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Immune response against trematodes with particular emphasis to Fasciola and Schistosomes

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Abstract

The impact of helminthic infections is more as a result of the large numbers of individuals infected, than that of the severity of the disease although some parasitized individuals can suffer from severe disease which may be fatal. Remarkable equilibrium between most hosts and parasites is the product of long-term co-evolution of the two partners and particularly of the immune response of the host and the immune evasion of the parasite. Trematodes express various carbohydrate-containing glycoconjugates on their surface and they release glycan-rich excretion/secretion products at each developmental stages of the parasite that can be very important in their life cycles and pathology, since they can participate in immune escape and are highly immunogenic in infected animals. These molecules also cleave host immunoglobulin and can inhibit in vitro attachment of eosinophils to newly excysted juveniles.Carbohydrate-signatures from parasites are decoded by the immune system through the interaction of several immune receptors. The immune responses of the hosts to trematode infection are generally characterized by a skewed Th2-like response. Trematodes can mediate the modulation of the activity or function of DCs which are potent antigen presenting cells that possess the ability to stimulate naive T cells. Trematode parasites such as *Fasciola* and *Schistosoma*species have developed several means of escaping these immune responses and scientists called them “masters of immunomodulation. These immune-modulatory abilities enable thesehelminthes to persist in the host for a long duration and can lead to interactions with inflammatory and immune mechanisms involved in other infections or to vaccines or in allergic and autoimmune diseases.

Keywords: Eosinophils; Fasciola; Immune response; Schistosoma

Introduction

Parasitic helminthic worms comprise a diverse group of metazoan organisms, which represent an enormous burden on human and ruminant health in most tropical countries and can cause serious disease in infected populations(Hewitson and Maizels, 2014). The impact of helminthic infections is more as a result of the large numbers of individuals infected, than that of the severity of the disease although some parasitized individuals can suffer from severe disease which may be

fatal(Van and Cummings, 2017; Mallevaey et al., 2003). While clinical symptoms of infection may not always be displayed by the infected individual, disease may arise from an overwhelming burden of infection, or as a result of an inappropriate immune response(Hewitson and Maizels, 2014; Krecek and Waller, 2006).Indeed, worms tend to be aggregated in their distribution, with a large number of hosts harbouring few parasites and few heavily infected hosts. This remarkable equilibrium between most hosts and parasites is the product of long-term co evolution of the two partners and particularly of the immune defense of the host and the immune evasion of the parasite(Vukman et al., 2013).

Trematodes express various carbohydrate-containing glycoconjugates on their surface and they release glycan-rich excretion/secretion products that can be very important in their life cycles and pathology, since they can participate in immune escape (Johnston et al., 2009). Carbohydrate-signatures from parasites are decoded by the immune system through the interaction of several immune receptors(Vukman et al., 2013). In particular, receptors of innate immunity that recognize glycan motifs consist of soluble or membrane-associated lectins, siglecs and scavenger receptors, among others. Notably, C-type lectin receptors (CLRs) have been described tomediate internalization of parasite glycosylated molecules as well as cell-surface signalling, modulating the host immune response(Vukman etv al., 2013; Johnston et al., 2009).

Evidence demonstrating that trematodes can mediate the modulation of the activity or function of DCs has also been reported. DCs are potent antigen presenting cells that possess the ability to stimulate naive T cells(Maizels and Yazdanbakhsh, 2010; Maizels and Hewitson, 2014). In response to infectious agents DCs undergo a maturation process during which they migrate to secondary lymphoid organs where they present captured antigens to naive T cells, for the triggering of specific immunity(Maizels and Yazdanbakhsh, 2010). This process is associated to an up-regulation of the expression of MHC molecules, adhesion molecules and co-stimulatory molecules (CD40, CD80 or CD86) as well as a down-regulation of their endocytic capacity(Maizels and Yazdanbakhsh, 2010). However in the presence of trematode antigens mature DCs express reduced levels of co-stimulatory markers and MHC class II molecules, as compared to DCs matured with Toll-like receptor (TLR) ligands such as lipopolysaccharide (LPS)(11). Also, these DCs are not capable of producing high levels of pro-inflammatory cytokines (IL-12, IL-6 or TNFα). In this sense, independent in vitro studies have reported that different F. hepatica components modulateTLR-initiated DC maturation and their stimulatory function(Maizels et al., 2012; Moreau and Chauvin, 2010).

Phagocytosis is the main innate immune response to parasitic infections but many parasites are able to escape the immune system. E.g. some helminths have thick teguments that enable them to evade the cytocidal mechanism of neutrophils and macrophages. Very few parasites have the potential to activate alternate pathway of complement system but the parasites that recoup from infected patients acquire resistance to complement mediated lysis(Gause et al., 2003; Trinchieri, 2014).

