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Review Article

Parasitic infection and immunomodulation: A possible explanation for the hygiene hypothesis in autoimmune and allergic disease

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ABSTRACT

Helminthic parasites have a long history of co-evolution with human beings. The incidence of helminthic infection has significantly decreased in developed countries due to better sanitary measures. However, epidemiological data suggest a corresponding increase in the incidence of autoimmune and allergic diseases in association with a reduction in helminthic infections in these societies. The immune response to helminthic infection involves both innate and adaptive processes, with a strongly polarised Th2 response being the most characteristic feature. However, there is a concomitant increase in the functional regulatory T cell responses. This might explain the paradoxical decrease in both Th2-and Th1-mediated diseases such as allergy and immune-mediated inflammatory disorders in populations with increased incidence of helminthic infection. Parasitic infection therefore appears to confer a degree of immunomodulation, and for this reason, utilising helminthic infection as a therapeutic modality for the treatment of allergic and autoimmune disease has been proposed. Improved understanding of the immunologic responses to helminth infection allows these mechanisms to be exploited, enabling manipulation of the immune response in Th1-dominant conditions such as inflammatory bowel disease and multiple sclerosis, and providing a new approach to treatment of these and other inflammatory and allergic conditions.

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1. Introduction

Helminthic parasites have a long history of co-evolution with human beings. Their presence has been demonstrated in the intestinal contents of Neolithic and Pre-Columbian American mummies.[1,2] Helminths continue to represent major pathogens, even in the current age, and infect billions of people and livestock in developing countries.[3] The incidence of helminthic infection has significantly decreased in developed countries, with the application of better sanitary measures and

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improved hygiene. However, there is large amount of epidemiological data that suggests an increase in the incidence of autoimmune and allergic diseases in association with a reduction in helminthic infections in these societies.[4] This points towards a mutually beneficial relationship between helminth and host. There is a strong T-helper 2 (Th2) immune response generated within the host to fight the parasitic infection, and in order to evade this response, parasites secrete novel immunomodulatory products. Interestingly, this leads to reduction in both T-helper 1 (Th1) and Th2 immune-mediated inflammatory diseases in the host, most likely due to generation of strong regulatory T cell (Treg) responses. Mechanisms of immune evasion by the parasite can be used to study and develop novel immune regulation strategies to treat these inflammatory diseases. This review will discuss the immune evasion strategies employed by helminths to promote their survival in the host, and its implications on the treatment and prevention of immune-mediated inflammatory diseases.

2. Helminthic infections and the immune response

Helminths are classified zoologically as nematodes (roundworms), cestodes (flatworms) and trematodes (fluke worms). Most parasitic helminths have multiple stages in their life cycle, which is typically completed within multiple hosts. They are usually transported from the environmental niche through the oral route to the gastrointestinal tract of higher organisms. They subsequently cross the mucosal barrier and gain access to other anatomical sites within the host by haematogenous spread. Multiple structural changes occur within the parasites during this evolution, and various secretory and excretory products are released in an attempt to achieve immune evasion.

The most characteristic host immune response following parasitic infection is a strongly polarised Th2 response with secretion of interleukins IL-4, IL-5, IL-6, IL-10 and IL-13, which results in production of IgE antibodies, mast cell activation and eosinophilia.[5] There is also concomitant suppression of the Th1 response. In addition to the generation of Th2 immune responses, helminths generate several other immunomodulatory reactions which result in relative immune suppression of the host. This can lead to increased morbidity and mortality during co-infection with other bacterial and viral infections.[6] However, these same phenomena result in a lower incidence of immune-mediated inflammatory diseases where the burden of infectious diseases is low.

3. Alteration of immune responses by helminth infection

There are numerous mechanisms documented for helminth-induced immunomodulation which helps promote survival of the parasite. It has effects on both the innate and adaptive immune systems, with the net result being a state of relative immune anergy, which is beneficial for the long-term survival of the parasite.

The most consistent observation in immunomodulation is the shift of the Th1/Th2 balance towards a robust Th2 phenotype. There are several mechanistic explanations for this phenomenon. T cells secrete cytokines which activate macrophages to function as effective phagocytic agents. Two types of macrophages have been described, and can be differentiated based upon their activating cytokines:

1) Classically activated macrophages, which are interferon gamma (IFN-γ) dependent
2) Alternatively activated macrophages (AAM), which are IL-4 dependent.

