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Immunosuppression in Helminth Infection

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1. Introduction

1.1 Parasitism

Parasitism is an antagonistic relationship between organisms of different species where the parasite benefits at the expense of the host. Helminths are long-living, multicellular parasites. There are two major phylla of helminths; Nematodes and Platyhelminthes. The nematodes contain the intestinal worms known as soil-transmitted helminths including hookworms, whipworms and the filarial worms that cause lymphatic filariasis and onchocerciasis. The Platyhelminthes, known as flatworms, include the flukes and the tapeworms. Both nematodes, flukes and tapeworms widely infect humans and animals (Hotez & Kamath, 2009). Most of the parasitic species causing weakness and disease survive in and explore the host as natural environment. Helminths can be found in a great variety of tissue niches, and although they cause very high morbidity, direct mortality of the host species remains low (Brooker, 2010). Human hookworm infection is a common soil-transmitted helminth infection that is caused by the nematode parasites *Necator americanus* and *Ancylostoma duodenale*. Hookworm infections are asymptomatic however substantially contributes to the incidence of anemia and malnutrition in developing nations (de Silva et. al 2003, WHO 2010).

Filarial diseases are rarely fatal and morbidity of human filariasis results mainly from the host reaction to microfilariae or developing adult worms in different areas of the body. Most of the filarial infected individuals have a subclinical condition associated with patent infection, and acute manifestations which are rarely life threatening. However, chronic manifestations, such as lymphedema (elephantiasis) and hydrocele, are debilitating (Keiser et al., 2002).

Schistosomes, the blood flukes reside in the mesenteric and vesical venules. They have a life span of many years and daily produce large numbers of eggs, which must traverse the gut or bladder tissues on their way to the lumens of the excretory organs. Many of the eggs remain in the host tissues, inducing immunologically mediated granulomatous inflammation and fibrosis (Warren, 1982). The relationship between the presence of schistosome infection and clinical morbidity revealed schistosomiasis-related disease and associated death (Van der Werf et al., 2003).

Worldwide, many cestode infestations occur with very low prevalence of infections and are asymptomatic. Nevertheless some of the more serious infestations result in symptoms from mass effects on vital organs, inflammatory responses, nutritional deficiencies, and the potential of fatal anaphylaxis (Del Brutto, 2005; Morar & Feldman, 2003; Ozturk et al., 2007).

1.2 The outcome of immunosuppression in population

However the immune system is the system responsible for protection against parasites, mlticellular helminths which actively destroy host tissue evolved in effective immune system; the aim of parasite-related suppression is to get the right environment for existence and survival. The number of larvae which successfully invade the host, the number of migrating parasites and the number of settled adult forms and their reproductive capacity depend on the activity of the host immune system. Immune recognition, effectiveness of immune reactivity and protective response are the mechanisms that affect parasite abundance and survival in the host. In response to the action of immune system, parasites induce a plethora of mechanisms which evade or manipulate host defence. All these reactions take place at the host–parasite interface and are regulated by gene products of both species. In the evolutionary sense both parasite products and host immune system are adjusted to their intimate relationship.

Genetic population studies shown that helminths have been a major selective force on a subset of interleukin receptor genes (IL genes) from which some genes, have been a target of balancing selection, a process that maintains genetic variability within a population (Fumagalli et al., 2009). Allele frequency, host behaviour and helminth distribution in population may influence of heritable factors both in patterns of infection and immunity (Ellis et al., 2007). It is reflected in the effect of helminths on individual host responses to other pathogens such as microparasites, which is considerable variable. In concurrent infections with multiple coinfecting species, parasites interact with one another through the host's immune system *via* mechanisms such as immune trade-offs and immunosuppression (Ezenwa & Jolles, 2011). A subset of immunomodulatory parasite species may have a key role in structuring other infections in natural vertebrate populations. Affecting expression of toll-like receptors (TLR) are important in initiating immunity; populations free from immunosuppressive parasites may exist at 'unnaturally' elevated levels of innate immune activation, leading to an increased risk of immunopathology (Jackson et al. 2009). The host immunocompetence may give some indications of the control of parasite infection and of the host mediation effect, through immunity, on the parasite community structure (Combes, 1997; Mouritsen & Poulin, 2005). Thus immunosuppression promotes over-dispersal of parasites and favours the most suitable genotype of the host for better propagation of the parasite. As intestinal mucins are an important component of innate defence even a single gene deficiency predisposes to infection with nematodes (Hasnain et al., 2010; McKay and Khan, 2003).

The distribution of parasites among different individuals in the host population, infected with the same helminth species is heterogeneous. A consequence of this is the aggregated distribution of helminth infection in endemic communities; a small proportion of hosts are rapidly, frequently, and/or heavily infected (May & Anderson, 1990). Such a pattern of distribution suggests that some individuals are predisposed to heavy infection and intensity of parasitic infections are also under genetic control (Iraqi et al., 2003, Stear & Wakelin, 1998). It is shown in humans as individual predisposition to infection, ethnic variation in susceptibility to disease and familial aggregation to infection (Quinnell, 2003). Genetic background determines both the favorable level of immune suppression necessary to sustain chronic infection as well as a highly active immune response to eradicate worms from the infected host. In lambs, naturally exposed to nematodes on pasture season, genetics acts mainly through the control of acquired anti-fecundity immune response (Stear et al., 1997). Moreover, as the consequence of anthropogenic changes in natural environment the

evolution of different traits in parasites e.g. specificity, virulence, and polymorphism may be influenced by humans (Lebarbenchon et al., 2008).

