CHAPTER 05

IMMUNE EVASION MECHANISMS OF PARASITES WITH SPECIAL FOCUS ON *FASCIOLA HEPATICA*

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INTRODUCTION

Parasites are the living organisms (eukaryotes) that depend upon their host (definitive or intermediate) for their survival (Chulanetra and Chaicumpa 2021). They may be unicellular or multicellular organisms such as protozoa and metazoan. Parasites that are responsible for manifestation of disease in humans and animals can be classified in three main categories such as helminths, protozoans and arthropods (ectoparasites). Helminths and arthropods belong to kingdom Animalia whereas protozoans are classified into kingdom Protista (Verma 2021). Helminths have been further categorized into two phyla. Nematodes belong to the phylum Nematoda while flukes and cestodes are classified into phylum Platyhelminthes. Parasites have remarkable diversity in their life cycle and host (Cribb et al. 2003).

Although there is diverse taxonomy of the parasites, they share same mechanism to evade, overcome, and decrease the immune response of host to maintain their life cycle and parasitism due to which they are considered as the most successful organisms on earth (Chulanetra and Chaicumpa 2021). This chapter describes the most significant tactics employed by selected protozoa and helminths with special emphasis on *Fasciola* species to avoid, resist, withstand, inhibit, and alter the host immunity which is mounted against them.

Circumventing the Physical/physiological Barriers of the Host

In most cases, healthy skin is a powerful barrier that serves as the first check point against pathogens attempting to enter in the host. However, several helminthic parasites may infect humans by penetrating straight through the epidermis. Hookworm larvae (*Necator americanus*) and *Strongyloides stercoralis* (threadworm) a filariform larva can enter cutaneous surfaces of humans walking barefooted on contaminated ground. At helminth-penetrating location, the larvae generate a focused irritating region (ground itch), as well as rashes and papules. Humans that swallow contaminated substances can be infected by *Ancylostoma duodenale* larvae. Hookworm larvae that penetrate the skin can result into cutaneous larva migrans, which looks like a snake's track (Albanese et al. 2001). Urocanic acid is a metabolite of histidine which attracts *Strongyloides* spp. and is high in human and animal host skin and skin secretions (Safer et al. 2007).

The larvae of the mammalian *Schistosoma* spp. enter the skin of humans after their escape from snail into water. These infective larvae grow into adult parasites inside the mammalian host, causing various kinds of schistosomiasis based on the species of invading flukes. Urogenital schistosomiasis is caused by *Schistosoma haematobium*, which can lead to development of cancer of bladder (Ajibola et al. 2019) whereas *S. mekongi*, *S. mansoni* and *S. japonicum*, lead to intestinal and hepatic schistosomiasis (Elbaz and Esmat 2013). Schistosomes of aviary birds and animals are capable to enter in skin of human beings, but unable to mature further. Instead, they are limited to the site of penetration and result in cercarial dermatitis (Kolarova 2007; Horák et al. 2015). While some parasites, like trypanosomatids (*Leishmania* spp., *Trypanosoma* spp.), *Babesia, Plasmodium* spp., and filarial worms (*Oncocerca volvulus, Brugia malayi, Wuchereria bancroft, B. timori, Loa loa*) need vectors (ticks, hematophagous flies, mosquitoes and bugs) to transmit their invasive stages into their hosts.

Plasmodium-positive *Anopheles* bite can deliver up to 200 sporozoites into skin of human (Gomes et al. 2016). In addition to sprozoites, biting mosquitos also inject a variety of salivary constituents into the skin, including antihistamines, immunomodulators, anticoagulants, vasodilators, and platelet agglutination inhibitors, all of which aid in survival of sporozoites (Zheng et al. 2014). Even though many *Plasmodium* sporozoites are eliminated by host's innate defence components at the inoculation site, others manage to evade the immune system by diverse mechanical tactics, such as fast intercellular gliding movements (Vanderberg 1974). Invasion movement to invade hepatocytes, where the erythrocyte-infecting form, merozoites, is produced (Yuda and Ishino 2004; Tavares et al. 2013; Risco-Castillo et al. 2015; Gomes et al. 2016). *Plasmodium* sporozoite and its secretory organelles have a protein called thrombospondin related anonymous protein (TRAP) that enables sporazoite to interact with molecules of host skin surface and provide it with gliding movement to leave the skin via blood capillaries

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(Müller et al. 1993; Gomes et al. 2016). The sporozoites enter liver from bloodstream by penetrating the sinusoidal cell layer of liver and infecting the hepatocytes. The sporozoites employ perforin-like protein (PLP1) to avoid breakdown by lysosomes of hosts during movement across the cell (Patarroyo et al. 2011). The surface coat of sporozoites, circumsporozoite protein (CSP), attaches to the highly sulfated glycosaminoglycan chains which are generated by stellate cells and hepatocytes (Menard et al. 2013). The sporozoites live within the parasitophorous vacuoles, where they produce a large number of blood-stage merozoites.