It has been shown that AAM generated in a Th2 milieu are capable of inhibiting Th1 cell proliferation by secreting large amounts of anti-inflammatory cytokines, such as IL-10, IL-13 and TGF-β.[7] This modulates inflammation and contains tissue damage through recruitment of Treg and Th2 cells. The induction of Treg, along with the Th2 response, provides a possible explanation for why humans and animals with parasitic infection do not develop Th2-driven allergic disease.[8] The polarisation of the immune response to a Th2 phenotype is also possibly influenced by the effect of helminth protein on antigen presenting cells. Exposure of dendritic cells (DC) to Th2-inducing soluble egg antigen of schistosomes leads to a Th2 response when these cells are co-cultured with naïve CD4 T cells in vitro.[9]

Th17 cells are a T cell subset, which are implicated in the pathogenesis of helminth-induced hepatic pathology. It has been shown that mice demonstrating a reduced Th17 response were more resistant to schistosomiasis.[10] IL-25 is an important cytokine which down-regulates Th17-mediated inflammation. Sources of this cytokine include Th2 cells, non-B and non-T lymphocytes and mast cells. Hence it is possible that parasite-derived IL-25 could lead to inhibition of harmful Th17 responses which are widely implicated in many human inflammatory diseases including Rheumatoid Arthritis, Multiple Sclerosis (MS), Type 1 Diabetes Mellitus and Inflammatory Bowel Disease (IBD).[11]

In addition to their effects on T lymphocytes, helminth infections are also known to affect the phenotype and function of B1 cells, a B cell subtype. These cells are normally present on serosal surfaces and are responsible for production of natural, auto-reactive IgM antibodies. Secretion of IL-9 in response to *Schistosoma mansoni* has been shown to expand this B cell subtype, and is required to prevent severe pathology.[12] These cells produce large amounts of IL-10 and drive Treg differentiation. They also cause T cell apoptosis by up-regulation of Fas-Ligand.[13] These findings may be responsible for the prevention of anaphylaxis in a murine allergy model.[14]

There is also evidence of alteration of innate immune responses by helminths. Toll-like receptor 2 (TLR2) is an important pattern-recognition receptor in innate immune cells. Binding of helminth-derived lipid molecules to this receptor activates the TLR2 signalling pathway, leading to induction of Treg cells and DC-mediated orchestration of the Th2 response.[15] The function of the complement system, which forms part of the effector arm of innate and adaptive responses, is also influenced by helminthic infection.

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Helminths secrete proteases which cause cleavage of the parasitic coat, reducing their detection and lysis, as well as affecting the rate-limiting enzymes of both the classical and alternate complement cascade, including C3 convertase. Helminths also acquire certain complement regulatory proteins on their cell surface, which play a very important role in the prevention of excessive complement activation.[16] Moreover, certain antigens on the cell surface of helminths have been shown to be receptors for C1q, which is required for initiation of the classical complement pathway.[17] These properties of various helminth proteins and antigens could be harnessed in diseases where complement-mediated lysis and tissue damage play an important role in pathogenesis, such as Systemic Lupus Erythematosus and MS.

4. Role of specific parasite-derived molecules in immune modulation

There is a significant body of published data on the effect of helminthic infections on host immune responses. Parasites secrete or express several molecules that could be responsible for these effects. They secrete a wide range of proteins, carbohydrates, lipids and glycoconjugates which have a potent effect on the immune system. These have been tabulated and described in a review article by Zaccone et al[18]

The best characterised helminth-derived protein, Cystatin, belongs to the family of cysteine protease inhibitors. This protein is secreted by several helminths, including *Brugia malayi*, *Onchocerca volvulus* and *Nippostrongylus brasiliensis*, and is a homologue of mammalian cystatin C found in immature DCs.[19] This protein has been shown to affect the intracellular antigen processing pathways by altering expression of HLA class 2 molecules. Moreover, it has also been shown to suppress T cell proliferation and up-regulate IL-10 expression.[19] Two families of lipid-binding proteins, fatty acids and retinols, have also been shown to have immunomodulatory properties. Ov20 is a retinol-binding protein secreted by helminths, which deprives immune cells of this important protein required for several immunologic functions.[20] *Taenia taeniaeformis* and *Brugia malayi* synthesise and release prostaglandins PGE2 and PGD2 which have been demonstrated to inhibit IL-12 production and drive Th2 differentiation.[21]