1.3 The outcome of immunosuppression in the host

Helminths tend to settle in privileged localization in the host which is reflected in the distinct location of larvae and adults in the host. Helminths need a suitable and non-destructive localization to propagate and transmit their offspring. The state of immune unresponsiveness protects growing larvae during migration through the host tissue. Some nematode species larvae such as *Ascaris* and *Strongylus* undergo extensive migrations which begin and end in the same location, the intestine. Nematodes which migrate during development are usually bigger than their closest relatives that develop wholly within the gastrointestinal tract. Time to reproduction is the same, indicating that worms with a tissue phase during development grow faster in the intestine. Because fecundity is intimately linked with size in nematodes, this provides an explanation for the maintenance of tissue migration by natural selection (Read & Sharping, 1995). For example *Trichinella spiralis* infection results in depression of various parameters of immunity, including delayed type hypersensitivity and responses to bacterial lipopolysaccharide (Barriga, 1978; Beiting et al., 2007; Gerencer et al., 1992). The nematode is a source of macrophage inhibitory factor (TspMIF) and is able to subvert host immunoregulation; MIF has been cloned and characterized with respect to structural, enzymic and cytokine properties (Tan et al., 2001). The maintenance of an immunosuppressed state in the host may improve the fitness of the parasite.

Immunosuppression induced by helminths not only affects the parasite which already has infected the host, but also promotes infection with further infectious larvae. Parasite acquisition is density-dependent and the number of parasites successfully establishing in the host may over time increase with the parasite burden in the host. In long-lasting infections, immunosuppressive mechanisms prevent or limit parasite killing and expulsion; the ongoing infections do not elicit a strong host effector response; infection with one species predisposes for infection with other species and polyparasitism is common (Blaxter, 2003; Ellis & McManus, 2009; Keiser et al., 2002).

2. When immunosuppression is expressed

Immunosuppression may be recognized as; (i) the state when immune system is not specifically suppressed but is not active. That has been characterized for young or older individuals and also with genetic defects resulted in dysfunction of immune system or is artificially induced with immune suppressant for different reason; (ii) suppression activated during immune response which regulates inflammatory reactions and inhibits specific response to sustain the state of physiological homeostasis.

2.1 When the immunosuppression is used

The steady-state of immunosuppression develops as a naturally occurring regulatory pathway resulting in antigen-specific inhibition (von Boehmer, 1991) and the lack of immune response to antigen. Physiological immune homeostasis depends on a balance between the responses to infection or neoplasia and the reciprocal responses that prevent inflammation and autoimmune diseases. These phenomena lead to immunotolerance; the immunosuppressed host fails to responds to the presence of specific antigens or fails to respond to specific antigen. The outcome of these immune-compromising may be beneficial

to the host, through limiting the immunopathology and also beneficial to the pathogen, through subversion of the protective immune responses of the host (Kingston & Mills, 2004). Helminths survive within the host because they may induce the state of physiological and immune compromise and may consequently evade immune attack and actively subvert the host immune response (Mitchell, 1991; Ogilive & Wilson, 1976).

The immune system does not function efficiently throughout the life of the host. Host individuals are more susceptible to infection when their immune system is less sensitive to antigenic signals and doesn't react as quickly or efficiently to infection (Matzinger, 1994). This immune suppression is related to the physiological state of the host and influences the pattern of infection in the population. Most parasitic species are propagated preferentially in young individuals when the immune system is not completely developed or educated (Roberts, 1999). Especially physiological immunosuppression associated with parturition and lactation and the immunological unresponsiveness of young ruminants allows parasites to increase transmission; these states are correlated with the unresponsiveness of lymphocytes to mitogens (Soulsby, 1987).

Neonatal exposure to antigens appears to develop immune tolerance (Billingham et al., 1956). From the neonate major environmentally associated changes in immune response phenotype occurred (Wilkie et al., 2011) and neonatal T cells were susceptible to induction of tolerance (Gammon et al., 1986). In such immune milieu morbidity is acceptable in the host population. From evolution, it is likely that immunosuppression in the meaning of unresponsiveness or selective mortality of the most sensitive individuals, protect the better (suitable) genotypes of the host which are able to tolerate surviving parasites.

Changes with age in the average intensity of *Ascaris* infection tend to be convex, rising in childhood and declining in adulthood (Bundy et al., 1987). Also piglets are more susceptible to *Trichuris suis* infection than adult pigs (Pedersen & Saeed, 2002). In contrast, hookworm frequently exhibits a steady rise in intensity of infection with age, peaking in adulthood (Hotez et al., 2008). Similarly, *Brugia malayi* infection establishes more rapidly in adults than in children (Terhell et al., 2001). Changes in cytokine phenotype, particularly CD4 T cells, contribute to age-associated switch from *Trichuris muris* resistance to susceptibility in mice (Humphreys & Grencis, 2002). As the parasite load gained through the life differs among parasite and host species, the establishment of infection may be therefore dependent not only on the host immune response but also on parasite–related factors which may actively modulate immune reactions.

