International Journal of Advanced Multidisciplinary Research
ISSN: 2393-8870
www.ijarm.com
(A Peer Reviewed, Referred, Indexed and Open Access Journal)
DOI: 10.22192/ijamr Volume 10, Issue 12 -2023

Review Article

DOI: http://dx.doi.org/10.22192/ijamr.2023.10.12.002

Review on immune response against Cestode infections

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Keywords

Cestode Infection,
Immune response,
Immunity,
Inflammation

Abstract

Cestode infections in animals are important because several species are zoonotic, causing cysticercosis and hydatidosis in man, and because of the economic losses incurred due to infections in livestock. Adult cestode worms are found in the small intestine; these infections are usually well tolerated or asymptomatic, but may cause abdominal distress, dyspepsia, anorexia (or increased appetite), nausea, localized pain, and diarrhea. While Larvae locate in extraintestinal tissues and produce systemic infections with clinical effects related to the size, number, and location of cysts. Host Defenses against Adult worms are probably only weakly immunogenic, although some evidence exists for a cell-mediated host response; moderate eosinophilia and increased IgE may occur. *Hymenolepis nana*, in contrast, elicits a strong immune response when directly infected by the eggs, since the larvae develop within the villi. Larvae elicit strong immunity against reinfection that is derived from both cell-mediated and humoral responses induced by antigenic stimulation of tissues. The immunology of hydatid disease has been divided conceptually into preencystment and postencystment phases, which are differentiated by the formation of the laminated layer around the hydatid cyst. This occurs between 2 and 4 weeks post infection in the animal intermediate or human host following ingestion of the egg and release of the oncosphere.Helminth parasites including cestodesare responsible for some of the most common human infections and cause significant health problems and economic difficulties in the developing areas of the world. The type 2 immune response, characteristic of helminth infections, has been associated with the development of protective immunity and reduced worm burdens in infected humans. Further, animal model systems have demonstrated that type 2 cytokine production and signalling are necessary to promote inflammation and parasite clearance. Despite significant advances in our understanding of the mammalian immune response to helminths, the molecular and cellular mechanisms that promote type 2 immunity remain to be fully defined. Emerging studies suggest that a series of highly coordinated events including the production of epithelial cell-derived alarmins, the activation of innate

immune cells (innate lymphoid cells, haematopoietic progenitor cells, mast cells, basophils, eosinophils, neutrophils and macrophages) and the subsequent activation of lymphocytes are required to promote antihelminth immunity.

Introduction

Adult cestode worms are found in the small intestine; these infections are usually well tolerated or asymptomatic, but may cause abdominal distress, dyspepsia, anorexia (or increased appetite), nausea, localized pain, and diarrhea. While Larvae locate in extraintestinal tissues and produce systemic infections with clinical effects related to the size, number, and location of cysts. *Taenia solium* cysticercosis (infection with the cysticercus larval stage) is often asymptomatic and chronic; neurocysticercosis, ophthalmic cysticercosis, and subcutaneous and muscular cysticercosis are, however, frequently reported. *Echinococcus granulosus* hydatid larvae may form massive cysts in liver, lungs, and other organs, including long bones and the central nervous system.Host Defenses against Adult worms are probably only weakly immunogenic, although some evidence exists for a cell-mediated host response; moderate eosinophilia and increased IgE may occur. *Hymenolepis nana*, in contrast, elicits a strong immune response when directly infected by the eggs, since the larvae develop within the villi. Larvae elicit strong immunity against reinfection that is derived from both cell-mediated and humoral responses induced by antigenic stimulation of tissues(Baron, 1996).

Helminth parasites are responsible for some of the most common human infections and cause significant health problems and economic difficulties in the developing areas of the world. The type 2 immune response, characteristic of helminth infections, has been associated with the development of protective immunity and reduced worm burdens in infected humans. Further, animal model systems have demonstrated that type 2 cytokine production and signalling are necessary to promote inflammation and parasite clearance. Despite significant advances in our understanding of the mammalian immune response to helminths, the molecular and cellular mechanisms that promote type 2 immunity remain to be fully defined. Emerging studies suggest that a series of highly coordinated events including the production of epithelial cell-derived alarmins, the activation of innate immune cells (innate lymphoid cells, haematopoietic progenitor cells, mast cells, basophils, eosinophils, neutrophils and macrophages) and the subsequent activation of lymphocytes are required to promote antihelminth immunity(Kakkos, Mouzaki, & Vagianos, 2001).

The immune system is a network of cells, tissues, and organs that work together to defend the body against attacks by “foreign” invaders. These are primarily microbes (germs)—tiny, infection-causing organisms such as bacteria, viruses, parasites, and fungi. Because the human body provides an ideal environment for many microbes, they try to break in. It is the immune system’s job to keep them out or, failing that, to seek out and destroy them.When the immune system hits the wrong target or is crippled, however, it can unleash a torrent of diseases, including allergy, arthritis, or AIDS(Works, 2003).

