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Review Article

Immune Response against *Haemonchus contortus* and the Th1-Th2 Paradigm in Helminth Infection

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Abstract

The adaptive immune response is mediated by CD4+ T lymphocytes, which act by either stimulating or inhibiting effect or mechanisms that specifically recognise, eliminate or restrict the action of agents that have attacked the host. The identification of these cell subpopulations began with the work of Mossmann and colleagues in 1986, who provided the initial postulation not only for the existence of such subpopulations, termed Th1 and Th2, but also their cytokine profiles. In the following decades, five other subpopulations and profiles were identified, commonly known as Treg, Th17, Th9, Th22 and THF. Despite these new discoveries, and evidence of the complex multifunctional behaviour of these cells, the Th1-Th2 paradigm remains valid. It is evident that the responses generated by these cells depend not only on the interaction between the host and each pathogen, but also the simultaneous interactions between these pathogens, and their combined interaction with the host, whether among macroparasites, among microparasites or between macro and micro parasites. For co-infections of helminths and other parasites, there are many studies in the literature that demonstrate the strong Th2 stimulation induced by these worms, and the consequent downregulation of the Th1 profile. In this review, we present the current research on various aspects of these interactions, by discussing the main mechanisms of immune response induced by the helminth *Haemonchus contortus*.

Keywords: *Haemonchus contortus; Immune Response Th1-Th2; Coinfection; Downregulation*

Introduction

When Mossmann., *et al*. [1] described two subpopulations of CD4+ T lymphocytes, naming them Th1 and Th2, the authors postulated that each produced cytokines, usually with antagonistic actions. These cytokines were suggested to be responsible for activating the response mechanisms of cell-mediated immunity, dependent mainly on the interferon γ (IFNγ) cytokine (Th1), and humoral immunity, mainly mediated by interleukin-4(IL-4) (Th2). Thus, it was believed that these two distinctive patterns of CD4+ T lymphocytes, once properly stimulated, were completely responsible for inducing the capacity of the immune response and resolution of infections caused by intracellular pathogens (Th1) or helminths and extracellular microorganisms (Th2). However, knowledge regarding these responses has advanced over the past three decades, with numerous studies showing the wide range of cytokines and functional flexibility of their producing cells, resulting in improved definitions of their phenotypes and clarification of their roles in different situations and microenvironments of the body. New subpopulations are now known, including the regulatory function of the CD4+ 25+ Foxp3 phenotype, better known as Treg [2] the Th17 [3]and Th22 [4] subpopulations, associated with the induction of inflammation and tissue repair, respectively,

in addition to important roles in antimicrobial defence, Th9 cells with antitumor and anthelmintic defence roles [5], and T cells from lymphoid follicles (TFH), which are mainly related to the maturation of B lymphocytes [6].

Although there is flexibility, and consequently, multifunctionality of each of these subpopulations [7], the general idea of a stimulation mediated by cells mechanisms on one hand, or mediated by antibodies (particularly IgE), on the other hand - and therefore, the Th1-Th2 paradigm - remains accepted. There is strong evidence for the induction of one or more of these subpopulations in response to different parasitic infections. One of the best examples is the immune response against helminths, where the pattern of predominantlyTh2 reactivity has been repeatedly confirmed, as initially described in the early work of Mosmann., *et al* [1]. This review discusses the approaches for study in haemonchosis as a model of the anthelmintic immune response, in addition to discussing the main events and consequences of co-infection of helminths and other parasites on the immune system of the host.

Method

An electronic search was conducted in Medline/Pubmed, Lilacs and Science Direct. The following keywords were used, in both Portuguese and their English equivalent: coinfection, subpopulations of T cells, Th1 lymphocytes, Th2, Th1downregulation, helminths, *Corynebacterium pseudotuberculosis*, and *Haemonchus contortus*. There was no limit for time period on the included studies.