The immune system is involved in creating a favorable environment in the tissue for the parasites. The compromise of immune responsiveness by the host endocrine system may support establishment, growth, reproduction and survival of helminths. The contribution of stress, host sex or age may also reflect neuroimmunoendocrine interactions. The gender-dependent immune regulation was identified; adult individuals of Senegalese population chronically infected with *Schistosoma haematobium* parasite presenting similar intensities of infection showed specific IgA response and production of TGF-β and IL-10 significantly higher in females compared to males. This specific profile was supposed to be associated with T helper type-3 (Th3) immune response. Nonimmunological factors like sexual hormones, were proposed to influence the chronicity of the infection (Remoué et al., 2001). Hormones are strongly involved in immune suppression observed in stress-fully conditions which predispose to greater and longer infection or make the host susceptible to infection (Hernandez-Bello et al., 2010). Increases in gastrointestinal nematode egg production in sheep with age were greatest among individuals that had experienced the highest degree of stress (Hayward et al., 2009).

2.2 When the immunosuppression is expressed

Immunosuppression may be reached by different mechanisms in response to a plethora of parasitic molecules and may be expressed at each point of infection; from the ongoing invasion to chronic prolonged infection (Robinson et al., 2010). When parasites enter host tissues, a balance between the host effector mechanisms and the defense by the parasite have to be established allowing the survival of a number of larvae that escape from the first immune attack, and as long as some parasites persist, are able to act as effectors to regulate immune responses. One of the possibilities to cope with host defence is to inhibit innate immunity. Helminth derived products are able to modulate the function of non-immune and immune cells (Perrigoue et al, 2008). T cell hyporesponsiveness to antigen-specific stimuli from the beginning of infection may support survival of the developing stages of the parasite (Schwartz, 2003; Taylor et al., 2009). Induced hyporesponsiveness of T cells as a defect in lymphocyte function may contribute to the failure of the immune system to eliminate filarial nematodes (W. Harnett & M.M. Harnett, 2008; W. Harnett & M.M. Harnett, 2006). In ruminants immunosuppression caused by parasites leads to reduced responsiveness of lymphocytes to mitogens (Soulsby, 1987).

Helminth infections induce regulatory T cells (Treg: Tr1, Th3) secreting IL-10 and transforming growth factor (TGF-β) (Doetze et al, 2000) as well as $CD4^+CD25^+$ Treg expressing the Foxp3 transcription factor in the host (Cervi et al.; 2009; Pacífico et al., 2009). These regulatory T cells can alter the course of inflammatory disorders by increased production of IL-10 and TGF-β, together with induction of $CD25^+CD4^+$ $Foxp3^+$ T cells (Correale & Farez, 2007). This also may represent a potential explanation regarding how exposure to a parasite could alter immune reactivity to unrelated stimuli.

Parasites release products whose molecular structure and specificity may be changed during infection and most parasite immune evasion mechanisms depend on a form of molecular recognition between parasite and host. Helminths especially in long lasting infection produce factors that interfere with the tissue of the host and for that many helminths-derived substances are considered as immune modulators (W. Harnett & M.M. Harnett, 2008; Harn et al., 2009; Imai & Fujita, 2004). Infection with helminths drives $CD4^+$ T cell biasing towards Th2-types and also induces the state of immunosuppression or anergy (Stadecker, 1992; Tawill et al., 2004).

From the beginning of infection down regulation of innate response may occur. Typically for helminthic infections, expanded populations of eosinophils, basophils, mast cells and macrophages appear (Anthony et al., 2007; Jenkins & Allen, 2010). Nitric oxide produced by activated macrophages, eosinophils and other myeloid cells, is involved in many signalling pathways and may mediate induction of immunosuppression (Stamler et al., 1992). Hookworm infection inducing NO production is associated with impaired function of antigen-presenting cells and depletion of lymphocyte subpopulations (Dondji et al., 2008); myeloid cells derived from helminth infected animals exhibit antiproliferative properties (Mylonas et al., 2000).

Myeloid suppressor cells displaying an alternative activation phenotype CD11b/GR-1 emerged gradually in progression of *Taenia crassiceps* infection and in the late stage of infection, the suppressive activity relied on arginase activity, which facilitated the production of reactive oxygen species including H_2O_2 and superoxide (Brys et al., 2005). These cells are potent to impair antigen-specific T cell responses (Terrazas et al., 2001). Helminth extracts activate various macrophage populations and the most active in regulation of immune response are alternatively activated macrophages (AAMΦ) (Herbert et al., 2004).

2.3 Immunosuppression for tissue repair

During helminth infections Th2 immune responses and parasitic-related products downregulate immunity; both of which minimize pathology in the host (Maizels & Yazdanbakhsh, 2003; Tawill et al., 2004).

Macrophages are frequently the most abundant cell type recruited to the site of helminth infection but their activation and role are strictly dependent on the stage of infection and localization of the parasite. In the construction of tissue homeostasis suppression of inflammation is propagated by AAMΦ as anti-inflammatory down-regulatory cells (Allen & Loke, 2001; Villanueva et al., 1994). These cells are sources of TGF-β and IL-10 (Mylonas et al., 2009; Loke et al., 2000) as well prostaglandins PGE2 (Rodriguez-Sosa et al., 2002) and the IL-1 receptor antagonist (Goerdt & Orfanos, 1999). AAMΦ are also involved in repairing tissue or wound healing followed migration of larvae through the host tissue (Gratchev et al., 2001; Munder et al., 1998). Activation of myeloid cells may represent not only the state of innate protection but also have been already activated by helminth products and represent suppressor or repair responses.