The causative agents of sleeping sickness (*Trypanosoma brucei*) use the tsetse fly (obligate hematophagous) as a vector to transfer their infectious trypomastigote stage into human skin as fly bites for taking blood meal. Saliva of Tsetse fly comprises of anti-hemostatic chemicals for successful blood feeding. In addition to this, saliva also contains other multifarious constituents that aid in establishing a proper infection by transforming the human skin microenvironment into a trypanosome-friendly one. Thromboregulatory chemicals 5′-nucleotidase-related apyrase and nucleotide deaminase found in tsetse fly mouth limit the platelet aggregation and blood coagulation at the puncture site (Caljon et al. 2010). Antigen 5 is another allergen found in fly saliva that can induce hypersensitivity (type-1) (Caljon et al. 2009). Another constituent, Gloss 2, of tsetse fly saliva suppresses immune response of host by reducing the release of TNF-alpha, IL-6, IFN gamma and IL-10 from the host. Trypanosome transmission and blood feeding by the fly is facilitated by these mechanisms (Bai et al. 2015). Growth and settlement of trypanosomes in the host is also facilitated by the kinesin heavy chain 1 and arginase 1 proteins in case of *T. brucei* infection via suppressing the inflammatory response by host immune system (De Muylder et al. 2013). Trypanosome lytic factors (TLF1 and TLF2) are poisonous to trypanosomes. TLFs are usually found in human blood (Thomson et al. 2009). *Trypanosoma brucei*, on the other hand, has acquired ability to resist TLFs by releasing serum resistant associated protein, which inhibits TLF function (Thomson et al. 2009). As a result, they can progress to create sleeping sickness, which is characterized by neuropsychiatric symptoms such as sleep disturbance, disorientation, exhaustion, and seizures. If not addressed, the sickness might be deadly. Triatoma bugs are carriers of *Trypanosoma cruzi* which causes Chagas disease. Triatomine bugs like to attack peoples face. When bugs defecate, trypanosomes present in feces enter in the bite wound (Montes et al. 2006).

Parasitic worms that cause infection in human hosts through the mouth must surmount acidic environment of host's stomach. Ingested cysts of *Entamoeba histolytica* and *Giardia spp.* can resist the low gastric pH, allowing the trophozoites to germinate and develop in the host. *Giardia lamblia* infests the small intestine, feeds on nutrients in the digestive fluids, producing giardiasis in humans (Schofield et al. 1992; Hemphill et al. 2019). Oocytes of *Cryptosporidium parvum* also cause diarrhea in immunocompromised individuals (Striepen 2013). Trophozoites of *E. histolytica* break MUC2 mucin using glycosidases and cysteine proteases to penetrate the mucus layer and populate in the colon by binding with strong affinity to mucosa with their surface lectin, producing amoebiasis (Moncada et al. 2003; Lidell et al. 2006; Nakada-Tsukui and Nozaki 2016).

Echinococcus granulosus uses components of bile acid to induce the development of eggs into oncospheres, which then travel to the hepatic system through portal and lymphatic channel, where they generally grow into *Echinococcus* cysts. Onchospheres of *E. granulosus* can occasionally enter the pulmonary tissue, bones, brain, or any other organ forming hydatid cysts (Wen et al. 2019). Many parasites elude host immunity by staying at anatomical regions that are free of the host immune factors, such as hollow organs or inside the cells of host. To avoid the complement system and antibodies of host, red blood cells (RBCs) infected with merozoites of the *Plasmodium* spp. create rosettes with noninfected counterpart (Moll et al. 2015). Merozoites are insensitive to major histocompatibility complex and lymphocytes mediated killing because human red blood cells lack MHC molecules (Bowen and walker 2005). According to one study, a splenectomized squirrel monkey exhibited less *Plasmodium*-infected erythrocyte sequestration than an untreated animal.