The immune system is amazingly complex. It can recognize and remember millions of different enemies, and it can produce secretions and cells to match up with and wipe out each one of them. The Immune response is the body's response caused by its immune system being activated by antigens. The immune response can include immunity to pathogenic micro-organisms and its products, as well as autoimmunity to self-antigens, allergies, and graft rejections. In this process the main cells involved are T cells and B cells (subtypes of lymphocytes), and macrophages (a type of leucocyte or white blood cell). These cells produce lymphokines that influence the other host cells' activities. B cells mature to produce immunoglobulins (also known as antibodies), that react with antigens. At the same

time, macrophages process the antigens into immunogenic units which stimulate B lymphocytes to differentiate into antibody-secreting plasma cells, stimulating the T cells to release lymphokines (Janeway Jr, Travers, Walport, & Shlomchik, 2001).

Cestode infections in animals are important because several species are zoonotic, causing cysticercosis and hydatidosis in man, and because of the economic losses incurred due to infections in livestock. Information on immunological diagnosis of and vaccination against cestode infection is restricted almost exclusively to the taeniid cestodes in which two groups of mammalian hosts are concerned: the intermediate host infected with the larval parasite and the definitive host infected with the adult tapeworm parasite(Janeway Jr et al., 2001).

Therefore the objective of this review is;to deal on immune response against cestode infection.

An overview on parasite recognition by host defense systems

Immune response is a general term referring to the capacity of an individual to mount an e cient immune response when challenged by pathogens. The immune system is complex, and therefore, immune function can be quantified in many ways. Invertebrates, two di erent types of indicators are commonly employed by ecologists to assess immune competence. First, monitoring measures such as white blood cell counts, haematocrit or sedimentation rate are relatively simple to obtain and provide integrative measures of the individual's health status. Secondly, measures of the host cellular or humoral immune responses to non-replicative antigens such as phytohemagglutinin (PHA) or sheep red blood cells (SRBC) respectively, test an individual's ability to mount an immune response while measuring the magnitude of that response. Despite the fact that these tools are frequently used in ecological studies, a central question remains unresolved: Do measures of immune indices reflect an individual's current status of pathogenic infection or its actual immune competence. For example, an elevated lymphocyte count can be interpreted as a good immune competence (i.e. an indicator of healthy individuals who highly invest in immune function to maintain low parasite levels, or as a sign of an ongoing infectious disease (i.e. a physiological response to infection in unhealthy individuals with high parasite levels. To solve this issue, most studies used a correlative approach, measuring immune indices and relating these measures to the prevalence of parasites or parasite load(Janeway Jr et al., 2001).

Parasites live either inside or outside cells. Intracellular parasites such as the organism that causes malaria can trigger T-cell responses. Extracellular parasites are often much larger than bacteria or viruses and require a much broader immune attack. Parasitic infections often trigger an inflammatory response when eosinophils, basophils, and other specialized granular cells rush to the scene and release their stores of toxic chemicals in an attempt to destroy the invader. Antibodies also play a role in this attack, attracting the granular cells to the site of infection(Works, 2003).

When a host has successfully been 'found', the parasite has to adapt to a completely new environment with different physiologies and particularly different immune systems the parasite has to adapt to.The immune system of the host is responsible for parasite recognition, and is traditionally differentiated into innate and adaptive immunity. Innate immunity is the early phase of the host response to infection in which a variety of innate mechanisms recognize and respond to the presence of a pathogen. In contrast to adaptive immunity, innate immunity is present at all times, does not increase with repeated exposure to a given pathogen, and does not discriminate between pathogens. Adaptive immunity, also known as acquired immunity, is the response of antigen-specific lymphocytes to antigen, including the development of immunological memory. The invertebrate immune system consists of innate immunity, whereas the vertebrate immune system comprises of both, innate and adaptive mechanisms.

Recently, evidence for the existence of specific immunological recognition and moreover of specific memory in the innate immune system of invertebrates is accumulating, challenging the dogma that specific recognition and immunological memory is confined to the adaptive immune system. The mechanisms leading to specificity in the invertebrate immune system are, as yet, not clear. However, specificity in innate immune systems is not based on the mechanisms that mediate specificity in vertebrates, i.e. diversified lymphocyte receptors and antibodies. Recent studies allude to the recognition of carbohydrate residues, probably by lectin-like proteins as mediators of specific recognition and memory in invertebrates. Pathogen-associated molecular patterns (PAMPs), mainly carbohydrate residues, can be bound by peptidoglycan recognition molecules and so invading microbes be recognized. These components of the innate immune system are highly conserved and are present in both, invertebrates and vertebrates(Janeway Jr et al., 2001).

After a parasite has successfully entered and established itself in the host, it starts exploiting the hosts' resources and thus causes irrevocable damage, often death. Why do parasites kill their hosts? Intuition suggests that parasites should evolve to be benign as long as the host is needed for survival, e.g. until transmission to the next host is accomplished. The question, why natural selection may favour virulent parasites over avirulent ones, is still unsolved and puzzles many scientists in that field. Several models were designed to deal with this problem, but experimental evidence is, as yet, scarce. Aside from an increasing academic interest, the evolution of virulence is probably the most important topic in evolutionary parasitology in the face of its medical and agricultural applications, e.g. designing better vaccines or prevent emergence of highly virulent strains.Helminth infections are typically associated with hypereosinophilia, considerable IgE production, mucous mastocytosis, and goblet cells hyperplasia. These immune parameters are involved in di erent e ector mechanisms highly depending on where the helminth is localized(Moreau & Chauvin, 2010).

