Intestinal Parasitic Infection And its Relationship with many Risk Factors and the Role of the Interaction Between Parasites and the Immune System in the Inability of the Host to Prevent Re-infection

A Review paper

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AbstractI

ntestinal parasitic infections (IPIs) contribute to a high global health burden, causing about 3.5 billion infections and 450 million clinical morbidities especially in developing countries in which public health standards are not as high as in developed countries. Intestinal parasitic infections (IPIs) comprise both protozoan parasites such *as Entamoeba coli ,Entamoeba histolytica/E.dispar, Giardia lamblia ,Endolimax nana, Cryptosporidium spp ,Blastocystis hominis, Isospora belli, Trichomonas hominis, Iodamoeba butschlii* and Helminths parasites such as *Ascaris lumbricoides, ,Trichiuris trichiura, Enterobius vermicularis Strongyloides stercoralis ,Taenia Spp, Hymenolepis nana* Some of these species are most common worldwide. The high prevalence of intestinal parasitic infection is closely related to many factors including behavioral, biological, environmental, socio-economic, health systems factors that influence the risk of infection, disease transmission and associated morbidity and mortality. In spite of the enormous efforts made by the World Health Organization (WHO), the exposure to parasitic infections is highly prevalent in developing countries, Parasites can cause persistent infection due to their ability to resist immune-mediated expulsion by modulating the host's immune response. Understanding the complex interaction between intestinal parasites and the immune system is of critical, importance, for the development of improved Anti-parasitic therapies, as well as for potential treatments targeting inflammatory and autoimmune disorders. The aim of this review is highlight on Intestinal parasitic infections (IPIs). And their association with many factors that influence the spread of the disease. In addition to understanding the complex interaction between intestinal parasites and the immune system is of crucial importance for the development of improved therapies and also for potential treatments targeting inflammatory and autoimmune disorders.

الملخص

تساهم العدوى الطفيلية المعوية (IPIs) في زيادة العبء الصحي العالمي ، مما يتسبب في حوالي 3.5 مليار إصابة و 450 مليون حالة مرضية سريرية خاصة في البلدان النامية حيث معايير الصحة العامة ليست عالية مثل البلدان المتقدمة. تشمل العدوى الطفيلية المعوية (IPIs) كلاً من الطفيليات الأولية مثل *Entamoeba coli ,Entamoeba histolytica/E.dispar, Giardia lamblia ,Endolimax nana, Cryptosporidium spp ,Blastocystis hominis, Isospora belli, Iodamoeba butschlii, Trichomonas hominis,* and Helminths parasites such as *Ascaris lumbricoides, Trichiuris trichiura, Enterobius vermicularis S*

trongyloides stercoralis ,Taenia Spp, Hymenolepis nana بعض هذه الأنواع هي الأكثر شيوعًا في جميع أنحاء العالم. يرتبط الانتشار المرتفع للعدوى الطفيلية المعوية ارتباطًا وثيقًا بالعديد من العوامل بما في ذلك العوامل السلوكية والبيولوجية والبيئية والاجتماعية والاقتصادية والنظم الصحية التي تؤثر على مخاطر

العدوى وانتقال المرض والمراضة والوفيات المرتبطة بها. على الرغم من الجهود الهائلة التي تبذلها منظمة الصحة العالمية (WHO) ، فإن التعرض للعدوى الطفيلية منتشر بشكل كبير في البلدان النامية ، يمكن أن تسبب الطفيليات عدوى مستمرة بسبب قدرتها على مقاومة الطرد بوساطة المناعة عن طريق تعديل الاستجابة المناعية للمضيف. يعد فهم التفاعل المعقد بين الطفيليات المعوية والجهاز المناعي أمرًا بالغ الأهمية ، لتطوير علاجات محسنة مضادة للطفيليات ، وكذلك للعلاجات المحتملة التي تستهدف الاضطرابات الالتهابية والمناعة الذاتية. الهدف من هذه المراجعة هو تسليط الضوء على العدوى الطفيلية المعوية (IPIs). وارتباطهم بالعديد من العوامل التي تؤثر على انتشار المرض. بالإضافة إلى فهم التفاعل المعقد بين الطفيليات المعوية والجهاز المناعي له أهمية حاسمة لتطوير علاجات محسنة وكذلك للعلاجات المحتملة التي تستهدف الاضطرابات الالتهابية والمناعة الذاتية.