Metazoan parasites localized in the tissue require a supply of nutrients and the removal of waste products therefore angiogenesis may be a key mechanism for helminth survival and presumably depend on the host tissue. The multifactorial induction of parasitic helminth-associated neovascularization could arise through, either a host-, a parasite- or a host-/parasite-dependent, angiogenic switch (Dennis et al., 2011). It is possible that mechanisms that downregulate the inflammatory reaction and support wound healing are the main outcome of immunosuppression in the host tissue. Upon immunosuppression, the activation or efficacy of the immune response is reduced. Some portions of the immune system itself have immunosuppressive effects on other parts of the immune system, and immunosuppression may also occur as an adverse reaction to treatment of other conditions. It is really that helminths inducing inflammatory responses provoke opposite or reverse reactions of immune cells (Erb, 2009). Depending on the parasite stages and their localization a distinct local and systemic immune reaction may be observed in the host tissue (Löscher & Saathoff, 2008). The rapid and persistent release of tegument glycoconjugates play a key role in immune evasion and life-long inflammation seen in many neurocysticercosis patients (Alvarez et al., 2008). The production of pro-inflammatory cytokines is often required to control parasites but the same cytokines contribute to immunopathology. In the tissue, cytokines and prostaglandins or glucocorticoid hormones may differentially suppress an inflammatory response provoked by the parasite (Dhabhar, 2009; Noverr et al., 2003; Wiegers & Reul, 1998).

The immunosuppressive effect may be also maintained by other mechanisms such as induction of immunosuppressive B cells (Wilson et al., 2010) and regulatory function in helminth infection is also pointed for B cells. IL-10 and TGF-β are secreted form B cells during *Schistosoma mansoni* infection (Velupillai & Harn, 1994) or in mice infected with *Brugia pahangi* (Gillan et al., 2005).

2.4 The action of immunosuppressive factors

Immune non-responsiveness may also be the result of particular external processes such as deactivation of immune molecules or factors by helminthic products. Helminth parasites secrete considerable quantities of proteins and glycoproteins into the host environment, many of which are capable of modulating antiparasite immunity. Such molecules interfere with crucial stages in the immune response such as extravasations (blocked by parasite lectins and glycans through binding to endothelial selectins), chemokine attraction

(hookworms release proteases capable of degrading eotaxin), release of host proteases (inhibited by helminth serpins), attack by reactive nitrogen and oxygen intermediates by eosinophils and other effector cells (inhibited by helminth antioxidants such as glutathione-S-transferase) (Falcone et al., 2004; Maizels et al., 2004).
Helminth parasites may also secrete cytokine homologues such as TGF-β and produce protease inhibitors that are capable of blocking peptide antigen presentation and of eliciting an IL-10 response from macrophages. Immune non-responsiveness may also be the result of deactivation of immune molecules or factors by helminthic products such as macrophage migration inhibitory factor (Vermeire et al., 2008). Lipid-like molecules of schistosomes such as lyso-PS can interact with dendritic cells to induce T regulatory phenotypes in naïve T cells (van der Kleij et al., 2002) and homologous molecules have been identified in *Ascaris.* Potent immunosuppressive effect of *Ascaris suum* extract components on the host immune system was related to their property of down-regulating the antigen presenting ability of dendritic cells *via* an IL-10-mediated mechanism (Silva et al., 2006). Filariae cystatin as immunoregulator exploits host signalling events to regulate cytokine production in macrophages (Klotz et al., 2011).
The efficiency of the innate response is crucial for invasion and survival of arriving larvae. Key attack points for selective immunoregulation conducted by parasites rely on (i) modulation of antigen recognition with changes in pathways of signal transduction; (ii) costimulation blockade; (iii) induction of regulatory cells; (iv) deviation to protective responses; (v) neutralization of proinflammatory cytokines; (vi) induction of anti-inflammatory cytokines and; (vii) modulation of leukocyte trafficking. Immunosuppressive action of parasites can be primarily directed to antigen-presenting cells (APC) and induction of suppressor/regulatory T cells and macrophages, with the common effect to selectively inhibition of local or systemic immune response.

2.5 How and when to get the immunosuppression

2.5.1 Innate and adaptive immune response

Innate immunity provides the first line of defence against invading pathogens. Excretory – secretory products released by helminths described as conserved molecular patterns associated with the pathogen (PAMP) may interact with the host pattern recognition receptor (PRRs) (Jackson et. al., 2009). Different carbohydrate moieties of helminths molecules are recognized by toll-like receptors (Medzhitov, 2007) and the C-type lectins receptors on dendritic cells and macrophages (Cambi et al., 2005). As a consequence of ligation, these DC will receive signals that are subsequently translated into different sets of Th1-, Th2-, or Treg-polarizing molecules. However, TLR ligation by helminth derived factors is recognized as a mechanism to limit of Th1 cytokine-mediated inflammation. Mature DC generated during helminth infection express relatively low levels of co-stimulatory molecules and proinflammatory cytokines promoting proliferation of CD4-positive T cells with Th2 phenotypes (MacDonald & Maizels, 2008; Semnani et al., 2008). Regulation of the host response starts from the recognition of the parasite; helminths products are able to stimulate partially activated dendritic cells with suppressed expression of TLRs and activate factors which promote Th2 and Treg phenotypes (Jackson et al., 2008). Some molecules which are released during tissue damage may interact with and induce anti-inflammatory effects (Ehlers & Ravetch, 2007).
Helminths strongly drive Th2-cell differentiation (Liu et al., 2005). Th2 related defence is involved in protective immune responses to helminths and is dominated by IL-4, IL5 and IL-

