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Immunomodulation by Filarial Parasites

Anuradha Rajamanickam, M.Sc, M.Phil. * and Subash Babu, *MBBS, PhD#*

Abstract — **Approximately 200 million people are infected with the major forms of filarial parasites causing the diseases - lymphatic filariasis, onchocerciasis, and loiasis. Even though infections by these pathogens are generally not fatal, they are associated with high rates of morbidity, and disability. Helminths are master regulators of host immune responses, developing complex mechanisms to dampen host protective Th2-type responses and favour long-term persistence. In order to chronically infect their hosts, filarial nematodes have produced a range of approaches to evade and down-modulate the host's immune system. Evasion mechanisms ensure mutual survival of both the parasite and the host. In this review we discuss recent findings on the cells that are targeted by helminths and the molecules and mechanisms that are induced during infection and also examine recent findings on helminth-derived molecules that can be used as tools to identify the underlying mechanisms of immune regulation or to determine new anti-inflammatory therapeutics.**

Keywords — **Filariasis, Helminth, Immuno modulation, Regulation.**

INTRODUCTION

HELMINTHS are multicellular organisms of which many species are parasitic. Those infecting humans are mainly found in two phyla; the phylum of Platyhelminths includes digenean flukes (trematodes) and tapeworms (cestodes), and roundworms belong to the phylum of Nematoda. Infections with filarial nematodes are a major problem of public health in tropical countries. According to recent estimates, 200 million people are infected with the major forms, lymphatic filariasis (by *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*), onchocerciasis or 'river blindness' (by Onchocerca volvulus), and loiasis (by Loa loa) [1-4][87,88,91]. Although infections by these pathogens are generally not fatal, they are associated with high rates of morbidity, and disability.[5] Helminths are long-lived organisms (up to 10 years for filarial worms) and mostly they are not able to replicate within their human host. Cells of the innate and adaptive immune system are important for the initiation of type 2 immunity, which are the hallmark of helminth infections. The key players in T helper (Th) 2-type immunity are CD4+ Th2 cells and involve the cytokines—IL-4, IL-5, IL-9, IL-10, and IL-13; the antibody isotypes—IgG1, IgG4, and IgE, and expanded populations of eosinophils, basophils, mast cells, and alternatively activated macrophages.[6,7] Helminths are thought to have developed different strategies for survival in their human host. Helminths can interact with the host adaptive immune response by down-regulation of T- and B-cell responses via the induction of regulatory T cells or the anti-inflammatory cytokines IL-10 and TGF- in the chronic phase of infection.[8]

A common feature is the fact that these infections are chronic and persist over many years, if not for a lifetime, yet they produce, in the majority of individuals, comparatively little signs of disease. Over the recent years, a large body of scientific literature has demonstrated that this is because of the capability of filarial nematodes to modulate the host's immune systems in such a way that it tolerates the parasites for a long time. Immunomodulation is hypothesized to be useful to both the human host and the parasite, as it could protect helminths from being eradicated, and at the same time protect the host from excessive pro-inflammatory responses. Immune hyporesponsiveness is evident mostly in cases of chronic or high level infections; upon infection the immune system will be activated and try to eliminate the worm, however, as the burden or time after infection increases, the worms seem to modify and down-regulate these responses in order to survive. Immunomodulation and suppression by filarial nematodes, however, although being antigen specific, has also been shown to spread to unrelated third-party antigens through a process that may initially be confined to antigen-specific T cells but then extends to antigen-presenting cells in the course of infection, and thus can have a broad impact on the whole immune system. Defining the cellular and molecular basis for helminth immunomodulation will provide both new

strategies for eradicating parasite infection [9] and new understanding of the intimate co-evolution between helminths and the mammalian immune system.[10,6]

Helminth induced immune response:

Cells of the innate and adaptive immune system are important for the initiation of type 2 immunity, which characterizes the response to helminth infection, as well as allergic reactions. The key players in T helper (Th) 2-type immunity are CD4+ Th2 cells and involve the cytokines interleukin (IL-) 4, IL-5, IL-9, IL-10, and IL-13 and immunoglobulin (Ig) E. Filarial parasites use intense immunoregulatory effects on the host immune system with both parasite antigen specific and more generalized levels of immune suppression.[11] Th2-type immune responses are composed of three major features[6] immunosuppression, immunological tolerance and modified Th2 response.