Keywords: Intestinal parasitic infection, sprotozoal parasitic infection , helminthes parasitic infection

Introduction

Intestinal parasitic infections constitute a global health burden in many developing countries (Harhay *et al*,2010). It is estimated that approximately 3.5 billion persons are affected worldwide and cause clinical morbidity in 450 million. Many of these are children from developing countries (Park,2005)..Intestinal parasitic infections (IP) are caused by intestinal helminths and protozoan parasites, which are the most common infections in developing countries(Haque , 2007).They cause over 33% of deaths worldwide (Mulatu *et al,* 2015).The transmission of the most intestinal parasitic infections occurs either indirectly via eating or drinking contaminated food or water, skin penetration or directly by fecal- oral route (Niyyati *et al*, 2009).

Intestinal parasitosis refers to a group of diseases caused by one or more species of protozoa, cestodes, trematodes or nematodes distributed with high prevalence throughout the world (Tadesse *et al,* 2008).The most important protozoan etiologic agents of IPIs are *Entamoeba histolytica* (affecting 50 million people), *Giardia lamblia* (affecting 200 million people), and also *Cryptosporidium spp*., *Cyclospora cayetanensis*, *Cystoisospora belli* and *Microsporidia spp*. in immune compromised patients (Pham *et al,* 2011).The most prevalent helminths parasites are *Ascaris lumbricoides*(*A.lumbricoides*), *Trichuris trichiura* (*T. trichiura*), and hookworm, which affect about one-sixth of the world'spopulation.(WHO,2022). Other common helminths in IPIs are *Enterobius vermicularies*, *Strongyloides stercoralis*, *Taenia spp*., *Schistosoma mansoni* and *Hymenolepis nana* (Mamo,2014).

Intestinal parasitic infection (IPI) is a common cause for abdominal disease worldwide (Faust *et al.*,1938). They are correlating to many symptoms such as abdominal/stomach pain, diarrhea, vomiting and nausea, weight loss, indigestion/dyspepsia, bloating and constipation (Haghighi *et al,* 2009). Parasitic infections are regarded as serious public health problem, as they cause iron deciency anemia, growth retardation, physical and mental health problems, loss of weight in pregnancy and low birth weight .patients. (Rodriguez-Morales *et al*,2006).

Epidemiological researches in different countries have shown that the socio-economic, sanitary and environmental conditions are important underlying causes in the endemicity of parasitic infections (Bakr *et al,* 2009). The high prevalence of intestinal parasitic infection is closely associated with poverty, population density(Unasho, 2013) climatic conditions, poor personal hygiene, poor sanitation, and unsafe drinking water (Wongsaroj *et al* ,2014).malnutrition, low host resistance(Unasho, 2013). and in some cases special political situations and the regional conflicts (Alum *et al*, 2010).

Children are more susceptible to parasitic infections because their immune systems are not fully developed and their activities and hygiene practices put them at greater risk of infection than older age group (Fabiano and Carolina, 2002). Moreover, IPIs can result in serious problems in gastrointestinal disorders patients, immunocompromised patients such as HIV positive, transplanted and haemodialysis patients (Haghighietal,2009).

Effective immune mechanisms against gut parasites and their regulation are important factors to human health and stability (Wang *et al*,2017). Importantly, many parasitic infections become chronic because of various immune evasion strategies developed by parasites that have coexisted with humanity for millennia (Massac and *et al*, 2009) resulting in persistent modulation of the immune system (McSorley and Maizels, 2012). And the inability of the host to prevent reinfection (Hotez *etal*,2008). The aim of this review is highlight on Intestinal parasitic infections (IPIs). And their association with many factors such as poverty, population density climatic conditions, poor sanitation, poor personal hygiene, and poor drinking water… ect. That influence the spread of the disease. in addition to understanding the complex interaction between intestinal parasites and the immune system is of crucial importance for the development of improved therapies and also for potential treatments targeting inflammatory and autoimmune disorders.