13 production (Finkelman et al., 2004). During Th2 related response, in addition to IL-4, IL-13, IL-5, IL-9, and IL-10 (Anthony et al., 2007). Th2 cells can make IL-25 and IL-33 (Fallon et al., 2006; Neill et al., 2010) which can further promote and/or regulate Th2 immune responses. IL-10 is differentially used by helminths to regulate immune response and as produced by different cells *in vivo* downregulates both Th1 and Th2 response (Hoffman et al., 2000; Taylor et al., 2006). Induction of type 2 immune responses may also be influenced by thymic stromal lymphopoietin (TSLP) synthesized by epithelial cells, and blocking IL-12 production can condition dendritic cells to promote Th2 cell development (Rimoldi et al., 2005). The innate cell sources of factors promoting Th2 and Treg response were only now proposed as a new innate type-2 immune effector leukocyte that were named the nuocyte. Nuocytes expand *in vivo* in response to the type-2-inducing cytokines IL-25 and IL-33, and represent the predominant early source of IL-13 during helminth infection with *Nippostrongylus brasiliensis* (Neill et al., 2010).

Apoptosis is mechanism which is involved in regulation of cell abundance during immune response. Cells induced to die release extramembrane phosphotidylserine which causes differentiation of immature dendritic cells to cells with a tolerogenic phenotype which favours anti-inflammatory responses (Steinman et al., 2000; Wallet et al., 2005). However, a plethora of helminths are able to modulate host apoptosis pathways to their own advantage. The involvement of apoptosis in immune regulation of the host immune function was proposed as one possible mechanism in creating the host−parasite relationship. The relative numbers of activated cells in both tissue and lymph nodes *via* the apoptotic pathway could determine pathology (Donskow-Schmelter & Doligalska, 2005). There is growing evidence that parasites can regulate apoptosis of T cells. Apoptosis can be triggered by diverse stimuli (Domen, 2001), including stimulation *via* T cells, Fas receptor, TNF receptors, glucocorticoids, removal of growth factors and enhanced expression of some proteases. In mice infected with microfilariae of the filariae nematode *B. malayi*, $CD4^+$ T cells showed high levels of apoptosis and displayed an antigen specific proliferative defect what is related to elevated macrophages activity (Jenson et al., 2002). Parasites may provoke apoptosis directly by secretion of active mediators or indirectly by producing an inflammatory milieu that promotes death of reactive T cells.

2.5.2 The regulation of immunosuppression by *Heligmosomoides polygyrus*

The *H. polygyrus* nematode is known to induce a dominant Th2 $CD4^+$ response and it provides an excellent example of downregulation of immune responsiveness. The adult worms had a potent immunosuppressive influence on the mouse host, but the histotropic L4 larvae provided the strongest signal for acquired immunity (Wahid & Behnke, 1992). In helminths, glycans provide a major contribution to the induction of Th2 development which is strongly skewed but the effectiveness of these responses for elimination or maintenance of the parasite is not fully elucidated. Additionally, in response to IL-4 and/or IL-13 producing cells, alternatively activated macrophages are activated, and express high levels of PRR. These population of cells produce high amounts of IL-10 and TGF-β but fail to generate NO (Gordon, 2003; Rodríguez-Sosa et al., 2002) and therefore may contribute to the general immune hyporesponsiveness observed in helminth-infected individuals (Leng et al., 2006; van Riet et al., 2007). Profoundly downregulatory cytokine TGF-β is critical to the immunosuppression induced by nematodes. Neutralization of these cytokines in human peripheral blood lymphocyte (PBL) cultures reversed antigen responsiveness toward filarial antigens (Cooper et a., 2001). Neutralization of TGF-β in BALB/c infected with *H. polygyrus* mice did not affect the Th2 related immune response (Doligalska et al., 2006). However

adult worms might express ligands from the TGF-β superfamily- TGH-2 to bind to mammalian TGF-β receptors which may induce naïve T cells to adopt a regulatory T-cell phenotype; thereby promoting long-term survival of parasites (Peng et al., 2004).