Parasite-derived carbohydrates and lipids have also been shown to have immunomodulatory properties. Schistosome egg antigen (SEA) contains Lacto-N-fucopentaose (LNFPIII), a tri-saccharide which binds to pattern-recognition receptors and stimulates intracellular signalling, resulting in secretion of anti-inflammatory cytokines.[22] The pathophysiology of this phenomenon is intriguing, as it involves signalling through toll-like receptor 4 (TLR4), which typically results in pro-inflammatory cytokine secretion. Finer dissection of this phenomenon may provide a better understanding of these intracellular signalling pathways, and useful insight into ways in which to modulate them. Another SEA component, Lysophosphatidyl serine, has a similar function but uses TLR2 binding to induce an IL-10-secreting Treg phenotype. ES-62 is a nematodal glycoprotein which has been shown to have strong immune suppressor properties. It modulates signalling through TLR4 and the B cell receptor by inducing negative regulators of intracellular signalling pathways.[21]

Lastly, helminths have been shown to possess certain cytokine equivalents which can bind to their respective cytokine receptors on host cells and modulate the immune response to their benefit. Two families of helminth-derived cytokines have been identified using extensive genetic studies. TGF-β and macrophage-migration inhibitory factor (MIF) have been the most extensively studied helminthic cytokines.[21] Helminth-derived TGFβ binds to its receptor and causes immune down-regulation. However, the role of MIF is still uncertain, as the mammalian MIF is known to be a pro-inflammatory cytokine. There is some emerging evidence suggesting that continuous secretion of this cytokine may result in immune suppression.[21] There have been some functional studies pointing towards the presence of other cytokines and chemokines of helminthic origin, however their presence and functional relevance have not yet been conclusively documented.[23]

5. Clinical implications

There is extensive published data based upon epidemiological observation suggesting that parasitic infection has a beneficial role in preventing autoimmune and allergic diseases. Low prevalence of helminthic infections in developed countries has been correlated with a higher incidence of allergic and inflammatory conditions.[4] It has been shown in an animal model of diabetes mellitus that development of hyperglycaemia in non-obese diabetic (NOD) mice can be prevented by infection with *S. mansoni*.[24] Similar studies have shown inhibition of MS progression in animal models after a parasitic infection. It has also been demonstrated that MS patients with parasitic infection had markedly improved clinical and radiological disease parameters as compared to non-infected patients.[25] The landmark study in human disease was performed in patients with IBD, where amelioration of colitis symptoms was demonstrated following treatment with pig whipworm (*Trichuris suis*) ova (TSO).[26] Several subsequent studies have demonstrated improvement of disease activity scores in patients with IBD receiving TSO therapy compared with those in the placebo group, with a favourable safety profile. Several larger randomised controlled trials are currently in progress to further evaluate efficacy of this therapeutic modality for IBD and MS.[27] Similar studies are planned for evaluation of helminth-based therapies in allergic disorders. However, the exact intervention will require a more innovative approach, as allergic disorders are inherently Th2-driven, as compared to IBD in which the pathophysiology is mediated by Th1/Th17 responses.[27] A recent trial investigating the use of TSO in a cohort of patients with allergic rhinitis did not demonstrate any therapeutic effect of this intervention.[28]

Aside from administering the parasitic agents themselves as therapy for allergic or inflammatory diseases, a proposed alternative modality is the administration of therapeutic agents which are based upon secreted parasitic glycoproteins such as ES-62.[29,30] However, the therapeutic applicability of such products is limited by large molecular size of these

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proteins and their potential immunogenicity, which may be overcome through the development of small molecule analogues which are currently under evaluation and show promise in mouse models.[30]

6. Conclusion

The co-evolution of helminth and man over an extensive time period is suggestive of a symbiotic relationship. Helminthic infections are a significant health issue in developing countries due to poor hygiene and a high community parasite burden. Conversely, with the reduction in prevalence of parasitic infections amongst populations in developed countries, there has been a rise in the incidence of immune-mediated inflammatory diseases. This supports the theory that "a few parasites are better than none". There has been great progress in understanding the host immune response to parasites, which has provided unique insight into the regulation of immune responses. The next step involves translating this knowledge into novel therapeutic approaches, utilising helminth-derived therapeutic strategies to develop specific agents for the treatment of autoimmune and allergic disease.

Conflicts of interest

All authors have none to declare.

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