Intestinal Parasitic Infections

Intestinal Protozoal Parasitic Infection

Infections caused by intestinal protozoan parasites (IPPs) are among the most prevalent human diseases that affect a large section of poor communities particularly in developing countries (Tegan *et al.*,2020) .It is estimated that IPIs result in 450 million illnesses with an average prevalence rate of 50% in developed world, and almost 95% in developing countries (WHO,1998). *Entamoeba histolytica*, which is mainly a cause of amoebiasis (amoebic bloody diarrhoea), involves primary pathogenic protozoans in the human body (Edrisian *et al.*, 2008).Most strains of *E. coli* are harmless but some serotypes act as pathogens, producing virulence factors allowing them to cause infections in intestine and other organs. (Singleton, 2004 The other members of the collection, infecting humans are *E. hartmannii, E. moshkovskii,,E. gingivalis, Iodamoeba butschlii and Endolimax nan*a (Alberta & Wellness,2011).

Giardiasis is a digestive zoonotic disease caused by the protozoan genus Giardia and the most frequent species is *G. duodenalis* (syn. *G. intestinalis, G. lamblia* (Acha Szyfres, 1992).Infections with *G. lamblia* casualties the intestinal mucosa and results in malabsorption of nutrients, especially carbohydrates, fat and vitamins, particularly vitamins A. It seems to be mostly seen in children with under nutrition and results in impaired growth and weight loss in children (Eckmann & Gillin, 2001). Giardiasis is reported to infect approximately 280 million people every year and about 2.5 million annual deaths. Annually, an estimated 1.2 million giardiasis cases occurred in globe (Kalyoussef & Goldman,2010).

Cryptosporidiosis is an infectious emerging and re-emerging protozoan zoonosis that has been described from the devil) opted as well as developing nations of the world (Pal *et al*, 2016). *Cryptosporidium spp.* is primarily affecting immunocompromised patients like HIV/AIDS patients (Lozano *et al.*, 2012).It occurs in up to 7% of children with diarrhoea in developed countries and up to 12% of children with diarrhoea in developing countries (Leav *et al.*, 2003.
Blastocysts species remains one of the most common intestinal parasites in humans(Taubert, *et al*,2009) .It is estimated that about one billion people in the world are infected with *B. hominies*, whose prevalence is much higher in developing countries (30.0%–100.0%) than in developed countries (1.5%–20.0%) (El Safadi *et al*, 2014). Isospora belongs to a subclass of coccidian in the family Eimeria. *Isospora belli* is known to infect humans only with *Isospora* (Bialek *et al*, 2002). Importantly, *C. belli* has been frequently detected in patients infected with HIV, human T lymphocyte virus type 1 (HLTLV1), Alzheimer's disease, and colorectal cancer, in addation to those who have undergone liver and kidney transplantation (Mahmoud and, *etal*,2019). .

Studies have authenticated that, the prevalence rates of protozoan infections are completely high in developing regions, especially Africa, and population there are frequently infected with one or multiple protozoan parasites. (Hajissa *et al*, 2022). Few studies have been done on the prevalence of intestinal parasitic infection in Libya (Bugharara *et al*, 2017).There are still several localities in the country for which parasitic infection information is not available.(Kassem *et al*, 2013). These studies were in different cities including: Benghazi (Hussain *et al*,2019). In Tripoli, about five studies were done, (Mohamed *et al*,2006). Three studies were studied in Sirt(Salem *et al*, 2006; Kasssem, *et al*,2007). In Zawia (El said,*et al*,2014) in Derna (Sadaga *et al*, 2007) in AlKhoms (El Ammari, & Nair. 2015) in Zliten (Abuhelfaia, & Dufani, 2005) in Wadi Al-Shati(Saad *et al*,2009) and in Nalout (Al Kilani *et al*, 2008). The widespread intestinal protozoan infections among Libyan population are *Blastocystis hominis* followed by *Entamoeba histolytica/Entamoeba dispar* or *Giardia lamblia* , *Endolimax nana Entamoeba coli* and *Chilomastix mesnil* (EI-Ammari, & Nair, 2003 ;Saleh,2007) *Cryptosporidium spp* infections have been reported in Libya among patient particularly in children with diarrhea(Ghenghesh, *et al*, 2016).