Mechanisms of immunity in Hydatid disease

Hydatid disease is a chronic, cyst-forming, parasitic helminthic disease of human beings as well as domestic and wild animals. It is caused by infection with the larval (metacestode) stages of dog/fox tapeworms (cestodes) belonging to the genus Echinococcus (family Taeniidae) and is also referred to as echinococcosis. The two major species of medical and public health importance are Echinococcus granulosus and Echinococcus multilocularis, which cause cystic echinococcosis (CE) and alveolar echinococcosis (AE), respectively. Echinococcus granulosus is a parasite causing hydatidosis, an infection characterised by a prolonged course attributed to some form of immunosuppression. Recent findings have increased our knowledge concerning the parasite-evading mechanisms, making more rational future therapeutic intervention. The most recent and important finding relating to improved parasite survival is the induction of a cytokine-related Th2 response, leading susceptibility to hydatid disease. Th1 response may co-exist and relates with protective immunity. The complete investigation of immunopathology may help management, improving the efficacy of the conventional therapeutic measures(Kakkos et al., 2001).

The Echinococcus organisms, the cause of echinococcosis (hydatid disease), are parasitic helminths with lifecycles involving a carnivorous definitive host (usually dog or fox) and an intermediate host (human, ungulate, or rodent).They are complex multi cellular pathogens that, despite being under constant barrage by the immune system, are able to modulate anti parasite immune responses and persist and flourish in their mammalian hosts. Understanding how the immune system deals with these parasites is a major challenge. Recent application of modern molecular and immunological approaches has revealed insights on the nature of immune responses generated during the course of hydatid infection, although

many aspects of the Echinococcus host interplay remain unexplored. This review summarizes current understanding of the immunology of echinococcosis, indicates areas where information is lacking, and shows how knowledge of host protective immunity has been translated into the design(Zhang, Ross, & McManus, 2008).

Immunity in the intermediate host

The immunology of hydatid disease has been divided conceptually into preencystment and postencystment phases, which are differentiated by the formation of the laminated layer around the hydatid cyst. This occurs between 2 and 4 weeks postinfection in the animal intermediate or human host following ingestion of the egg and release of the oncosphere.Very little is known about the factors affecting innate susceptibility to infection with E. granulosus following ingestion of the infective egg stage and establishment of the primary cyst. Host age, sex, and physiological state may influence the innate susceptibility or resistance to infection. Furthermore, experimental infections of mice with eggs or oncospheres of E. granulosus showed that susceptibility varies with different strains of mice. It is noteworthy that although cattle are naturally susceptible to infection with E. granulosus, the resultant cysts are invariably infertile and do not produce brood capsules or PSC. In contrast, sheep cysts are generally fully fertile, with brood capsules asexually budding from the germinal layer and PSC developing from the inner wall of the brood capsules. It has been suggested that this difference may be due to parasite strain variation, but the same situation applies in cattle and sheep from the same area of endemic infection. This implies that cattle may have some natural immunity that inhibits the development and growth of PSC. In contrast, sheep appear to be highly susceptible to infection. Experimental infection of sheep with eggs showed that a high percentage (32 to 48%) of oncospheres survived and developed, suggesting that naive sheep may have only a limited resistance to primary infection(Zhang, Li, & McManus, 2003).

After infection, the earliest detectable immunoglobinG (IgG) response to hydatid cyst fluid (HCF) antigens occurs after 2 to 11 weeks in mice and sheep, respectively, and after 4 weeks in vervet monkeys. Early infections may be associated with a significant cellular inflammatory response that may cause pathologic changes since there is an increased leukocytosis, mainly of eosinophils, lymphocytes, and macrophages. With oncospheres, necrosis of surrounding cells is followed by infiltration of neutrophils and macrophages 3 to 5 days after infection in sheep. Experiments in vitro have shown also that neutrophils, in association with antibody, can bring about the killing of E. granulosus oncospheres, suggesting a possible role for antibody-dependent cell-mediated cytotoxicity reactions. At the early stages of disease, there is a marked activation of cell-mediated immunity to the parasite(Zhang et al., 2003, 2008).

In experimentally induced secondary infections in mice, intraperitoneally injected PSC are surrounded by a considerable cellular infiltration within 3 days, initially involving activated macrophages and subsequently including neutrophils, eosinophils, and lymphocytes. Interleukin-10(IL-10), IL-4, andIL-5secreted invitro by splenocytes can be detected as early as week 1 post infection. High levels of tumor necrosis factor alpha(TNF), gamma interferon (IFN), IL-6, and specific IgG1 were detectable in serum, and IgG3 was measurable in the peritoneal cavity using protoscolex somatic antigens. These data suggest that polarized Th2 reactions are evoked at the very beginning of the immune response to secondary infection. E. granulosus PSC contain immunogenic T-independent antigens. Primary antibody responses to protoscolex somatic antigens and the production of IgM and IgG3 in early infection appear to be stimulated mainly by a T-independent mechanism(Tamarozzi, Mariconti, Neumayr, & Brunetti, 2016).

