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A Concise Overview of Immunological Aspects and Immune Polarization against Soil-Transmitted Helminths (STHs)

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ABSTRACT

Introduction: Soil-transmitted helminths (STH) represent a common group of parasitic infections that commonly contract humans as their definitive hosts. This parasite has been declared the third most prevalent neglected tropical diseases (NTDs) globally. The intricate interplay between these parasites and the host immune response necessitates a comprehensive exploration of the immunological dynamics governing the response to STH for prospective insights.
Main Text: This review aims to elucidate the immunological facets of STH during host infection, delving into the intricate pathologic interactions underscored by the multifaceted involvement of adaptive and acquired immune responses. This immune interaction produces two major outcomes, chronic infection and worm expulsion depending on immune predominant response (type 1 versus type 2 immunity). Type 1 immunity is notable for its function against intracellular pathogens yet unsuitable for parasitic infection. Meanwhile, type 2 immunity is typical for macro parasite. However, attention recently has been dragged towards the study of the immunomodulatory properties inherent to STH, as recent reports leverage this characteristic to discern immune responses and functions against various parasitic diseases. Immunomodulation properties of STH are primarily mediated by the presence of Excretory/secretory proteins (ESPs) and soluble products (SPs) which act as a double-edged sword, enhancing parasitic invasion yet blunting immune response.
Conclusions: Understanding the immunological aspects of STH is imperative for fostering comprehension and effective management in the contemporary era, as the goal of eradicating STH as a neglected tropical disease remains distant. In addition, its immunomodulation properties bring several implications, particularly to the advancement of treating other diseases, such as autoimmune diseases.

INTRODUCTION

Parasitic infection also gives the world population a high burden of diseases notwithstanding its category as neglected tropical diseases (NTDs). Helminth infections are the top three parasitic infection which has DALYs of 5.16 million just behind cryptosporidiosis, but below Leishmaniasis, schistosomiasis and lymphatic filariasis (Pisarski, 2019). Soil-transmitted helminth also stands as one of the most predominant types of neglected tropical diseases (NTDs) infecting 24% of the global population or 1.5 billion infected people. Massive campaigns to eradicate its prevalence ensued to prevent soaring disability-adjusted life years (DALYs) among high-risk populations, including school-aged children (Mitra and Mawson, 2017). Major

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species in the STH group include *Ascaris lumbricoides* or roundworm, *Trichuris trichiura* or whipworms, and hookworm (two common species: *Necator americanus* and *Ancylostoma duodenale*). STH development involves humans as the definitive host throughout the life cycle yet necessarily soil contact is indispensable to establish a fertile egg that is subsequently ingested in the form of a fertilized egg or infective larva stage depending on the species. Furthermore, STH also denotes a helminthic group with similar diagnostic procedures as well as good responses to similar therapeutic agents (Jourdan et al., 2018).

Notably, the host's immune response determines the relationship between STH and the host. Host response will determine the fate of STHs infection whether it ultimately promotes chronic infection or direct worm expulsion based on the fate of immune polarization. The development of infection and immune response becomes the utmost important aspect to determine future infection and stratify host risk to produce more severe infection (Colombo and Grencis, 2020). Another essential aspect is the immunomodulation properties of STHs that are not uncommon in producing deviant immune responses. STHs will reside in the human body for a longer period, and turn into an adaptive process to support their proliferation and development via secreting several proteins as well as molecules, which is mentioned as immunomodulation properties (Loukas et al., 2021).

Nevertheless, not all helminth infections have immunomodulation properties in skewing the immune response of their host. From the recent reports, nematode intestinal infections, including *Trichuris trichiura, Ancylostoma sp*, and *Ascaris lumbricoides* are the most reported species triggering immunomodulation in their hosts. This article highlights a novel mechanism of parasitic infection that manipulates host immunity to enhance its invasiveness. Additionally, the parasite induces immune polarization to create conditions favorable for a successful infection, thereby supporting worm proliferation. Two modes of pathogenesis are presented as state-of-the-art discoveries in the parasitology field, yet they remain frequently overlooked by researchers.

OVERALL IMMUNE RESPONSE AGAINST STH INFECTION

The immune system will provoke against the presence of STH infection mainly using IgE-based response and type 2 immunity. The macroscopic appearance of STH infection will be easily recognized by the immune system. In the gut, STH presence induces alarmin secretion, including thymic stromal lymphopoietin (TSLP), Interleukin-25, and IL-33.