Parasites also exhibit diverse adaptive immune response. Cell mediated immunity is the principal defense mechanism against parasitic infections(Correale and Farez, 2007). Stimulation of macrophages by Th1 cell derived cytokines is especially directed by cell mediated immunity to neutralize the antigens. Trematodesare removed by IgE antibody and eosinophil-mediated killing as well as other leukocytes(Esser et al., 2015; Maizels and Yazdanbakhsh, 2008).

The immune responses of the hosts to trematode infection are generally characterized by a skewed Th2-like response. Trematodeshave developed several means of escaping these immune responses; and scientists called them “masters of immunomodulation(Rook, 2009). These immunomodulatory abilities enable the worm to persist in the host and can lead to interactions

with inflammatory and immune mechanisms involved in other infections or to vaccines or in allergic and autoimmune diseases(Cervi et al., 2009).

Immune response against trematodes

Immunology againstFasciola infections

Although many mammalian species may be infected with *Fasciola*, there is variation in the degree of susceptibility to infection, and the ability to mount an effective immune response. For example, sheep often die from acute fasciolosis, while some infections may last for as long as 11 years(19). Different genetic backgrounds may be causative in the differing levels of susceptibility to infection. In contrast, cattle rarely die from infection with liver fluke, and display a “self cure” between 9 and 26 months after infection. This self-cure may be due to the observed thickening by calcification of the bile duct walls, in chronically infected cattle. This immune strategy employed by cattle is not observed m sheep, and may explain the higher mortality rates associated with infection of sheep(Ayaz et al., 2014; Cwiklinski et al., 2019).

Infection with *F hepatica* induces a predominant Th2 response. It has been observed that Th cell clones specific for *F hepatica* enhanced IgG synthesis through IL-4 expression, a characteristic Th2 cytokine response. The capacity to produce IgG_2 is associated with the production of IFN-y, and as a result of a polarized Th2 response, the production of IFN-y, and consequently IgG_2 is inhibited(Espino et al., 2007; Hamilton et al., 2009).

The immune response induced during natural infectionhas been well characterized in ruminants for F. hepaticaalthough there are increasing studies on F. gigantica thatreport similar findings(Vicente et al., 2016). During the acute stagesof infection, cattle exhibit a mixed immune response withelevated IL-10, TGF-β, IL-4 and IFN-c. However, asinfection progresses Th2/Treg immune responses becomemore dominant(Flynn and Mulcahy, 2008). During the later chronic stages,Treg cells release cytokines that inhibit inflammatoryTh1/Th2 cytokines; PBMCs isolated from F. hepatica -infected cattle produced enhanced levels of IL-4 andIFN-c cytokines when cultured in vitro in the presenceof TGF-β and IL-10 neutralizing antibodies(Giron et al., 2007). Thisimmune profile is similar in sheep infected with F. hepaticaas they also present a mixed Th1/Th2 cytokine profilein the spleen at week 3 after infection and asinfection progresses enhanced gene expression of Th2 butnot Th1 cytokines is observed (Flynn and Mulcahy, 2008).

Interestingly,although an overall systemic Th2 immune response dominates,different cytokines are expressed at differentanatomical locations; in sheep, IL-5 can be detected inthe hepatic lymph nodes, while IL-10 is primarilyobserved in the spleen, whereas in goats, IFN-c and high levels of IL-4 can be detected in both the hepatic lymph node and liver(Rivera and Espino 2016). The potent suppression of host Th1 immune responses during active infection of both natural hosts and experimental rodent models has been attributed to the development of a strong regulatory/Th2- type immune response(Dalton et al., 2013; Cwiklinski et al., 2016).

While Th2 and regulatory T-cell cytokines are important in downplaying host protective Th1 responses during infection with F. hepatica, it seems that the parasite also influences various cells of the innate immune response(Dowling et al., 2017). Firstly, in experimental mouse models, CD11c+ dendritic cell (DC) populations are increased during Fasciola infection displaying an immature phenotype with lower expression of co-stimulatory markers (CD40, CD80 and CD86), MHC class II, increased expression of CCR5 and are hyporesponsive to TLR activation. These cells express enhanced levels of intracellular IL-10 and ex vivo suppress the secretion of antigen specific IL-17 and IFN-c from naıve DO11.10 OVA TCR Tg CD4+ T cells independent of IL-10 and TGF-β(Dowling et al., 2017).

Secondly, the induction of macrophages with a regulatory/M2 phenotype is common in both large animals and rodents infections. This switch occurs within the first 3 days of murine infection and similar to DCs activated by Fasciola antigens, M2 macrophages are hyporesponsive to TLR ligands, suggesting a reduced ability to promote the differentiation of host Th1 immunity. In addition, it has been shown that M2 macrophages isolated from mice during infection with *F. hepatica* promote the polarization of Th2 cells(Lund et al., 2014).

Thirdly, there is a significant increase in the number of mast cells observed at the site of infection and in the gut mucosa. While mast cells are critical to the expulsion of gut helminths, their role in *Fasciola* infection is not clear, although we hypothesize that given that mast cells have an important role in wound healing and tissue remodeling, they are recruited to combat the extensive tissue damage caused by migratory flukes(Vukman et al., 2013).