Similar to E. granulosus, differences in susceptibility to E. multilocularis have been shown in both primary and secondary infection of different mouse strains. Susceptibility and

resistance are based on the activation of different CD4 T-cell immune responses. Experiments with mice infected with eggs showed that IFN-gamma-, IL-2-, and IL-4-expressing cells in the parasitic lesions were not detectable at the early phase of the infection but were present at the end. Similarly, low levels of cytokines in the sera were measurable at the beginning of the infection and high levels were detectable subsequently. IL-10 was the most prominent cytokine measurable throughout the course of the infection. Correspondingly, only small amounts of IgM, IgG1, IgG2a, and IgG3 could be detected early on, and higher levels were detectable later. A strong, specific intestinal immune response was found in the early stage. Both subsets of CD4 Tcells(Th1andTh2)areinvolvedinprimarymurine alveolar echinococcosis(Tamarozzi et al., 2016).

Inhibition of Cyst Growth; It is generally accepted that Echinoccocus is unaffected by the immune response during the developing stage. However, natural infections in sheep indicate that some cysts can be killed during the latter stages of development, with the relatively frequent occurrence of dead, calcified metacestodes or necrotic cysts. These are due to the primary cyst having degenerated, leaving the cavity full of host leukocytes and protoscolex-derived daughter cysts. There is no direct evidence that the death of such cysts is due to an immunological phenomenon, but it is a likely possibility. If a progression in cyst degeneration does take place, then the immune response may play a role in the death of the parasite. This may signify increased immunological stimulation with cyst progression. Unfortunately, there are no detailed studies of immunological events associated with the degeneration of different types of cyst, and it is therefore unknown which mechanisms may be involved. This is clearly an area for future study. One aspect that is likely to be important is the influence of CD4. The lymphocytes on the control of such immunological mechanisms. In addition, IFN- and nitric oxide production may play a role. Complement through C5-mediated effectors contributes to host defenses by both restricting the establishment of infection and controlling the growth of established cysts. This contribution may be associated with the ability of C5a to promote eosinophil infiltration. Lysis in both immune and normal serum is antibody dependent and complement mediated. Protoscoleces of E. multilocularis and E. granulosus are lysed by fresh serum of many different species of mammals. The presence of Echinococcus cysts appears to deplete host complement. The rapid development of E. multilocularis infection is associated with depletion of serum complement; the use of cobra venom factor to deplete complement results in faster growth of E. multilocularis cyst masses. In hydatid infections, IL-6 seems to be produced nonspecifically whereas IL-5 production appears antigen specific. The effect of IL-5 on human B cells is controversial, but a significant correlation between IL-5 production and IgE and IgG4 expression has been found in hydatid disease patients. When CE cysts grow, IgG1 andIgG4 levels are elevated, whereas the concentrations of specific IgG1 and IgG4 decline(Zhang et al., 2003).

Immunity in the definitive hosts

Immune reactions of canid definitive hosts to Echinococcus infections have been comprehensively reviewed. There is now quite an extensive literature, but until the 1980s, little research had been performed on immune responses to Echinococcus and other taeniid cestodes in their definitivehosts. This may be because the adult worms, being parasites of the gut lumen, were thought unlikely to evoke systemic immune responses and also because of the lack of knowledge of host-protective immune responses to reinfection with taeniid cestodes at the time. Mucosal immunity in animals is now recognized as an important phenomenon. In sheep, clearance of the parasitic nematodes Trichostrongylus colubriforms and Haemonchus contortus is associated with the sensitization of mucosal mast cells (MMC), measured by the release of sheep mast cell protease and the number of globular leukocytes, which are possibly degranulated by MMC. These cell types are more numerous in the regions of the gastrointestinal tract where these parasites reside.

An increase in the level of immune mediators, sheep mast cell protease larval migration inhibition components, and peptidyl leukotriene is correlated with the clearing of T. colubriforms infection and a reduction in fecal egg counts. The secretion of leukotrienes and larval migration inhibition from MMC is thought to be a major mechanism of parasite removal. IgA and IgE are important in mucosal immunity since they bind directly to antigens and also attract effector cells that bind the constant region of the antibody. Eosinophils and MMC bind immunoglobulin constant regions via Fc receptors, becoming activated to degranulate when bound to the opsonized parasite. This method of antibody-dependent cell mediated cytotoxicity is well established as an important mechanism by which the host can damage a multicellular parasite. As reviewed by Heath, the scolex of adult Echinococcus worms is normally in close contact with the canine intestinal submucosa, but mucosal immune responses, leading to the production of neutralizing IgA antibodies to deal with the secretions of the strobila, have no effect on the scolex. The scolex is in intimate contact with the systemic circulation, even in the Peyer's patches, and it appears to maintain its privileged integrity by suppression of cytotoxic and effector cell activity in the region of the scolex(Baron, 1996; Parvathi & Karemungikar, 2011; Tamarozzi et al., 2016; Works, 2003; Zhang et al., 2003, 2008; Zhang & McManus, 2006).