Intestinal submucosa	Reference	**Mesenteric lymph node**	Reference
L3 Larvae			
Neutrophils↑	Morimoto et al., 2004	T cells proliferation↑	Doligalska et al., 2006
Eosinophils↑	Morimoto et al., 2004	$CD4^+$ T cells apoptosis↓	Doligalska et al., 2006
AAMΦ↓	Morimoto et al., 2004		
Basophils↓	Anthony et al., 2006		
Mast cells↓	Morimoto et al., 2004		
$CD4^+$ T cells↑	Morimoto et al., 2004		
$CD8^+$ T cells↓	Liu et al., 2007		
B cells↓	Liu et al., 2007		
Cytokines & chemokines		*Cytokines & chemokines*	
IL-4↑, IL-13↑, IL-6↑	Donskow-Schmelter et al., 2008	IL-4↓, IL-6↓	Doligalska et al., 2007
IL-2↑, IL-12p70↑, IFN-γ↑	Donskow-Schmelter et al., 2008	IL-2↓, IL-12 p70↓, IFN-γ↓	Doligalska et al., 2007
TNF-α↑, IL-10↑, MCP-1↑	Donskow-Schmelter et al., 2008	TNF-α↑, IL-10 , MCP-1↑	Doligalska et al., 2007
		TGF-β↓	Doligalska et al., 2006
L4 Larvae			
AAMΦ↑	Kreider et al., 2007	T cells proliferation↓	Doligalska et al., 2006
CAMΦ↓	Donskow-Schmelter et al., 2008	$CD4^+$ T cells apoptosis↓	Doligalska et al., 2006
$CD4^+$ T cells↓	Kreider et al., 2007		
$CD8^+$ T cells↓	Kreider et al., 2007		
Cytokines & chemokines		*Cytokines & chemokines*	
IL-4↓ , IL-13↓, IL-6↑	Donskow-Schmelter et al., 2008	IL-4↓, IL-6↓	Doligalska et al., 2007
IL-2↓, IL-12p70↑, IFN-γ↑	Donskow-Schmelter et al., 2008	IL-2↓, IL-12 p70↓, IFN-γ↓	Doligalska et al., 2007
TNF-α↑, IL-10↓, MCP-1↑	Donskow-Schmelter et al., 2008	TNF-α↑, IL-10↓, MCP-1↓	Doligalska et al., 2007
		TGF-β↑	Doligalska et al., 2006
Adult worms			
Eosinophils ↓	Doligalska et al., 2006	T cells proliferation↓	Donskow et al., 2011
AAMΦ ↑	Anthony et al., 2006	$CD4^+$ T cells apoptosis ↓	Donskow et al., 2011
$CD4^+$ T cells ↓	Doligalska et al., 2006	$CD8^+$ T cells apoptosis↓	Donskow et al., 2011
$CD8^+$ T cells↑	Metwali, 2008	$CD4^+CD25^{hi}$ Treg apoptosis↓	Donskow et al., 2011
$CD4^+CD25^{hi}$ Treg ↑	Metwali, 2008		
Cytokines & chemokines		*Cytokines & chemokines*	
IL-4↑, IL-13↓, IL-6↓	Donskow-Schmelter et al., 2008	IL-4↓, IL-6↑	Doligalska et al., 2007
IL-2↓, IL-12p70↑, IFN-γ↓	Donskow-Schmelter et al., 2008	IL-2↓, IL-12 p70↓, IFN-γ ↑	Doligalska et al., 2007
TNF-α↓, IL-10↑, MCP-1↓	Donskow-Schmelter et al., 2008	TNF-α↑, IL-10↑, MCP-1↑	Doligalska et al., 2007
IL-5↑	Doligalska et al., 2006	TGF-β↑	Doligalska et al., 2006
IL-17↓	Elliott et al., 2009	IL-17↓	Elliott et al., 2009

Table 1. Cellular and cytokines responses to *H. polygyrus* infection in BALB/c mice. *H. polygyrus* is trichostrongylid nematode parasite used as a model of human gastrointestinal nematode infection. Within 24 hrs of infection by gavage larvae, the stage L3, penetrate the submucosa of duodenum. The fourth larval molt takes place about 90-96 hrs after infection and larvae reside in for 8 days. Pre-adult stage re-enter the lumen of the intestine and mature to adult stages. *H. polygyrus* infection in BALB/c mice is widely used for studies of parasite immunomodulation. BALB/c mice moderately respond to *H. polygyrus* infection and the immunoresponsiveness of this strains is well documented (Donskow-Schmelter et al., 2008). The *H. polygyrus* causes chronic, asymptomatic infection. Primary exposure to L3 larvae results in an upregulation of the Th2 cytokine response, minimal damage in the tissue provoked by L4 larvae and significant reduction of inflammation by adult stages. AAMΦ, alternatively activated macrophage; CAMΦ, classically activated macrophage

The induced immunosuppressive mechanisms including apoptosis of activated cells is dependent on the host genotype (Donskow-Schmelter et al., 2007). The other immune response of fast FVB responder and slow C57Bl/6 responder mice during infection with *H. polygyrus* is associated with differences in apoptosis of $CD4^+$ T cells in mesenteric lymph nodes (MLN). The apoptosis of these lymphocytes at the beginning of infection, when the first immune signal is given by infective L3 larvae, might play an important role in the modulation of the response in C57Bl/6 slow responder (Donskow-Schmelter, et al., 2007) but not in fast responder mice.

The expression of host-protective immunity to *H. polygyrus* was dependent on the development of resistance to the immunomodulatory factors secreted by the worms (Behnke & Parish, 1979). The differences in sensitivity of T cells to apoptosis is provoked by distinct protein production by *H. polygyrus* worms in different strains of mice (Morgan et al., 2006). Calreticulin or other proteins produced by *H. polygyrus* (Morgan et al., 2006; Rzepecka et al., 2006) in slow responder mouse could be responsible for the observed apoptosis in C56Bl/6 mice. The recombinant form of human hookworm calreticulin can disturb the complement cascade and induce cell apoptosis *in vitro* (Kasper et al., 2001; Chow et al., 2000) thereby supporting chronic infection (Donskow-Schmelter et al., 2007).

Interestingly, in resistant strains immunosuppression during infection does not affect the outcome of parasite-induced apoptosis, but results from a hyporesponsiveness experienced by $CD4^+$ T cells during *H. polygyrus* infection (Doligalska et al., 2006). In the prepatent and chronic phase of infection, $CD4^+$ T cells that are leaving the MLN survive better, do not proliferate and already have a hyporesponsive or anergic phenotype induced by $CD4^+$CD25hi T cells which increased in number (Donskow et al., 2011).

