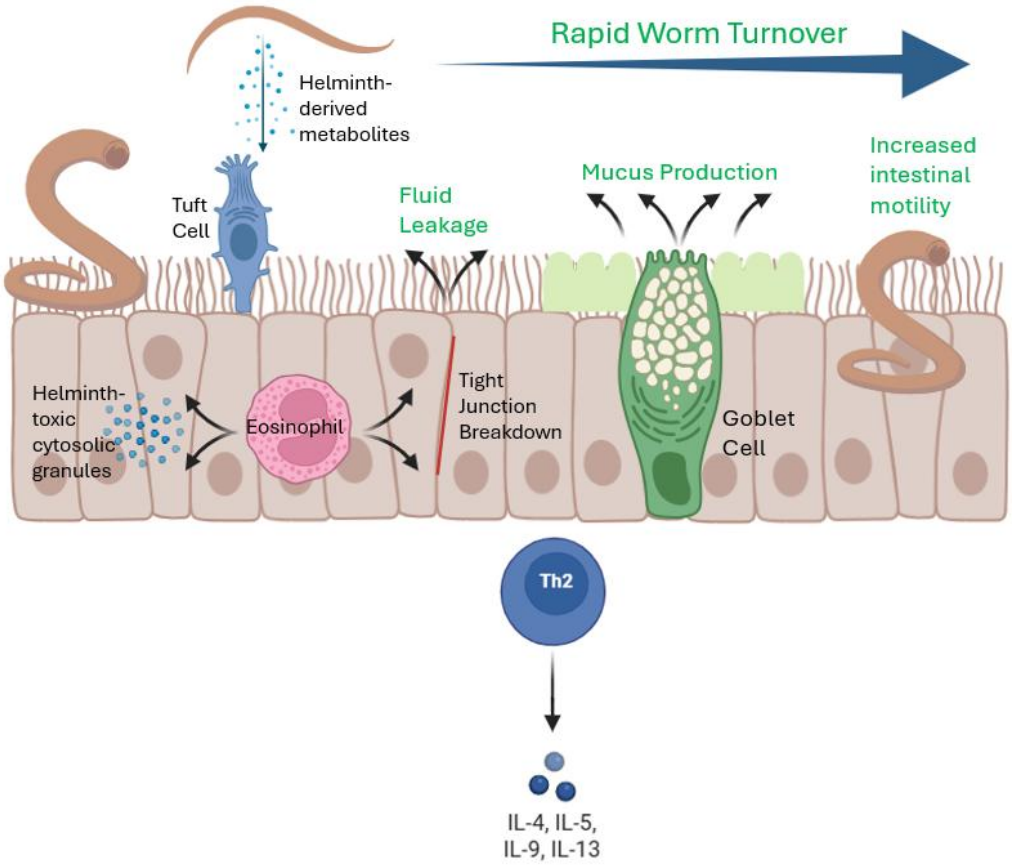

Figure 3. The Weep and Sweep Mechanism (19)

If helminth clearance is unsuccessful, the Th2 response must be attenuated by the regulatory response, to enable tissue repair and maintain the integrity of the intestinal barrier. Type 2 cytokines such as IL-4 drive nearby macrophages to adopt an anti-inflammatory 'M2' tissue-repairing phenotype and induce expansion of regulatory T cells (Tregs), that have been shown to limit the collateral damage caused by unrestrained Th2 and Th1 responses (10). Evolutionarily, this induced immunosuppression enables helminths to establish long-term residence within their host and successfully reproduce whilst minimising pathology. Although this biology could be beneficial in the context of autoimmune disease, it can be detrimental in the context of intracellular infections (e.g. Tuberculosis), vaccination (e.g. BCG), and tumour immunotherapy where a potent Th1 response is needed for efficacy (Figure 4). Thus, it is a double-edged sword.