Experiments with immunosuppressed golden hamsters subsequently infected with E. multilocularis showed that worms developed faster than in normal animals. In addition, dogs that were immunosuppressed and then challenged with PSC of E. granulosus were shown to harbor more worms than did non treated dogs, suggesting that the definitive host may have some innate resistance to infection by adult worms. Cells from Peyer's patches of dogs infected with E. granulosus produce specific immunoglobulin in vitro. Infection depresses the ability of unstimulated cells to proliferate in response to HCF protein but enhances the response to ConA. Dogs with enhanced reactivity to ConA and another mitogen, phytohemagglutinin, have significantly fewer worms and a lower number of mature worms than do dogs with less reactivity. After infection, the concentrations of IgG and IgA increased in serum and IgA levels increased in feces. Dogs with high-titer anti-HCF antigen serum antibodies were better protected than were dogs with low titers in serum(Zhang et al., 2003).

Immunology/host defense against adult echnococosis

Host defense against Echinococcus granulosus

The migrating and growing larvae, and antigens that leak from the cyst, induce a strong immune response—but rarely one capable of penetrating and destroying the cyst. Ruptured cysts may cause anaphylaxis and the appearance of new cysts in other sites, suggesting an active but ineffectual immune response(Baron, 1996).

Innate immunity**;** the factors involved in innate susceptibility/resistance (s/r) to *Echinococcus* infections are largely unknown. Different strains of mice infected with eggs, hatched eggs, or activated oncospheres of *E. granulosus* showed differences in s/r. Cotton rats (*Sigmodon hispidus*) treated with nonspecific Ags such as bacillus Calmette-Guérin (BCG), BCG cell walls, or phytohemagglutinin were protected against inoculated proliferating *E. multilocularis* metacestodes, indicating that protection against echinococcosis can be induced nonspecifically, with protection correlating with increased numbers of monocytes and macrophages. Congenic C5-sufficient mice were shown more resistant to *E. granulosus*infection than C5-deficient mice, suggesting that the alternative complement pathway contributes to s/r. There is significant evidence showing that infiltration of neutrophils and macrophages occurs during the early phases of *E. granulosus* and *E. multilocularis* infection followed by leukocytosis, resulting in an increased number of myeloid such as eosinophils, lymphocytes, and macrophages. Pronounced pathologic changes then follow. It is noteworthy that eosinophils have been implicated as potent effector cells in innate immunity against the infective larval stages, but not adults, of most

helminth parasites, including *E. granulosus*(Zhang et al., 2003).