It also appears that during infection of mice withF. hepatica, T cells are induced to enter an anergic state asmarkers of anergy were observed in CD4+ T-cell populations and may explain why these cells become hyporesponsive to antigen stimulation in the late stages of infection(36). This anergic state, as shown by decreased cytokine responses and reduced proliferative activity, could be reversed with the addition of IL-2 to cultures. The presence of anergic T cells is yet to be demonstrated in ruminants (and humans); however, the lack of IL-2 reported in the local HLN of infected sheep supports such a mechanism of immune inactivation(Walshe, 2003; Aldridge and O'Neill, 2016).

Susceptibility to a secondary infection and chronicity is a common feature of *Fasciola*infection. For example, the relationship between pathogenesis of disease and host immune responses was observed in primary and secondary *Fhepatica* infections of goats(Walshe, 2003). The extent to which infection had been established, measured as the percentage of recovered flukes at the necropsy, was similar m animals during primary and secondary infections, however liver damage was much more severe m secondarily infected animals. Primary infection was observed to evolve to chronic fasciolosis that did not induce the development of resistance, as animals were highly susceptible to secondary infection, exhibiting severe and acute hepatic lesions that ultimately led to the death of some of the animals(Eman et al., 2012).

Eosmophiha is a common feature of *Fasciola*infection, and eosinophilshave been observed in close association with the surface of damaged newlyexcysted juveniles (NEJ), suggesting a role for this cell type in resistance to*Fasciola*infection(Dusak et. al., 2012). Furthermore, it has been demonstrated *in vitro* that eosinophils fail to induce irreversible damage on NEJ of *F hepatica.* The fact that the immune responses are induced, but are ineffective against *Fasciola*implies that the immune response is ineffective due to a defensive capability of the parasite(Vegu et al., 2003).

Role of Excretory/ Secretory Products of Fasciola on Immunity

Proteases catalyse the cleavage internal peptide bonds between peptides and proteins and are involved in a wide range of eukaryotic processes. Proteases are also known to require for the virulence of pathogenic agents including helminth infections(Dowling et al., 2010). It has been demonstrated that immature and mature flukes secrete endo-protemases into culture medium when maintained *in vitro* (Eman et al., 2012). Several functions have been suggested for the role of these enzymes including functioning in migration through host tissue, the acquisition of nutnent and evasion of host immune responses. Two cysteine proteases were isolated and characterized as having physiochemical properties similar with the mammalian lysosomalcathepsin L protemases. The two enzymes were observed to differ m their specificities for hydrolysing peptide bonds and as a result were termed cathepsm LI and cathepsm L2(Dar et al., 2016).

Another antigen containing a haemgroup was isolated from flukes maintained m culture medium which was shown to be liver fluke haemoglobin(34). Hb is involved in theaerobic respiration of immature flukes and egg production in adult flukes. Because the cathepsm LI, cathepsm LI and Hbmolecules are involved m processes functional in the survival of the parasite in thehost, they have been used as potential targets for liver fluke(Dowling et al., 2012).

Investigations havebeen earned out to test the viability of these molecules for use as vaccines where individual molecules and combinations of the moleculeswere given to cattle, to investigate their immunoprophylactic potential(Dalton et al., 2013). It wasobserved that cattle immunised with cathepsm LI induced protection against experimental challenge of 53.7%, while animals vaccinated with cathepsin L2 andHb were also protected. A combinational vaccine containing cathepsin L2 and Hb induced the highest level of protection (72. 4%). Flukes recovered from this group were smaller in size than that of control groups, indicating that vaccination had stunted fluke growth, and as a result less liver damage was observed(Tallima et al., 2014).

Cathepsin LI, one of the major molecules of fluke excretory/secretory product, is secreted at each stage in the development of the parasite, and has shown to be highly immunogenic in infected animals. This molecule has the ability to cleave host immunoglobulin and can inhibit in vitro attachment of eosinophils to newly excysted juveniles(Falc et al., 2010).

Cathepsin LI is also capable of degrading extracellular matrix and basal membrane components and thus aids in parasite migration through the tissue of the host. The ability of cathepsin LI and cathepsin L2 to produce vasoactive kinnms in alkaline pH may qualify them as factors of virulence in fascioliasis, since the intrinsic vasodilation activity exhibited by kirnns, associated with endothelial leakage and anti-aggregationplatlet activity might assist m the migration and survival of the parasite in the tissue of hosts(Rodr et al., 2017).

Adult flukes secrete a cysteine protease capable of cleaving host IgG close to the papain binding site, and this hampers the host's immune response to the invading parasite. Immature flukes also secrete a papain or cathepsin B-like proteolytic enzyme which cleaves immunoglobulins of mice, rats and sheep *in vitro* (Dar et al., 2012).

