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Review

Immune Response and its Effects on the Host during Helminthic Infections

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ABSTRACT

Helminths are multicellular organisms causing chronic infections affecting nearly one-third of the global population. They are experts at immunomodulation, and pathologic outcomes are generally observed in patients with immunodeficiencies or with exaggerated levels of anti-helminth immune responses. Elimination of helminths is usually mediated by T-helper type-2 (Th2) immune responses, characterized by the induction of Immunoglobulin E (IgE) release, increase in eosinophil and mast cell levels, and elevation in the production levels of Th2 cytokines. However, the triggered mechanisms may also depend on the location of the parasite. This is because tissue invasion, an immune evasion strategy for parasites, was considered to activate more Thelper type 1 (Th1) cells in tissues. During chronic infections, immune response regulatory pathways become more influential, thereby reducing the levels of the peripheral T-cell-mediated responses against parasitic antigens. The resultant immune response is termed as "modified Th2 response" and is characterized by enhanced levels of anti-inflammatory cytokine production and regulatory immune cells as well as high IgG4/IgE ratios. Immunomodulation during chronic helminth infection is not limited to only parasite-specific responses. It can influence the efficiency of vaccination, host susceptibility to infections, and allergen or autoantigen responses. This review discusses anti-helminth immune responses. Moreover, it highlights current literature on the effects of chronic helminth infections on host health as well as their possible use as a treatment strategy against autoimmune, autoinflammatory, and allergic diseases.

Keywords: Co-infection, helminth, immune response, therapy, vaccine

INTRODUCTION

Helminths are parasitic multicellular organisms that include nematodes, cestodes, and trematodes (1). Although they are one of the most common infectious agents infecting nearly one-third of the global population today, they cause mostly asymptomatic infections (2,3). Pathologic outcomes can be observed in immunocompromised individuals and also in those with high levels of immune response triggered against low parasitic burden (3).

Helminths can exploit the host immune system for their own benefit and can survive within the host for weeks, months, or even years. They can utilize a wide range of immunomodulatory mechanisms, such as the secretion of molecules, that inhibit immune cell function and induce regulatory pathways (3). Since they are considered as experts in immunomodulation, helminths are currently being studied for their use in the treatment of allergic and autoimmune diseases. Autoimmune and abnormal T-helper type-2 (Th2 cells) cell-related disease (such as asthma or allergic rhinitis) levels in helminth-infected populations are relatively low (4). According to the "old friend" hypothesis, microorganisms, including helminths, evolved along with mammalian hosts over the ages and acted as triggers of immunomodulator mechanisms required for the development of a healthy immune system (1).

CLINICAL AND RESEARCH CONSEQUENCES

Effective Immune Response Triggered Against Helminths

Helminths are generally associated with host Th2 immune responses, which can be initiated to repair tissue damage as well as in disease states such as allergy and asthma (5). Because of this association, Th2 cells are thought to be triggered to improve resistance to helminths as well as to repair tissue damage caused by helminths colonizing tissues (3). The response is characterized by Immunoglobulin E (IgE) release, eosinophilia, mastocytosis, goblet cell differentiation, increased mucus production, and the production of Th2 cytokines such as interleukin-4 (IL-4) and IL-5 (6).

Although T-cells were initially thought to be the only source for Th2 cytokines, innate immune cells can also function as a reservoir

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for these cytokines. For example, previous studies have revealed that basophils, eosinophils, multipotent progenitor type 2 cells (MPPtype2), and type 2 innate lymphoid cells (ILC-2) are important sources for IL-4, IL-13, and IL-5 (7). Among those, ILC-2 was shown to be dependent on adaptive immune cells such that in the absence of B-cells and T-cells, they failed to facilitate worm expulsion from the host (8, 9). In addition to these cells, intestinal epithelial cells (IECs) were also shown to engage in the development of Th2 immune responses (10). Inability to develop Th2 immunity during helminth infections in mice has been associated with the disappearance of intestinal protective properties and subsequent fatal sepsis, resulting in intestinal bacterial infection (3).