Appropriation in Host

Several parasites elude host immunity by staying at immunological favored areas/regions that are free of the host's defense mechanism, such as within the host cells or body cavities. Blood cells lack major histocompatibility complex due to which parasites are able to survive within blood cells (Bowen and Walker 2005). Most of the life forms of blood parasites are not available in blood circulation after maturity (trophozoites and schizonts). This is made possible through a process known as sequestration which is also an immune evasion mechanism of the parasites (Miller 1969). *Babesia* spp. infect erythrocytes and generate molecules on their surfaces, causing infected red blood cells to attach to the vascular wall (Allred and Khedery 2004). In this way, they escape the elimination of themselves by the spleen.

Trichinella species, including *T. spiralis, T. britovi, T. nativa,* and *T. nelsoni* develop L3 larvae in muscle cells of the host that give rise to nurse cells which shield the parasites from host immunological identification while simultaneously supplying them with nutrients obtained from the host (Wu et al. 2008). Several parasites, such as *Taenia* spp., *Ascaris* spp., and *Opisthorchis viverrini,* reside in the host's body cavities, such as the gut lumen. They cannot be accessed by the immunoglobulins at these places, and the secretory IgA produced in the mucosal cells cannot activate the complement system. In addition, the epithelium of intestine produces many factors that have the potential to neutralize complement protein molecules (Sun et al. 1999; Andoh et al. 2001).

Antigenic Disguise

Several parasites have the host components in their coat such as carbohydrate conjugates and proteins to avoid being detected as foreign particles by the host immune cells. To escape the recognition by host immune system, adult flukes acquire antigenic proteins of the host such as erythrocyte associated antigens, integrins, complement proteins, collagen, monoclonal antibodies, CD44, and MHC (class-1) (Goldring et al. 1976; Snary et al. 1980; Braschi et al. 2006). *Schistosoma* spp. generate paramyosin muscular protein that interacts to host Fc segments of antibodies and complement 1 (C1) and complement 9 (C2) for antigenic disguise and action against complement (Laclette et al. 1992).

Onchocerca volvulus microfilariae (causative agent of river blindness) cover themselves with factor H which helps them to mask surface antigens (Meri et al. 2002). The host cells produce the outermost layer that encases the *Echinococcus* hydatid cyst developed in host organs. In this way, the pericyst is vital not only in parasite growth and sustainability, but also in escape from immune response by the antigenic masking process (Golzari and Sokouti 2014).

Different Developmental Forms of Parasites

Almost all parasites have a complicated lifecycle that includes many growth phases or variations that exhibit various surface antigens, driving the host to generate diverse/specific immune responses. In most cases, the immunity to one epitope of antigen is useless against the other epitopes.

Adult male and female parasites have different secretory and excretory products and protein profile as indicated by a proteomic study (Moreno and Geary 2008). Out of 228 proteins in microfilarial worm in a study, only 32 proteins are shared by male and female parasites (Moreno and Geary 2008). Different proteins in larval and adult parasite in both male and female indicate their different mechanisms for survival within the host (Reamtong et al. 2019). This antigenic variety renders them excellent escape from host's immune system. *Schistosoma* species have complex life cycle and includes various stages such as miracidium, sporocyst, cercariae, schistosomulae and adult (Khurana et al. 2005). After infection in the host animal, *Schistosoma* spp. express different proteins that have different biochemical composition (Gryseels et al. 2006; Colley et al. 2014; Smit et al. 2015).

Common Antigens of Host and Parasite

Many parasites have the ability to produce antigens that have molecular similarity with mammalian host components. By doing this, they are recognized as self and secure themselves from the host's immune response. Human *Schistosoma* spp. possess CRIT gene that has 98% similar nucleotide sequence with mammalian analogue (Inal 1999). Eggs and cercariae of *Schistosoma* are rich in CRIT (Deng et al. 2003). *Plasmodium* sporozoite protein has composition similar with host thrombospondin (Robson et al. 1988).

Resisting Killing by the Host

To finish the life cycle, parasites can avoid immune system by competing with phagocytic activity and avoiding the very deadly oxidative radicals and digestive enzymes of host cells in their surroundings.

