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2.1 Parasites

In this chapter, I will explore the advances made in understanding the molecular pathogenesis and basic immunological principles of the most common protozoan and metazoan organisms that affect the lungs. Needless to say, these eukaryotic organisms are far more complex genetically than their bacterial and viral counterparts. Genome sizes range from 7,000 to 20,000 protein-encoding genes [1]. During the past 10 years, genome sequences of helminthes and protozoans have been completed or are underway. To date more than 1,000,000 ESTs (expressed sequence tags) are available at GenBank (excluding *Caenorhabditis elegans*) [2]. This level of complexity is needed in order to survive through multiple stages of development that occur in intermediate and definitive hosts. As a rule, most parasitic diseases lead to chronicity, suggesting that the host-parasite relationship enters a level of “tolerance” that we are beginning to understand at the molecular level through a complex interaction between parasite-derived immunomodulatory products and the host immune response.

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2.2 Principles of Parasitic Molecular Pathogenesis

The term pathogenesis encompasses several steps including transmission, entry, initial spread from point of entry to other organs, contact with target cell/organ, survival within the host (immune evasion and adaptation to the host environment), and extension of the niche (multiplication, survival, and modulation of host biology).

Mechanisms of transmission and entry of pulmonary parasites are as diverse as the parasites capable of causing pulmonary disease (see mode of transmission under each pathogen heading). Most of the discussion in this section will focus on the interaction between the parasite and the host, with special emphasis on the immune response as a pathogenetic mechanism in some of these infections.

Human parasitic infections range from asymptomatic carriers to lethal infections. This variability is determined by several factors including host response, virulence factors, and infectious dose. From the immunological point of view, responses to parasites follow the usual Th1 and Th2 types [3]. Th1 responses are associated with the activation of cells by IFN- γ (gamma) and IL-2, induction of cytolytic CD8+ T-cells, and production of complement-fixing antibodies. Th1 responses are very useful when the host is battling an intracellular infectious agent [4]. Th2 responses are driven by IL-4,

IL-5, IL-10, and IL-13 and are characterized by high levels of neutralizing antibodies and cell-bound antibodies, activation of mast cells, and eosinophils. Th2 responses are most useful for extracellular organisms. Both responses can become detrimental to the host if unchecked due to side effects produced by their effectors such as NO, ROS, and TNF- α (alpha) in Th1 responses and formation of immune complexes, complement activation, and hypersensitivity reactions in strong Th2 responses. As a rule, the host tries to strike a balance between these two responses. Inhibitors of the Th1 response include IL-10, TGF- β (beta), and IL-4; the Th2 response is mostly controlled by IFN- γ (gamma), IL-12, and IL-10. Experimental rodent models have shown that IL-10-deficient mice have increased mortality with normally avirulent *Toxoplasma gondii* (an intracellular protozoan) due mostly to overproduction of IFN- γ (gamma), TNF- α , and IL-12 [5–7]. At the same time, *T. gondii* levels in these animals were lower than their control counterparts. On the other hand, Th2 responses can also be beneficial and detrimental. It has been widely believed that *Schistosoma* spp. cause disease due to the granulomatous response to egg deposition in tissues, especially in the mesenteric circulation and liver leading to scarring and subsequent portal hypertension. In these cases, the host develops a strong Th2 response driven mostly by IL-4 leading to granuloma formation around the eggs. However, in animal models where the IL-4 response is nonexistent, and therefore granuloma formation is markedly impaired, the host succumbs to acute infection rapidly, for the most part due to the deleterious effects of a sustained proinflammatory cytokine response [8–10]. Even though these animal models illustrate the protective role of the Th2 response during the early phases of the infection, the sequelae in the liver during chronic infections, namely, hepatic fibrosis, seem to be driven by IL-13, a potent fibrogenic Th2 cytokine [11]. It appears then that in these animal models, polarized Th1 and Th2 responses are detrimental to the host, whereas a balanced Th1/Th2 response is necessary for the control of egg-induced immunopathology [10, 12].

2.2.1 Innate Immunity to Parasitic Infections

The traditional view of innate immunity playing a small role in parasitic infections has changed in recent years. Innate immunity plays a very important role in determining the class of the adaptive immune response, be it Th1 or Th2 dominated. Innate immunity operates through both humoral and cellular mechanisms. One of the best-studied humoral mechanisms is the activation of the complement cascade through the alternative pathway (parasite membrane components) or lectins present on the parasite surface. Activation of the classical pathway requires parasite Ag/Ab complexes and therefore occurs when adaptive immunity is already active and production of antibodies is underway. Parasites have developed different strategies present at certain developmental stages that prevent killing by the activated complement cascade and include expression of parasite-derived regulatory proteins (gp160 or gp63) or acquisition of regulatory proteins from the host on the parasite surface such as decay accelerating factor (DAF) and factors H and I which inhibit formation of the membrane attack complex (MAC) by acting on C3b [13]. The glycoprotein gp160 present in trypomastigotes of *Trypanosoma cruzi* is homologous to DAF and therefore binds to C3b or C4b, inhibiting the downstream members of the cascade. On the other hand, gp63 present on *Leishmania* spp. can cleave C3b to its inactive form, iC3b, and prevent deposition of the C5b-C9 attack complex [13]. Other examples include the cleavage of C3 by a cysteine proteinase from *Entamoeba histolytica* that leads to complement activation via the alternative pathway, but it also inactivates C3a and C5a, preventing immunoregulatory and chemotactic functions of these two molecules [14]. Amebas and certain helminths like *Echinococcus granulosus* can also acquire host regulatory proteins on their surface [14, 15]. Larvae and adults of *S. mansoni* can also express DAF on their tegumental surfaces [15].

Examples of evasion of innate cellular mechanisms include the ability of *Leishmania* spp. to survive in the macrophage after phagocytosis due

to internalization via complement receptors CR1 and CR3, which fails to trigger the respiratory burst [16]. *T. cruzi* escapes the phagosome by expressing a C9 homolog that disrupts the phagosomal membrane [17]. *T. gondii* prevents acidification of the parasitophorous vacuole [18]. The host at the same time responds to intracellular pathogens by producing IL-12, which activates NK cells and macrophages to control the intracellular pathogen. IL-12 is produced by several cells including macrophages, dendritic cells, and neutrophils. The most studied molecule in protozoans that is thought to be responsible for the production of proinflammatory cytokines is the lipid molecule known as glycosylphosphatidylinositol (GPI) [19, 20]. On the other hand, LPG and GPIs of *Leishmania* spp. have been shown to downregulate production of IL-12 and TNF-R, therefore favoring the parasite in its initial interaction with the host [21, 22].

NK cells seem to play a very important role in the initial response to parasitic infections. The early production of IFN- γ by these cells seems to prevent the parasite from rapid proliferation in the host [23]. Ultimately, adaptive immunity takes over, and T-cells are the main players in controlling intracellular protozoan infections.