Immunology of Schistosome

Immune Response against Cercariae and Schistosomula

The entry of the schistosomula through the skin does not go unnoticed by the host immune system. It elicits an inflammatory response due to infiltration of polymorphonuclear and mononuclear cells that is followed by the localized production of pro-inflammatory cytokines (IL-1b, IL-12, TNF-a, and MIP-1a and IL-6) as well as immunoregulatory mediators such as IL-10 and prostaglandins [PG] E2 and D2(Kuria et al., 2012). The invasion and consequent infection by the schistosomes leads to a predominantly Th2 immune response, in contrast to the expected pro-inflammatory Th1 response. This skewing of the cytokine response is a rather complex and intriguing process by the virtue of which the parasite thrives and survives within the host immune system(Nayak and Kishore, 2013).

One of the main immunomodulatory cytokine induced following exposure to cercariae is the anti-inflammatory IL-10. The source of IL-10 in the skin is not clear, although reports do suggest that keratinocytes might be the major source along with dendritic cells (DC), macrophages and B1 lymphocytes(Colley and Secor, 2014):). In addition to IL-10, other inhibitory molecules are also produced followed by stimulation by the cercarial ES products. These molecules include prostaglandins such as prostaglandin E2 (PGE2) and parasite-derived prostaglandin D2 (PGD2) in all *Schistosomaspp*and IL-1ra (IL-1 receptor antagonist) in *S. mansoni*and *S. haematobium.* The production of the prostaglandins leads to an

increased production of IL-10 in the skin. PGE2 aids the production of IL-10 through a cyclooxygenase 2-dependent pathway. Mouse studies have shown that PGE2 is the main immunoregulator in the skin in *S. mansoni*induced inflammation(Alebie, 2016).

Interestingly, parasite-derived prostaglandins play a huge role in the immunomodulation within the host(48;49). The cercariae upon penetration into the skin turn themselves into schistosomula. This change of stage is also concomitant with the production of PGE1, PGE2, 5-HETE, and 15-HETE by the parasites(Janssen et al., 2016). Studies have demonstrated the abilityof schistosomula to induce PGE2 production by human keratinocytes(El Ridi et al., 2014). The schistosomula might be favoring the induction of increased production of PGE2 in the skin milieu for various reasons. First, schistosomula-induced overexpression of PGE2 plays a role in the production of IL-10 by host cells. Second, PGE2 acts as a potent vasodilator which might facilitate the easy passage of the parasite into the circulation(Tallima et al., 2017).

The *S. mansoni*schistosomula, following entry into the skin, remains in the skin for up to 3 days afterwhich it gets into the circulation and progresses toward the other organs(He YX, Chen and Ramaswamy, 2002). Cytokineanalysis shows a rapid increase in the levels of IL-10 within a few hours of the parasiteentry into the skin, along with significant reduction in the levels of IL-1a and IL-1b andincreased levels of IL-1ra. Yet another prostaglandin, PGD2, is produced as part ofthe ES components of the schistosomula(Nayak and Kishore, 2013).

Parasite-derived PGD2 has been reported to inhibit migration of epidermal Langerhans cells to the site of invasion. Physiologically, Langerhans cells are found anchored to neighboringkeratinocytes and when the skin is penetrated by parasites, both keratinocytes and Langerhans cells produce pro-inflammatory cytokines such as TNF-a and IL-1b(Nayak and Kishore, 2013). The expression of these cytokines, in turn, leads to the diminished expression of E-cadherin and stimulates actin-dependent movements of the Langerhans cells. However, during a schistosomal infection, the migration of Langerhans cells is inhibited due to the parasite-induced production of PGE2 by the host cells and parasite-derived PGD2 that both lead to an increased production of IL-10(Giera et al., 2017). IL-10 impedes migration of Langerhans cells by downregulating the production of IL-1b and TNF-a by epidermal cells. Thus, the purpose of the schistosome-induced IL-10 production is to create anti-inflammatory cytokine environments which can downregulate the host immune response against the invading parasite. The interruption of the migration of antigen presenting cells from site of exposure to the draining lymphoid tissue is another strategy adopted by the parasites to modulate the host's immune response(Smits et al., 2005).

The schistosomula also adopt additional strategies to evade the host immune response. The ES products from the schistosomula can induce in vitro mast cell degranulation, and hence, lead to production of IL-4, release of histamine and 5-hydroxytryptamine in an IgE-independent manner(Janssen et al., 2016). One of the components of the ES products, termed *S. mansoni* apoptosis factor (SMAF), has been shown to induce apoptosis specifically in the CD4+ lymphocyte population via a Fas-FasL interaction (James and Green, 2004). The CD4+ apoptosis allows the schistosomula to escape detection by the host immune system. Once the schistosomula have evaded the immune response, it gains entry into the portal veins and remains in the circulatory system. Within 1–3 weeks, it turns into a sexually active adult that adheres to the inner lining of the veins(Zakeri, 2017).