Hemozoin, a substance produced by some blood parasites, interfere the phagocytic activity of the macrophages (Belachew 2018). *Leishmania* spp. produce nuclease that causes the digestion of neutrophil (Guimarães-Costa et al. 2014). Sand flies possess endonuclease in their saliva that also increase the chances of survival of *Leishmania* parasite (Chagas et al. 2014). *L. donovani* outer membrane is composed of lipophosphoglycan which prevent the phagosome maturation and neutrophil mediated damage. Promastigote is a life cycle stage of the *Leishmania* that survives within macrophages by this mechanism (Holm et al. 2001). *T. gondi* employs a number of mechanisms to evade of killing by the host cells and can enter host tissue directly via actin-based movement known as gliding motility (King 1998).

Avoiding Complement Mediated Killing

To avoid complement-mediated elimination, parasites have developed a number of ways. One of the mechanisms is the production of parasite proteins conjugating to complement components and impede the actions of the complement proteins. *Trypanosoma cruzi*, and the worms such as *Brugia malayi* and *Tichinella spiralis* avoid detection by the mammalian complement system by generating vertebrate calreticulin homologs which indirectly causes the suppression of complement classical pathway (Ferreira et al. 2004; Valck et al. 2010; Zhao et al. 2017). In human serum, *T. cruzi* calreticulin interacts with ficolins and mannose-binding lectin (MBL) and bring about inhibition of the lectin route for activation of complement (Sosoniuk et al. 2014).

T. cruzi also produces regulatory proteins for complement pathway and decay accelerating factors to suppress the complement activation (Norris and Schrimpf 1994; Shao et al. 2019). *T. cruzi* also enhances the survival by producing microvesicles that interact with complement 3 (C3) convertase enzyme (Cestari et al. 2012; Wyllie and Ramirez 2017; Shao et al. 2019).

Taenia solium and *Schistosoma* spp. are equipped with the mechanisms for complement inactivation. They perform this activity by producing paramyosin (Parizade et al. 1994) which bind with C3 and C8 causing the inhibition of membrane attack complex (MAC) formation.

Parasite's immune evasion strategies that have been included in this manuscript are summarized in Table 1.

Review of *Fasciola* Immune Evasion Mechanisms

Fascioliasis is one of the helminths borne zoonotic diseases of the livestock caused by *F. hepatica* and *F. gigantica* (Mas-Coma et al. 2005). The disease leads to high mortality and morbidity causing a huge impact on livestock business and is of great veterinary concern. (Mas-Coma et al 2019). *Fasciola* infection has recently been added to the World Health Organization's list of neglected illnesses, with clinical cases found in the America, Asia, Africa, Europe, and Oceania as well as other temperate countries (Mas-Coma et al. 2014; Mehmood et al. 2017; Mas-Coma et al. 2019). This is a major foodborne disease that is currently thought to impact approximately two million people in over 70 countries, with developing countries more severely affected (Mehmood et al. 2017; Mas-Coma et al. 2018).

The life cycle of *Fasciola* species is completed in two hosts. Sheep and cattle are their definite host while snails serve as the intermediate host (Bethony et al. 2006; Jourdan et al. 2018). It spread by the ingestion of encysted metacercariae. In the small intestine, metacercariae excyst, and change into new form called excysted juveniles (Moazeni and Ahmadi 2016). Furthermore, this infective stage of the parasite moves towards the liver through the intestinal wall of the animal. (Mas-Coma et al. 2014; Cwiklinski et al. 2016). The parasite causes many destructive changes in the host body leading to inflammation and finally reaches the bile ducts of host liver where it attains adult size having the ability to lay eggs. Different strategies are adopted by the parasites to hide/evade from immune response as shown in Figure 1.