Regarding helminths, innate humoral mechanisms are associated with resistance to such infections. T-cell-dependent mast cell responses play a role in infections caused by nematodes. Eosinophils are also important in resistance to helminthic infections during their larval stages, which requires IL-5 production by T-cells and opsonization (antibody production). Other components of the innate immune response that have been shown to play a role in protection against parasites include B1 cells (B-cells that express the CD5 molecule and are mostly present in body cavities) and γ (gamma) δ (delta)-T-cells which seem to play an important role in epithelial mucosal barriers [23].

2.2.2 Adaptive Immune Response

The ultimate effector mechanisms that control parasitic infections depend largely, like with

any other infectious agents, on location within the host (organ and intracellular versus extracellular), life cycle stages within the host, and evasion strategies of the parasite. IL-12 plays a critical role in starting protective immune responses against intracellular parasites. IL-12 upregulates production of IFN- γ and therefore favors Th1 responses [24]. The main sources of IL-12 are macrophages and dendritic cells which secrete IL-12 after ingestion of whole parasites or parasite products. Other sources include T-cells through ligation of CD40 by CD40 ligand and ligation of CCR5 on dendritic cells by MIP1a and MIP1b ligands [4, 25, 26]. Killing of parasites present in macrophages is achieved mostly through activation of these cells by IFN- γ (gamma) and TNF- α (alpha). Activated macrophages then produce both reactive oxygen intermediates (ROI) and reactive nitrogen intermediates (RNI). In protozoan infections that target other cells different than macrophages, the immune system has to eliminate the parasites from non-phagocytic cells. CD8+ T-cells seem to play a critical role in this situation since they recognize antigen in the context of MHC class I molecules which are expressed by all cells in the body. In these cases, CD8+ T-cells aid macrophages by producing IFN- γ (gamma) [4]. Humoral immunity also has the potential of playing a role in infections produced by intracellular parasites. Antibodies act in different ways by lysing the pathogen directly, playing a role in opsonization, promoting antibody-dependent cell-mediated cytotoxicity, and blocking invasion [4].

Th2 responses are important in infections produced by intestinal nematodes. Studies rely on animal models, especially rodents, and have revealed that the two most important cytokines are IL-4 and IL-13 in the process of expulsion of intestinal nematodes from the host [27]. Recently, IL-9 has been implicated and seems to play also an important role in the expulsion process [27]. However, the effector mechanisms responsible for the parasite clearance are not clear. The role of eosinophils and antibodies seems nil or absent. In some animal models of helminth infection, mast cells present in the intestinal mucosa may

play an important effector role in clearance of intestinal nematodes by production of specific proteases [28]. Other studies have suggested the role of subtle chemical changes in goblet cells in the intestinal mucosa making the microenvironment for worm survival less amenable [28]. Another important observation is the effect of type 1 responses. Both IL-12 and IL-18 suppress or downregulate the type 2 response leading to delayed expulsion of intestinal nematodes. Most certainly, other factors are in play such as host nutrition. Gut nematodes can also produce immunomodulatory molecules that would tip the balance towards a type 1 response by an IFN- γ (gamma) mimic in *Trichuris muris* infections [29]. Other observations have implicated the size of the initial inoculum as an important determinant of susceptibility or resistance. In cases where the host is infected by a low-level inoculum, susceptibility develops, whereas a large inoculum is associated with a very strong type 2 response followed by expulsion from the host [4].

After successful entry into a host, bacterial and viral infections are usually followed by rapid replication that leads to tissue damage and therefore disease. The outcome is either recovery if the immune system is able to control the infectious burden or the host's demise if the bacterial/viral burden is overwhelming to the host. In some cases, chronic infections arise, in which the host tolerates a certain amount of infectious burden. For parasitic infections, most of these principles apply to protozoan pathogens. In humans, many protozoan infections are followed by a rapid expansion of the infectious agent within the host followed by chronic infection. Chronicity is due to either antigenic variation or the parasite becoming quiescent or dormant. In helminthic infections, expansion of the initial infectious burden is much more complex due to the life cycle of most helminths. For most helminths, adults mate and try to produce eggs or larvae capable of infecting new hosts. In most cases of human infection, these stages are the ones responsible for the pathology observed in human hosts.

An interesting working model for the understanding of immunity in parasitic infections has

been proposed [30–32]. The model proposes a 2D immunological map with an inflammatory-regulatory axis and a type 1 and type 2 axis. Four quadrants would result with four possible immune profiles: type 1 inflammatory (autoimmunity and acute bacterial infections), type 1 regulatory (chronic protozoan and mycobacterial infections), type 2 inflammatory (chronic allergies and fibrosis), and type 2 regulatory (helminth infections). The central elements of type 1 and type 2 inflammatory and regulatory responses are Th1, Th2, Th17, and Treg cells, respectively. Each of these cells is driven by signals from the innate branch of the immune system, and they recruit a characteristic set of effector cells (PMNs, alternatively activated macrophages, eosinophils, mast cells, and basophils). Furthermore, Th1, Th2, and Th17 negatively regulate each other, and Treg cells suppress all the other three subsets.

Another level of control of the immune response during protozoan and helminth infections exists in the form of negative costimulators such as cytotoxic T-lymphocyte antigen 4 (CTLA-4 also known as CD152), programmed death-1 (PD-1 or CD279), and B- and T-lymphocyte attenuator (BTLA or CD272). Blockade of these substances would lead to an enhanced immune response and decreased parasitemia, but potential immunopathology in tissues is affected. On the other hand, activation of the negative costimulatory pathways would lead to a decreased immune response, increased parasitemia, and decreased immunopathology [33].

2.2.3 Parasitic Proteases and Their Role in Pathogenesis

A common theme in protozoan and helminthic infections is the presence of proteases which play an important role in virulence and pathogenesis (Tables 2.1 and 2.2). Their roles have been described in establishing, maintaining, and expanding or exacerbating infections [34–36]. Larval stages of several helminth nematodes directly invade the human host through the skin (*Schistosoma*, *Strongyloides*, and *Ancylostoma*)

Table 2.1 Summary of representative parasitic proteases, protease inhibitors, and immunomodulators identified in protozoan pulmonary pathogens

Protease	Parasite	Mechanism(s) of action
EhCP1	<i>E. histolytica</i>	Inflammatory dysregulation
EhCP2	<i>E. histolytica</i>	Cytotoxic. Disruption of intestinal epithelium Enhancement of chemokine activity (CXCL8)
EhCP5	<i>E. histolytica</i>	Enhancement of cytokine activity (IL-1 β) Inactivation of IL-18 Caspase 3 activator (apoptotic signal)
Toxopain 1	<i>T. gondii</i>	Cysteine protease. Rhoptry biogenesis, protein processing
TgSUB1	<i>T. gondii</i>	Serine protease. Host cell invasion
Microneme processing proteases (TgMPP1-3)	<i>T. gondii</i>	Host cell invasion
Toxomepsin II	<i>T. gondii</i>	Aspartyl protease. Host cell invasion
ROP16 (rhoptry kinase)	<i>T. gondii</i>	Down-modulation of IL-12
Microneme protein protease 1 (MPP1)	<i>T. gondii</i>	Host cell invasion
Formin/profilin (TgPRF)	<i>T. gondii</i>	Host cell invasion, gliding motility, and exocytosis
Myosin motors and associated proteins (TgMyoA, TgGAP45, and TgGAP50)	<i>T. gondii</i>	Parasite motility and invasion
TgMIC1/MIC4/MIC6	<i>T. gondii</i>	Attachment, internalization
CAD98424	<i>C. parvum</i>	Aspartyl protease. Host cell invasion