Parasites have developed various strategies to modulate the immune system and ultimately suppress host protective Th2-type immune responses for example, by induction of innate and adaptive regulatory cells, anti-inflammatory cytokines and specific inhibitory antibody isotypes[12] effector responses are dampened by immunoregulatory cytokines released by regulatory lymphocytes through different mechanisms. In immunological tolerance, effector Th2 cells enter a state of anergy and fail to develop specific T effector cells that would mediate resistance to infection. One strategy of immune regulation that has evolved is the secretion of a wide range of immunoregulatory molecules, which are able to target various host cells and alter them to induce a highly directed host response known as a modified Th2-type response. In immunological terms, the modified Th2 response is defined by the development of specific antibody isotypes, including induction of IgG4 accompanied by a decrease in IgE, as well as IL-4 and IL-5, while IL- 10 levels from different regulatory cell sources increase [13,6] and also in addition some measurable attenuation in responses to bystander antigens and routine vaccinations.[14] Among the mechanisms utilized by parasites to avoid immune-mediated elimination are those of suppression, regulation, or blockade of immune effector pathways [14] can lead to attenuation of pathology and tolerance, and ultimately persistence of the worm, which is associated with a hyporesponsive immune system. Asymptomatic infection assures long-term survival of the parasite within the host and therefore sustains parasite-feeding, completion of the life cycle, and successful reproduction.[8,6] Many studies of animal and human helminth infections have shown their potential for down regulating the immune system. Helminths and helminth-derived products that play a role either in induction of Th2 responses and immune modulation in parasitic infections or in down regulation of bystander Th2-type immunopathology like allergy and asthma.

Filaria induced Immunoregulation:

Immunoregulation in filarial infection was first recognized in early human studies, because peripheral T cells in infected patients were frequently unresponsive to parasite antigens and responses to bystander antigens (including allergens and vaccines) were also reduced.[10] Among the host factors influencing immunoregulation, the key players are the induction of regulatory T cells, modulation of effector T cells, and antigen-presenting cells and apoptosis of responder cells.[11]

Th2 responses induced by filarial parasites is a conventional response of the host, its initiation requires interaction with many different cell types, most notably: (1) stromal cells; (2) dendritic cells and macrophages; (3) eosinophils; (4) mast cells; (5) basophils, and (6) epithelial and innate helper cells.[6]

Filarial parasites induce a specific immune phenotype in the majority of persons that allows for establishment of infection while simultaneously preventing or reducing signs of disease in the host.[90] Ottesen-*et-al*. described antigen-specific cellular hyporesponsiveness for filarial infections for lymphatic filariasis in Cooks Island. In this study lymphocytes from adults infected with the filarial species *W. bancrofti* showed significantly lower levels of proliferation in response to filarial antigen compared with endemic controls that were negative for all signs of infection or disease but constantly exposed to infection and, therefore, putatively consistently exposed to the antigens.[15] Another study from the same group examined the difference between microfilariae (mf) positive asymptomatically infected persons and mf negative patients showing clinical symptoms of filariasis (e.g., elephantiasis or hydrocele).[16] The data suggested that the disease outcome depends on the host response together with a mechanism of immune modulation induced by the parasite.[17] Endemic normal individuals are continually exposed to the parasite but show no signs of infection or disease; this group develops an opposite response, defined by equal proportion of Th1, Th2 and T regulatory cell with a balance of IgG4 and IgE levels. Asymptomatic infection results in hyporesponiveness, which allows the presence of productive adult worms. This group has high levels of regulatory cells and IL-10, leading to a modified Th2 response. Finally, a small proportion of patients develop a hyperresponsive phenotype (characterized by an immunopathological response) [11][18][15] In *W. bancrofti*, and *B. malayi* infections, the main pathological response is a result of over reactive T cell responses that cause inflammation and injure the host. This group exhibits increased IgE responses, and the Treg compartment is greatly diminished. In *W. bancrofti* and *B. malayi* infections, this can result in elephantiasis, whereby the lymphatic tissue becomes dilated and hypertrophic. Parasite death leads to the release of antigenic material that causes lymphatic obstruction in the vessels and chronic inflammation. A second, rare result of these infections is tropical pulmonary eosinophilia (TPE) characterized by chronic lung obstruction, peripheral blood eosinophilia, and

extremely elevated levels of IgE, greater than in elephantiasis.[15][84][93] This is accompanied by strong Th2 responses, including IL-4, IL-5, and IL-13. Thus a fine balance of different aspects of immunity is required to develop a response beneficial to the host.