Those alarmins will eventually lead to the differentiation as well as mounted type 2 immune response. Subsequently, the hallmark cytokine of type 2 immunity is the production of IL-4, IL-5, IL-9, and IL-13 (Figure 1). There are wide arrays of these interleukin effects that could change the host environment to promote worm expulsion. Antibodies class switching ensues galvanising the anti-helminth effect via the IL4R/STAT6 signalling pathway, by increasing the production of IgE and IgG4 (Darlan et al., 2021).

B cell activation and humoral responses are stated as the most functional immune cells for macroparasite. Helminth invasion induces B cell activation and IL-10 production. Type 2 immunity and B cell activation are inseperable entities to promote worm expulsion. In a study, mice B cell deficiency lead to the disastrous infection of T.muris, H.polugyrus and Litomosoides sigmodontis, since no antibody production occur to coat helminth cell surface to promote effective opsonization and ultimately worm expulsion. IgG demonstrates excellent antibody protection against helminth infection, and IgM, commonly produce without T cell involvement, aims to eradicate filariasis (Harris and Gause, 2011).

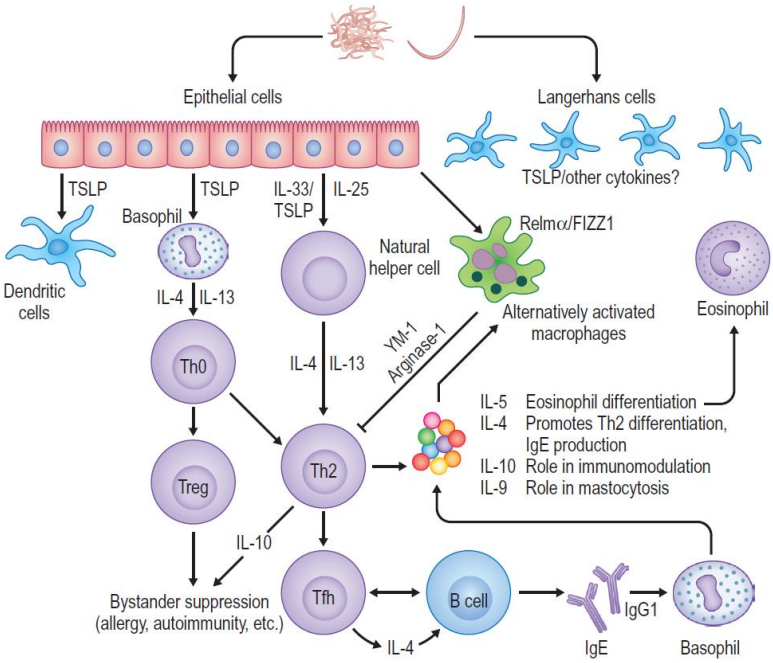

Figure 1. Overall immune response against STHs (IL, interleukin; Th0, precursor T-helper cell; Th2, T-helper 2 cell; Treg, Regulatory T cell; TfH, T-follicular helper cell, RELM-α, Resistin-like molecule-α; Chi3l, Chitinase 3 like protein; IDO, indoleamine 2,3 dioxygenase; TSLP, thymic stromal lymphopoietin (Babu and Nutman, 2019).

By the presence of an immune response, STH will forcefully produce modulation properties against host immunity to support its proliferation and development. The properties of immunomodulation of helminth infection through various ways of secreted substance preventing inflammatory response during the multiple steps of host immune response against STH infection (Loukas et al., 2021). To elaborate details about helminth immunomodulation properties, researchers frequently delve into the mimicry species of helminth infecting humans, including *Necator brasiliensis* for *N.americanus* infect mice and *Ancylostoma duodenale* in humans, Mice trichurid or *Trichuris muris* for *Trichuris trichiura* for humans, porine ascarid infection or *Ascaris suum* for *Ascaris lumbricoides*. Those species bear similar developmental stages to their human species counterpart opening the opportunity to study the details of STH infection without inhibition by ethical issues (Montano et al., 2021).

IMMUNE POLARIZATION: CHRONIC INFECTION VERSUS WORM EXPULSION

Conventional delineation of immune response separated into humoral (B cell responses) and cell-mediated immunity (T cell responses). Dating back to the early 1980s when 2 major subsets of lymphocytes had been discovered: T helper cells which conceived CD4 and T cell bearing CD8 markers mentioned as Cytotoxic T cells. Two different immune cells provoke two distinct downstream implications, CD4 can induce antibody production through B cell activation while CD8+ cell promotes cell lysis primarily against intracellular pathogens. In the recent era, T cells have had a major function in both humoral and cellular immune response primarily since the discovery of the CD4 cell subset population, Th1 and Th2.

