Parasitology Research (2020) 119:3165–3180
https://doi.org/10.1007/s00436-020-06841-x

IMMUNOLOGY AND HOST-PARASITE INTERACTIONS - REVIEW

Granulomas in parasitic diseases: the good and the bad

Selma Giorgio[1] · Pedro Henrique Gallo-Francisco[1] · Guilherme Augusto Sanches Roque[1] · Marina Flóro e Silva[1]

Received: 7 April 2020 / Accepted: 2 August 2020 / Published online: 13 August 2020

Abstract

Parasitic diseases affect more than one billion people worldwide, and most of them are chronic conditions in which the treatment and prevention are difficult. The appearance of granulomas, defined as organized and compact structures of macrophages and other immune cells, during various parasitic diseases is frequent, since these structures will only form when individual immune cells do not control the invading agent. Th2-typering various parasitic diseases are frequent, since these structures will only form when individual immune cells do not control the invading agent. The characterization of granulomas in different parasitic diseases, as well as recent findings in this field, is discussed in this review, in order to understand the significance of the granuloma and its modulation in the host–parasite interaction and in the immune, pathological, and parasitological aspects of this interaction. The parasitic granulomatous diseases granulomatous amebic encephalitis, toxoplasmosis, leishmaniasis, neurocysticercosis, and schistosomiasis mansoni are discussed as well as the mechanistic and dynamical aspects of the infectious granulomas.

Keywords Granuloma · Granulomatous amebic encephalitis · Toxoplasmosis · Leishmaniasis · Neurocysticercosis · Schistosomiasis mansoni

Introduction

The term granuloma was first coined by Rudolf Virchow in 1863 to refer to usual "tissue granulation" found in tuberculous lungs (tubercle) and some tumors (Turk 1998; Klippe et al. 2004). At the end of the nineteenth century, other pathologists defended the use of granuloma instead of tubercle and associated other infectious diseases with granuloma formation (Turk 1998; Klippe et al. 2004).

Some definitions of granuloma found in important reviews are cited below and complement each other. Boros (1986) defined it as a chronic, mainly mononuclear, inflammatory tissue response to slowly degradable or insoluble live or inanimate agents. For Mariano (1995), the granulomatous inflammation is the morphological substrate for many infections and non-infectious agents. The unique morphological characteristic of the granuloma is the occurrence of epithelioid cells and the concentric appearance of the whole lesion. For Seitzer et al. (2001), the term granuloma is applied to any small nodular delimited aggregation of mononuclear inflammatory cells or a collection of modified macrophages, usually surrounded by a rim of lymphocytes and often containing multinucleated cells. Recently, Págan and Ramakrishnan (2018) based in Adams and Williams' definitions (Adams 1976; Williams and Williams 1983) concluded that granuloma is a compact, organized aggregate of macrophages, frequently with characteristic morphological changes, and other immune cells, that arise in response to a persistent stimulus; what distinguishes granuloma formation from a chronic inflammatory aggregation is the characteristic organization of macrophages into a compact structure. For these authors, granulomas are enigmatic immunological structures, since many aspects of their development are not known (Págan and Ramakrishnan 2018).

Granuloma formation could be initiated by various non-infectious agents mainly with characteristics of insolubility and/or low degradability, such as silica, talc, and metal salts (Boros 1986), and inflammation and autoimmune diseases (e.g., Crohn's disease and systemic lupus erythematous) (Shah et al. 2016). The infectious granulomas are caused by

Section Editor: Ramaswamy Kalyanasundaram

✉ Selma Giorgio
sgiorgio@unicamp.br

[1] Department of Animal Biology, Biology Institute, State University of Campinas, Campinas 13083-865, Brazil

various virus, bacteria, fungi, protozoa, nematodes, and trematodes (Zumla and James 1996; James 2000; Guarner 2012; Págan and Ramakrishnan 2018). The latter three groups of organisms are traditionally placed among parasites.

There have been excellent recent reviews dealing with granuloma biology and infectious granulomas, but these addressed each specific disease or infectious diseases in general (for example, Guarner 2012; Chensue 2013; Guiraldo and Schlesinger 2013; Moore et al. 2013; Shah et al. 2016; Págan and Ramakrishnan 2018). The parasitic diseases affect more than one billion people worldwide, some are considered neglected tropical zoonotic diseases and most of them are chronic conditions (Pisarski 2019). The damaged associated with pathogen persistence that occurs because the immune response was unable to eradicate the parasite induces granulomatous responses, which in turn can shape the disease outcome. This outcome can be the eradication or parasite persistence (chronicity).

The characterization of granulomas in different parasitic diseases, as well as recent findings in this field, is discussed in this review in order to understand the significance of the granuloma in the host–parasite interaction and in the immune and pathological aspects of this interaction. This review is organized into items; the first item is about the general characterization of the granulomas; this is followed by discussions of specific parasitic granulomatous diseases (granulomatous amebic encephalitis, toxoplasmosis, leishmaniasis, neurocysticercosis, and schistosomiasis mansoni). Most of these parasitic diseases have tractable experimental models for the study of mechanistic and dynamical aspects of the granuloma.