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Table 2.2 Summary of representative parasitic proteases and protease inhibitors identified in helminth pulmonary pathogens

Protease	Parasite	Mechanism(s) of action
Elastase-like serine proteases	<i>S. mansoni</i>	Immunoglobulin degradation
900 kDa glycoprotein ECF-SjE	<i>S. japonicum</i>	Eosinophil chemotaxis
440 kDa JAE-H/JAE-L glycoproteins	<i>S. japonicum</i>	Eosinophil and neutrophil chemotaxis
Surface glycans	<i>S. mansoni</i>	Decreased phagocytosis
Schistosome secreted proteins alpha-1 and omega-1	<i>Schistosoma</i> spp.	IL-4 release, basophil degranulation. Favorable Th2 environment
Phosphatidylserine (PS)	<i>Schistosoma</i> spp.	DC polarization (IL-4, IL-10 production)
Lyso-phosphatidylserine (lyso-PS)	<i>Schistosoma</i> spp.	Increased IL-10 production from Treg cells
Onchocystatin	<i>O. volvulus</i>	Inhibition of host cysteine proteases Decreased antigen presentation by APCs and T-cell hyporeactivity Cuticle molting
Bm-CPI-1	<i>B. malayi</i>	Inhibition of host cysteine proteases. Unknown
Bm-CPI-2	<i>B. malayi</i>	Inhibition of host cysteine proteases (cathepsins L, S, AM) T-cell hyporeactivity via altered MHC antigen presentation
Bm-SPN-1	<i>B. malayi</i>	Inhibition of host serine proteases. Regulation of proteolysis
Bm-SPN-2	<i>B. malayi</i>	Unknown
SMpi56	<i>S. mansoni</i>	Inhibition of host serine proteases Possible inhibition of coagulation cascade and complement activation Inhibition of host neutrophil elastase

(continued)

Table 2.2 (continued)

Protease	Parasite	Mechanism(s) of action
MIF homologue	<i>B. malayi</i>	Synergy with IL-4 to increase alternatively activated macrophages (AAMs)
SHSPI	<i>S. haematobium</i>	Inhibition of host serine proteases Same as SMpi56
Excreted-secreted proteins (ESPs)	<i>Paragonimus</i> spp.	Cysteine proteases. Tissue degradation
Strongylastacin	<i>S. stercoralis</i>	Metalloproteinase. Skin invasion
Calreticulin	<i>N. americanus</i>	C1q binding, procoagulant sequestration
Macrophage migration inhibitory factor (MIF)	<i>T. spiralis</i>	Regulation of host macrophage responses
Glycosphingolipids	<i>Echinococcus</i>	Decreases macrophage activation
Glycans	<i>Echinococcus</i>	Decreased PMN chemotaxis, modulation of dendritic cells Increased production of IL-4 and IL-13

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[37]. The third stage of larval maturation is the invasive one, and several serine and metalloproteases have been found to be expressed during this stage of development. Likewise *Onchocerca* migrates extensively within the body once the infection is established after a vector bite [38]. Tissue migration is indeed mediated by proteases expressed in the mature microfilaria. Trematodes such as *Fasciola* spp., *Paragonimus* spp., and *Clonorchis* spp. also produce several proteolytic enzymes during the tissue invasive stage of the life cycle in order to form a niche in their target organs [39, 40]. In addition, proteases can also play a role in the immunomodulatory process by degrading immunoglobulins or altering cytokine production, especially IL-8 [41]. As a general rule, proteases produced during the larval stage play an important role in tissue invasion or immune evasion, whereas proteases produced during the adult stage primarily degrade gut proteins (those who use the bowel as niche for adult stages) and have roles in anticoagulation and immune evasion.

The best-studied proteases are the ones produced by schistosomes and have been described in several stages of development [42]. They can be present in the parasite gut and excreted or present on the surface of the parasite where they can coat it and play roles in anticoagulation or degradation of immunoglobulins. Some of the proteases are also potent immunogens and could be used as vaccine candidates [43].

Another kind of proteins produced by helminths is protease inhibitors that play an important role in perpetuating these infections for the entire life span of the host. Molecules released from filarial parasites such as phosphorylcholine can interfere with activation and proliferation of T- and B-cells and favor T-helper responses towards the Th2 type. Inhibitors of cysteine and serine proteases, known as cystatins and serpins, respectively, can also have a role in immunomodulation [43].

The best-known cystatin is the one found in *Onchocerca volvulus* (onchocystatin) and is responsible for inhibition of protease activity in antigen-presenting cells (APCs) leading to low T-cell responses [44]. Other cystatins have been described in *Brugia malayi* which inhibit host cathepsins leading to altered digestion of antigens necessary for presentation of antigen-derived peptides to immune cells via MHC molecules [45]. Serpins have been described in *Schistosoma* spp. and are possibly responsible for anticoagulation. *Ascaris* spp., and *Ancylostoma* spp., secrete protease inhibitors that might be responsible for inhibition of host enzymes such as trypsin and chymotrypsin in the gut lumen and inhibition of key coagulation factors [46].

Protozoans also produce potent proteases that play an important role in pathogenesis and immune response. For example, the genome of *E. histolytica* is thought to contain up to 20

proteases, three of which are very well studied and they all belong to the family of cysteine proteases: EhCP1, EhCP2, and EhCP5. Two of them, 1 and 5, are actually absent in other nonpathogenic amebas [47]. They are cytolytic and therefore contribute to intestinal layer degradation and trigger strong inflammatory responses via enhanced activity of chemokines such as CXCL8. Other protozoan proteases have been described in *T. gondii* and their role elucidated during entrance and exit from parasitized cells. Examples include cell surface proteins such as Tg MIC (*Toxoplasma* microneme protein) and TgAMA1 (*T. gondii* apical membrane antigen); proteins present in the rhoptries such as Tg toxopain I and Tg SUB1 and 2, important in processing and targeting rhoptry proteins ROP2, 3, and 4; and proteins of the aspartyl protease group such as toxomepsin II, are also important for invasion [43].