The distribution of intestinal protozoan infection depends on many factors, these include socio-demographic variables as well as unpredictable factors such as natural disasters contribute to the problem (Thapar & Sanderson, 2004). Children are more likely to be infected with intestinal parasites, a study conducted by Kassem *et al* (Kasssem *et al*, 2007),in Sirte showed that the social and economic status of parents was related to the prevalence of intestinal parasites and their immature immune system (Jemaneh,1998). the epidemiological patterns of parasitic diseases in a rapidly developing country like Libyaare further complicated by the arrival of large numbers of migrant workers leading to destabilizing effects on the normal pattern of disease transmissions (EI-Ammari, & Nair, 2003). It is noticed that the dominating infections are the protozoan parasites and that the females is the most affected group by them. Shawesh *et al*, 2019.The absence or scarcity of water in some parts of Zawia is another reason for the spread of the infection among the ladies, especially in the sectors where water is scarce Shawesh *et al*, 2019).

Helminths intestinsl parasitic infection

Helminth parasitic diseases are the topmost neglected tropical diseases (NTDs) comprised 24% population in the world reported to be infected with helminth transmitted from soil. Numerous helminthes inhabit the intestinal tract of human and those of large, health importance include nematodes (roundworms) such as *T. trichchiura, A. lumbricoides*, hookworms (Ancylostoma duodenale and Necator americanus) and *S.stercoialis*, trematodes (flukes) such as *Clonorchis sinensis, schistosomes, Fasciola spp*. (*F. hepatica and F. gigantica*) *Opisthorchis viverrini* and cestodes (tapeworms) such as *Taenia. saginata, T. solium, Diphyllobothrium latum, E. vernicularis* and *H. nana* (Odening, 1976). Morbidities from the commonest infectious intestinal helminthes including Ascaris lumbricoides, Hookworm and Trichuris trichiura (collectively referred to as soil-transmitted helminths, STHs) (Yadav & Prakash, 2016).Other species that have been reported but not very popular, include *Taenia spp*, *Dicrocoelium traspes* and *Hymenolepis nana* (WHO, 1994).

At center stage are the three common soil-transmitted, intestinal nematodes, *Ascaris lumbricoides, Trichuris trichiura* and hookworm, that are estimated to infect 1.4, 1 and 1.2 billion people, respectively, representing (Crompton, 2001). Acute *Ascaris* infections cause about 60,000 deaths per year, mainly in children due to intestinal obstruction (Scott, 2008). *T. trichiura* was one of the highly prevalent soil-transmitted helminths (STH) until the 1970s in the Republic of Korea (= South Korea)(Hong *et al*, 2006.Most *T. trichiura* infections lack symptoms; only patients with heavy infections are symptomatic.(Joo *et al*, 1998; Elsayed *et al*, 2004).
In the addation to Pinworm *(Enterobius vermicularis*), is a common nematode parasite among children. Although pinworm infection (enterobiasis) is not commonly serious but usually common parasitic infection (Cadwell, 1982).

Strongyloidiasis is caused by two types of intestinal nematodes. The most popular, and globally spread, human pathogen of clinical importance *is stercoralis*

strongyloides. Other of *Strongyloides fuelleborni* are found sporadically in Africa, New Guinea and Papua (Grove, 1996). Hymenolepiasis is cestode infection with *Hymenolepis nana* (the dwarf tapeworm) as etiologies (Sungkar *et al*, 2017).

The greatest numbers of soil-transmitted helminths infections occur in tropical and subtropical regions of Asia, especially China, Saharan Africa(Hotez *et al*, 2003) . Parasitic worms reported in stool samples of school-aged children in Tripoli (Mohammed *et al*, 2017). In south western Libya who reported only one stool sample showed the egg of Ascaris lumbricodesamong HIV/AIDS patients . While did not find helminthes infections among outpatients in Sebha and school aged children in Tripoli respectively (Saleh, 2007). In Houn city, Libya, the helminthes infections are uncommon probably due to climatic conditions (dry, hot and sandy soil) of this region(Zaed, 2018). Lower spread rates of helminthes infections have been found in Tripoli (Ben Mousa *et al*, 2007) and in Derna (Sadaga & Kassem, 2007) Benghazi (El-Buni, *et al*, 1998) . However, paradoxical results were reported by Ben Mousa, (Ben Mousa *et al*, 2007) who found that prevalence of *A. lumbricoides* (20.0 %) was higher than the other parasites detected (2 % *Taenia saginata*, 6 % *H. nana*, 4.0 % *E. vermicularis*, 14 % *T. trichiura*, between school aged children in Tripoli. comparatively little infections rates of helminthes have been reported in this country (Abahussain,2005).