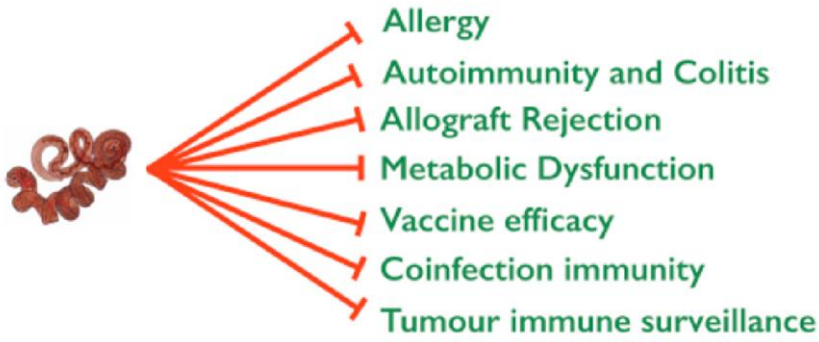

Figure 4. The Effect of Worm Secretions (Artavanis-Tsakonas, 2024)

The Impact of Helminth-Induced Immune Modulation

The ability of helminths to induce a modified type 2 response with systemic immune suppression has encouraged researchers to test whether exposure to these pathogens can be beneficial to treat autoimmune diseases such as inflammatory bowel disease (IBD) (e.g. ulcerative colitis, [UC] and Crohn's disease [CD]) (20). IBD is proposed to result from a failure to downregulate a chronic Th1 intestinal inflammatory process (21). Induction of a Th2 immune response by intestinal helminths diminishes Th1 responsiveness so in theory could treat IBD.

A promising study in 2003 showed that the pork whipworm *Trichuris suis* could be a safe and possibly effective treatment for IBD (20). 7 patients with UC and CD received weekly oral doses of *Trichuris suis* eggs (TSO) and reported their symptoms using the Inflammatory Bowel Disease Quality of Life Index. Results were impressive with 9/11 participants achieving disease remission. However, a more rigorous randomised double-blind placebo-controlled trial in 5 developed countries in 2016 failed to replicate this result. (22). A cohort of 252 participants with CD received TSO or a placebo solution. Although safe, TSO showed no clinical superiority over the placebo group for inducing remission in mildly-to-moderately active CD, which has stalled the research into the future of this treatment.

The underwhelming results using TSO could be because these helminths are adapted to pigs and are not 'old friends' of humans. Indeed, they only transiently colonise the gut before being shed, rather than inducing long-term immunosuppression (23). Furthermore, more recent research has challenged the concept that CD is only associated with Th1 cells and shown that Th17 cells are implicated as well (23). If TSO suppresses Th1 but not Th17 responses, there could still be a source of intestinal inflammation following treatment. Therefore, it could be worthwhile to use a combination therapy of helminth products to target Th1 as well as humanised monoclonal antibodies to target IL-23, which activates Th17 cells (24).

In the discussion of therapeutic helminth infection, a drawback is that uncontrolled worm secretions can have undesirable immunological effects. By inducing a state of systemic immune suppression, helminth infection may blunt responses to a variety of vaccines or infections in the real-world setting. Consistent with this, there is evidence demonstrating that vaccine efficacy is alarmingly reduced in tropical low-income countries where helminths are endemic. Vaccines designed to protect against intracellular pathogens, such as Tuberculosis, Malaria and COVID, require a strong cell-mediated Th1 response in order to achieve effective host protection (25). By blunting Th1 immunity, chronic helminth infection attenuates vaccine responsiveness (25). Indeed, a randomised control trial performed across helminth-endemic islands of Lake Victoria, Uganda has demonstrated that intensive de-worming significantly improved the response to the BCG vaccine (26). Thus, whilst helminths or their excretory-secretory product may be of benefit in some autoimmune diseases, the clinical evidence supporting this is limited and impact of chronic infection on public health can be significant.