2.3 Molecular Pathogenesis of Pulmonary Protozoan Pathogens

2.3.1 Toxoplasmosis

Toxoplasmosis is a systemic disease due to an obligate intracellular coccidian named *Toxoplasma gondii* which is a very homogeneous species with only three strains worldwide, responsible for more than 95 % of infections. Its distribution is worldwide and the range of animal species that can be affected by it is broad [48]. The life cycle involves a wide range of mammalian intermediate hosts [48]. *T. gondii* is found in three forms in nature, namely, tachyzoites (asexual forms), tissue cysts enclosing bradyzoites (found mostly in the brain and muscle), and oocysts containing sporozoites (sexual forms). The invasive form in humans and other hosts is the tachyzoite and is also the form responsible for cellular and tissue damage. Tissue cysts containing bradyzoites serve as reservoirs for tachyzoites and therefore play an important role in disease transmission (ingestion of contaminated meat) and latent infection. Oocysts with sporozoites are only found in the definitive hosts, the wild and

domestic *Felidae*, where they are produced in the intestinal epithelium and then shed in the stool. After sporulation, the cysts are infectious and can then be ingested/inhaled by humans. Other routes of transmission include ingestion of raw or undercooked infected meats, perinatal exposure from infected mothers, transfusion of infected blood products, and transplantation of infected organs. Regardless of the route of infection, tissue cysts or oocysts are digested in the GI tract, and bradyzoites (tissue cysts) or sporozoites (oocysts) are released in the intestine where they invade neighboring cells and become tachyzoites. Invasion of the eukaryotic host cell is an active process mediated completely by the parasite's cytoskeleton [49, 50]. The host cell cytoskeleton does not play any role nor does phosphorylation of any proteins upon attachment of the parasite to the host cell via glycosaminoglycans and sialic acid [51]. The ubiquity of the receptor explains the wide distribution of the parasite in human infections. The parasite adhesins also play an important role in entry. They are not displayed continuously on the surface, as opposed to bacterial and viral adhesins. Instead, the adhesins are contained in cytoplasmic structures called micronemes that discharge their contents upon contact mediated by a controlled release of calcium from the parasite [51]. A "baseline" secretion of the adhesin is sufficient for the initial interaction followed by a dramatic increase in microneme secretion. Such secretion is only apical facilitating interaction in a polarized way that is necessary for entry. The best characterized of the microneme proteins is MIC2 which belongs to the TRAP (thrombospondin anonymous repeat protein) family of proteins [51, 52]. Type A domains (or Von Willebrand factor-like domains) interact with heparin-like molecules and GAGs and therefore are important as adhesins. After apical secretion, MIC2 is transported to the posterior pole of the parasite via the actin cytoskeleton where it is cleaved and released from the cell surface. MIC2 in turn is tightly related to an accessory protein (M2AP) that is also necessary for upregulation of MIC2 secretion from the micronemes. The cytoplasmic domain of MIC2 in turn binds aldolase in the host cell, and

this complex is able to recruit actin monomers [51]. The actual protein responsible for the gliding motility in *T. gondii* is a class XIV myosin that is present beneath the plasma membrane named TgMyoA [53]. This protein is anchored to the inner membrane complex by accessory proteins, and myosin filaments can propel actin filaments recruited by the aldolase-MIC2 complex and induce motility. Entry also depends on a calcium-regulated secretion of the parasite [54]. However, calcium signals in the host cell do not play a role in entry either. Since entry relies completely on active motility of the parasite, research into this area has been active and has elucidated some molecular mechanisms responsible for the unique “gliding” motility seen in all apicomplexans. *T. gondii* motility is highly predictable and consists of circular gliding (counterclockwise) and helical gliding (clockwise). Once inside the cell, *T. gondii* resides in a modified vacuole that does not fuse with any of the endocytic or exocytic vesicles. Most of the vacuolar membranes come from apical organelles called rhoptries which secrete their contents after entry. The main component identified so far is a transmembrane protein called ROP2 which mediates interactions between the vacuolar membrane and the host cell’s mitochondria and endoplasmic reticulum [55]. Another component of the vacuolar membrane is the host’s glycosylphosphatidylinositol (GPI)-anchored proteins. The damage during the acute infection is due to cell death of parasitized cells and a vigorous inflammatory reaction which initially is neutrophilic in nature and turns lymphocytic when acquired immunity sets in. Most human hosts control the disease in the acute phase, and critical determinants are IL-12 and IFN- γ (gamma) followed by CD8+ T-cells [56, 57]. Antibodies are also capable of neutralizing or killing circulating tachyzoites [58]. Tissue cysts containing bradyzoites then form and tissue integrity is usually restored completely. In some cases, infection persists in the lymph nodes leading to chronic lymphadenopathy, usually in the cervical region accompanied by mild constitutional symptoms. The spectrum of disease ranges from asymptomatic infections (the most common form) to severe disseminated disease seen mostly

in immunocompromised patients. In the lungs, the main presentation is that of a diffuse confluent bronchopneumonia that appears secondary to hematogenous and lymphatic dissemination, followed by shock. In AIDS, pulmonary toxoplasmosis is seen in up to 3 % of cases and CD4+ T-cells are usually below 100 cells/ μ l.

2.3.2 Amebiasis

Pulmonary amebiasis is due to *Entamoeba histolytica*, a protozoan primarily responsible for colonic infections in humans. Pulmonary infections are the result of complications seen in cases of intestinal amebiasis in which *E. histolytica* becomes systemic after invasion of the colonic mucosa, spreading to the liver, lungs, and other organs. Most of these infections occur in the tropics in developing countries. The life cycle of *E. histolytica* comprises an infective cyst and an invasive trophozoite. Cyst formation appears to be mediated by quorum sensing triggered by a lectin (Gal/GalNAc) on the parasite’s surface [59]. Excystation occurs in the intestine and eight trophozoites are produced from each cyst which then invade the colonic mucosa leading to ulcer formation. Killing of host cells occurs only after contact of trophozoites with the host cell, and adhesion is mediated by an amebic adhesin, the Gal/GalNAc lectin, referred to above. The lectin recognizes N- and O-linked oligosaccharides on the cell surface. This lectin also appears to be cytotoxic since monoclonal antibodies directed against certain epitope block cytotoxicity in vitro although adhesion is conserved [59]. Invasion and hematogenous spread activates the immune system, and in cases of amebiasis, both the alternate and classical complement pathways are activated. However, trophozoites are resistant to the C5b-C9 attack complex which is inhibited by the abovementioned lectin [60]. Mechanisms of cell killing by *E. histolytica* are under intense scrutiny and may include dramatic rises in cytoplasmic calcium upon contact leading to cell blebbing and death, apoptosis, and a pore-forming protein isolated from ameba [61]. Amebic cytoplasm also contains collagenases and cysteine proteases

that also play a role in pathogenesis by degrading extracellular matrix and producing cell detachment, respectively [43].