Table 1: Summary of immune evasion tactics of the parasites

Evasion Strategy	Evasion Mean	Parasite	Factor/ Mechanism Involved	References
Overcoming host's physical and physiological barrier	Skin penetration	Hookworms	Larvae enter in skin through minute break in skin	Albanese et al. 2001
		Strongyloides stercoralis	Urocanic acid, a histidine metabolite that attracts	Safer et al. 2007
	Vector and Vector's salivary factors	*Plasmodium* spp.	Biting mosquitos inject antihistamines, immunomodulators, anticoagulants, vasodilators, and platelet agglutination inhibitors	Zheng et al. 2014
		T. brucei	Tsetse fly release thromboregulatory compounds	Caljon et al. 2010
	Mechanical damage by the vector	*T. cruzi*	Biting wound caused by triatomine bug	Montes et al. 2006
	Resistance to serum toxic molecules	*T. brucei*	Serum resistance associated proteins	Thomson et al. 2009
	Tolerate gastric acidity	*Giardia lamblia, Entamoeba histolytica, Cryptosporidium parvum*	Cysts; modification of microenvironmental condition in intestinal mucosa	Schofield et al. 1992; Striepen, 2013; Hemphill et al. 2019
	Breach intestinal mucosa	*Entamoeba histolytica*	glycosidases and cysteine proteases	Moncada et al. 2003; Lidell et al. 2006; Nakada-Tsukui and Nozaki 2016
	Digesting extracellular matrix	*Entamoeba histolytica*	Many kinds of proteases	Nakada-Tsukui and Nozaki 2016
	Exploit Bile acids and salts	*Echinococcus granulosus*	Development of its ingested eggs into oncospheres in the small intestine, which then travel to the hepatic system through portal and lymphatic channel, where they generally grow into Echinococcus cysts. Onchospheres of *E. granulosus* can occasionally enter the pulmonary tissue, bones, brain, or any other organ forming hydatid cysts	Wen et al. 2019
Sequestration in host's immunological privileged sites	Reside in blood cells	*Babesia* spp.	GPI anchor surface protein. Microneme proteins	Allred and Khedery, 2004
	Sequestration	*Babesia* spp.	Parasite induced red blood cells membrane proteins	Allred and Khedery, 2004
	Nurse cells	*Trichinella* spp.	Parasite induced host process that involve muscle cell response (de-differentiation and arrest)	Wu et al. 2008
	Reside in hollow organs	*Taenia* spp., *Ascaris* spp., and *Opisthorchis viverrine*	Avoid effective serum IgG and IgM Anti-complementary activity	Sun et al. 1999; Andoh et al. 2001
Antigenic disguise	Masking host/ host derived molecules	*Schistosoma* spp.	Erythrocyte associated antigens, integrins, complement proteins, collagen, monoclonal antibodies, CD44, and MHC (class-1)	Goldring et al. 1976; Snary et al. 1980; Braschi et al. 2006
		Schistosoma spp.	Paramyosin, Fc fragment of immunoglobulin and complement C1 and C9 protein	Laclette et al. 1992
		Onchocerca volvulus	Factor H	Meri et al. 2002
		E. granulosus	Host cells form outermost layer	Golzari and Sokouti, 2014
Parasites exist in different developmental forms	Different morphological forms	*Schistosoma* spp., *Trypanosoma* spp. and many others	Parasites exist in various forms and shapes. They express different genes during their life which in turn changes surface antigenic proteins	Gryseels et al. 2006; Moreno and Geary, 2008; Colley et al. 2014; Smit et al. 2015; Reamtong et al. 2019
Sharing of antigen between host and parasite	Complement resistance	*Schistosoma* spp.	Complement C2 receptor inhibitory trispannin (CRIT)	Inal, 1999; Deng et al. 2003
Resist killing by the host	Interrupt phagocytic activity, resistance to toxic chemical synthesis	*Plasmodium*	Hemozoin	Belachew, 2018
	Neutrophil resistance	*Leishmania* spp.	Nuclease/ nucleotidase	Chagas et al. 2014
Prevention of complement mediated killing	Interfere classical pathway	*Trypanosoma* spp.	Calreticulin homologs	Ferreira et al. 2004; Valck et al. 2010
		Trypanosoma spp.	microvesicles interact with complement 3 (C3) convertase	Cestari et al. 2012; Wyllie and Ramirez, 2017; Shao et al. 2019
	Inhibition of membrane attack complex (MAC) formation	*Taenia solium* and *Schistosoma* species	Production of paramyosin	Parizade et al. 1994