State of the Art

Immune response against *Haemonchus contortus*

The *Haemonchus* genus, possibly originating in Africa, contains several important species, including *Haemonchus contortus* [8]. *Haemonchus contortus* is a blood-sucking nematode of the Trichostrongylidae family (Strongylida order), and is one of the most pathogenic helminths that infect ruminants. In these animals, the stomach is the target organ for their parasitic activity, where they attach to the mucosa of the and feed on the blood of the host. They also use this site formating, and the females release approximately 10,000 eggs per day. Its life cycle includes five larval stages, beginning in the stool. The infecting form is the L3 larvae, which loses its cuticular membrane in the gastric environment and advances to the L4 larval stage, and the latter mature into adults [9].

Innate and adaptive mechanisms against the parasite have been described in response to their somatic and secreted antigens. Both mechanisms are essential for eliminating the pathogen, the former is associated with rapid clearance, particularly naturally resistant animals, while the latter requires a preliminary contact [10]. A major difficulty for the effectiveness of the adaptive immune response involves the different antigens that are presented by this worm throughout their life cycle, as each larval stage presents specific antigens [11]. Many animals are naturally resistant to this helminth, although the mechanisms underlying such resistance remain unclear. It is certainly an individual characteristic, related to the age, breed and condition of infection or reinfection [12]. A study using microarray and bioinformatic techniques was able to identify various genes related to the maintenance of homeostasis and the immune response in T lymphocytes of infected sheep, obtained at specific periods of nematode infection, in addition to identifying genes responsible for changes at the molecular level of these cells [13]. As with other helminth infections, the control of *Haemonchus contortus* infection by the host's immune system depends mainly on the Th2 response [14].

Antibody Response

The IgG, IgM, IgA and IgE antibody isotypes have been detected in the serum, faeces and mucosal secretions of ruminant animals infected with *Haemonchus contortus* [12]. In two similar studies which evaluated the presence of cells that produce antibodies against the parasite in the abomasal mucosa detected and quantified plasma IgA+ in both sensitive and resistant animals, reporting similar levels in both groups, leading them to conclude that the increase in these cells was not correlated with resistance to the pathogen [25,26]. However, other study show that IgA and IgG1 antibodies of sheep, in the serum and faeces, were positively correlated with resistance and negatively correlated with the number of parasite eggs that were eliminated in each gram of faeces (OPG). In similar experiments, others have reported a significant increase in the cells expressing IgG in their membranes [27]. In a study by Guo [30] that evaluated the ability

to fight infection of two breeds of sheep, Canaria Hair and Canaria, a negative correlation was found between the length of the adult larva and mucosal IgA levels in the susceptible Canaria sheep and mucosal IgA levels.

The response of IgE antibodies is the most typical example of Th2 stimulation [28] and several authors have demonstrated the importance of these molecules in the adaptive immune response to *Haemonchus contortus* in small ruminants. Assessing the response of mixed breed sheep against this helminth, de la Chevrotière., *et al*. [29] showed that the response of IgA antibodies was not correlated with indicators of protection, and the opposite was observed for the response of IgE antibodies. By assessing the response in young sheep, found that the inability to mount a specific Th2 response against these worms, particularly with the synthesis of IgE antibodies, made these animals vulnerable to infection [31]. It have been reported that animals aged 3, 6 and 9 months had a greater ability to generate a protective Th2 response, as well as increased ability to produce antigen-specific IgE antibodies [32]. Investigating the antibody response for each class, it was possible to identify anα1→3-fucosedomainon the surface of *Haemonchus contortus*, which was recognised by these antibodies. This epitope is found on the surface of other helminths, as well as other animals and plants, and is associated with the induction of type I hypersensitivity reactions [33].

Various immunization protocols against *Haemonchus contortus* have been conducted in sheep, and these utilise antigens on the external and intestinal surface, as well as secreted antigens. Most of these methods are intended to stimulate the production of antibodies that can trigger mechanisms such as mast cell degranulation or cytotoxicity by eosinophils. We identified 95 studies in the literature that describe these protocols, the first of which was published in 1961 [34] and the most recent in December 2014 [35]. Many of these studies have attempted to induce immunoprotection in order to neutralise hemoglobinase, an enzyme which is essential for helminth nutrition. An example of this involved the immunization of sheep with the H-gal-GP complex glycoprotein of this worm that demonstrated the induction the production of specific IgG and IgE antibodies against hemoglobinase, which increased the immune protection of the immunized animals [38].