The male and female adult schistosomes form a pair and can reside adhered to their chosen vein lining, escaping the host's immune response for decades. *S. mansoni*and *S. japonicum*adhere to the inferior and superior mesenteric veins, respectively, while *S. haematobium*adheres to the venous plexus of the bladder(Brant and Loker, 2013). The adult pairs then produce 300–3000

eggs, depending on the species. The eggs are the second stage in the schistosomal life cycle that elicits an inflammatory response within the host body(Isnard et al., 2010).

Immune Responses Triggered by Schistosomes Eggs

The onset of egg production by the adult schistosomes is associated with the skewing of the CD4 response toward the Th2 polarization, characterized by production of IL-4, IL-5 and IL-13. IL-4 is one of the key cytokine that plays a role in the regulation of the development of the Th2 response (Alebie, 2016). IL-4 is produced in small amounts by naive CD4 cells. This IL-4 in turn acts in an autocrine manner to induce GATA3 expression, and hence, establish the Th2 phenotype. The resultant IL-4/IL-4R/Stat6 signaling pathway plays an important role in stabilizing and expanding the Th2 cell populations. In mouse models in which the egg antigens were injected, rapid induction of strong Th2 responses were observed(Smits et al., 2005).

Dendritic cells, as the most potent antigen presenting cells and the sentinels of cell-mediated adaptive immunity, are known to play a central role in initiation and polarization of T-cell responses (Rossi and Young, 2005). *S. mansoni*eggs preparations have been shown to prime Th2 cells through the functional modulation of DCs.Although the identity of the molecules responsible for this priming is still unclear, recent studies have reported Omega-1 and *S. mansoni*glycoprotein w-1 to be inducers of Th2 responses(Guermonprez, et al., 2002). One direct correlation of Th2 polarization is the presence of M2 macrophages in the granuloma, which undergo alternative activation by IL-4 and IL-13, important for the immune response to parasites as opposed to the classical macrophage activation induced by IFN-g, which triggers a pro-inflammatory response that is required to kill intracellular pathogens(Rossi and Young, 2005).

Granulomas in Acute and Chronic Schistosomiasis

Acute schistosomiasis, also called Katayama syndrome, is due to primary infection by the parasites and is observed in travelers visiting affected places and non- immune people(67). This phase of infection is usually asymptomatic but clinical manifestations can occur including fever, nausea, headache, irritating cough, blood-and-mucous-ridden diarrhea for several months. Acute toxaemic schistosomiasis by *S. mansoni*and Katayama syndrome by *S. japonicum*are systemic reactions against the first cycle of eggs laid by the adult schistosomes, usually after 28–90 days of infection(Lambertucci, 2010). Granulomas form around eggs that are trapped in the intestinal and liver wall leading to hepatosplenomegaly and leucocytosis with eosinophilia(De'Broski et al., 2008).

Chronic schistosomiasis with complications occurs in affected individuals living in endemic areas. Intestinal schistosomiasis is the most frequently diagnosed form of chronic schistosomiasis. Schistosome eggs that have entered into circulation reach different organs including the intestinal wall(King and Dangerfield-Cha, 2008). The eggs that get trapped in the intestinal wall provoke inflammation. Hepatointestinalschistotomiasis is due to embolisation of schistosome eggs in the liver and is the leading cause for hepatomegaly(69). In patients with severe longstanding infection, periportal collagen deposits lead to progressive obstruction of blood flow and portal hypertension (hepatosplenic form). *S haematobium*eggs, on the other hand, cause inflammation in the bladder and ureteral wall which can lead to haematuria and dysuria. With progressive involvement, fibrosis and calification can occur, resulting in obstructive uropathy(King and Dangerfield-Cha, 2008).

Chronic disease caused by schistosome species is due to the immune response against entrapped eggs within tissues. Liver is the main organ that gets affected in *S. mansoni* and *S. japonicum*infections as the sinusoids of the liver

are too small for the eggs to pass by. Contrastingly in *S. haematobium* infections, the bladder is affected as the eggs traverse across the bladder wall. Once trapped within the sinusoids, death of the eggs can cause the stimulation of the host response against the egg antigens(De'Broski, et al., 2008).

Granulomatous lesions, which comprise of collagen fibers and cells like macrophages, eosinophils and CD4+ T cells, form around the live eggs(King and Dangerfield-Cha, 2008). Once the eggs die inside the granuloma, the resolution of the granuloma occurs leading to the formation of fibrotic plaques. The liver can become fibrotic, congested and harder to perfuse due to the granuloma-induced fibrotic plaques and this can in turn lead to an increase in the portal blood pressure(Gryseels et al., 2008).Ascites and portal-systemic venous shunts are also caused that can lead to excessive bleeding that could be life threatening. Infection with *S. haematobium*can lead to very serious diseases such as bladder cancer and genital schistosomiasis(King and Dangerfield-Cha, 2008).