It was later mentioned as type 1 immunity for Th1-based immune response (hallmark cytokines: IL-2, IFN-y, LT-α/TNF-β) which has more profound cell-mediated immunity but weak humoral; subsequently leading to chronic STH infection. In contrast, type 2 immunity inundated

by cytokine based on Th2 cells (hallmark cytokines: IL-4, IL-5, IL-9, IL-10, and IL-13) will promote worm expulsion via suppressing cellular mediated immunity but strong humoral immune response and antibody switching to IgG2,4 and IgE. Type 2 immunity is an effective immune response in eradicating or halting the STH infection process but what urge immunity type activation is still under research area (Spellberg and Edwards, 2001). But one for sure, complex interactions from innate until adaptive immune responses are responsible for the fate of worm expulsion or type 2 immunity. In the context of responding against infection, the immune system could tend to activate one of the predominant immune responses, this is defined as immune polarization (Gause et al., 2020).

FACTORS INFLUENCING IMMUNE POLARIZATION

The fate between Th1 and Th2 predominant immune response is determined by priming cytokines, hormones, antigen doses, antigen-presenting cells and the strength of the signal. These five major factors are associated with the immune polarization of naïve T cells when activated into a more mature form of Th1 or Th2 cells. During the first 48-72 hours of T cell activation, immunity type would be subsequently determined. Cytokine for priming type 1 immunity is IL-12 while IL-4 is an essential cytokine for type 2 immunity inducer. This polarization will not occur unless naïve T cells sense predominant priming cytokine into a targeted area of injury or infection. When arriving, exposing naïve T cells to an IL-12-rich area could polarize the immune response to type 1 immunity or type 2 if the infection area is full of IL-4 (Yamaguchi et al., 2015).

Hormonal regulation also weighs as an important indicator promoting type 1 or type 2 immunity. Steroid is the sole hormones and powerful stimulators for triggering type 2 immunity, they directly induce IL-4 and IL-10 secretion from lymphocytes as well as antigen-presenting cells. Although type 2 immunity is evident as an effective immune response against STH, administering steroids will not ultimately eradicate the parasite; it becomes clear evidence that complex interaction between type 1 and 2 still took part to achieve worm expulsion (Roved et al., 2017).

Mode of infection is another indicator that could skew immune polarization against STH. According to several reports, trickle infection could cause desensitization of immune cells against parasitic infection. This state of infection predominantly provokes type 1 immunity which later failed to eradicate STH infection. Large burdens of antigen doses could prevent Th1 priming cytokines and subsequently promote resistant phenotype against STH infection (Glover et al., 2019). In addition, innate lymphoid cells (ILCs) as part of innate immunity also plays important primordial responses in promoting excellent outcome against STH infection. ILC2 activation would later promote worm expulsion but the triggering factors of this cell activation have not yet been elucidated (Nausch et al., 2015).

In recent reports, immune polarization is a debatable issue since two distinct types of immunity are not feasible to be separated, particularly in response to macro parasites. All types of immune responses are orchestrated to the successful outcome of worm expulsion. An investigational study proved that type 1 immunity is the primary response during the early invasion of parasites. Type 1 immunity can mount type 2 immunity in certain pathways, primarily if there is a priming cytokine for type 2 immunity, IL-4. Subsequently, the adequate response of IL-4 will provoke further type 2 immunity in the later phase of infection. Therefore, there is a hidden mechanism that could define the fate of worm expulsion versus chronic infection not merely of immune polarization (Chakraborty et al., 2023).