The Impact of Helminths on Metabolism and Nutrition

The prevalence of metabolic diseases such as obesity, non-alcoholic fatty liver disease and type 2 diabetes mellitus (T2DM) has risen dramatically in developed nations and in developing countries that have recently experienced rapid urbanisation (27). In 2020, 38% of people over 5 years of age worldwide were overweight or obese, with projections to reach 51% by 2035 (28). Risk factors for these disorders include hyperlipidaemia, abdominal obesity, hypertension and insulin resistance and are collectively described as the metabolic syndrome (Figure 5) (29).

In recent years, landmark studies have highlighted a link between metabolism and immunity. The fruitfly (*Drosophila melanogaster*) incorporates energy storage (fat), and innate immunity into a single organ called the 'fat body', where pro-inflammatory cytokine signalling can induce systemic insulin resistance with impact upon distant organs (Figure 5) (30). The metabolic impact of pro-inflammatory cytokines (*termed metainflammation*) is evolutionarily conserved in mammals and is inappropriately up regulated in states of nutrient excess (31).

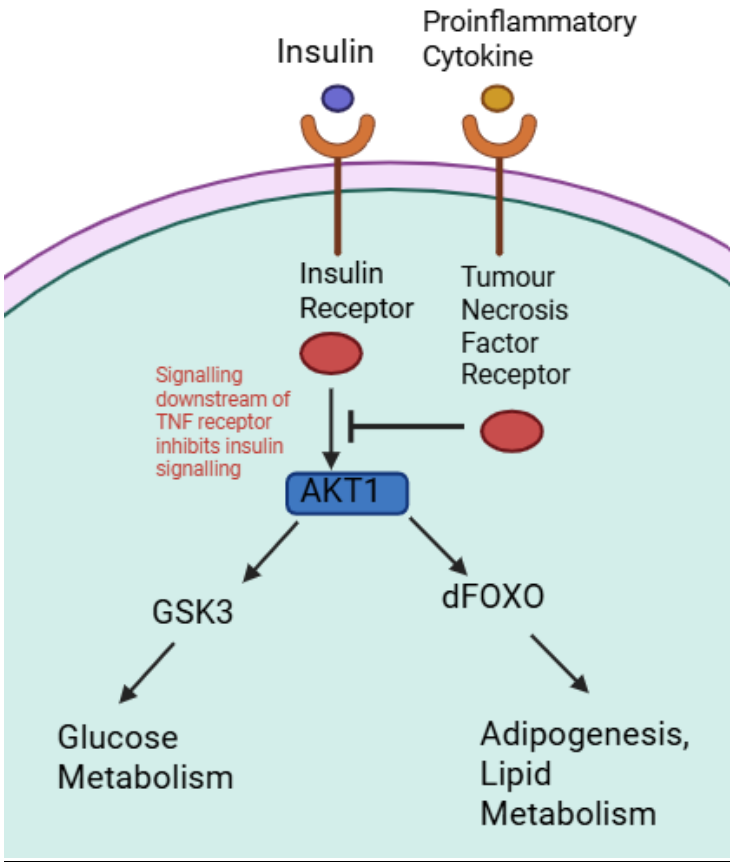

Figure 5. The interaction of pro-inflammatory cytokines with the insulin signalling pathway (31)

In mammals, there are two types of adipose tissue. White adipose tissue (WAT) stores energy, whereas brown adipose dissipates energy to generate heat (32). During healthy metabolic homeostasis, WAT is enriched for ILC-2, M2 macrophages, Eosinophils and Tregs. Similar to the immune response to intestinal helminth infection, IL-5 and IL-13 produced by ILC-2 in WAT attract eosinophils, which secrete IL-4 and drive macrophages to adopt an M2 phenotype (33). M2 macrophages are particularly important for metabolic homeostasis as they consume/buffer excess lipid released during adipocyte lipolysis (34). However, in obesity, the balance is perturbed (Figure 5). Prolonged caloric excess causes adipocytes to hypertrophy and outgrow their blood supply with resultant hypoxia and lipid cell necrosis (32). The increased spillover of lipid and free fatty acids contributes to macrophage-driven inflammation (35). Consequently, WAT becomes enriched in pro-inflammatory M1 macrophages and Th1 cells but depleted in Tregs and eosinophils (36). Such 'meta-inflammation' induces systemic insulin resistance and predisposes to the metabolic syndrome. Hence, mice rendered deficient in pro-inflammatory cytokine (i.e. TNF-α) production or signalling display increased sensitivity to insulin (Figure 6) (37).