Immune response by CD4+ T lymphocytes

In the 1990s, the first studies showing the involvement of CD4+ lymphocytes in the adaptive immune response against *Haemonchus contortus* were published [39,40]. These studies reported that infection with the larvae of this parasite caused an increase in the amount of CD4+ lymphocytes on the surface of the abomasal mucosa, the lymph nodes that drain the abomasum, and in the bloodstream. Animals that had been infected with this worm and treated with monoclonal antibodies against these cells showed significant inhibition of the antibody-specific response, as well as the infiltration of mast cells and eosinophils into the abomasum mucosa [25,41]. A significant reduction in resistance to infection by this pathogen was also observed after depletion of the CD4+ T cell population in a resistant sheep breed that had been infected with this worm [43].

Although these studies confirm the importance of CD4+ T lymphocytes against this infection, the Th2 subpopulation is also known to play a central role [12]. Furthermore, pioneering experiments that evaluated theTh1 and Th2 populations in sheep showed that the Th2 cells in pathogen-resistant animal breeds predominantly produce IL-4, IL-5 and IL-13, whereas susceptible animals breeds mainly produce IFN-γ [43]. A more recent study on the dendritic cells of sheep reported that while Salmonella antigens induced the production of IFN-γ and IL-17 by these cells *in vitro*, stimulation with *Haemonchus contortus* antigens inducedIL-4 and IL-13 [44]. However, a study that used a microarray approach to analyse the expression of various cytokine genes of sheep infected with this parasite showed much higher expression of IL-17 compared to other cytokines in the abomasum mucosa [45].

In addition, more recent studies that investigated infected sheep demonstrated that CD4+ T cells that produce IL-17 (Th17) are converted into CD4+ lymphoid follicle cells (THF), to provide the maturation of lymphocyte B IgA-specific for this parasite [46]. Controversial results have been reported in similar experiments with *Teladorsagia cimcurcincta*, which is also a parasite of the abomasum, similar to *Haemonchus contortus*. This study used polymerase chain reaction to quantitatively assess the expression of IL-6, IL-21 and IL-23 cytokines, and showed that the expression in the lymph node that drains the abomasum was positively correlated with OPG and negatively

correlated with the serum IgA concentration [47]. According to the authors, these results are consistent with the hypothesis that the Th17 population of these lymphocytes have an inhibitory effect on the immune response against this worm.

Evidence of negative regulation induced byTh1 helminth infections

The first study to investigate the negative regulation on the immune response induced by helminth infection, specifically the Th1immune response, was published in the early 1990s and experimentally evaluated the vaccination of mice with *Schistosoma mansoni* larvae. This study observed that the Th2 response induced by the parasite eggs inhibited the protective Th1 response against the larvae of this flatworm [48]. In the same year, another important publication, also focussed on the vaccination of mice with the same antigen, reported that inhibition of the Th1 response resulted from the action of IL-10. They also demonstrated *in vitro* inhibition of the production of this cytokine by spleen cells of mice by blocking the monoclonal antibodies directed against it, which led to the significant production of IFN-γ [49]. The same researchers later demonstrated for the first time the co-infection of this helminth and a vaccine containing a virus that expressed HIV-1 proteins in a murine model. The virus persisted for a long period, however, was rapidly eliminated in the absence of co-infection with the helminth. This inability to eliminate the virus was shown to occur via the inhibition of the cytotoxic activity of CD8+ lymphocytes by IL-10 [50]. Experiments conducted on Balb/c mice that were co-infected with *Fasciola hepatica* and *Bordetella pertussis* demonstrated that the bacterial infection progression rapidly, which was found to be dependent on Th1 mechanisms. Such an occurrence is not only found in animals co-infected with the bacterium, but also in IL-4 knockout mice [51].