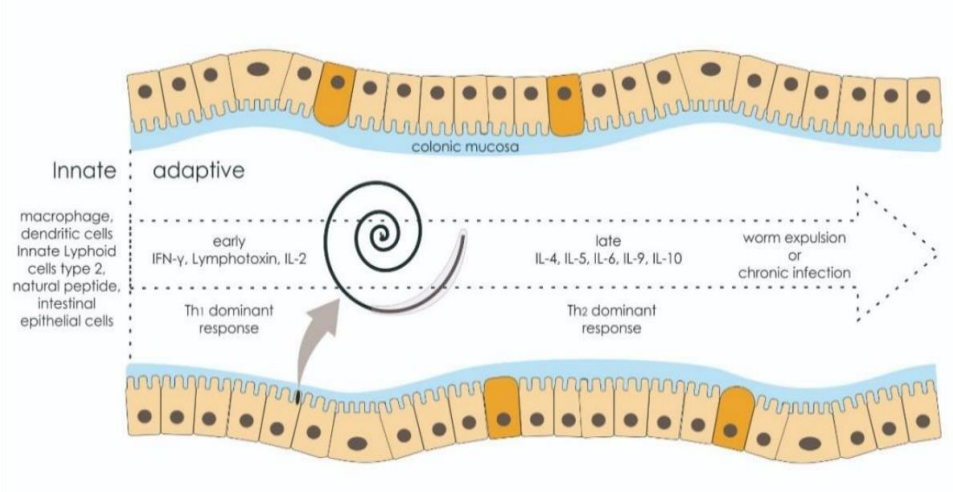

Figure 2. Two scenarios between worm expulsion versus chronic infection based on the type of immunity activation (Darlan et al.,2021)

STH AND IMMUNOMODULATION PROPERTIES

The basic concept of immunomodulation is a function of one substance could skew immune response through the secretion of any proteins or substrate. It also refers to the process of modifying or regulating the immune system's response. In several studies, several STH species secretes proteins or substance that is associated with immunomodulation properties during the infection process. These substances can affect the immune system locally and systemically to support worm proliferation in the host. A group of proteins or substances that is secreted during infection is also under investigation but grouped into one entity, mentioned as Exctretory-secretory (ESPs) and Soluble Products (SPs). This defence mechanism is also stated as the causative factor bore by STH to produce chronic infection and long-term establishment in the human body.

Immunomodulation properties of STH span from innate to adaptive immunity. In the previous part, alarmin from disrupted epithelial becomes the incitement of the immune cascade against parasitic invasion. In murine study, *Heligmosomoides polygyrus* (murine nematode) released IL-33 inhibitor, encoded as H.polygyrus alarmin release inhibitor (HpARI). This ESP will inhibit IL-33 release as the most important alarmin. Besides, HpARI also decreases IL-33 production at a genetic level, consequently, it increases worm burden. In addition, ESPs and SPs administration also transform classical monocyte response (inflammatory) into non-classical monocyte which has no expression of CCR2 and CD14 (Yeshi et al., 2022).

In another study, *Trichuris trichiura* is predicted as having similar characteristics to its murine counterpart, *T.muris*, inducing immunomodulation via several mechanisms. The product of ESPs and SPs of Trichurid species affect the level of recognizing pattern recognition receptors (PRR), such as retinoic-acid inducible gene (RIG) like receptor (RLRs) and toll-like receptors. ESPs of *T.suis*, swine trichurid, prevent TLR4 of human dendritic cells (DCs) from sensing their surface while invading epithelial barriers. No sensing from TLR4 brings a blunt inflammatory response during the subsequent infection process, which means worm survival and pro-proliferation (Leroux et al., 2018).

At the cellular level, immunomodulation properties have a deleterious effect in skewing cytokine responses. ESPs trigger TGF-β, IL-35, and IL10 secretion which has a paramount effect in promoting an anti-inflammatory state yet IL10 have multiple pleiotropic effects caused by a

wide array of its receptor, it depends on which receptor is activated during the immune response (Chakraborty et al., 2023).

STH AND AUTOIMMUNE DISEASES

The topic of STH infections and autoimmune diseases has been discussed in the last two decades since both areas attract researchers to elaborate on which one is impacting the others. These two distinct areas of medical research are distinct but similarly have significant implications for public health. Autoimmune diseases are represented by the failure of the immune cell to recognise the self-antigen of the human body provoking an immune reaction that finally turns it into a disease. Surprisingly, recent evidence has suggested that autoimmune disease might be influenced by the presence of parasitic infection. Recent experimental studies demonstrated that secreting products of helminths could ameliorate the autoimmune process in vitro, modulating the immune system, and provoking anti-inflammatory responses. Therefore, there was an emerging beneficial effect of helminth in treating autoimmune conditions and became one of the therapeutic approaches to curing autoimmune diseases (Fleming and Weinstock, 2015).

Researchers even delve into the intricacies of parasitic infection influencing the natural history of autoimmune disease that leads to the most prominent properties of parasitic infection, immunomodulation and anti-inflammatory substances. Through this pathway, theoretically, the parasitic infection could change, transform and modulate the natural history of several autoimmune diseases. The interaction between these unexpectedly affects one another and it is far more complex than previously thought. While parasites have traditionally been associated with causing various diseases, there is growing recognition that their presence can also modulate the immune system, potentially influencing the development as well as the treatment of autoimmune disorders (Loukas et al., 2021).