Immunity to amebic infections is usually both humoral (secretory IgA antibodies directed against the surface lectin) and cell mediated in the form of cytokine activation of macrophages and neutrophils which become amebicidal after stimulation by IFN- γ (gamma), IL-12, and TNF- α (alpha) [62–64]. Most infections are acquired via the fecal-oral route, but cases can also be acquired via the anal route in homosexual men. Pleuropulmonary complications of amebiasis are seen in cases on hepatic amebiasis (up to 20 %) or invasive colonic amebiasis (up to 3 %). Multiple forms have been described including a pleuritis that results from the inflammatory reaction in the liver “traveling” via the right dome of the diaphragm, empyema or pulmonary amebic complications (pneumonitis, abscess, or fistulas) secondary to rupture of a hepatic abscess, and hematogenous spread.

2.3.3 Microsporidiosis

Phylum Microsporidia are spore-forming, obligate intracellular protozoans that reside in the intestine, liver, kidneys, brain, and other tissues of wild and domesticated mammals and several other animal species. Eight genera out of more than 144 (containing more than 1,000 species) have been documented as human pathogens, namely, *Encephalitozoon*, *Enterocytozoon*, *Pleistophora*, *Brachiola*, *Nosema*, *Trachipleistophora*, *Vittaforma*, and *Microsporidium* [65]. Of these, *Encephalitozoon hellem*, *E. cuniculi*, and *Enterocytozoon bienersi* have been documented as the main culprits in pulmonary microsporidiosis. Microsporidia in general are rare pathogens in humans that have received attention due to the increased incidence of infections present in patients with AIDS. In cases of pulmonary microsporidiosis, there usually is intestinal involvement and in many cases systemic involvement. Histologically, the microsporidia are seen as faintly basophilic intracellular round structures in the apical portion of the cell

measuring 1–1.5 μ m in diameter inside epithelial cells lining the bronchial and bronchiolar epithelium. Microsporidia are eukaryotes with Golgi apparatus, mitochondrial remnants, a double-layered spore structure (exo- and endospore layers), and a typical extrusion apparatus anchored to the anterior end of the spore by a disc [65]. Upon invasion of the host cell, the sporoplasm is extruded through the polar tube, which pierces the phagocytic vacuole, into the cytoplasm of the host cell [66]. Spores gain access to humans via ingestion or inhalation. Once they germinate in the host, the sporoplasm undergoes merogony, in which proliferation occurs (meronts), followed by sporogony, in which the membranes thicken again and form sporoblasts that turn into mature spores and are released from the distended cell and into the environment to complete the cycle. Characterization of the process of extrusion of the sporoplasm is lacking. Early events in the process include rupture of the anterior attachment complex upon host cell attachment and cell penetration. So far three polar proteins have been identified and are known as PTP1, PTP2, and PTP3 [66]. PTP1 is O-mannosylated, a post-translational modification that seems to be necessary for its function [67]. PTP1 represents at least 70 % of the polar tube mass. Furthermore, it has been demonstrated in humans that PTP1 is one of the immunodominant proteins that triggers formation of neutralizing antibodies of the IgG type in humans [68]. The major epitope is indeed the posttranslational carbohydrate modification, namely, O-mannosylation. PTP2 is also immunodominant and PTP3 seems to be involved in sporoblast-to-spore polar tube biogenesis [69]. PTP1 and PTP2 contribute to the high tensile strength of the polar tube via extensive disulfide linkages [69]. Another mechanism of infection is phagocytosis upon attachment of the microsporidia to the host cell. In these cases, penetration of the host cell by the polar apparatus and extrusion of the spore contents do not occur on the cell surface. Instead, the spore is phagocytosed and some of them extrude their contents using the polar tube, thus escaping the endosomes [70]. The spores that remain in the endosomes at some point fuse with lysosomes

and disappear after 72 h. The phagocytosis route was ten times more effective than the attachment followed by extrusion in an in vitro model using *E. cuniculi*. Adhesion mechanisms have also been studied with *E. intestinalis*, and host cell glycosaminoglycans seem to play an important role in the adhesion process. Another interesting pathogenetic mechanism is manipulation of the host cell cycle. In models using *Encephalitozoon*, it has been shown that levels of cyclin D1 are decreased and cyclin B1 are elevated suggesting that host cells can go into arrest to ensure optimal growth of the parasitophorous vacuole in a non-dividing cell [71].

2.3.4 Cryptosporidiosis

Cryptosporidium was first diagnosed as a human pathogen in 1976 in two immunocompromised patients in whom persistent diarrhea developed. The largest outbreak occurred in Milwaukee in 1984 and involved 400,000 people most of whom recovered completely [72]. However, in immunocompromised patients, the diarrhea persists for weeks or months and is debilitating. Currently the main risk factor is the presence of HIV infection/AIDS. Cryptosporidiosis is endemic in developing countries and is responsible for childhood diarrhea. Respiratory cryptosporidiosis results in cough, dyspnea, fever, and chest pain and is always associated with gastrointestinal symptoms. Histologically, there is tracheitis, bronchitis, and bronchiolitis with mild to moderate mononuclear inflammatory infiltrate in the mucosa and submucosa. The organisms are usually seen in the epithelial surface and rarely in submucosal glands. *Cryptosporidium* belongs to the phylum *Apicomplexa* (some other members of the phylum include *Toxoplasma*, *Plasmodia*, and *Babesia*) and is a monoxenous genus (complete developmental cycle occurs in one host) [73]. Oocysts are ingested by the host and release in the small bowel lumen four sporozoites (infective form). Upon attachment, sporozoites form an intracellular/extracytoplasmic parasitophorous vacuole in which they evolve into trophozoites and then into meronts (schizonts). Schizonts

undergo three nuclear divisions and become type I merozoites that invade neighboring cells and develop into type II merozoites or into trophozoites. The merozoites can infect other cells and restart the asexual part of the cycle. Type II meronts can also undergo two nuclear divisions and release 4 type II merozoites that invade other cells and become macro- and microgametocytes which can then form a zygote (sexual reproduction). The zygote ultimately becomes an either thin-walled oocyst (autoinfectious) or a thick-walled cyst shed in feces. There are several species within the genus, and the ones known to infect humans include *C. parvum* (humans and bovines), *C. hominis* (humans), *C. meleagridis* (turkeys and humans), and *C. felis* (cats and humans) [73]. Infectious doses are very low. As few as ten oocysts are capable of starting an infection in humans. In addition, cysts are extremely resistant to chlorination treatments and pass through filters relatively easily. Forms of the disease include endemic childhood diarrhea in developing countries, traveler's diarrhea in visitors to endemic countries, chronic diarrhea in immunosuppressed patients, and diarrhea outbreaks in developed countries.