Cellular basis of Immunomodulation

The immune response against filarial parasites involves a remarkable range of innate and adaptive pathways for the induction and strengthening of highly powerful effector mechanisms. These potentially pathogenic responses also have to be regulated by the host immune system through counterbalancing immunoregulatory mechanisms.

Dendritic Cells

Filariasis is one of the most complex infections of humans. The infection is initiated by mosquito-derived third-stage larvae (L3) deposited in the skin, itself an immunologic organ, containing Langerhans cells (LC) and keratinocytes (KC) among other cells. LC are bone marrow-derived cells that are present in all epithelial tissues[19][89] and are essential for the initiation and dissemination of immune responses against foreign Ag in the skin. Before contact with Ag, LC express low levels of MHC class II and co- stimulatory molecules and are poor stimulators of unprimed T cells. Upon contact with Ag, these cells become activated and migrate to the regional lymph node, where they act as mature APC[20] It has been suggested that TNF-α and IL-1β are the two independent cytokine signals required for migration of LC. Both are up regulated following various forms of skin trauma and result in necessary physiologic changes to allow for migration from the skin to the draining lymph nodes.[21] LC produce a variety of mediators, including cytokines such as IL-1 , IL-6, IL-12, and IL-18 that are capable of playing a role in the initiation and modulation of immune responses in the skin.[22] LC exposed to the L3 stage of *B. malayi* have shown a relatively latent response of the LC to this infective stage of the parasite. This latent response augments to the increasing evidence that LC have many different functions in the skin other than priming the adaptive immune response, that these functions depend on the type and nature of the stimulus, and that skin-transiting helminths have evolved methods for by- passing the hosts' first line of immune defense by failing to fully activate LC.[23]

The initiating step in the adaptive immune response to infection is an antigen-presenting cell (APC, usually a dendritic cell – DC), taking up, processing and presenting antigen to T cells. DCs up regulate expression of surface ligands and soluble mediators, which activate antigen-specific T cells through their co-stimulatory and cytokine receptors. This interaction can also direct the qualitative nature of the response, for example towards a dominant Th1 or Th2 mode.[24] DC's are the main messenger cells to communicate with T cells and initiate an immune response, interference with their functions represents a key mechanism for helminths to induce an environment conducive to their survival.[25] The down regulation of

proinflammatory cytokines appears to be a frequent feature in helminth-mediated modulation of the Th2-type response.[29] Human DCs exposed to *B. malayi* mf showed higher levels of apoptosis and decreased production of IL-12 and IL-10.[26][81] In fact when human monocytes that were being differentiated to DCs in vitro were stimulated with *B. malayi* mf antigen, they produced significantly decreased levels of IL-12p40, IL- 12p70, and IL-10 in response to bacterial adjuvant.[27][86] Combined with suppression of proinflammatory cytokines, a key aspect in modulation of DCs is the down regulation of co-stimulatory molecules; leading to induction of a Th2 response.[28] Tolerogenic DCs exhibit little evidence of maturation (up-regulation of CD40, CD80, CD86, and major histocompatibility complex (MHC) class II), whereas microbial TLR ligands strongly induce these markers. Helminth molecules interfere with the ability of DCs to respond to TLR ligands and to produce IL-12 in response to stimulation.[29][30-31] Live filarial parasites have the capacity to downregulate TLR expression (specifically TLR3 and 4) on dendritic cells as well.[32] This is accompanied by an impaired ability of dendritic cells to produce IFN- , MIP-1 , IL-12, and IL-1 in response to TLR ligands. The diminished expression and function of TLRs on immune cells is thought to be a likely consequence of chronic antigen stimulation and probably serves as a novel mechanism to protect against the development of pathology in filariasis.[33] The ability of TLR2, TLR7, and TLR9 agonists to induce enhanced levels of Th1 and other pro-inflammatory cytokines,[34][82] While the TLR adaptors are not differentially induced, TLR2 and 9 ligands were shown to induce significantly higher levels of phosphorylated extracellular signal-related kinase 1/2 (ERK 1/2) and p38 mitogen-activated protein kinases (MAPK) and cause increased activation of NF-kB[35] Thus, downregulation of proinflammatory cytokines seems to be a frequent mechanism in immune modulation by helminths.