Thus, the causative factor for the hepatosplenomegaly and fibrosis is the immunopathology due to uncontrolled inflammatory response involving granulomatous formation induced by the trapped eggs in the tissues. The eggs generate a typical Th2 response that also includes infiltration of eosinophils, mast cells, and alternatively activated macrophages, followed by fibroblasts leading up to fibrosis(Pearce, 2005).

It is unclear whether granuloma formation is beneficial for the human host as the egg sequestration may reduce further tissue damage. For instance, mouse models that were tolerised against *S. mansoni*egg antigen did not develop granuloma but had severe hepatotoxic liver damage, which may be due to hepatotoxins secreted by the eggs(Pearce and Mac-Donald, 2002). Granulomas along with egg-antigen specific antibodies are likely to sequester these hepatotoxins away from the hepatocytes.

However, what is evident via murine experiments is that the parasite uses host immune response for its proliferation, survival and excretion of eggs(Pearce and Mac-Donald, 2002).

The murine models using wild out bred strains-MOLF mice (as compared with inbred strains) appear to express more appropriate human immunopathology that coincides with the appearance of IL-17 producing CD4+ T cells (Th17 cells) (74;75). IRAK-2 gene has been linked with severe immunopathology (than Th2 alone that induces only mild disease in murine models) since it appears to promote IL-1b-mediated Th17 cell development(Booth et al., 2004).

Within 5 weeks of parasite infection, the immune response is characterized by a heightened Th1 response (IL-12 and IFN-g). As soon as female parasite starts to churn out eggs, there appears a shift Th polarization from a Th1 to Th2 phenotype. The egg antigen induces production of IL-4, IL-5 and IL-13, and elevated IgE levels and Eosinophilia(Schramm et al., 2007). There appears to be a direct correlation between the intensity of the Th2 response against egg antigens and severity of granulomatous inflammation in murine models, which declines in the chronic phase (3 months)(Burke et al., 2009).

Thus, mice genetically deficient in IFN-g or IL-12p40 show no changes in granuloma formation following infection whereas IL-4 deficient mice generate impaired granuloma and develop severe pathology(Pearce, 2005). The modulation of T-cell polarization from Th1 to Th2 response is due to secretory egg protein (SEA) that can suppress maturation of and subsequent cytokine production by DC (Dendritic cells co-pulsed with microbial and helminth antigens undergo modified maturation, segregate the antigens to distinct intracellular compartments, and concurrently induce microbe-specific Th1 and helminth-specific Th2 responses(Schramm et al., 2007).

Immunological evasive strategies of trematodes

Fasciolahost immune evasion strategies

Flukes may persist in their definitive hosts for extensive periods of time and therefore must possess means of evading prolonged attack from the hosts' immune system. *F hepatica* has developed various mechanisms of immune modulation allowing its establishment and survival in the liver causing a severe hepatic disease(Ravid ert al., 2016).

While the parasite ultimately resides in the bile duct of the liver, it must first find safe passage as it migrates through the intestinal wall and liver tissue. Adult worms are generally more resistant to immune effector mechanisms than the earlier larva stages, suggesting that it has developed more efficient mechanisms for evasion of the hosts' immune response(Ravid et al., 2016a). As the tegument of the liver fluke is involved m most of the interactions between the parasite and the host, the liver fluke surface plays an important role m protection against immune attack. Liver fluke tegumental membrane is covered by a poly anionic glycocalyx consisting of ganglioside terminating in sialic acids(Ravid et al., 2016b).

Experimental approaches have demonstrated the significance of glycosylation inhelminth infections. First, immunodominant glycosylated epitopes are often the major targets of natural and experimental host humoral responses, as demonstrated by the loss of antibody recognition through deglycosylation of the parasitic glycoprotein antigens or destruction of the glyco-epitopes by periodateoxidatio. Second, immuno-staining by glycan-recognising monoclonal antibodies or lectins against whole parasite or parasite derived extracts may show developmental stagespecific expression profiles of glycosylation(Espino et al., 2007).

The tegumentalglycocalyx may aid in immune evasion in several ways, (1).Antigen switching, composition of the glycocalyx changes during the development of the parasite m the host, thus presenting the hosts' immune system with a changing target. For example, the glycocalyx coat changes in composition from Tl-type tegumental cells to T2-type tegumental cells as the fluke migrates from liver tissue to that of the bile duct(Ravid et al., 2016a). Changes in the fluke surface are reflected in changes in the immune system. Host antibodies specific to the Tl-denved components peak between 3 and 5 weeks after infection, and following their decline, anti-T2 antibodies can be observed. Anti-T2 antibody production in infected rats declines after the parasite has entered the bile duct(Vukman et al., 2013).