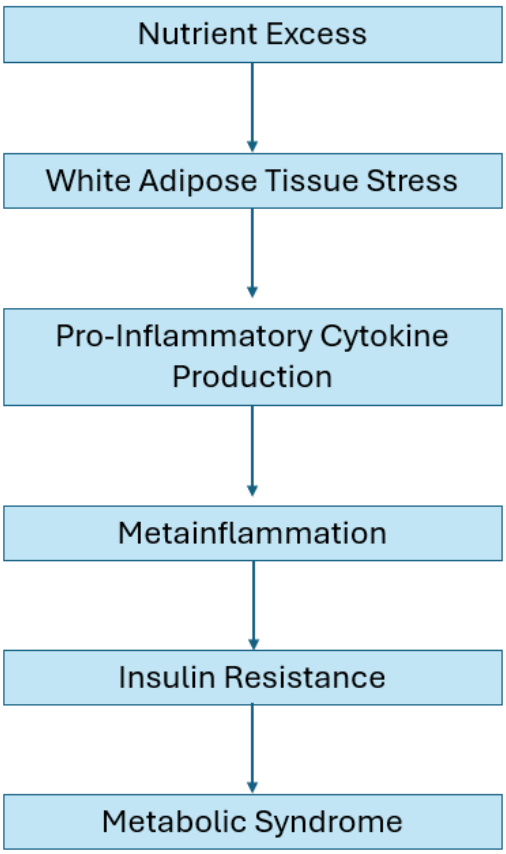

Figure 6. Schematic highlighting the role of inflammation in insulin resistance (38)

Given the systemic regulatory impact of helminth infection on host immunity, it has been proposed that therapeutic exposure to these pathogens may protect against the metabolic syndrome (Figure 7). Indeed, mice rendered transgenic for IL-5, harbour a constitutive eosinophilia that is associated with reduced accumulation of visceral adipose and enhanced sensitivity to endogenous insulin during glucose challenge (36). Provocatively, a comparable phenotype could be induced in wild-type mice upon infection with the gastrointestinal roundworm *Nippostrongylus brasiliensis* (36)(39). Infected mice displayed increased abundance of eosinophils in WAT and enhanced insulin sensitivity (36)(40). Similarly, infection with *Heligmosomoides polygyrus*, was associated with reduced adiposity in mice fed a high fat diet (HFD), which correlated with an increase in M2 macrophages and expression of uncoupling protein 1 (UCP1) in WAT (41). UCP1 is a mitochondrial membrane protein present in brown adipose tissue that is involved in utilisation of lipids for thermogenesis (42). However, this beneficial effect of helminth infection was lost through pre-treatment with broad spectrum antibiotics (43), suggesting that interactions involving the host intestinal microbiome may be key to the systemic metabolic impacts of helminth infection.