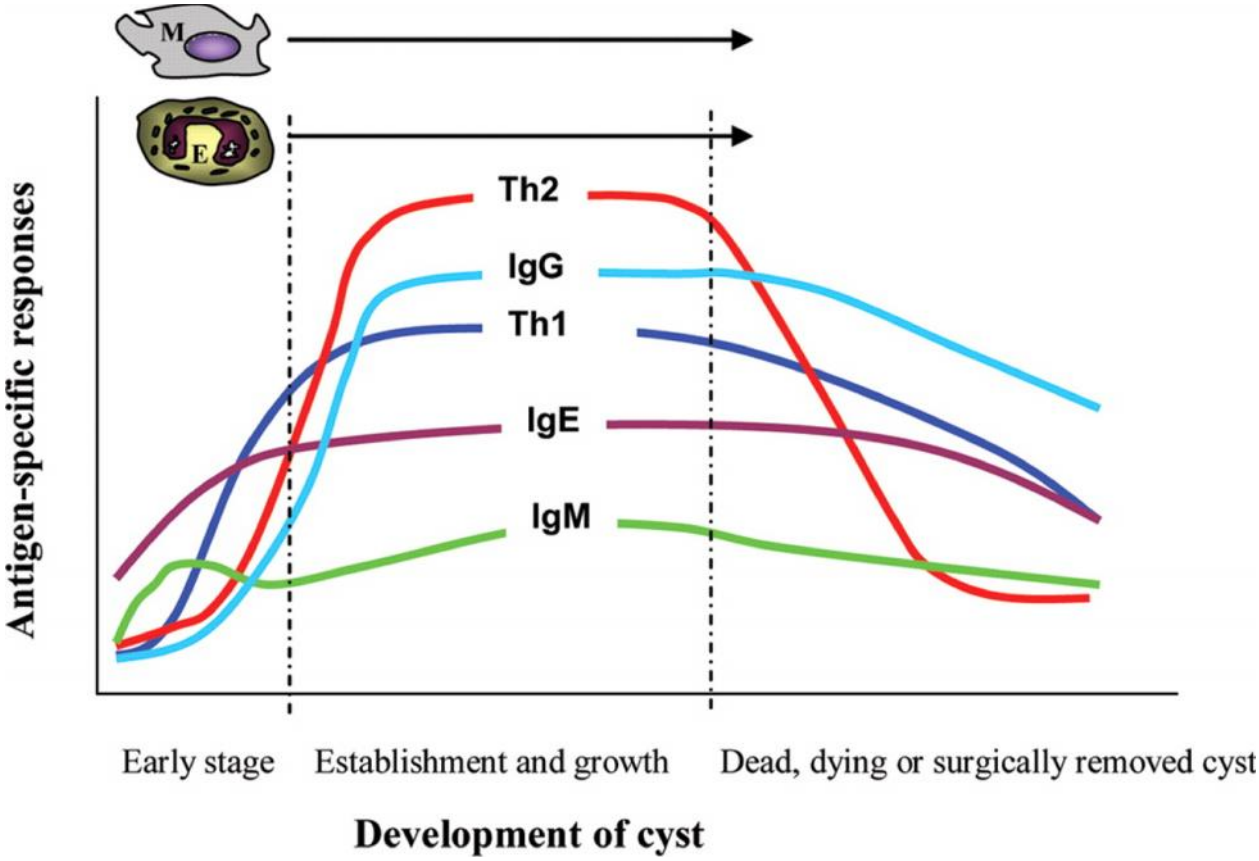

Figure 1.

Immune responses during the development of a hydatid cyst of *E. granulosus* in the intermediate host. In the early stage of infection the oncosphere is transported to a host organ such as the liver or lung, where it develops into a hydatid cyst. The immature cyst has to overcome host, mainly cell-mediated, immune responses, especially the infiltration of macrophages and eosinophils and low level polarized Th1 responses. About 8- to 10-wk post infection in mice, cyst growth is maintained and complex echinococcal Ags are released from the cyst. These Ags stimulate complex immune responses. These include polarized Th2 responses balanced with Th1 responses. At this time, the parasite produces significant quantities of Ags that help to modulate the immune response, which may benefit both host and parasite; IgG, especially IgG1, and IgG4, IgE, and IgM levels are elevated. When the cyst is dead, dying, or surgically removed, the Th2 responses drop rapidly whereas the Th1 responses drop slowly, then becoming polarized. IgG can be maintained in the human host for many years after the cyst is surgically removed. Once an infected patient has relapsed, the Th2 responses recover very quickly whereas other responses are elevated slowly. M, Macrophage; E, eosinophil.

In chronic stage CE, as well as neutrophils and macrophages, there is cellular infiltration of eosinophils and fibrocytes into the outer adventitial layer of human hydatid cysts, leading to fibrosis/necrosis and bile duct and vessel obstruction. Eosinophils degranulate at the host-*Echinococcus* interface, and eosinophil cationic protein, a major component of eosinophil granules, reaches levels in hydatid cyst fluid harmful to the parasite. There have been few studies that have investigated NK cells in *Echinococcus* infection, although these cells

are known to be instrumental in innate immune responses against intracellular pathogens including viruses, bacteria, and protozoa. Patients with active CE cysts were shown to have proportionally more NK cells ($CD56^{+}CD8^{-}$) in their PBMC than controls , but no functional studies or in situ analysis of the cells at the periphery of the cysts were undertaken, so their role in the outcome of hydatid disease was not determined. In contrast, patients with AE infection had a lower level of PBMC NK activity than healthy controls and subjects with nonparasitic biliary disease; this could be due to a lower percentage of NK cells circulating in the blood of the AE patients or to the presence of serum inhibitory factors such as immune complexes or Abs. It has been hypothesized that in AE the MHC class I chain-related molecules A and B (MICA/B), induced by *E. multilocularis*, skew the NKG2D activation pathway on NK and CD8 T cells, inhibiting NKG2D-dependent cytotoxicity and thereby contributing to the longevity of the parasite.A regulatory role for IL-12 in innate resistance in intermediate hosts against *Echinococcus* infection has been suggested. Mice injected with an expression vector encoding IL-12 or treated with rIL-12 were protected against secondary CE and AE, respectively, and this was accompanied by a Th1 response. TLR is believed to play a key role in the innate immune system, but there is limited information on its involvement in innate resistance against *Echinococcus* infection. As is discussed later, *E. granulosus* Ags can modulate the maturation of dendritic cells (DC) via TLR thereby limiting antiparasite immune responses(Tamarozzi et al., 2016; Works, 2003; Zhang & McManus, 2006).

Adaptive immunity; Although the data are limited, there is, nevertheless, clear evidence from experiments with animals challenged with *E. granulosus/E. multilocularis* eggs or oncospheres that infected hosts produce significant immune responses, including Ab and T cell responses generated by lymphocytes. Understanding the mechanisms whereby these immune responses are produced, particularly the role of protective Abs against the oncosphere, has been of fundamental importance in developing highly effective recombinant vaccines against both *E. granulosus* and *E. multilocularis.* Antibody response; The earliest IgG response to hydatid cyst fluid and oncospheral Ags appears after 2 and 11 wk, respectively, in mice and sheep challenged with eggs or oncospheres of *E. granulosus*. As will be described below, these anti-oncospheral Abs play a major role in parasite killing and are central to the protective immune response against *E. granulosus* and *E. multilocularis*. In the chronic phase of CE, elevated levels of Ab, particularly IgG, IgM, and IgE, occur in humans, with IgG1 and IgG4 being predominant. Ab responses to protoscolex Ags are relatively weak and delayed in the early stage of *E. multilocularis* infection in mice but are increased later; IgG1 and IgG3 levels increase significantly at 8 wk postchallenge and remain elevated thereafter. T cell responses**;** Early Th1-polarized cytokine production, which can kill the metacestode at the initial stages of development , shifts to a predominant Th2 cytokine response in the later chronic stage and is characteristic of *E. granulosus* and *E. multilocularis* infection. Very little is known of cytokine production in the early phases of a primary (oral challenge with eggs) *E. granulosus* infection, although both Th1 and Th2 cytokine levels are low in the early stages of a primary *E. multilocularis* infection but are raised subsequently. As well, it is thought the Th2 cytokines are responsible for inhibition of parasite killing because of the anti-inflammatory action of IL-10*(Zhang et al., 2003).*