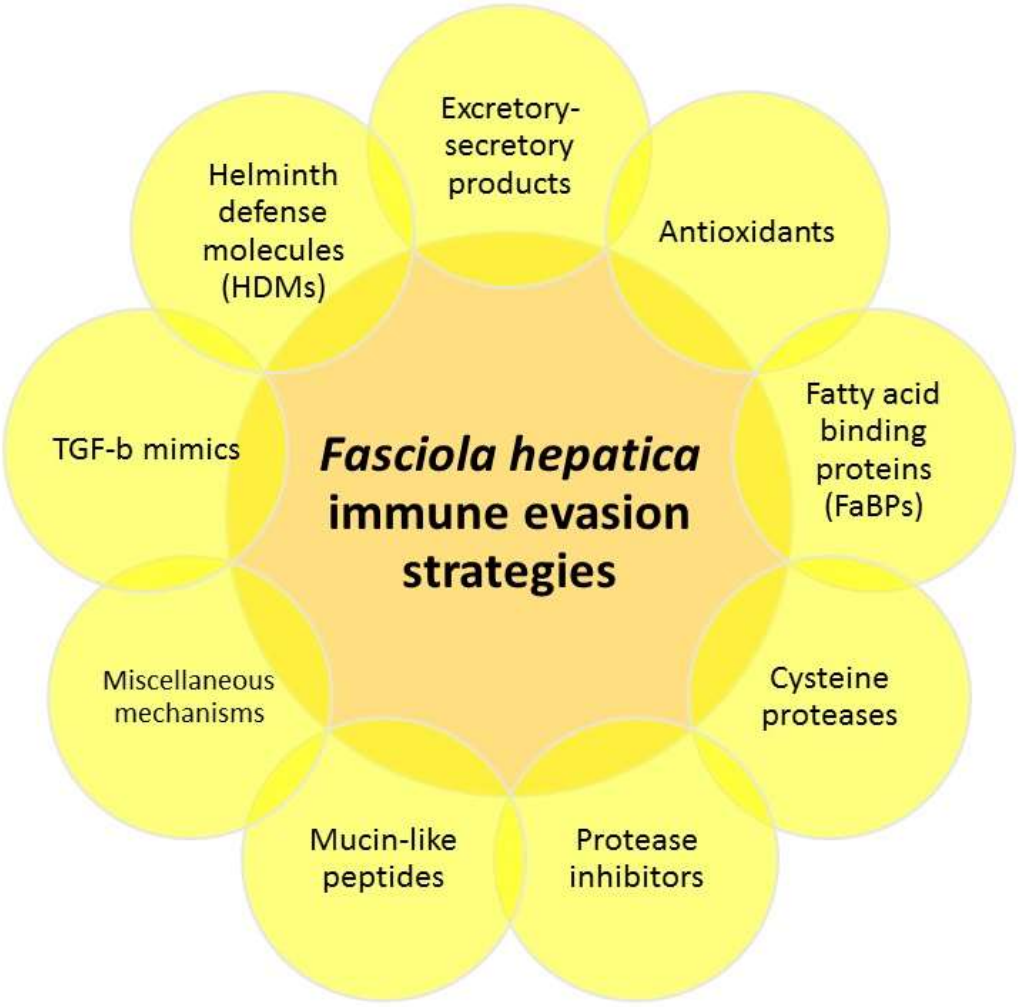

Fig. 1: *F. hepatica* immune evasion ways/ mechanisms.

Fatty Acid Binding Proteins (FaBPs)

Fasciola hepatica has FaBPs that arbitrate the lipid response in cells and is linked with metabolism and inflammation (Furuhashi and Hotamisligil 2008). Till now, there are four fatty acid binding proteins found in the excretory products of *F. hepatica* which have two roles *viz*. antioxidant and nutritive role for the *F. hepatica* (Robinson et al. 2009). Moreover, experimentally induced infection of *F. hepatica* causes decline of the immune system of host especially circulating cytokines (Ramos-Benítez et al. 2017).

Mucin-like Peptides

Some mucin-like peptides formed in the host's body act like excretory products and save the *F. hepatica* from the host immune system. These proteins are functionally and chemically similar to mucin (Cancela et al. 2010; Cancela et al. 2015). Experimental studies reveal that synthetic mucin quantity increases in the peritoneal cells of infected mice with *Fasciola hepatica* (Noya et al. 2017).

Excretory-secretory Products

F. hepatica releases various immunomodulatory molecules in the host body which are known as excretory-secretory (ES) products that alter the immune system of the host. These excretory-secretory products play an important role in the survival of the parasite in the host body. FhTLM, FhKTM, FaBP, TPx, Prx, and FhGST are the important excretory-secretory products of *F. hepatica* released in the host body (Jefferies et al. 2001).