The parasitic relation of worms with human has been influenced by global changes in the human sociocultural spectrum (Gizaw *et al*,2019). Libyan is a developing country, and population, in usually communities have high level,of cleanliness, general good health, clean water supply and appropriate sewage discarding (El-Buni & Khan,1998). An enormous raise in the number of expatriates is a result of economic development of Libya. The spread of intestinal parasites has been found higher in expatriates forthcoming from developing countries (Emad& Haytam, 2007) whole information about intestinal parasites in Libyan is lacking despite some reports(Ben Mousa *et al*, 2007). .

The immune mechanism against Intestinal Parasitic Infections
Intestinal Helminthic Infections.

The immune response is a biological process to protect the host from infections. A healthy immune system can recognize and differentiate self-antigens and antigens belonging to microorganisms such as parasites. Immunity pursues pathogen clearance and preserves tissue homeostasis through a wide range of complex networks that involve cellular and humoral components with regulatory feedback systems (Villani *et al*, 2018). A variety of inflammatory and suppressive responses are generated following infection or injury to restore the homeostatic conditions. The host exerts intrinsic control between both responses to achieve pathogen elimination while simultaneously preventing collateral damage.

The first cell to arrive at the inflammation site is the neutrophil, which employ an extracellular ATP-dependent mechanism to generate a chemotactic gradient and

orientate its migration (Junger,2008). Remarkably, the purinergic system regulates many effector functions of neutrophils, such as phagocytosis, oxidative burst, degranulation and neutrophil extracellular traps (NETs) formation (Wang &Chen ,2018). After its death, apoptotic neutrophils release ATP to stimulate mononuclear phagocytic cell infux and promote engulfment and clearance functions (Elliott *et al*, 2009). Extracellular ATP triggers multiple immune efector functions to inhibit infections and is primarily a pro-inflammatory metabolite (Corriden& Insel ,2010).

Parasitic nematodes constitute one of the major threats to human health, causing diseases of major socioeconomic importance worldwide. Parasitic helminthes include a diverse group of intestinal worms that are one of the most successful pathogens of the animal kingdom. Current estimates indicate that over 1.5 billion people and many other agricultural and wild mammalian species are infected with at least one species of intestinal helminthes (Wakelin, 1993).

Immune response to nematodes

The most common intestinal parasitic nematodes of humans include the roundworm *Ascaris lumbricoides*, the whipworm *Trichuris trichiura* and the hookworm Necator *americanus.* To propagate their species, these enteric worms have developed mechanisms to invade the host via the skin and/or ensure their survival passage through the oral cavity and stomach until they arrive within the intestinal tissue where they produce eggs that are shed via host feces (Grencis ,2015).when they upon entry into the intestine, epithelial cells (IECs) are critical for initiating a type 2 immune response.IECs release damage-associated molecules such as ATP as well as the cytokines interleukin (IL)-25 and thymic stromal lymphopoietin that, in combination with diverse sources of IL-33, stimulate tissue-resident type 2 innate lymphoid cells (ILC2s) to produce IL-4, IL-5, and IL-13 (Peterson & Artis,2014). These quint essential type 2 cytokines rapidly recruit eosinophils and alternatively activated macrophages (AAMacs) with tissue reparative properties to the site of infection that feedback on to the epithelium to fortify the intestinal barrier by stimulating the production of mucus and anti-microbial peptides as well as enhancing the shedding of dead enterocytes (Peterson & Artis,2014). Increased IL-25 stimulated the proliferation of IL-13 producing ILC2s that, in turn, induced goblet cell hyperplasia, intestinal remodeling, and enhanced immunity to subsequent *N. brasiliensis* infection (Schneider *et al*,2018).