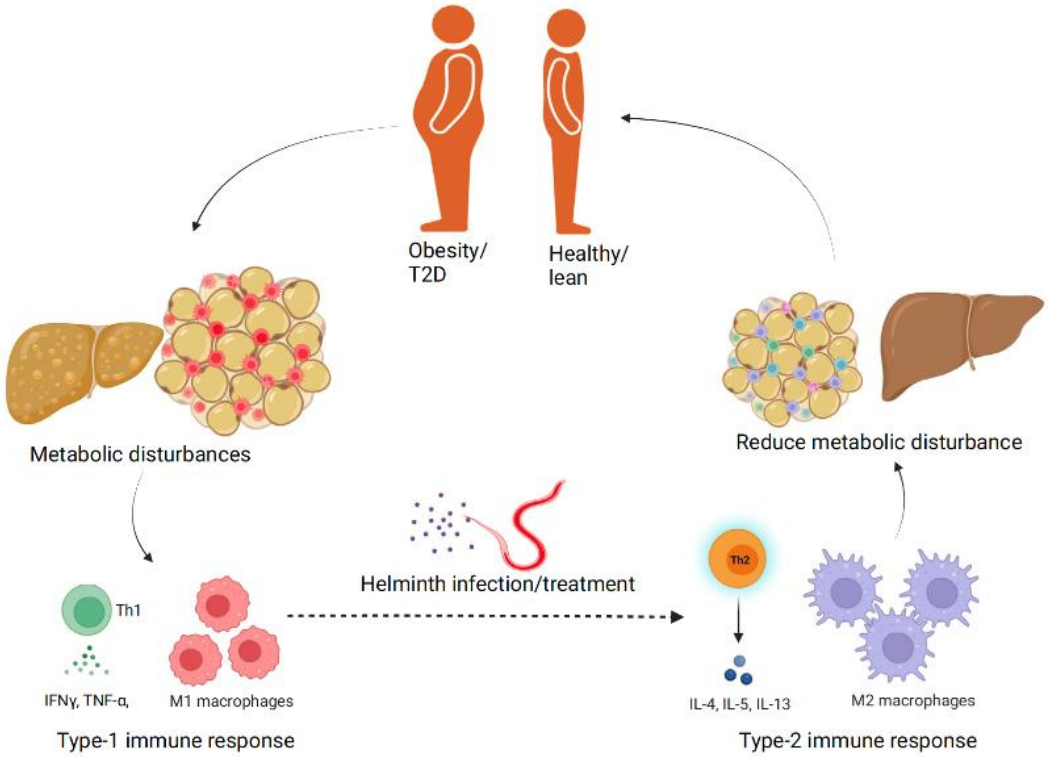

Figure 7. The immune response to metabolic syndrome and helminth-treatment (44)

In humans, helminth infection has been variably associated with increased insulin sensitivity (45), and protection against the development of T2DM. Furthermore, a small early phase trial recruiting patients diagnosed with metabolic syndrome showed that experimental infection with the hookworm (*Necator americanus*) induced systemic eosinophilia and elicited a modest reduction in fasting plasma glucose and improvement in insulin resistance relative to placebo (46). However, 44% of participants reported gastrointestinal side effects, some of which required deworming treatment.

Recently, the use of glucagon-like peptide-1 receptor agonists has been highly effective at improving glycaemic control, inducing weight loss and treating T2DM; however, these drugs require constant administration and have gastrointestinal side-effects (47). Instead, several anti-diabetic drugs (i.e. Metformin, Thiazolidinediones) successfully use modulation of M1/M2 macrophage phenotypes to suppress obesity-induced inflammation (48). Therefore, through this mechanism, helminths and their secretory products could be a next-generation treatment for T2DM.

Malnutrition Associated with Endemic Helminths

In nutrient excess, helminth infection can provide a countermeasure to protect against the metabolic syndrome (31). However, nutrient scarcity is a threat to survival and more often occurs in helminth-endemic settings where these infections can exacerbate

malnutrition. Fundamentally, these parasites not only scavenge nutrients from their host, but they also induce tissue damage, blood loss and can cause chronic intestinal inflammation impairing nutrient absorption (6). Females of child-bearing age are particularly vulnerable with respect to protein and iron-deficient malnutrition because of their monthly menstrual cycles and pregnancy. During pregnancy, maternal malnutrition and iron deficiency anaemia has adverse impacts on foetal development, which adapts by diverting its circulation to the developing central nervous system at the expense of other organs (i.e. smaller nephrons in the kidney, thinner myocardium in the heart) (49). Consequently, babies experience intrauterine growth restriction and have reduced birth weights (50). Curiously, if such children are exposed to nutrient excess in later life, their adaptations to the nutrient-deprived womb predisposes them to increased fat storage and metabolic syndrome (51). This hypothesis is called the developmental origins of health and disease and is believed to underlie a significant burden of non-communicable diseases globally (49). Therefore, helminth-endemic and undernourished populations may be predisposed to metabolic syndrome.