Effector T Cells

A major hallmark of longstanding filarial infection is the down regulation of parasite antigen driven Th1 differentiation. This is manifested by a significantly lower production of IFN-γ and IL-2 upon filarial antigen stimulation in asymptomatic-infected compared to diseased individuals.[36] Human filarial infection is known to be associated with down regulation of parasite-specific Th1 responses and T cell proliferation and but with augmented Th2 responses.[13] Human lymphatic filarial infection is associated with an antigen specific expansion of Th2 cells (mostly defined by IL-4 expression) and enhanced production of IL-4 and IL-13.[13] However, antigen– driven IL-5 production has been shown to be diminished in patently infected individuals[37,38] in some studies. The induction of classical Th2 response with high IL-4, IL-5 and IL-13 secretion has long been considered to be the hallmark of active infection in human filariasis.[13] However,not all studies have consistently shown a predominant classical

Th2 response in filarial infections. A recent study in Mali suggested that patent long-standing filarial infection is associated with expanded adaptive regulatory T cell cells rather than an expansion of classical Th2 cells environment.[39] Previous studies have reported a down regulation of IL-5 upon parasite stimulation.[37][38][40] Recent data using multi-color flow cytometry has shown that the frequency of Th1 cells (CD4+ T cells expressing either IFN-γ or IL-2 or TNF-α) is significantly enhanced in filarial lymphedema patients, while the frequency of Th2 cells (CD4+ T cells expressing IL-4 or IL- 5 or IL-13) is significantly diminished in comparison to asymptomatic, infected individuals both at homeostasis and following parasite antigen stimulation (Babu, S et al., unpublished). The increase in Th17 cells has also been confirmed by findings that chronic pathology individuals have higher frequencies of CD4+ T cells expressing IL-17 and IL-22 when compared to asymptomatic individuals (Unpublished data).

Effector T cell responses can be turned off or modulated through a variety of mechanisms including through CTLA-4 and PD-1.[41] CTLA-4 may also be an important inhibitor of effector T cell signaling, as in lymphatic filarial patients, peripheral T cells challenged with parasite antigen in the presence of anti-CTLA-4 antibodies showed improved responsiveness. Increased expression of CTLA-4 and PD-1 has been demonstrated in filarial infections, and blocking of CTLA-4 can restore partially a degree of immunological responsiveness in cells from infected individual.[40][42] Besides, T cells have decreased induction of T-bet, the Th1 master transcription factor, indicating a failure at the transcriptional level to differentiate into Th1 cells.[43] T cells from filarial- infected individuals exhibit classical signs of anergy including diminished T cell proliferation to parasite antigens, lack of IL-2 production, and increased expression of E3 ubiquitin ligases.[40] Evidence that helminth parasitic infection actively suppresses immune responses also comes from studies in which responses to parasite antigens increase after the drug-induced clearance of parasites. After drug treatment of filaria-infected patients[44][83], immune responsiveness to the respective antigens is restored.