Host defense against Echinococcus multilocularis

Echinococcus multilocularis, which normally follows a fox-rodent cycle in northern Siberia and North America, is occasionally conveyed to human fur trappers via fox pelts. In humans it causes a frequently fatal form of echinococcosis. The appearance and life cycle of this cestode closely resemble those of *E granulosus*, except for the restricted range and small number of hosts. The cyst, however, is extremely dangerous as it lacks the laminated membrane that confines the cyst of *E granulosus*, and develops an invasive,

uncontrolled series of connected chambers (hence the designation “multiloculate” and the alternative name *alveolar hydatid*). It therefore resembles a malignant growth, capable of budding off to cause metastatic spread. The primary cyst usually forms in the liver. The disease is usually diagnosed late, when it is inoperable, and ends fatally. Early radiologic imaging by US, CT, or MR is essential. Serological tests, particularly with purified *E multilocularis* antigens, are sensitive and highly specific. Treatment with mebendazole, albendazole, or praziquantel, and surgery should follow(Baron, 1996).

Host immune defense against cysticercosis

Cysticercosis involves a complex host-parasite relationship in which the participation of the immune response may be decisive; the disease constitutes a serious threat to human health in underdeveloped countries. It is also a major problem in the production of meat and thus affects the food industry. It is generally observed with Taenia that exposure of the host to different forms of the parasite's antigens induces resistance to subsequent challenge, although the degree of resistance may vary. The main findings in the different species studied are presented briefly in the following paragraphs. In a study of the pig's immune response to infection with eggs of Taenia solium , it was observed that the animals that received a single dose of eggs had more cysticerci than those that received two doses, indicating that larger doses gave better immunity. Protection of cattle against Cysticercus bovis has been attempted in many ways, using as vaccine: live or irradiated embryos, viable or irradiated eggs, secretions and excretions of cysticerci, or whole cysticerci. In most cases, exposure to the antigens reduced somewhat the number of cysticerci found after challenge. In some experiments, when the vaccine consisted of live or irradiated embryos implanted intramuscularly, there was considerable reduction in the number of cysticerci that established after challenge, but usually the effects of vaccination have been very variable. When live embryos have been used as vaccine they usually developed into cysticerci and survived apparently well at the inoculation site, even in those animals that showed resistance to subsequent challenge with eggs. The route and the frequency of administration of vaccine seem to be important: the intramuscular route proved to be more effective than the subcutaneous one for embryos as well as for eggs, while repeated injections were more efficient than a single one. Some authors favour the concept that cattle acquire natural immunity to cysticercosis, based on the fact that younger cows, especially those not exposed to natural infections are more susceptible to challenge with T. saginata than older ones(Flisser, Pérez-Montfort, & Larralde, 1979).

The human neurocysticercosis (NC) is caused by the presence of the larval form of Taenia solium in the central nervous system, after the consumption of water or food contaminated with parasite eggs. The prevalence of NC is related to socioeconomic and cultural factors, representing an important public health problem in countries with deficient sanitary conditions, and in industrialized countries receiving immigrants from epidemic areas. The disease is one of the most severe parasite infections affecting the central nervous system, with complex biological parasite-host interactions due to the occurrence of different parasite antigens in different stages of evolution, and individual genetic variations interfering with the host response, impairing the understanding of the dynamics of parasite survival and host defense mechanisms(Flisser et al., 1979).

Because of its limited contact with the epithelial lining, the gut-dwelling adult tapeworm induces little host inflammatory, allergic, cell-mediated, or humoral response. The sucking action of the scolex appears to have relatively limited immunogenic effect. The long life span of the worm suggests the absence of an effective inhibitory mechanism(Baron, 1996).

Owing to the systemic migration and tissue localization of the cysticerci, cysticercosis elicits considerable host sensitization. This response is usually insufficient to block the initial infection but probably renders the normal host immune to a subsequent one. Much of the damage from

cysticercosis is caused by the severe inflammatory host response that occurs after the death and disruption of the parasite(Terrazas, Satoskar, & Morales-montor, 2010)

The adult worm of *Taenia multiceps* is found in dogs or wild canids. The larva is a bladder worm with multiple scoleces—from a few to 100 or more—in an encysted vesicle. This vesicle, usually 2 - 5 cm in diameter, is called a coenurus. The usual intermediate host is the sheep. Human infection can occur from accidental ingestion of dog feces containing the eggs. Infection in humans usually occurs in the brain in temperate areas, and in the eye or subcutaneous tissues in tropical areas. Diagnosis and treatment are similar to those for *Echinococcus* infection, which may be difficult to distinguish from coenurus infection. Treatment is chiefly surgical, although the drugs used for cysticercosis may also be effective against coenurus infection(Baron, 1996).