Several mechanisms have been suggested to explain the relationship between helminth infections and autoimmune diseases. These include the modulation of immune cell balance, alteration of cytokine profiles, changes in gut microbiota composition, and disruption of immune tolerance mechanisms. In the immune response, there are several basic mechanisms triggered by the presence of helminthic infection producing a delinquent immune response to accommodate their survival in the host environment; it includes an anti-inflammatory response, cytokine manipulation, evasion of immune recognition, host tissue modification, and regulatory T cell (Treg) inductions. These mechanisms are worth noting for deciphering the complex interactions between parasitic infections and autoimmune diseases (Colombo and Grencis, 2020).

CONCLUSION

STHs are one of the major neglected tropical diseases (NTDs) among the global population. Immune response against this parasite has long been acknowledged as the most efficient type of immunity during the infection process which produces long-term and chronic infection. Hence, imperative to achieve a profound comprehension of the immune response and its polarization is the prerequisite for acquiring comprehensive insights. This understanding is pivotal not only to facilitate eradication strategies but also for potential applications in diverse areas of expertise, such as autoimmune diseases.

REFERENCES

Babu S, Nutman TB. (2019). Immune responses to helminth infection. In:*Clinical Immunology*. (p. 437-47). New York: Elsevier.

Chakraborty P, Aravindhan V, Mukherjee S. (2023). Helminth-derived biomacromolecules as therapeutic agents for treating inflammatory and infectious diseases: What lessons do we get from recent findings?. *International Journal of Biological Macromolecules*,124649.

Colombo SA, Grencis RK. (2020). Immunity to soil-transmitted helminths: evidence from the field and laboratory models. *Frontiers in immunology,* 11:1286.

Darlan DM, Rozi MF, Yulfi H. (2021). Overview of immunological responses and immunomodulation properties of Trichuris sp.: Prospects for better understanding human trichuriasis. *Life*, 11:188.

Fleming JO, Weinstock JV. (2015.) Clinical trials of helminth therapy in autoimmune diseases: rationale and findings. *Parasite immunology,* 37: 277-92.

Gause WC, Rothlin C, Loke PN. (2020). Heterogeneity in the initiation, development and function of type 2 immunity. *Nature Reviews Immunology*, 20:603-14.

Glover M, Colombo SA, Thornton DJ, et al. (2019). Trickle infection and immunity to Trichuris muris. *PLoS Pathogens*, 15:e1007926.

Harris N, Gause WC. (2011). To B or not to B: B cells and the Th2-type immune response to helminths. *Trends in immunology,* 32:80-8.

Jourdan PM, Lamberton PH, Fenwick A, *et al*. (2018). Soil-transmitted helminth infections. *The Lancet*, 391:252-65.

Leroux LP, Nasr M, Valanparambil R, *et al*. (2018). Analysis of the Trichuris suis excretory/secretory proteins as a function of life cycle stage and their immunomodulatory properties. *Scientific Reports*, 8:15921.

Loukas A, Maizels RM, Hotez PJ. (2021). The yin and yang of human soil-transmitted helminth infections. *International journal for parasitology*, 51:1243-53.

Mitra AK, Mawson AR. (2017). Neglected tropical diseases: epidemiology and global burden. *Tropical medicine and infectious disease,* 2:36.

Montaño KJ, Cuéllar C, Sotillo J. (2021). Rodent models for the study of soil-transmitted helminths: A proteomics approach. *Frontiers in Cellular and Infection Microbiology*, 11:639573.

Nausch N, Appleby LJ, Sparks AM, *et al*. (2015). Group 2 innate lymphoid cell proportions are diminished in young helminth infected children and restored by curative anti-helminthic treatment. *PLoS neglected tropical diseases*, 9:e0003627.

Pisarski K. (2019). The global burden of disease of zoonotic parasitic diseases: top 5 contenders for priority consideration. *Tropical medicine and infectious disease,* 4: 44.

Roved J, Westerdahl H, Hasselquist D. (2017). Sex differences in immune responses: Hormonal effects, antagonistic selection, and evolutionary consequences. *Hormones and behavior*, 88:95-105.

Spellberg B, Edwards Jr JE. (2001). Type 1/Type 2 immunity in infectious diseases. *Clinical Infectious Diseases,* 32:76-102.

Yamaguchi T, Takizawa F, Fischer U, et al. (2015). Along the axis between type 1 and type 2 immunity; principles conserved in evolution from fish to mammals. *Biology*, 4: 814-59.

Yeshi K, Ruscher R, Loukas A, *et al*. (2022). Immunomodulatory and biological properties of helminth-derived small molecules: Potential applications in diagnostics and therapeutics. *Frontiers in Parasitology*, 1:984152