Regulatory Cells

The suppressive T- cell populations recently termed regulatory T cells, which are induced by filariae, most likely by adult MF producing female worms and/or the MF themselves. The concept and the term 'regulatory T cells' was introduced into filariasis research in 2000, when it became possible for the first time in infectious diseases to isolate and clone filarial antigen-specific T cells having a regulatory phenotype.[45] The host factors influencing immunoregulation, the key players are the induction of regulatory T cells, modulation of effector T cells, and antigen-presenting cells and apoptosis of responder cells.[11] Recently, a number of regulatory factors, including Tregs, IL-10, TGF-beta, CTLA-4, and PD-1, have been implicated in the establishment of chronic viral and bacterial infections.[46] Evidence for the involvement of regulatory T cells in helminth-mediated down modulation of the immune response has been accumulating in recent years.[41] Treg populations can be defined, in particular "natural" Tregs, which express the transcription factor Foxp3 following their development in the thymus; "induced" Tregs, which switch to Foxp3 expression in the periphery; and Foxp3- type 1 regulatory (Tr1) cells. One of the major cell types now known to regulate effector CD4+ T cell responses is the subset of regulatory T cells (Tregs), characterized by surface expression of CD25 and the transcription factor FoxP3.[47] All these Treg populations can produce IL-10 and TGF-beta in different settings.[48] IL-10 and TGF-beta, both factors associated with regulatory T cells, are elicited in response to helminth infections and in vitro neutralization of IL-10 and TGF-beta, at least partially restores T cell proliferation and cytokine production in lymphatic filariasis.[13][49,50] The importance of suppressive cell subsets in human helminth disease was evident, in assays of T cells from hyporesponsive Mf+ *B. malayi* infected individuals.[16] An important role for IL-10 in preventing pathology was described several years ago by the finding that significantly increased levels of IL-10 was induced upon filarial antigen stimulation in asymptomatic, infected patients but not in those with chronic pathology.[18] In addition, blockade of IL-10 could partially reverse the impaired proliferation and Th1 differentiation of PBMC in infected individuals.[50] Asymptomatic Mf+ individuals show elevated levels of IL-10[18] and a suppression of Th1 inflammatory cytokines (such as IFN-γ) as well as key Th2 components such as IL-5.[37] Conversely, those individuals succumbing to lymphatic pathology have significant Th1 and Th17 components.[80] By flow cytometry, recent studies have established higher frequencies of CD4+ CD25+ CD127- Foxp3+ Tregs in filariasis Mf+ cases than in controls.[40] Effector T cell responses can be turned off or modulated through a variety of mechanisms including through CTLA-4 and PD-1.[41] Increased expression of CTLA-4 and PD-1 has been demonstrated in filarial infections, and blocking of CTLA-4 can restore partially a degree of immunological responsiveness in cells from infected individuals.[40][42] It was suggested that CTLA-4 and PD-1 (programmed cell death 1) may be involved in blocking inflammatory bystander responses in infected patients.[51] Recently, regulatory T cells from microfilaremic individuals, but not those from uninfected individuals, were shown to suppress both Th1 and Th2 PBMC cytokine production, providing further evidence of a link between Tregs and the hyporesponsive state.[52] On the other hand, PBMCs from filaria-infected individuals with chronic pathology fail to up-regulate Foxp3 in response to filarial antigen, potentially indicating that Tregs are deficient in these patients,[51] although this is subject to the limitation that Foxp3 can also be activation induced in humans.[53] During infection, Tregs may therefore be seen as important effector cells required to prevent or reduce pathology in

the host by modulating the ensuing Th2 response, thereby simultaneously allowing establishment of chronic infection. The frequency of CD4+ T cells expressing IL-10 also appear to be significantly elevated in infected individuals in comparison to both uninfected individuals and those with chronic pathology.[39][54] It has also been clearly demonstrated that the main source of IL-10 in infected individuals are CD4+, CD25- T cells and not the nTregs.[39][55][85] Though, nTregs are not the major source of IL-10 in infections, they might still have an important role to play in the prevention of pathology as individuals with filarial lymphedema exhibit an inability to up regulate Foxp3 expression in response to filarial antigens.[51] In addition, nTregs might also contribute by helping turn off exuberant immune responses by their capacity to up regulate CTLA-4 and PD-1 surface expression and to produce TGF-beta, a molecule known to be induced by parasite antigen stimulation in infected individuals but not in those with filarial pathology.[39][51]