Studies of the T-cell-independent innate response have shown elevations in IL-5 and IL-9 in *H. polygyrus*-inoculated (Schneider *et al*,2018) . The differentiation of an IL-4 producing T cell is an important step in the development of an effective host protective response. IL-4 can directly mediate worm expulsion mechanisms, and it is required for the amplification of Th2 cells, which also produce IL-5, IL-9 andIL-13; in vivo, IL-10 is not elevated in the *H. polygyrus* response (Schneider *et al* ,2018) and *al* is normally only slightly elevated in the *N. brasiliensis* response (Nadjsombati *et* ,2018). The *N. brasiliensis* Th2 response is currently unique in that CD4 T cells,

producing IL-4 and IL-13, can develop that mediate worm expulsion when B7-1–B7-2 costimulatory, molecules are inhibited (Schwartz *et al* ,2014).

IL-10, although not generally elevated during the *trichostrongylid* responses, is elevated in the *T. muris* responses and is important in maintaining host protection, probably through the downregulation of the Th1 inflammatory response(Schopf *et al*, 2002) as in schistosomes (Stadecker *et al* ,1994). B cells could still have a role in the initiation of the Th2 response, either as antigen-presenting cells (APCs) or as additional sources of Th2 cytokines (Harris *et al*, 2000).

In parallel to ILC2 activation, *T. muris* has been shown to stimulate production of thymic stromal lymphopoietin by IECs that condition intestinal dendritic cells (DCs) en route to the draining lymph nodes to polarize CD4+ T cells into Th2 cells that home to the intestine and amplify the ongoing type 2 response (Zaph *et al* ,2007). DCs have also been shown during *H. polygyrus* infection to initiate the differentiation of T follicular helper cells that migrate to the B cell follicles and drive a humoral immune response skewed toward the generation of IgG1 and IgE antibody-secreting plasma cells (Meli *et al*, 2016). This antibody response enhances the effector functions of macrophages, mast cells and basophile populations through Fc-mediated clearance of cellular debris and release of histamines and eicosanoids that maintain or enhance gut contractility and intestinal blood flow (Esser-von Bieren *et al*, 2013). Helminth-specific immunoglobulins have also been shown to directly bind and limit parasite motility (Esser-von Bieren *et al*, 2015), the latter being necessary for parasite survival. .

Early responses to helminth infection may simultaneously involve components of a type 1 and type 2 immune response that not only limit microbial invasion during a helminth-induced barrier breach but also promote tissue repair/regeneration and limit tissue damage, yet have minimal effect on parasite burden.

The vertebrate innate immune response to parasitic nematodes is complex and varies greatly with the species and severity of nematode infection. Invasion of the host tissues by parasitic nematodes activates the complement system, a collection of proteins responsible for identifying pathogens and directing the innate immune response. Leukocytes are recruited to the site of infection and are responsible for enhancing the inflammatory response and release of cytokines, among a variety of other processes (Martinez *et al*, 2009).

Mast cells, elevated in Th2 responses to parasites (Knight *et al* ,2000). Recruitment of other types of leukocytes, such as neutrophils, macrophages, basophils, innate lymphoid cells and dendritic cells, leads to the production of toxic free radicals, phagocytosis, and eventually, the development of an adaptive immune response (Grencis , 2015).Production of reactive oxygen intermediates that damage the worm and changes in mucous quality that facilitate mucous entrapment could also contribute to viable worm expulsion (Finkelman *et al* ,1997).Tumor necrosis factor-a

(TNF-a) might also have a role in accelerated worm expulsion, either through direct effects on gut epithelial cells or through enhancement of the Th2 response (Artis *et al* ,1999).Mast cells, elevated in The responses to parasites (Knight, *et al* ,2000).

However, certain vertebrate-parasitic nematodes have evolved immunomodulatory mechanisms that promote nematode infection by interrupting one or more effectors of the innate immune response (Maizels *et al*, 2004).