Various isotypic responses are observed as a result of parasite-induced stimulation of different lymphoid compartments. IgE responses are significantly greater in the hepatic lymph nodes m comparison with that of the mesenteric lymph nodes or the spleen, while IgA responses are higher in the mesenteric lymph nodes(Dalton et al., 2003). This provides evidence of a unique regulation of the cytokines secreted by T cells in each of these micro-environments. It has been suggested that by migrating between different tissue types, which are predisposed to a specific type of immune response, the flukes may be protected from tackling a single immune response that would otherwise become increasingly efficient as the parasite migrates(Moreau and Chauvin, 2010).

Antigen shedding, as a result of the flukes altering glycocalyx, antibody-bound immune effector cells, such as eosinophils and neutrophils may not bind sufficiently with the parasite to allow degranulation and damage to the to the surface, but are shed with the glycocalyx. Glycocalyx turnover slows down once the bile duct is reached, as migration is completed and the fluke is no longer under such vigorous attack(Walshe, 2004).Antigen decoy, shed products of the glycocalyx may act to "mop up" circulating anti-fluke antibodies preventing their participation m direct attack on the fluke(Walshe, 2004).

Newly excysted juveniles are highly resistant to complement. Terminal sialic acids in the glycocalyx prevent the activation of complement by the alternative pathway. The shedding of antibody from the fluke's surface may prevent activation of complement by the classical pathway(Finlay et al., , 2014).

It has been observed that immune inflammatory cells are rarely found m close association with the flukes, which would otherwise be expected to be instrumental m mounting a destructive strategy towards the invading pathogen(Burke et al., 2009). This suggests an evasive strategy employed by the fluke in avoiding contact with the immune inflammatory cells. This may be explained by the lack of CD3+ T cells in the infiltrate surrounding tracts made by migrating parasites inhibits immune inflammatory cells from migrating through the liver parenchyma(Zhang et al., 2005). This hypothesis is supported by the involvement of *Fasciola* excretory/secretory products in the suppression of peripheral blood lymphocytes(Flynn and Mulcahy, 2008).

A further possible evasion strategy employed by the fluke is the rapid migration by the parasite through the liver, which has been reported in goats and sheep which makes it impossible for the leucocytic infiltration around the parasite(Dalton et al., 2010). Liver flukes also possess an ability to disable immune effectors cells, for example by inactivating the toxic reactive oxygen products of the respiratory burst of leukocytes (eosmophila and neutrophils) and macrophages or reactive nitrogen intermediates generated by macrophages(Smooker et al., 2010). Oxygen scavenging *enzymes such* as superoxide dismutase (SOD) may be involved in the inactivation of oxygen species. Researchers have been observed increased activity of SOD in extracts of newly excysted juveniles(Piedrafita et al., 2007). SOD has also been detected in the excretory /secretory product of adult flukes. It has been observed that adult flukes release a peroxiredoxin-like enzyme which may protect flukes against hydrogen peroxidase and other reactive oxygen intermediates(Hewitson et al., 2009).

Researchers have demonstrated that liver flukes secrete two cysteine proteinase activities which are involved in host tissue penetration and feeding as well as immune evasion. Subsequent studies showed these enzymes were cathepsm L proteinases, termed cathepsin LI and cathepsinL2. These molecules can specifically cleave immunoglobulins. It was also demonstrated that purified cathepsm L could inhibit the antibody mediated attachment of eosinophils to newly excysted juveniles(Eman et al., 2010).

Schistosoma host immune evasion strategies

The schistosome-induced pathogenesis consists of evasion of the host immune system by the cercariae, the adult and the egg during different stages: penetration through the skin, migration through the circulation, incubation of the adult schistosomes, production of eggs and excretion of the eggs(Nayak and Kishore, 2013). Most immune responses are widely observed in chronic schistosomiasis when compared with acute schistosomiasis(King and Dangerfield-Cha, 2008)).

During the earlier stages of the pathogenesis, the schistosome ES (excretory/secretory) products are involved in modulating the immune response while soluble egg antigens (SEA) are involved in the later stages of immune modulation (Finlay et al., 2014). Schistosomal ES products are released or secreted from epithelial surfaces of the gut and/or tegument as well as other specialized ES organs throughout almost all life stages of the parasite(Tallima et al., 2014).

The production and secretion of these products might be induced by factors present in the host fluid such as blood cells, phagocytic cells, hormones and complement proteins(Hewitson et al., 2009). Due to the complexity in collection and harvesting of ES products from host tissue and the inability to mimic in vivo environment in an in vitro environment, studies on the immune modulation by ES products is a daunting challenge for researchers(Jenkins et al., 2005). In the adult worms, ES products are mostly secreted by the excretory cells and co-localized to the

tegumental and sub-tegumental region along with the gut epithelium(Aldridge and O'Neill, 2016). Six of these ES products have been suggested as potential vaccine targets (Paramyosin, glutathione S-transferase, IrV-5, Triose phosphate isomerise, Sm23 and Sm14)(Janssen et al., 2016).