B cells

Host protection as well as regulation by antibodies and B cells is being recognized as an essential component in Th2 responses in helminth infections.[56] Blockade of B cell production resulted in high levels of the proinflammatory cytokines IFN-γ and IL-12 but low levels of the Th2 cytokines IL-4 and IL-10 in acute infection.[57] IgG4 and IgG1 elevated in chronically filarial infected humans.[58] High levels of IgG4 but low levels of IgE are found in the blood of hyporesponsive, asymptomatic persons infected with *B. malayi*, *W. bancrofti,* and *O. volvulus*.[59,60][92] IgG4 correlates with high levels of IL-10 and the presence of adult worms in hyporesponsive persons. In Bancroftian filariasis, high levels of IgG4 but low levels of IgE were found in mf positive individuals compared to patients with clinical disease (Elephantiasis & TPE). One of the most consistent findings in filarial infections is the elevated level of IgE that is observed following exposure.[61] Interestingly, these IgE antibodies persist many years after the infection has been treated, indicating the presence of long-lived memory B cells or plasma cells in filarial infections.[62] Inhibitory IgG4 may prevent immunopathological responses in helminth asymptomatically infected individuals and can simultaneously provide an indication of the clinical outcome in infected persons

Alternatively Activated Macrophages

Macrophages that are activated by the Th2-type cytokines IL-4 and IL-13 develop an alternatively activated phenotype and have a well-described role in helminth infections.[63,64] Alternatively activated macrophages (AAMs) are recruited in large numbers to the sites of helminth infection where they can proliferate.[65] AAMs are important in tissue homeostasis, downregulation of the adaptive immune system, acting as effector cells against parasites, and to reduce or heal any ensuing damage caused by infection.[66] AAMs are distinct from macrophages activated through IFN-γ in expressing high levels of arginine-metabolizing arginase 1 which is important for wound healing,[67] the chitinase-like molecule Chi3L3 (Ym1), and the resistin-like molecule RELM-α.[68] Immunosuppressive effect was attributed to macrophages in mice peritoneally implanted with adult *B. malayi* filarial parasites.[69] The *in vitro* suppressive nature of *B. malayi*-induced AAMs, together with the induction *in vivo* of Foxp3+ Tregs by the same parasite,[70] suggests that these macrophages fulfill an immunoregulatory role. AAMs recruited during *B. malayi* infection have been demonstrated to drive CD4+ Th2 responses, deviating the immune system from inducing a proinflammatory Th1 response that could be detrimental to parasite survival.[71] In human filariasis, alternatively activated macrophage markers are up regulated in the blood of asymptomatic microfilaremics, the category displaying T cell hyporesponsiveness.[51] Thus, in filarial infections at least, AAMs appear to suppress the immune response against the parasite, promoting anergy and/or tolerance.

Filaria derived molecules:

Among the notable immune-evasion strategies, a key one is the secretion of products that modulate host immune function[9] Phosphorylcholine (PC) is a small hapten like moiety present in the excretory/secretory products of many helminths which has anti inflammatory property and one particular PC containing molecule called ES-62 from filarial worms has been shown to have a wide variety of immunomodulatory properties.[72] Other modulators from helminths, such as prostaglandins, membrane derived arachidonic acid might have the ability to alter the T-cell phenotype, *B.malayi* able to synthesis, release PGE2 provides direct route for immunomodulation of APCs in this parasitic infection.[73]

The cystatins and serpins are the best-characterized protease inhibitors of helminths that have immunomodulatory potential. Mammalian cysteine proteases are essential for efficient processing and presentation of antigen on MHC class II to induce an appropriate adaptive T cell response. Mammalian cystatins play a vital role in regulating these pathways; however, helminth cystatins from *B. malayi*, *O. volvulus* have been shown to interfere with this process to dampen antigen-dependent immune reactions.[74] Bm-CPI-2, a cystatin from *B. malayi*, was demonstrated to interfere with antigen processing, which led to a reduced number of epitopes presented to T cells in vitro.[75] Studies demonstrated that onchocystatin (rOv17) from *O. volvulus* reduced antigen-driven proliferation of peripheral blood mononuclear cells in a monocyte-dependent manner.[76] Similar to cystatins, serpins (serine protease inhibitors) have important roles in mammalian biological processes including regulation of complement activation, inflammatory pathways, and cell interactions. Bm-SPN-2 is a serpin expressed by *B. malayi* microfilariae, which could inhibit proteases of