Cysteine protease inhibitors, or cystatins, produced by parasitic nematodes have been identified as a major class of molecules with immunomodulatory properties. Cystatins secreted by nematodes have been shown to inhibit two classes of cysteine proteases: legumains , and cathepsin L and S . Inhibition of legumains is especially relevant to nematode infection because it prevents the generation of MHC class II molecules that recognize nematode antigens, thus preventing the induction of an adaptive immune response (Dall& Brandstetter, 2016). However, cystatins strongly enhance the production of IL-10, which in turn restricts the activity of T cell-mediated responses (Schierack *et al*, 2003). A cystatin secreted by *Heligmosomoides polygyrus* modulates the activity of dendritic cells during the anti-nematode immune response in mice (Sun *et al*, 2013). Dendritic cells exposed to recombinant cystatin expressed fewer MHC-II molecules as well as reduced CD40 and CD86, two proteins necessary for T-cell differentiation. The interference with antigen processing generated by the cystatin ultimately results in an immune response modulated in favor of nematode infection. Recombinant cystatin induces downregulation of iNOS as well as COX-2, both proinflammatory cytokines. It also induces the upregulation of IL-10, further promoting an anti-inflammatory effect upon microglia stimulated with lipopolysaccharide.

Intestinal Protozoal Parasitic Infection

Immune responses against E. *histolytica*

E. histolytic contains several virulence factors that allow it to persist and survive within the host. Although more than 90% of *E. histolytica* infections are asymptomatic and remain as commensals within the host's gut environment, under certain circumstances, the parasite invades the host epithelium and becomes pathogenic (Verkerke *et al*,2012). The intestinal tract provides the first line of defense, where mucus prevents ameba penetrance into the intraepithelial cells. Gal-lectin of *E. histolytica* binds mucosal matrix and uses its cysteine proteases to cleave mucin to gain access to the intestinal epithelial cells (IECs) (Moncada *et al* ,2003).The intestinal tract is also filled with antimicrobial compounds and secretory immunoglobulin A (sIgA) that provide additional protection against *E. histolytica*. As such, deficiency in antimicrobial protein REG1 or s IgA renders the host highly susceptible to *E. histolytica* infection (Peterson *et al*, 2011). IECs recognize LPPG associated with *E. histolytica* and produce several chemokines and cytokines, including TNF-α, IL-6, and GM-CSF, to recruit neutrophils and monocytes (Becker *et*

al ,2010). Thus, neutrophil-depleted mice have more intestinal lesions and higher susceptibility to *E. histolytica* than do wild-type (WT) mice (Rivero-Nava *et al*,2002). LPPG also activates dendritic cells through TLRs, increasing their expression of costimulatory molecules such as CD80, CD86, and CD40 and promoting cytokine production (Vivanco-Cid *et al* ,2007).

Macrophages also play an important role during *E. histolytica* infection. Macrophages express Toll-like receptors (TLRs) that can recognize *E. histolytica* virulence factors to initiate amebicidal immune responses. TLR2 and TLR4 recognize *E. histolytica* LPPG, whereas TLR9 recognizes *E. histolytica* DNA (Ivory *et al* ,2008). Cytokines such as interferon (IFN)-γ further activate macrophages to produce nitric oxide synthase (NOS) and prevent *E. histolytica* infection (Seydel *et al* ,2000). Deficiency of either IFN-γ or NOS results in severe liver infection with *E. histolytica*, demonstrating the importance of these critical cytokines(Guo *et al* ,2009).With regard to adaptive immunity, protection from or resistance to *E. histolytica* also seem to depend on Th1 responses. Patients who were infected with *Entamoeba* but were asymptomatic had higher levels of IFN-γ, suggesting a protective role for Th1 responses and patients with invasive amebiasis had increased levels of the Th2-associated cytokine IL-4 (Sanchez *et al* ,2002). .

Production of IFN-γ by T cells is associated with protection against *E. histolytica* infection (Guo *et al* , 2008). More importantly, the protection observed in susceptible mice immunized with Gallectin was due to the production of IFN-γ and IL-17 by CD4+ and CD8+ T cells (Guo *et al* ,2011). Taken together, these results demonstrate that protection against *E. histolytica* requires a balance of Th1 and Th2responses.

previous studies showed that the cysteine proteinase EhCP5 of *E. histolytica* can cleave and inactivate recombinant IL-1β and IL-18 (Que *et al* ,2003). The Gal-lectin of *E. histolytica* induces robust caspase-1 activation and subsequent IL-1β and IL-18 production in mouse macrophages (Mortimer *et al* ,2014). Given that Gal-lectin induces inflammasome activation (Mortimer et *al*, 2014) and protective CD4 and CD8 T-cell responses (Guo *et al*, 2011), the NLRP3 inflammasome may be involved in regulating adaptive immune responses.