While Th2 cells rarely kill parasites, they limit the infection, reduce the viability and reproductive properties of helminths, and physically remove them from the mucosal membranes (11). Nevertheless, the effector mechanisms may vary depending on the location of the parasite, whether in the duct lumen or in the tissue. Removal of parasites from lumenal regions depends on IgE-mediated mast cell degranulation and intestinal anaphylaxis, which is responsible for muscle contractility, fluid stimulation, vascular permeability enhancement, immune cell recruitment, and mucus secretion (11). Although the expulsion was triggered by Th2 cytokine release (6), it was mediated in the absence of adaptive immune system by IECs (8). Immunoglobin A (IgA) antibodies, another mediator, released during Th2 immunization are essential for the neutralization of metabolic enzymes as well as influence parasite nutrition (11).

Furthermore, tissue invasion, which is considered as a strategy for the parasite to evade from anti-helminth Th2 responses, activates T helper type 1 (Th1) immunity in these regions (11). Trematode strains such as *Schistosoma* spp. were suggested to require collaboration between Th2 and Th1 responses for effective protection (11). Th1 immunity mainly targets adult parasites, and the Th2 skewed response is initiated after parasite's eggs are produced (12). The absence of effective Th2 immunity at this stage may result in granulomatous inflammation mediated by Th1 and T helper type 17 (Th17) cells, thereby causing severe damage and death to the surrounding tissues (12). Effector mechanisms against helminths in tissues mainly include antibody-dependent cellular cytotoxicity, nitric oxide release by classically activated M1 macrophages, and granuloma formation (11).

Granuloma formation is frequently associated with Th1 immunity; however, it may also be detected during Th2 immune responses (11). Neutrophils and macrophages are among the first line of defence. They are responsible for the rapid development of a granulomatous build-up involving Th2 cells, eosinophils, and alternatively activated M2 macrophages (12). As time elapses after granuloma formation, fibrous extracellular matrix levels in granulomas increase. Controlled fibrogenesis are beneficial because of the limitation of granulomatous content, thereby preventing inflammation and damage caused by the spread of toxic egg products (13). Excessive fibrosis can be a serious complication, and stimulated tissue fibrosis may become pathologic (14). In addition, neutrophils may be invoked by helminths and may be effective against the parasites (15).

Main Points:

- While the elimination of helminths is mainly mediated by the induction of Th2-mediated immune response, tissue invasion can lead to activation of more Th1 cells.
- "Modified Th2 response", which is observed during chronic helminth infections, is characterized by enhanced levels of anti-inflammatory cytokine production and regulatory immune cells as well as high IgG4/IgE ratios.
- The immunomodulation during chronic helminth infection can influence the efficiency of vaccination, host susceptibility to infections, and allergen or autoantigen responses.

In contrast to classically activated M1 macrophages associated with high expression levels of pro-inflammatory cytokines and Th1 responses, M2 macrophages that are differentiated during the T_H2 immune responses participate in tissue remodelling and tumour progression as well as in anti-parasitic immunity (16). In addition to the contribution of control of parasitic tissue damage, M2 macrophages were also shown to be effective in providing protection against helminth infections by influencing the effects of Th2 cytokines, intestinal smooth muscle contractility, and worm expulsion (17).

The importance of the dendritic cells (DC) during the antigen presentation process in the initiation of anti-helminth immune responses is under debate (7). A recent study emphasized that basophils are involved in antigen presentation during *Trichuris muris* (*T. muris*) infection (18). Selective elimination of basophils from mice considerably reduced the levels of IL-4 mRNA expression and Th2 cytokine-dependent goblet cell hyperplasia in mice. In the same study, basophils were reported to induce CD4+ T cell proliferation in an MHC class II-dependent manner *in vitro* (18).