Fox and colleagues [40] used a murine model to demonstrate atrophy of the gastric mucosa as a result of *Helicobacter pylori* infection, which is known to be induced by Th1 cytokines, and showed that the infection progressed in animals without coinfection but regressed in animals co-infected with intestinal helminths. In their review, published in the 1990s, on the inhibition of the immune response, mainly against HIV, *Mycobacterium tuberculosis* helminth or other parasites, Bentwich and colleagues [41] asked "Can eradication of helminthic infections change the face of AIDS and tuberculosis?". Following the same line of questioning, Bundy., *et al*. [42] reviewed the evidence for whether helminth infections are advantageous to the host in an article titled, "Good worms or bad worms: do worm infections affect the epidemiological patterns of other diseases?". This review focussed on the effect of infections on reducing the inflammatory process, similar to that observed in allergic diseases, as well as the disadvantages, such as co-infection with HIV and Koch's bacillus.

Around the same time, Yazdanbakhsh and colleagues [43,44] reviewed the consequences of Th2 hyperstimulation by addressing the main stimulatory mechanisms for this cytokine profile that could affect the development of atopy and other inflammatory processes, also triggered by the Th2 response. They discussed the basis of the "hygiene hypothesis", which postulates that short parasitic infections reduce the inflammatory manifestations, for example, the aforementioned atopy. Another important publication around this time evaluated an experimental model of murine autoimmune encephalitis, and showed that co-infection with *Schistosoma* and *Mycobacterium* affected the course of the inflammatory process [45].

Following the initial discussion of the hygiene hypothesis by Yazdanbakhsh [43,44], hundreds of articles in the literature have discussed this proposal. Recent publications continue to contribute to this hypothesis, such as a study by Figueiredo., *et al*. [46], in which the authors collected information about the immunological phenotype, habits, living conditions and allergies in a sample of 1127 children from Salvador (Bahia) Brazil. Another recent publication [47], based on an epidemiological survey of 1029 children, showed that children from families that manually washed their dishes had a much lower prevalence of allergic diseases than those who used dishwashing machines. The authors suggest that this may be explained by increased exposure to pathogens, thereby reducing the prevalence of allergies.

In relation to possibilities for different co-infections and their consequences over the course of the infection, the previously mentioned literature, in addition to more recently published studies, among these is a consistent review by Helmby [48], which describes several examples of the positive and negative effects of helminth infection on human and animal hosts, as well as identifying 15 areas that need better clarification, ranging from issues related to the biology of the parasite, genetic issues of the host, and experimental approaches. Concluded this review with, "So the question remains: are helminths friend or foe?". Another recent publication addressed the effects of helminth infection on the course of human tuberculosis, including neonatal effects in mothers infected with parasites [49]. These authors

also focussed on the Th1, Th2 and Treg aspects of the immune response as the basis for the ability of helminth infection to suppress immunity against *Mycobacterium tuberculosis*, and highlighted the need for further research on this topic. Finally, studies by Osborne., *et al*. [50] and Reese., *et al*. [51] which further investigated the helminth-virus murine model, began to uncover the underlying mechanisms for the hyperactivation of Th2 and inhibition of Th1from the identification of molecules, such as Ym1, which is one of the alternative STAT-6-dependent macrophage activation products, and is possibly one of the mediators of this inhibition.

Experiments are currently underway in our laboratory, not yet published, focussed on aspects of the immune response resulting from the coinfection of *Haemonchus contortus* and *Corynebacterium pseudotuberculosis* in sheep and goats. This will certainly provide further information on the possible effects of the strong Th2 stimulation induced by this helminth over the course of *C. pseudotuberculosis* infection, as discussed earlier in this review.

Conclusions

The literature discussed in this review, identified by searching for the keywords mentioned previously, provide information on the innate and adaptive immune responses to *Haemonchus contortus.* These studies report outcomes from the rapid or delayed removal of this worm, and also demonstrate strong stimulation of Th2 mechanisms, and their important consequences for the control of this helminth. These studies have also addressed the effect of the strong stimulation of the Th2 response rather than Th1 in experimental animal models and in humans, and while further studies are required to better understand this negative regulation, current information suggests that helminth infection allows for progression of the concomitant infection, the control of which relies mainly on the Th2 response.

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