Complement Evasion by Schistosomes Paramyosin

Schistosomula and adult worms also evade the immune system by developing resistance to complement attack(Deng et al., 2007). Complement system comprises of three different pathways; the classical pathway, the lectin pathway and the alternative pathway. All three pathways involve cascades of events that eventually attempt to the lysis of the target cell/pathogen or opsonisation and phagocytosis. The three complement activation pathways converge on the formation of C3 convertase(Deng et al., 2007).

*Schistosoma*evades the complement attack and survives within the host system for years and the complement evasion mechanisms are yet to be fully understood. However, studies have been performed understand how the parasite escapes from or offers resistance to the complement-mediated killing at every step of its life cycle within the mammalian host(Braschi and Wilson, 2006). Following host skin penetration by the schistosomal larva, it undergoes a change from being sensitive to complement attack to gaining resistance to the complement system(Liu et al., 2009). This is made possible by the shedding of the glycocalyx coat by the larva that otherwise contains strong complement activators. Once inside the host, the other life stages of the parasite employs several strategies to evade the hosts' complement attack system. Parasitic proteins have been shown to bind to complement proteins such C1, C2, C8 and C9(Zhao et al., 2014).

An important schistosomal protein that has been studiedextensively as a complement pathway evader is a 97-kDa protein named paramyosin(Pmy), a major core protein of thick filaments of invertebrate muscle. Immunolabellingstudies in adult schistosomes have localized the detection of Pmy in regions just belowthe parasitic surface i.e., either the tegument or muscle layers of the male and femaleadult schistosome(Hao et al., 2014).

Earlier studies identified a schistosome complement inhibitor, SCIP-1, on the surface of *S. mansoni*larvae and adult worms which was later shown to be the exogenous form of Pmy(Nayak and Kishore, 2013).Pmy binds to C1q, the initial subcomponent of the classical complement pathway, in solution and this interaction fails to activate C4 and the MAC formation on sheep red blood cells (Nayak and Kishore, 2013). This suggests that the inhibition of the complement mediated killing of the parasite is modulated by paramyosin at the initial phase. Pmy has also been shown to bind to other complement proteins such as C8 and C9. Thus, Pmy appears to inhibit complement activation, and hence complement-mediated killing of schistosomes, by binding to at least three complement proteins. Binding of C1q might inhibit the initial activation of the classical complement pathway and binding to C8 and C9 might ensure that the MAC is not generated(Mowafy and Abdel-Hafeez, 2015).

Paramyosin (Pmy) also shows binding ability to the Fc portion of IgG, which might possibly mask the surface of the parasite and block the binding of specific antibodies(Mowafy and Abdel-Hafeez, 2015). Thus, Pmy is an attractive candidate for developing a potential vaccine against schistosomiasis. Trials in various animal models have demonstrated that immunization with native or recombinant paramyosin can substantially reduce the worm burden and liver/faecal egg counts in the infected animals(Nayak and Kishore, 2013). Yet another protein, Sh-TOR, from the surface of *S. mansoni*has been shown to be a functional receptor of human complement protein C2. Sh-TOR is likely to inhibit the classical complement pathway by preventing C2 from binding to C4b(Liu et al., 2009).

Conclusive remarks

Among the major neglected tropical diseases (NTD) ofhumans are a group that results from infection with thetrematode parasites mainly,Fasciola (liver flukes) and Schistosoma (blood flukes) and many others.Fasciolosis has a strong effect on the functionality of the cells from innate immunity such as eosinophils, macrophages as well as dendritic cells. Once the parasite enters the host tissues, a delicate balance between the host effector mechanism and the defense by the parasite is established, allowing the survival of a number of flukes that escape from the immune attack, and as long as some parasites persist, are able to act as effectors to regulate immune responses. The understanding of the molecular basis by which ESP or other helminth products modulate the functionality of eosinophils, macrophages and dendritic cells, has an enormous potential since the modulation of these cell activities has a strong impact on the type of the adaptive immune response as well as in tissue repair.

The schistosomes have developed three strategies to “cheat” its host’s immune system: utilization of parasitic proteins to gain entry, mimicry of the host proteins to establish itself within the host body and enable persistence by evasion of the host immune system. The survival of the host is dependent on the Th balance that in turn can affect the development of granuloma. The main characteristic lesion in schistosomiasis is the granuloma formation induced by the eggs laid by the adult worms that can persist in the host for up to 30 years. These granulomatous lesions can induce heavy inflammatory reactions that can cause fibrosis in the organs afflicted. Thus, by controlling the development of granuloma formation and consequent fibrosis, acute and chronic forms of the disease can be controlled. Renewed efforts to study the resistance and susceptibility phenotypes in intermediate and mammalian hosts can help control the infection by trematode parasite. Studies to understand the host-pathogen interactions in both intermediate and mammalian hosts can pave way for better therapeutic approaches to cure infections and subsequent control. At the same time, identification and characterization of target proteins in both host and the parasite do have paramount import ace in the development of effective vaccines against these parasites.

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