Regulatory Immune Response Triggered by Helminths

Peripheral T cells are known to be rendered insensitive to parasite antigens during chronic helminth infections (2). Helminthic parasites can directly act on the host immune cells to block their function and modify the immune response for their own survival within the host. The regulatory pathways triggered for this purpose causes the development of a host immune response known as the "modified Th2 response." This response, associated with anti-inflammatory cytokine production, such as IL-10 and Transforming Growth Factor (TGF)-β, and high IgG4/IgE ratios, besides regulatory immune cells, is likely involved in the Th2 immune reaction and play an active role in limitation of the overt symptoms frequently seen in helminth disease (4, 11).

Among the regulatory immune cells activated during the anti-helminth immune response, regulatory T-cells (Treg cells) comprise various subgroups. The cells in which Foxp3 transcription factor expression is initiated following the developmental stages in the thymus are called "natural" Treg (nTreg); cells that initiate Foxp3 expression in peripheral tissues are termed "induced" Treg cells. Treg cells such as type 1 regulatory (Tr1) cells do not possess any detectable level of Foxp3 expression. All these Treg populations can exert immunosuppressive effects by releasing IL-10

and TGF-β cytokines (19). Among those populations, in particular, Foxp3+ Treg cells have an important role in the development of self-tolerance, such that mutations affecting Foxp3 expression were shown to cause autoimmune diseases by influencing Treg cell expression and/or functional levels (19).

Microfilaremic filariasis (Mf) patients were previously reported to have higher Foxp3+ Treg cell levels than the control group patients (20). In addition, an *in vitro* study revealed an elevation of Th2 in Mf-positive patients when Treg cells were depleted (21). Although an increase in nTreg marker expression levels was observed during asymptomatic infection, such an increase was not observed in patients with filarial lymphedema (22). Therefore, the pathogenesis of lymphatic pathology during filarial infections is associated with the strengthening of pro-inflammatory responses and lowering of anti-inflammatory cell subset levels (22).

Tr1 cells have also been implicated in immunosuppression during infection with *Onchocerca volvulus* (*O. volvulus*), another parasitic filarial nematode worm (23). Peripheral blood mononuclear cells from individuals suffering from general oncocytosis produce higher levels of IL-10, and the observed decline in T-cell proliferative levels in this group can be reversed by anti-IL-10 and anti-TGF-β antibodies (24). In addition to these cases, Treg cells have also been associated with the pathogenesis of *Schistosoma mansoni* (*S. mansoni*), *S. Haematobium*, and hookworm infections (2).

There are other adaptive immune cells called regulatory B-cells (Breg) that are effective in the modulation of the immune responses. Like Treg cells, Breg cells were shown to be influential in the suppression of autoimmune diseases (25). Similar to Treg cells, Breg cells are thought to suppress pathogenic T cells and autoreactive B cells via cellular contact and release of cytokines such as IL-10 and TGF-β (25). Besides, they are also known to suppress immune responses by inducing Treg differentiation, suppressing the DC antigen-presentation function and releasing anti-inflammatory antibody isotypes such as IgG4 (26). In mouse experiments, the induction of Breg cells has been previously documented during infections with *S. mansoni* and *Heligosomoides polygyrus* (2).

DCs play an important role in immune responses induced by helminths. Accordingly, mice injected with DCs treated with helminth extracts *in vitro* have been reported to induce Th2 immunologic responses (27). In contrast, DCs have also been reported to trigger mechanisms responsible for the regulation of the immune responses (28). Currently, the mechanisms that induce Th2 or Treg differentiation are not yet fully clarified. However. the maturation levels in tolerance-inducing DCs are low, and helminth products were shown to inhibit IL-12 secretion by DC (2). Furthermore, some helminth products have been shown to interfere with DC function by blocking host antigen processing or inducing mRNA degradation (2).