Immune responses against T. *gondii.*

Innate immune responses are critical for protection against *T. gondii* infections, as shown by the results of studies in mice lacking critical cytokines and molecules, including IFN-γ (Scharton *et al* ,1996), IL-12 (Gazzinelli *et al* ,1993), and iNOS (Scharton *et al*, 1997).

TLRs play an integral role
in innate recognition of T. gondii–associated PAMPs and in initiating cytokine responses by the innate immune cells. Several TLRs, including TLR2, TLR4, TLR7, TLR9, and TLR11, are involved in innate recognition of *T. gondii* and promote production of IL-12 and IFN-γ (Yarovinsky,2014) .More recently, the *T. gondii*–

secreted protein profilin was shown to be the specific ligand for TLR11, suggesting that TLR11 is the principal innate sensor (Yarovinsky *et al* ,2005).

T cells are essential for providing complete protection against *T. gondii*, Both CD8+ and CD4+ T cells are important for controlling *T. gondii* infection, and IFN-γ production by these cells is critical for protection (Gazzinelli *et al* ,1992).

In addition to NOD2, both NLRP1b and NLRP3 are also involved in protection against *T.gondii*. Single-nucleotide polymorphisms in the NLRP1 gene are associated with increased susceptibility to toxoplasmosis in humans (Witola *et al*, 2011). These findings were further confirmed via RNA interference–mediated knockdown of NLRP1 in human monocytic cell lines. Activation of the inflammasome during *T. gondii* infection in human monocytes was determined via short hairpin RNA–mediated knockdown of ASC and caspase-1 (Gov *et al*, 2013). The involvement of the NLRP1 inflammasome during *T. gondii* infection has also been confirmed in both murine and rat models (Ewald *et al*, 2014). These studies' results show that the activation of caspase-1 and subsequent production of IL-1β and IL-18 in human cells in response to *T. gondii* infection are mediated by the NLRP1 inflammasome. (Gorfu *et al*, 2014).

Conclusions

Intestinal parasitic infections (IPIs) are one of the major causes of human mortality and morbidity particularly in developing countries. Intestinal parasitic infections (IPIs) comprise both protozoan parasites such *as Entamoeba coli ,Entamoeba histolytica/E.dispar, Giardia lamblia ,Endolimax nana, Cryptosporidium spp ,Blastocystis hominis, Isospora belli, Trichomonas hominis, Iodamoeba butschlii* and Helminths parasites such as *Ascaris lumbricoides, ,Trichiuris trichiura, Enterobius vermicularis Strongyloides stercoralis ,Taenia Spp, Hymenolepis nana* Some of these species are most common worldwide. The high prevalence of intestinal parasitic infection is closely associated with risk factors including contaminated food and water, poverty, population densitypersonal hygiene, climatic conditions, Contaminated soil and vegetables and in some cases special political situations and the regional conflicts, These factors must be considered for appropriate implementation of any prevenation and control strategies related,the intestinal parasitic infection. Informing the public by press and mass media can be efficient in reducing the contamination and also for reducing the intestinal parasitic infection. Furthermore, a comprehensive epidemiological studies are needed to pilot decision makers in the pertinent sectors to control intestinal parasites.
Children are most volatile to parasitic infections because their immune systems are not completely developed and their activities and practices impose them at major risk of infection than older age bracket.

A host try to eliminate parasites through an epithelial barrier, innate immunity and acquired immunity; however, parasites can avoid and regulate immune responses and become chronic with humanity for years. The host is able to regulate its immune responses to evict the parasite without excessive self- disadvantage and to obviate excessive suppression that would reduce, its ability to protect against reinfection or against other pathogens the understanding the complex interaction between intestinal parasites and the immune system may lead to the development of therapeutic methods and improved therapies to effectually eliminate parasites.

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