The pathogenesis of these infections is virtually unknown. Several mechanisms have been proposed such as malabsorption produced by villous inflammation and blunting, prostaglandin secretion at the local levels, cellular damage secondary to IL-8 and TNF- α (alpha) secretion, and substance P release in the microenvironment [74–78]. Entry into the unique compartment (intracellular/extracytoplasmic) requires protein kinase C activation and actin rearrangements in vitro [79]. In cultured biliary epithelial cells, *C. parvum* has been shown to induce apoptosis via Fas/FasL interactions [79]. In fact, *C. parvum* is responsible for cases of ascending cholangitis in immunocompromised patients. Full genomic sequence of *C. parvum* “type II” isolate was finalized in 2004 and revealed in 9.1 Mbp in eight chromosomes, coding for approximately 3,807 proteins [80]. *Cryptosporidia* lack mitochondria and apicoplasts, unlike *Plasmodia* and *Toxoplasma*, making the genomes simpler and smaller. Its metabolic pathways are very efficient

and rely mostly on glycolysis as a source of ATP due to absence of mitochondrial genes. Because of its unique intracellular but extracytoplasmic location, several genes are present for transport of sugars and amino acids into the parasitophorous vacuole. Motility and adhesion seem to be mediated by a family proteins known as thrombospondin-related adhesive proteins or TRAPs. In the adhesion process, an apical complex glycoprotein (CSL) has been shown to play an important role and its receptor is an 85-kDa protein in intestinal epithelial cells.

Cell-mediated immunity is important in controlling infections and the most important cytokine seems to be IFN- γ (gamma) [81]. Humoral response appears to be irrelevant. Elevated levels of IL-15 in the intestinal mucosa seem to correlate with no fecal shedding in human volunteers infected with cryptosporidia [82]. Other cytokines elevated found in Haitian children include IL-8, IL-13, and TNF- α (alpha) [74].

2.4 Molecular Pathogenesis of Pulmonary Helminthic Pathogens

2.4.1 Nematodes

2.4.1.1 Filariasis

These infections can be divided into lymphatic filariasis and zoonotic filariasis. The first one is caused by *Wuchereria bancrofti*, *Brugia malayi*, and *B. timori*. The latter is caused by filarial parasites that usually infect other animal hosts, and humans become accidental hosts.

Lymphatic filariasis is the cause of recurrent lymphadenitis leading to sequelae such as elephantiasis and hydrocele due to lymphatic obstruction. In some individuals infected with *W. bancrofti* or *B. malayi*, a distinct asthma-like syndrome develops, known as tropical pulmonary eosinophilia, in which there is paroxysmal cough and wheezing (typically at night due to nocturnal filarial periodicity), low-grade fever, and weight loss. Typically, the blood reveals severe eosinophilia ($>3,000/\mu\text{l}$) and elevated IgE levels in serum [83]. If not treated, the condition can

develop into restrictive pulmonary disease with interstitial fibrosis. The life cycle [83] of lymphatic filariae is very long and starts with the biting of a patient with circulating microfilariae. Once in the mosquito, they develop into first through third stage larvae in the thoracic muscles which then introduce infective third stage larvae into the human circulation. Larvae migrate to lymphatics where they mature and differentiate into adult females and males which then mate and start releasing microfilariae after 5–10 years. Up to 10,000 parasites can be released per day from pregnant female worms.

Initial immune responses to the third and fourth larval stages (early in human infection) are both proinflammatory Th1 and Th2 type of responses [84]. By the time microfilariae appear in the blood, several years later, there are markedly diminished antigen-specific T-cell responses, especially IFN- γ (gamma) and IL-4 [85]. Mechanisms for immune tolerance are multiple and poorly studied but include genetic predisposition, suppressor T-cells, increased expression of downregulatory molecules such as CTLA-4, and high levels of regulatory cytokines such as IL-10 and TGF- β (beta) [86, 87]. Another potentially important pathogenetic mechanism is the presence of large numbers of the endosymbiont *Wolbachia pipientis* in filarial parasites that probably modulate the parasite's life cycle. Dying parasites probably release large numbers of *Wolbachia* cellular products triggering an inflammatory reaction [88–90].

The best-known zoonotic filariasis is the one caused by *Dirofilaria immitis* [91]. These are all transmitted to humans by an infected arthropod and lead to a solitary (sometimes multiple) “coin lesions” in the lungs that are easily confused with neoplastic processes on chest X-rays. Patients are usually asymptomatic and the diagnosis is made when the lesion is taken out for histologic examination. Peripheral eosinophilia can be seen in blood smears. Pathogenetically, the lesion appears as a reaction around a dead or dying worm. *D. immitis* is mainly a dog pathogen although it can infect other mammals such as cats. This nematode has a similar life cycle as described for the lymphatic filariasis. However,

D. immitis is mostly a vascular pathogen [92]. In humans who are resistant to chronic infections, the microfilariae lodge into pulmonary vessels and subcutaneous vessels, and the immune system destroys the parasite, time at which the histopathology appears.

2.4.1.2 Strongyloidiasis

This disease is caused by *Strongyloides stercoralis*. The genus contains more than 40 named species and only one is capable of completing its cycle in humans [93]. The disease is mostly tropical but endemic foci can be seen in temperate areas. The infection is acquired at the time filariform larvae enter the human body via the skin (usually the lower extremities) and gain access to vascular or lymphatic channels that take them to the lungs where they rupture the capillaries and gain access to alveolar spaces. Location of the adequate host depends on detection of thermal and chemical signals by the larvae using specialized amphidial neurons located in the amphidial channel [94]. A metalloproteinase expressed in the third larval stage, named strongylastacin, is possibly responsible for skin penetration. This protein belongs to the metzincin superfamily of zinc metallo-endopeptidases [95]. From the lungs, they migrate up to the bronchi, trachea, and upper aerodigestive tract where they are swallowed and develop into hermaphroditic adults in the small bowel mucosa. The adults then penetrate the mucosa and release eggs that hatch into rhabditiform larvae. At this point of the cycle, two possible scenarios come into play: (1) larvae are shed in the stool and develop into free living male and female adults which mate and release eggs into the soil, followed by hatching of rhabditiform larvae which then develop into filariform larvae (indirect or heterogonic development), and (2) larvae shed in stool develop directly into filariform larvae (direct development). In addition, a third possible scenario is that of autoinfection in which rhabditiform larvae in the bowel lumen mature into filariform larvae which then can invade the body through bowel mucosa or perianal skin. The latter scenario is the one responsible for the so-called pruritic larva currens syndrome and hyperinfection leading to systemic

disease (pneumonitis, colitis, polymicrobial sepsis, and meningitis) [93].

Chronic infections with *S. stercoralis* are as a rule asymptomatic. However, in cases of hyperinfection, dissemination is marked, and in the lungs it can lead to diffuse bronchopneumonia, often with intra-alveolar hemorrhage or abscess formation. These infections are usually mixed with intestinal bacteria carried by the parasites in their cuticles. Rhabditiform larvae, filariform larvae, and even eggs can be seen in tissue sections. The mortality rates for hyperinfected patients approach 90 % and are usually associated with administration of exogenous steroids for conditions such as asthma and COPD. Steroids seem to upregulate metabolism of ecdysteroids (molting hormones) in the parasite, via receptor-mediated uptake of the corticosteroid by the parasites [96, 97]. Eggs and rhabditiform larvae receive molting signals, and the number of filariform larvae increases dramatically. Intestinal populations in these cases approach 100,000 adults, and even if steroids are discontinued, and molting rates are low, the burden of adult worms is so high that population growth cannot be arrested. The described developmental processes might be regulated by a family of transcription factors that control genes in response to fat-soluble hormones such as steroids. A gene homolog of *daf-12* present in *Caenorhabditis elegans* has been described in *S. stercoralis* [98]. Such gene plays an important role in the development of *C. elegans*.