Additionally, M2 macrophages, another innate immune cell, have also been reported to suppress T-cell responses (29). The human patent filariasis infection pathogenesis was shown to be related with the induction of M2 macrophages (30, 31). Monocytes from non-endemic donors directly inhibit CD4+ T cell proliferation and cytokine production in IL-10 or PD-1-mediated manner when stimulated with Mf-lysates (32).

Effect of Chronic Helminth Infection on Host Bystander Responses

Immunosuppression during helminth infection is not limited to only parasite-specific responses, and chronic helminth infections have also been reported to impact the efficiency of vaccination, host susceptibility to infections, and allergen or autoantigen responses. The effects of helminths on the immune responses can be classified into two distinct categories: inhibitors of Th1, Th2, and Th17 immunoreactivity through regulatory mechanisms (eg., Treg cells) and inhibitors of Th1 and Th17 mediated responses by activating the Th2 responses (33).

Efficiency of Vaccination

Levels of Th1 cytokines released in response to oral cholera vaccination drop in the presence of parasitic infection, and anti-parasitic worm therapy before challenge partially reverses this reduction (34). The same effect was also observed in the immune responses induced by the tetanus vaccine, and the level of Th1 response triggered was found to be lower in patients with schistosomiasis, onchocerciasis, and lymphatic filariasis (35-37). In addition, low Bacillus Calmette–Guérin vaccine immunogenicity level was observed in helminth-infected individuals (38).

Co-Infection

Due to the above-mentioned effects on the immune system, helminths are believed to provide resistance to Th2-responsive pathogens and increase host sensitivity to pathogens that induce Th1 immune responses (11). Accordingly, an increase in the prevalence of bacterial infections such as malaria, HIV/AIDS, and tuberculosis was detected in areas where helminth infection was endemic (39). Patients suffering from helminth infection have lower levels of immune responses against malaria, HIV, and tuberculosis than the control group (40-43).

Allergic, Autoinflammation, and Autoimmune Diseases

According to the "hygiene hypothesis," decreased exposure to childhood infections due to increased hygienic conditions in the Western and developing countries reduces the possibility of cross infection and prevents the development of a healthy immune system, increasing the chances of autoimmune and allergic diseases in later ages (1). In accordance with this view, many studies have observed relatively low levels of autoimmune and abnormal Th2-related disease (such as asthma or allergic rhinitis) cases in helminth-infected populations (4).

Epidemiological and immunological evidence has led to the use of helminth parasites to carry out many clinical trials for the treatment of diseases such as allergy, autoimmunity, and autoinflammation. Studies with the administration of *Trichuris suis* (*T. suis*) eggs (TSO) for the treatment of inflammatory bowel diseases, Crohn's disease, multiple sclerosis, and colitis reported a reduction in disease severity (44-47). Besides, a study using human hookworms also reported a reduction in the levels of pathologi-

cal Th1/Th17 immune responses responsible for celiac disease by the induction of Th2 and IL-10 pathways (48). Another study also revealed that Necator americanus may be effective against food allergies via induction of Treg cells (49).

On the other hand, there are also studies in the literature showing that using helminths for treatment has no effect on the patients monitored. These conflicting findings can be explained by the helminth genus used (1). Studies focusing on the therapeutic use of helminth or helminth derivative products still continue today (50).

CONCLUSION

Helminths can manipulate the host immune system for their own benefit and survive in the host for a long time. Due to these excellent immunomodulatory properties, chronic helminth infections can influence vaccine efficacy as well as susceptibility to pathogens in the environment and is held responsible for the increased prevalence of allergic and autoimmune diseases observed, especially in developed countries. Therefore, helminths and immunomodulator products they express are probably future anti-inflammatory molecules to be used against autoinflammation, autoimmune diseases, and allergies. Since the effects of helminths on the host immune system cannot be generalized among species, future work on the immune responses induced by candidate therapeutic agents will be a unique contribution to this area.

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