Discussion

Based on the current literature, helminths can be both friend and foe to humans. On one hand, they can exacerbate malnutrition, reduce vaccine efficacy, and may predispose children born to nutrient-deprived mothers to the metabolic syndrome. The Global Burden of Disease study reported that a quarter of the global population (1.5 billion people) suffer from anaemia, hypoproteinaemia, and loss of disability-adjusted life years caused by soil-transmitted helminth infections (52). On the other hand, the impact of helminth infection on immunity and metabolism present tantalising therapeutic opportunities to treat the rise in inflammatory and metabolic diseases. The nuance between friend and foe can be explored through our evolution with helminths, the basis of the 'old friends' hypothesis'.

Human evolution and parasitic infections have run hand in hand. Homo sapiens emerged in East Africa ~150,000 years ago and migrated out of Africa in waves ~60,000 years ago to occupy almost all the Earth's land ~15,000 years ago (53). Throughout this process, humans have carried heirloom parasites, inherited from primate ancestors, and souvenir parasites acquired from contact with animals during migration and agricultural practices (54). The development of settlements and cities in the Neolithic Revolution intensified the transmission of parasitic infections between humans (1), and the opening of trade routes, including the slave trade, spread new parasites from the New World to the Old World (55).

Building on this legacy, the 'Old Friends' hypothesis (5) proposes that the human immune system has evolved a dependence on microbes during our migration and

history. Microbe exposure induces immunological tolerance, preventing hypersensitive immune responses to harmless or self-antigens, seen in allergy and autoimmunity respectively. Hence, the loss of interaction with diverse microbiota, such as helminths, underlies the increase in chronic inflammatory disease in wealthy urbanised societies (56).

However, there is a challenge in applying this hypothesis to helminths. The principle of genetically evolved dependence assumes that helminth infection was inevitable for most humans throughout evolution and selected for genes that regulate the immune system in the presence of helminths. New research challenges this, and suggests that helminth burdens vary, with high intensity infections usually only concentrated in a small proportion of individuals in endemic areas (57), and that each species has a unique mechanism to suppress inflammation (58). If this is the case, there is no consistent pressure for helminth-dependent genes to be selected for in a population, so helminth-free populations are not evolutionarily disadvantaged. Therefore, the assumption of evolutionary dependence on helminths is a lot less convincing.

Conclusion

I propose that the relationship of helminths with humans must be looked at from 2 perspectives, a global health and then a therapeutic perspective.

From a global health perspective, the eradication of helminths should be pursued. Human health is intricately connected to those of other animals and the environment that they inhabit (59): it is the inhabitants of low-to-middle economic regions - such as sub-Saharan Africa, South America, and Asia – that are endemic for helminthiasis due to low access to clean water, sanitation, and hygiene (56). Therefore, development of these regions will inevitably include an eradication of human helminth infection, and elimination of the malnutrition and illness that these organisms cause.

Despite this, there is sufficient data to suggest that helminths and their interactions with the human immune system present significant therapeutic potential in the management of non-communicable metabolic and inflammatory diseases. Further study of this host:parasite interaction and better understanding of the factors responsible for the provocative observations made in model organisms with IBD or metabolic disease are sure to yield new therapeutic targets in the future. With molecular pathways better understood, it is possible that the therapeutic impact of helminth infection can be mimicked by targeted drugs. Helminths may not be our old friends, but their study could still be rewarding to future patients.

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