Host immune defense against Dipylidium infection

D. caninum, the double-pored tapeworm, is present in dogs and cats. Fleas are the intermediate host. Ingestion of an infected flea, usually by a young child, causes an asymptomatic, self-limited infection, but proglottids (tapeworm segments) may be seen in stool. *Dipylidium caninum* causes a cosmopolitan infection of dogs and cats. Fleas are the intermediate hosts in which the infective cysticercoids develop. Children in close and continuous contact with pets are occasionally infected as a result of the accidental ingestion of an infected flea. The infection is usually asymptomatic and is self-limited, although praziquantel would probably be an effective treatment. Flea control of pets would largely eliminate the infection from household pets and children(John, Petri, Markell, & Voge, 2006).

Infection with this tapeworm usually produces no pathology, although the minor symptoms are occasionally present. Megaloblastic anemia (“tapeworm anemia”), which is exacerbated by the worm's uptake of vitamin B12, is now seldom seen, as a result of improved diet, prenatal care, and ready treatment. This condition was formerly most common in Finland. Little or no protective immunity develops, owing to the lack of an intimate tissue phase in the human host. Reinfection is common(Baron, 1996).

Immune defense against Hymenolepis infection

Little or no pathology occurs from development of cysticercoids in the villi, and only after a heavy infection (perhaps produced by auto reinfection) do symptoms develop from the adult worms. Children may be particularly subject to massive worm loads and show the most severe intestinal symptoms. The tissue phase of the direct cycle of *H nana* infection and initiates a profound cellular and humoral response, rendering most hosts immune to subsequent infection (as demonstrated experimentally in rodents). In contrast, the indirect cycle through infected insects does not involve mucosal embryogenesis in humans and induces little or no immunity, even permitting occasional massive internal reinfection to occur. The immune response is seldom effective against the initial infection because the tissues have already been invaded and a protective cyst formed by the time the response develops(Baron, 1996). Lymphocytes, the immunocompetent cells, are responsible for the immune response of the host. Increase in the lymphocyte count, Lymphocytosis, reflects the host's immune response to overcome parasitic stress, after the phagocytic neutrophils failed in checking the invading parasites. Here is also an increase in the eosinophil count in infected host blood. Eosinophilia is a hallmark of helminthiasis. There is also an increase in the eosinophil count in infected host blood. The increase in monocytes, Monocytosis, too, is an immunological response of the infected host to combat hymenolepiasis(Parvathi & Karemungikar, 2011).

The rat tapeworm, which is larger than *H nana* (up to 40 cm long), has a life cycle involving grain insects, similar to the indirect cycle of *H nana*. *H diminuta* rarely infects humans, but may do so if a human eats an insect

carrying cysticercoids of this worm. The infection is most common in children, causes a mild diarrhea, is diagnosed by finding the characteristic eggs in the stool, and is readily treated with praziquantel(Baron, 1996).

Conclusive remarks

The immune system is a network of cells, tissues, and organs that work together to defend the body against attacks by "foreign" invaders. These are primarily microbes (germs)—tiny, infection-causing organisms such as bacteria, viruses, parasites, and fungi. Because the host body provides an ideal environment for many microbes, they try to break in. It is the immune system's job to keep them out or, failing that, to seek out and destroy them.Cestodes are multicellular organisms which can colonize almost any tissue in their hosts. Given the big size they can reach, the immune response against these infections is very complex. Worms infect millions of people and animal worldwide, and they can go since ino ensive until highly dangerous and, in some cases, threatening for humans and animals. As many pathogens is highly immunogenic for human and animal host. Thus, the host immunity play a most important role in host-parasite relationship in ehinococcosis and cysticercosis. The secretory and excretory products from parasite influences immune and immune competent cells in host and stimulate humoral and proinflammatory cell-mediated immune responses, releasing of significant antibody production, and activate T cells and other antigen presenting cells in host. The understanding of the immune mechanisms is of fundamental importance for revealing of a basic protective process for cestode infection. No doubt that protective antibody is also extremely important for development of a new more effective vaccine against Echnococcosis, cystcercosis and other parasites. Furthermore, knowledge of immune events as a response to infection with a helminth parasite could be used to reduce the intensity of undesired immune and autoimmune reactions such as a variety of auto-inflammatory diseases and allergy.

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DOI:10.22192/ijamr.2023.10.12.002	

How to cite this article:
Yacob Hailu Tolossa and Berhane Wakjira. (2023). Review on immune response against Cestode infections. Int. J. Adv. Multidiscip. Res. 10(12): 16-28.
DOI: http://dx.doi.org/10.22192/ijamr.2023.10.12.002