Chronic helminth infections are associated with a general hyporesponsiveness in which the activity of regulatory T cells can induce peripheral tolerance and constrain mucosal reactivity. However, little is known about particular helminth molecules that can induce Treg cells but characterization of some of them has started. The role of native and adaptive regulatory T cells and $CD8^+$ lymphocytes have been elucidated. The *H. polygyrus* downregulation of immune responsiveness, is attributable in part to the activity of host natural Treg cells with the $CD4^+$CD25hi phenotype (Finney et al., 2007) and regulatory $CD8^+$ T cells (Metwali et al., 2006). The expansion of $CD4^+$CD25hi Treg cells in mice MLN is a consequence of inhibited apoptosis of this subpopulation regulated by glucocorticoid during the infection (Donskow et al., 2011). *H. bakeri* antigen modulates CD4- positive T cell resistance to glucocorticoid induced apoptosis by inducing overexpression of Bcl-2 and FLICE-like inhibitory protein (FLIP). They are transcriptionally regulated by the transcription factor, nuclear factor kappa B (NF-κB) (Doligalska, unpublished data).

Additionally colonization with *H. polygyrus* induces a mucosal $CD8^+$ T cell that inhibits proliferation of CD4+ T cells and CD8+ T cells through a contact and transporter associated with antigen processing (TAP)-dependent mechanism (Metwali et al., 2006). These observations have far-reaching implications. Undoubted host parasite relationships are complex and there may be several mechanisms by which parasites could protect host from inflammation.

Helminths and their hosts need to achieve a state of homeostatic balance in which regulatory mechanisms operate for the survival of both the parasite and the host. Molecular signalling and cross-talk between cells of the endocrine, neuronal or immune systems and secreted factors such as hormones, neuropeptides, cytokines and chemokines influence the course of infection and severity of disease. Neural pathways regulate immune response at

regional, local and systemic levels through neurotransmitters and neuropeptides, and may have variable effects on immune cell activation and cytokine production. In turn, cytokines and chemokines produced both at peripheral inflammatory sites and/or locally in the CNS can modulate neural tissue function and hormonal secretion by endocrine glands (Delgado et al., 2004; Escobedo et al., 2005; Hernandez-Bello et al, 2010). One consequence of the invasion of nematode larvae is inflammation and tissue damage which provokes immunosuppression and analgesia. An increased number of neuronal opioid receptors on neurons is necessary for analgesic effects of opioids and their expression on immune effector cells allows immunomodulatory effects.

H. polygyrus is a strictly intestinal nematode and displays no systemic migration during its development in the host. L3 larvae briefly inhabit the duodenal wall and during this period the inflammation provoked by the larvae is regulated by opioids (Donskow-Schmelter et al., 2008). The endogenous opioid peptides have a wide array of immunomodulatory effects on the immune system, directly through MOR opioid receptor of macrophages and indirectly through the hypothalamic-pituitary-adrenal (HPA) axis. The administration of naltrexone (NLX), an oral antagonist of opioid receptors which completely blocks the effects of opioid agonists in mice infected with L4 larvae, caused a dramatic increase in classically activated macrophages (CAMΦ) activity; NO and cytokine production and migration. Additionally, as end-effectors of the HPA axis, endogenous glucocorticoids play an important role in the suppression of immunity by induction of $CD4^+CD25^+$ Treg lymphocytes. The opioid action is strictly determined by tissue damage; adult worms in the intestinal lumen inhibit inflammation without opioid receptor-linked mechanism activation (Donskow-Schmelter et al., 2008).

2.5.3 "Therapeutic helminths"

Nematode suppress the immunity generated by infection and also affect systemic responses to other non-nematode antigens (Barthlott et al., 2003). For this reason there has been a dramatic increase in the prevalence of immune-mediated diseases in areas where previously common exposure to helminths is now rare. These observations suggest that the parasites produce a natural governor that helps to prevent autoimmune disease such as inflammatory bowel disease (IBD), asthma, autoimmune diabetes (type I) or multiple sclerosis (Yazdanbakhsh et al., 2001). Laboratory and clinical studies confirm that nematodes can both prevent disease onset and reverse ongoing diseases.

The development of immunologically well-defined laboratory models of nematode infection helps to understand the immunological basis of effector mechanisms operating during these and other infections. Infected mice develop immunological characteristics which are very similar to those observed in m infection in man. *H. polygyrus* infection in mice is a laboratory model which generates new information in the wider fields of allergic and autoimmune inflammatory disorders.

Nematode infection of humans and animals induce immune responses which are characterized by the production of Th2 associated cytokines IL-4, IL-5, IL-10, IL-13 and Treg associated cytokines IL-10 and TGF-β. This type of response generally down regulates the Th1 immune responses and persists for the duration of the infection. *H. polygyrus* infection suppresses asthma in a murine model by induction of $CD4^+CD25^+Foxp3^+$ regulatory T cells and IL-10 production (Wilson et. al., 2005). In ovalbumin (OVA) induced asthmatic mice infected with *H. polygyrus* reduced Th2 responses and eosinophil responses by down-regulation of eotaxin concentration, reduced CCR3 chemokine receptor expression on

eosinophils and decreased chemotactic activity of these cells toward eotaxin (Rzepecka et al., 2006). The suppression of OVA-induced inflammation by *Nippostrngylus brasiliensis* is additional strictly mediated by IL-10 (Wohlleben et al., 2004). IL-10 which is a component of the natural host response to infection with enteric helminth parasites could be the key for therapeutic benefit.

T. spiralis, Trichuris trichiura and *H. polygyrus* infection protects animals from IBD (Eliott et. Al., 2007), but the complex pathways activated by nematodes to regulate the host's immune system, especially during *colitis,* is unknown. The combined induction of both Th2 (Setiawan et al., 2007) and Treg cells (Eliott et al., 2005) provoked by concurrent infection with *H. polygyrus* only partly explain the beneficial effects in mice with *colitis*. The inflammatory infiltrate in *colitis* is both Th1- and Th2-mediated. Therefore, additional parasite-induced mechanisms reduce inflammation.