TGF-β mimics

Bioinformatics approaches have shown that there are three transforming growth factor β (TGF-β). During parasitic development, TGF like molecules have a very important role, for example, recombinant *F. hepatica* TGF like molecules assist newly excysted juveniles (NEJ) sustainability and development by decreasing the nitric oxide (NO) production by the microphages (Sulaiman et al. 2016).

Antioxidants

F. hepatica has thioredoxin peroxidase/peroxiredoxin (TPx/Prx) antioxidant which detoxifies the metabolites of the immune system of the host increasing the survival chances of the parasite in the host body (McGonigle et al. 1997; McGonigle et al. 1998). *F. hepatica* produces Glutathione S-transferases (GSTs) which comprise about a total of four percent of their protein part and act as ES product protecting the parasite from free radicals (Chemale et al. 2006; LaCourse et al. 2012). *Fasciola hepatica* uses an important

antigen namely nFhGST which stops the Th1 responses as well as suppresses NF-kB pathway through JAK/STAT (Aguayo et al. 2019).

Cysteine Proteases

Cysteine proteases are the major part, about 80%, of ES product of *F. hepatica.* It plays an important role in the infestation of the *F. hepatica* (Robinson et al. 2008). A total of 5 classes of Fasciola cathepsin have been identified in which 2 are associated with the juvenile infective stage of the animal while three are specific to adult stage infection. FhCL1, FhCL2, and FhCL5 are found in adults while FhCL3 and FhCL4 in juveniles. FhCL3 secretion increased in the initial stage of immature juvenile infection which help the parasite in blocking the host immune system especially eosinophil (Carmona et al. 1993).

Protease Inhibitors

Kunitz serine protease has been recognized in *F. hepatica* (Bozas et al. 1995). Moreover, *F. hepatica* Kunitz type molecule (FhKTM) has exception against cysteine proteases (Smith et al. 2016). FhKTM has a specific role to deceive the immune system by impairing Th1 and Th17 responses by inducing a regulatory change in IL-27.

Helminth Defense Molecules (HDMs)

Helminths including *Schistosoma mansoni*, *Paragonimus westermani*, and *Schistosoma japonicum* have helminth defense molecules as secretory products which help the parasite to destruct the immune system of the parasites. It seems that the parasite secretes 8kDa protein during the whole life of infestation which acts as HDMs. Furthermore, HDMs divide into three groups: *Fasciola*/Asian fluke HDMs, Schistosome HDMs, and Sm16-like molecules. These groups have a unique structure, they have N-terminal peptide and helical structure which also contain hydrophobic C-terminal sequence (Donnelly et al. 2005). HDMs have a special feature that during parasitic infection. There is always secondary bacterial infections occurring at the parasitic site, but the host immune system does not trigger although there is tissue damage. It seems that the host immune system is suppressed (Onguru et al. 2011).

Miscellaneous Mechanisms

F. hepatica usually causes chronic infection in the animal due to the T helper cell 2 (Th2)/ regulatory response in the animal which helps the parasite and host tissue for support and integrity (McNeilly and Nisbet 2014; Dowd et al. 2017). In the initial phases of infection, immune response by T helper cell 2 and T helper cell 1 (Th1/Th2) gets activated along with cytokines including TGF-beta, IFNγ, IL-10, and 1L-4 activation. As *Fasciola* infection increases, the Th1 is suppressed and Th2 is amplified (O'Neill et al. 2000). Cytokines, IL-10 and IFNγ, are increasingly influenced by the mixed response at the initial stage of infection (Clery and Mulcahy, 1998). Sometimes in acute and chronic infections, TGF-β modulates IL-4 while IL-10 causes modulations in IFNγ (Donnelly et al. 2005; Flynn and Mulcahy, 2008). Another strategy adopted by *F. hepatica* to evade immune response of the host is the induction of the apoptosis of eosinophils (Escamilla et al. 2016).

Conclusion

In this manuscript, we have discussed various escaping mechanisms of parasites from host's immune response with special emphasis on *Fasciola hepatica* at molecular level. It has been revealed that parasites are endowed with diverse tactics/ mechanisms/ ways to overcome the cell mediated and humoral immune response. Moreover, these molecular entities/ factors and mechanisms can be targeted by designing novel vaccines and drugs to prevent and control disease against the respective parasite.

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