Other risk factors include HTLV-1 infections, autoimmune diseases, hematologic malignancies, and solid organ allografts [93]. However, the common denominator in many of these conditions seems to be steroid administration. In HTLV-1 infections, it has been demonstrated that the cytokine profile in humans infected with this retrovirus favors the parasite by way of high levels of IFN- γ (gamma) and TGF- β (beta) leading to decreased levels of IL-4, IL-5, IgE, and IL-13 [99]. Interestingly enough, *S. stercoralis* has also been shown to decrease the period of time to develop acute T-cell lymphoma/leukemia (ATLL) in patients infected with HTLV-1. In such cases, *S. stercoralis* induces a significant expansion of restricted T-cell clones infected with HTLV-1

[100]. In average, the incubation period of ATLL is decreased by 30 years in patients infected with HTLV-1.

Other nematodes include (*Ascaris lumbricoides*), hookworms (*Ancylostoma duodenale*, *Necator americanus*), *Toxocara canis* (visceral larva migrans), and *Trichinella* spp.

A. lumbricoides and hookworms are acquired through the mouth, and once eggs hatch in the intestines, larvae migrate throughout the body including the lungs where they cross from capillaries to airways and migrate up to the upper airways to be ingested and mature into adults in the intestine. The larval stage is capable of producing mechanical damage to tissues in the lungs and hypersensitivity reactions elicited by larval antigens leading to pulmonary and bronchial lesions rich in neutrophils, eosinophils, and macrophages (eosinophilic pneumonitis). Pulmonary signs and symptoms are known clinically as Loeffler's syndrome which tends to be more severe in cases of ascariasis. Toxocara infections tend to be as severe as ascariasis and can also lead to acute or chronic eosinophilic pneumonitis whose severity also depends on the larval burden. Trichinellosis is also a nematode that can affect several organ systems including the lungs and its presentation is similar to the above-described syndromes.

2.4.2 Trematodes

2.4.2.1 Paragonimiasis

The best-known pathogen in the genus *Paragonimus* is *P. westermani*, although seven more species have been described as human pathogens: *P. westermani* is mostly found in the far east (from India to Japan and the Philippines), *P. heterotremus* in China and southeast Asia, *P. skrjabini* and *P. hueitungensis* from China, *P. miyazakii* from Japan, *P. uterobilateralis* and *P. africanus* from central and western Africa, *P. mexicanus* from Central and South America, and *P. kellicotti* from North America [101]. The life cycles are very similar but the best-well-studied one is *P. westermani*. The cycle [102] starts with ingestion of metacercariae in uncooked crab or crayfish. The metacercariae are then excysted

in the stomach and small bowel and migrate through the bowel wall, mesenteric fat, and diaphragm until they reach the pleural cavity and lungs where they mature into hermaphroditic flukes that cross-fertilize. Human tissue surround the parasites with a capsule that then cavitates causing hemoptysis and cough. Adults lay eggs after fertilization which are found in sputum and feces if swallowed. The eggs then embryonate in water and miracidia are released which then penetrate *Thiara* or *Semisulcospira* snails. Once in this intermediate host, miracidia turn into sporocysts, rediae, and then short-tailed cercaria. The infected snails are then ingested by crabs or crayfish and cercariae encyst as metacercariae in gills and muscles of these crustaceans. The spectrum of disease ranges from pleuropulmonary infections due to *P. westermani*, *P. heterotremus*, *P. africanus*, and *P. uterobilateralis* to mostly cutaneous manifestations due to *P. skrjabini*. Adults can live up to 5–10 years in human tissues, and acute disease manifestations can happen any time during this period, but usually acute symptoms occur days after ingestion. They include diarrhea and abdominal pain, followed days later by fever, chest pain, fatigue, urticaria, and cough which can turn productive with rusty-colored sputum [102]. Pathologically, the lesions consist of cavitary lesions when adult flukes appear. Excised lesions reveal adult worms with fibrous cysts and egg-induced granulomas. Bronchiectasis, vasculitic lesions, and consolidation can also occur. Other organs affected include the skin, brain, liver, spleen, and peritoneum.

Paragonimus spp. secrete several biologically active molecules called excretory-secretory products (ESPs), and several of them are cysteine proteases whose role is probably host tissue degradation [102, 103]. In addition, they might play a role in immune modulation. In vitro, microglial cells exposed to low levels of ESPs secrete NO, while at high levels microglial cells die [104]. Likewise, co-incubation of eosinophils with ESPs induces rapid degranulation and elevated levels of granule products such as eosinophil-derived neurotoxin [105]. In addition, ESPs can also induce apoptosis in eosinophils via caspase 3 activation, facilitating survival of parasitic

larvae early in the infectious process [106]. Another important mechanism of survival is production of a copper/zinc containing superoxide dismutase at various stages of development including the adult stage [107].

Cytokines and chemokines found elevated in human serum or pleural effusions of humans infected with *Paragonimus* spp. included thymus and activated-regulated chemokine (TARC), eotaxin, RANTES, and IL-8 [108]. The immune response in general is that of a Th2-dominated response with an IgG4 subclass.

2.4.2.2 Schistosomiasis

This is one of the main human helminthiasis around the world with approximately 200 million people infected worldwide. The main human pathogens are *S. mansoni*, *S. japonicum*, and *S. haematobium*. Two other species, *S. intercalatum* and *S. mekongi*, have been described also in humans although their geographic distribution is more limited [109]. The life cycle [110] starts with penetration of the host's skin by forked-tail cercaria after which they shed their tail and become schistosomulae. At the site of penetration, they induce an inflammatory response known as "swimmers' itch." The schistosomulae then migrate to the portal circulation in liver where they become adults who start to mate for the life of the parasite (3–30 years). Mating adults of *S. mansoni* and *S. japonicum* migrate to the mesenteric venules of bowel and rectum where females start laying eggs that reach the liver and eventually the stools. *S. haematobium* adults migrate to the venous plexus of the bladder where females lay eggs leading to bacterial infections in the bladder, hematuria, and later in the disease process scarring and calcification of the venules. Eggs are shed in the urine. In cases with heavy parasitism, eggs can embolize to other parts of the body including brain and lungs. Once eggs are shed in stools or urine, they hatch in the outside environment and release miracidia which then penetrate the different snails (*Bulinis*, *Biomphalaria*, and *Oncomelania*) in which they develop as two generations of sporocysts. When mature, the snails release the forked-tail cercaria to restart the cycle.