human neutrophils, thereby interfering with and potentially circumventing the most abundant leukocyte to encounter mf in the bloodstream.[77] Another study disputes the enzymatic activity of Bm-SPN-2.[78] Recent genome study shows that analysis of *L. loa* genes identified a number of human cytokine and chemokine mimics and/or antagonists, including genes encoding macrophage migration inhibition factor (MIF) family signaling molecules, transforming growth factor- and their receptors, members of the interleukin-16 (IL-16) family, an IL-5 receptor antagonist, an interferon regulatory factor, a homolog of suppressor of cytokine signaling 7 (SOCS7) and two members of the chemokine-like family. *L. loa* genome encodes 17 serpins and 7 cystatins, which have been shown to interfere with antigen processing and presentation to T cells, 2 indoleamine 2,3- dioxygenase (IDO) genes, which encode immunomodulatory proteins implicated in strategies of immune subversion, and a number of members of the Wnt family of developmental regulators, which typically modulate immune activation.[79]
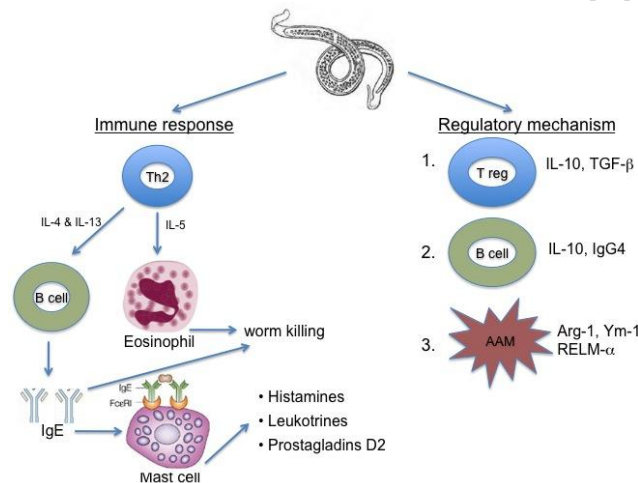
Th2 immune response in helminth infection

Helminth infection induces a protective Th2 immune response. Professional antigen presenting cells process helminth antigens and exhibit them to CD4+ T cells that differentiate into polarized Th2 cells. Th2 cells produce cytokines such as IL-4, -5, and -13 that activate and attract macrophages, eosinophils, and other innate immune cells as well as B cells. IL-4 and -13 induce differentiation of antigen-specific B cells and production of large amounts of antibodies (normally IgE). Antibodies opsonize the helminths leading to killing by antibody-dependent cellular toxicity (ADCC). IgEs bind to Fcε-receptors (FcεRI) on mast cells (MCs). Sensitized MCs secrete large amounts of histamine and other mediators and facilitate the attraction and accumulation of further immune cells, which result in larvae killing.

Regulatory mechanisms in helminth infection

Helminths induce immunoregulation through modulation of immune cells primarily to alternatively activated macrophages (AAMs), regulatory T cells (Treg),

and B cells. AAMs in mice express among others arginase-1 (Arg 1), resistin-like molecule-α (RELM-α), Ym-1, Ym-2, IL-10, and TGF-β and subsidize to wound healing. Treg produce IL-10 and transforming growth factor-β (TGF-β), whereas B cells can stimulate regulatory mechanisms via IL- 10. These cellular changes lead to modified Th2 immune responses and larvae survival as well as blocking of unrelated inflammation such as allergic immune responses.

CONCLUSIONS

In this review we have focused on the immune response, immune regulation, and also it has helped to further develop the general immunological concepts of regulatory T cells, alternatively activated macrophages, TLR stimulation by helminths, how filarial nematodes modulate the immune system of their hosts to their favour is an exciting area of research. Parasitic helminths produce a numerous of immunomodulatory molecules to suppress anti-parasite and immunopathological responses at multiple levels, from the very early initiating events in innate immunity to the final effector mechanisms in established adaptive responses.

Research should focus on studying the immunomodulatory effects of helminth-derived products on filariasis and struggle to develop new therapeutic strategies by identifying the mechanisms and pathways utilized by such molecules in mediating their immunomodulatory effects.

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