Such regulatory cells can control self-reactive T cells and are functionally important in limiting inflammation in various animal models of IBD. In addition, *H. polygyrus* suppression of *colitis* requires $CD8^+$ T cells, suggesting that such these population of T cells may be important for this protection (Metwali et al., 2006). Furthermore, a resistance of *Schistosoma mansoni* infected mice to *dextran* sulfate sodium (DSS) induced *colitis* is macrophage dependent but not mediated by alternatively activated macrophages in the colon (Smith et al., 2007). *H. polygyrus* reduced established *colitis* by proopiomelanocortin-alpha (Pomc-a) and MOR opioid pathway (Donskow, unpublished data).

Recently treatment with living helminths such as *T. suis* or *N. americanus,* was initiated to control Cohn's disease, ulcerative colitis and asthma in human (Ruyssers et al., 2008). The opportunity to reveal novel ways to manipulate the human immune system to treat autoimmune inflammatory diseases by utilization of the natural response of the host to infection is exciting. In order that they may survive for long periods in an adverse and aggressive environment, nematodes secrete several soluble factors that interact with host cells. Some of these molecules may modify host-cell homeostasis and increase the susceptibility to infection and oncogenic factors. Undoubtedly, host parasite relationships are complex and there may be several mechanisms by which parasites induce immunosuppression and modulate host cells. Therapeutic helminth infection of humans needs to be closely examined for potential adverse side effects. For this reason the complex pathways that nematodes activate to regulate the host's immune system need further investigation.

3. Conclusions

Helminth infections are widely distributed. The extended survival of parasitic worms suggests that they are successful in an evolutionary sense. It is because they survive in and explore the host as natural environment. Helminths are often long lived and support tolerogenic reactions in host tissue rather than devastating immune reactions; they may induce the state of physiological and immune compromise and may consequently evade immune attack and actively subvert the host immune response. The immunosuppressive reactions provoked by different stages of the parasite in different periods of the host life span are embroiled in the host-parasite relationship and in this sense sustain the state of physiological homeostasis.

Helminths seeking for survive themselves using a plethora of mechanisms have been a major selective force for the host population and may influence of heritable factors both in patterns of infection and host immunity. The state of immune unresponsiveness in the host

protects growing larvae during migration through the tissue and allow for non-destructive localization of adults to propagate and transmit their offspring. The maintenance of an immunosuppressed state in the host may improve the fitness of the parasite, promotes infection with further infectious larvae. Infection with one species predisposes also for infection with other species. As the parasite load gained through the life differs among parasite and host species, the establishment of infection may be therefore dependent not only on the host immune response but also on parasite–related factors which may actively modulate immune reactions. Immunosuppression may be reached by different mechanisms in response to a plethora of parasitic molecules and may be expressed at each point of infection. Helminths especially in long lasting infection produce factors that directly interfere with the tissue of the host and for that many helminths-derived substances are considered as immune modulators.

The efficiency of the innate response is crucial for invasion and survival of arriving larvae. Key attack points for selective immunoregulation conducted by parasites rely on: modulation of antigen recognition with changes in pathways of signal transduction; costimulation blockade; induction of regulatory cells; deviation to protective responses, neutralization of proinflammatory cytokines, induction of anti-inflammatory cytokines and modulation of leukocyte trafficking. Immunosuppressive action of parasites can be primarily directed to antigen-presenting cells (APC) and induction of suppressor/regulatory T cells and macrophages with the common effect to selectively inhibition of local or systemic immune response. The development of immunologically well-defined laboratory models of nematode infection helps to understand the immunological basis of effector mechanisms operating during hyperactive or auto-destructive disorders. *Heligmosomoides bakeri* related mechanisms involved in suppression of immune response in mice as representing for regulation of the host immune response are proposed. Helminths and their hosts need to achieve a state of homeostatic balance in which immunosuppressive and regulatory mechanisms operate for the survival of both the parasite and the host.

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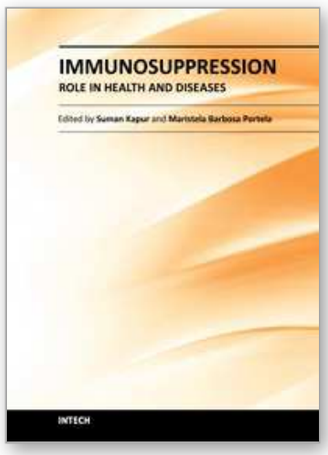

Immunosuppression - Role in Health and Diseases
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A need for a book on immunology which primarily focuses on the needs of medical and clinical research students was recognized. This book, "Immunosuppression - Role in Health and Diseases" is relatively short and contains topics relevant to the understanding of human immune system and its role in health and diseases. Immunosuppression involves an act that reduces the activation or efficacy of the immune system. Therapeutic immunosuppression has applications in clinical medicine, ranging from prevention and treatment of organ/bone marrow transplant rejection, management of autoimmune and inflammatory disorders. It brings important developments both in the field of molecular mechanisms involved and active therapeutic approaches employed for immunosuppression in various human disease conditions. There was a need to bring this information together in a single volume, as much of the recent developments are dispersed throughout biomedical literature, largely in specialized journals. This book will serve well the practicing physicians, surgeons and biomedical scientists as it provides an insight into various approaches to immunosuppression and reviews current developments in each area.

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