The disease itself is divided into the acute and chronic phases. During the acute phase, the

patient develops dermatitis, and the circulation of schistosomulae through the hepatic and pulmonary vascular beds followed by maturation and initial oviposition induces a systemic response that includes fever, chills, sweats, cough, and headaches (only seen in *S. japonicum* or *S. mansoni* exposure) [111]. Lymphadenopathy and hepatosplenomegaly can also be seen. The chronic phase is characterized by a granulomatous response to eggs deposited in the intestinal, portal, or urinary tract veins. Pulmonary schistosomiasis is the result of egg deposition in the pulmonary vascular bed resulting in granuloma formation and fibrosis [111]. If a large area of the pulmonary circulation is involved, secondary pulmonary hypertension can ensue. Eggs reach the pulmonary circulation via urinary veins draining into the inferior vena cava or bypassing the liver through porto-systemic collaterals in cases on *S. mansoni* and *S. japonicum* infection in which liver damage has led to portal hypertension [112].

One of the main driving forces in mouse models of schistosomiasis *mansoni* behind the formation of liver granulomas once eggs are deposited in the hepatic microcirculation is IL-13 and the IL-13R complex [11]. Liver fibrogenesis is greatly decreased in animals deficient in IL-13 or treated with IL-13 antagonists. It has been shown that IL-13 promotes expression of arginase in myofibroblasts, a step necessary to increase collagen production. Other important mediators include IL-4/IL-4R α (alpha) and Stat-6, IL-5, and IL-17 [10, 113]. In fact, granulomas evolve in two phases: during the early stages, a short-lived type 1 cytokine response predominates, whereas in later stages a type 2 response takes over and is long-lived [12]. The immune response to the eggs is necessary to neutralize an uncontrolled inflammatory response to egg antigens leading to even death in the early stages of the disease. The most important cell at this stage is the CD4+ Th2 cell. From the parasite's point of view, several molecules have been described as important in skewing the immune response towards the Th2 phenotype. An area of intense research is now focused on the role of several schistosomal glycans including Le^x and LNFPIII conjugates. These molecules act via toll-like receptor-4 or TLR-4 and possibly C-type lectins [114].

In regard to the acute phase of the disease known as “snail fever” or “Katayama fever” or acute toxemic schistosomiasis, it is widely accepted that the signs and symptoms are due to large amounts of circulating immune complexes and elevated levels of proinflammatory cytokines and low type 2 responses [115]. In fatal animal models, an overwhelming type 1 response is usually seen which can be controlled by IL-4 and IL-10. IL-4 in vitro is necessary for development of CD4+ Th2 cells.

The genome sequences of *S. japonicum* and *S. mansoni* have been completed and analyzed. Comparative genomics have also revealed abundant clues of the host-parasite relationship. For example, the schistosome genome has lost approximately 1,000 protein-encoding domains, out of approximately 6,000, most likely due to the parasitic lifestyle. These domains include basic metabolic pathways and defense mechanisms (synthesis of fatty acids, sterols, and purines). At the same time, other gene families have been expanded such as metalloproteases genes which total up to 12 family members in schistosomes and only one orthologue in humans [116, 117]. These metalloproteases are involved in skin penetration and tissue invasion.

Other interesting findings include the presence of genes encoding signaling pathways such as Wnt, Notch, Hedgehog, and TGF- β (beta). Most of the signaling molecules in these pathways (epidermal growth factor, fibroblast growth factor, SAMD, and Ras-Raf-MAPK) have a high degree of homology with mammalian molecules, suggesting that the parasites might utilize the mammalian molecules in addition to theirs [116, 117]. Genes related to immune regulation have also been identified such as cytokine homologs, glycoconjugates, and small lipid moieties, all of which have the potential to subvert the immune system when needed [2].

2.4.3 Cestodes

2.4.3.1 Echinococcosis

This disease is caused by cestodes belonging to the genus *Echinococcus* to which more than five species have been described, namely, *E.*

granulosus, *E. multilocularis*, *E. oligarthrus*, *E. vogeli*, and *E. shiquicus* [118]. The first four are well known as human pathogens, but the newly described *E. shiquicus* is of unknown human pathogenicity. *E. granulosus* contains several strains (G1–G10) based on their definitive host isolation [118]. The classic form of the disease (cystic echinococcosis) is due to *E. granulosus*. Another form of the disease known as alveolar echinococcosis is a highly lethal and infiltrative disease in humans caused by *E. multilocularis*. Infections by *E. vogeli* and *E. oligarthrus* lead to polycystic echinococcosis. The latter three are far less frequent in humans due to their host specificity limited to wild animals as opposed to *E. granulosus*. The life cycle of all of them involves two mammalian hosts. Definitive hosts are carnivores in which adult worms live in their intestines. The eggs from adult worms are shed in the environment and when ingested by intermediate hosts (like humans), hatch and liberate embryos that migrate to extraintestinal tissues (liver, lungs, brain, etc.) and turn into metacestode or larval forms. It is these larval forms that are known as hydatid cysts that take different morphologies when causing disease (polycystic, alveolar, or cystic) [119]. In nature, the passage from intermediate host (except for humans) to definitive host is the result of predator–prey interactions between those two hosts.

E. granulosus, as mentioned above, is the most common in humans because dogs are one of the definitive hosts. Infected dogs can harbor up to 40,000 tapeworms which in turn can release up to 1,000 eggs each per day. Fecal-oral transmission is therefore relatively easy if close contact with the dog is present. Indirect transmission via arthropods, fomites, soil, water, and vegetables is also possible. Other hosts besides dogs include sheep, cattle, camels, pigs, and cervids.

Signs and symptoms are extremely variable and depend on the localization of the cyst (lungs, brain, liver, etc.), size of the cyst, and its condition (intact versus ruptured). Conversely, in the brain and eyes, signs and symptoms appear more quickly. Cyst rupture can cause a variety of complications including mild to severe allergic reactions, chest pain, coughing, dyspnea, and hemoptysis. The immune response is usually

biphasic. The first phase is directed against the oncosphere or egg hatching in the intestine and penetrating the gut wall. This response is far more effective in controlling the infection since the metacystode in the extraintestinal tissues has more means of evading the immune response.

Conclusions

The classic triad of infectious agent, host, and environment plays a key role in parasitic as well as in any other infectious agents. The geographic distribution seen with some of the parasitic diseases, especially the ones due to helminthes, is in large part due to the complex life cycles that most of the helminthic parasites need to survive in nature. The interplay between host and parasites is also a very complex system in which virulence factors, developmental cycles, parasite nutrition, host immune response, and immune modulation by the parasite interact in a complicated network that we are beginning to elucidate at the molecular level. The availability of small animal models has provided great insights into the pathogenesis of these diseases. Likewise, with the help of powerful molecular techniques, both in vivo and in vitro experiments can now be designed to elucidate the host-parasite relationship and move the research to a new level.

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