General characterization of granulomas

There are several ways to classify granulomas, though some of them are confusing. However, two schemes of classification are more informative and based on the stimulus that induces granulation formation (infectious or non-infectious; for examples, see above) and the turnover of macrophages in granuloma (high or low). In the high-turnover type, the invoking agent is toxic to granuloma macrophages, leading to their death and replenishment by newly arrived macrophages; in this case, stimulus is still present (Págan and Ramakrishnan 2018). Examples of high-turnover granulomas are infectious granulomas. In the low-turnover-type granuloma, inert substances are surrounded by long-lived macrophages that are not replaced. As already mentioned, the predominant cell of a granuloma is the macrophage. During the evolution of infectious granuloma, macrophages respond to many stimuli (Ramakrishnan 2012) and change their morphology, resembling epithelial cells. Histologically, they have a flattened appearance, indistinct cell boundaries which are usually found aggregated into cluster within certain granules, abundant eosinophilic cytoplasm, and elongated or ship-shaped vesicular nucleus with prominent nucleoli (Yadav and Ramam 2018). An important ultrastructural observation is that these cells form interdigitated cell membranes in zipper-like arrays (Págan and Ramakrishnan 2018); the macrophage transdifferentiation into epithelioid cells is related to epithelial reprogramming to express epithelial structures (e.g., E-cadherin) (Van den Bossche et al. 2015; Nathan 2016; Págan and Ramakrishnan 2018) as studied in granulomas induced by *Taennia crassicpes* and *Schistosoma mansoni* infection (Van den Bossche et al. 2015; Díaz et al. 2017; Págan and Ramakrishnan 2018). Multinucleated giant cells, which are formed by the fusion of macrophages and are typically large with nuclei arranged in complete or partial wreaths at the periphery in cells (Yadav and Ramam 2018), are also seen in infectious granulomas; their development is mediated by interacting cell surface proteins present on the fusing macrophages, and it has been proposed that adhesion molecules and fusion regulatory proteins are involved in fusion and multinucleation (Helming and Gordon 2008; Págan and Ramakrishnan 2018). Other cells may be a part of a granuloma: lymphocytes, eosinophils, neutrophils, dendritic cells, and fibroblast.

The idea that granulomas represent a homeostatic mechanism for the neutralization of pathogens or foreign invaders and that this has been maintained during their evolution is largely accepted by researchers in the field. In fact, an evolutionary precursor or at least an analog response is observed in various phyla. For example, zebra fish infected with *Cryptococcus neoformans* produces macrophage aggregates consistent with granuloma observed in mammals (Tenor et al. 2015); the formation of a granuloma-like structure was observed in *Biomphalaria alexandrina* (mollusk intermediate host for *S. mansoni*) exposed to parasite miracidia (Ghoname et al. 2017), while the *insect Galleria mellonella* infected with *Mycobacterium abscessus* showed cellular structures resembling the granulomatous structures seen in human infection (Meir et al. 2018).

As will be seen in the following items, although granulomas are designed to be protective to the host, i.e., controlling the spread of the parasite, in various parasitic diseases, the associated tissue injury is often responsible for a profound degree of pathology (Ito et al. 2013). In addition, granuloma due to cell recruitment and containment in that space can also avoid a more potentially tissue-damaging effector mechanisms. For some chronic parasitic diseases examined here, granulomatous responses can shape the disease outcome, i.e., the eradication or parasite persistence (chronicity or latency). Thus, from the parasite perspective, granuloma can have a role in the onward transmission, i.e., an impact on its life cycle. These points are discussed below.

Granulomatous amebic encephalitis

Acanthamoeba and *Balamuthia* are free-living amebas distributed in various environments and contain species that are pathogenic to humans. *Acanthamoeba* may cause localized amebic keratitis and chronic granulomatous amebic encephalitis (GAE), more often in immunocompromised individuals and otherwise debilitated individuals (Perez and Bush 2007; Visvesvara et al. 2007). The routes of infection are by direct contact, through a break in the skin, or through the nasal cavity or respiratory tract. *Balamuthia mandrillaris* may also cause GAE in immunocompromised and immunocompetent individuals who have a breach in natural protective barriers, such as a break in the skin, or by pulmonary inhalation (Perez and Bush 2007). Both organisms have two life cycle stages, trophozoite and cyst. The infective form is trophozoites that can migrate to the central nervous system (CNS) via the blood stream and olfactory neuroepithelium (in the case of *Acanthamoeba* infection), where they proliferate, inducing a rare granulomatous inflammatory reaction that progresses for a period of weeks or months. Although GAE cases have increasingly been reported, they are often under-diagnosed and the pathogenesis of GAE is not fully understood (Kalra et al. 2020). The disease usually starts with headaches, nausea, and low-grade fever, and progresses to other neurological symptoms such as altered mental state, diplopia, and ataxia, leading often to death within a few months of symptom onset due to increased intracranial pressure (Duggal et al. 2017; Kalra et al. 2020). It is likely that circulating amebas cross the blood–brain barrier to enter the CNS; attach to a host cell, phagocyte, and "bite off" cells; secrete toxins such as extracellular proteases which are necrotic as well as apoptotic agents; and damage the brain tissue. Studies supporting this hypothesis are carried out with numerous in vitro assays, *various cell lines from different embryonic origins*, and *Acanthamoeba* (Pettit et al. 1996; Khan 2003). In a recent article, Shah et al. (2016) reviewed histologic patterns seen in a variety of clinical conditions and associated infections by *Acanthamoeba* and *B. mandrillaris* with the presence of suppurative granulomas, defined by a collection of epithelioid histiocytes and multinucleate giant cells with a central collection of polymorphonuclear leukocytes (PMNs), possibly occurring in association with necrotizing or non-necrotizing granulomatous inflammation (Kinard et al. 2016; Shah et al. 2016; Thomas et al. 2018). In fact, parenchymal necrosis and granulomas with variations in the amount of inflammation that are dependent on the immunological status of the host are found in the biopsy of brains. It has been postulated that the impairment of host defense mechanisms in immunocompromised individuals results or contributes to infection and GAE, since a well-developed granulomatous reaction may not occur in these patients and well-developed granulomas that form around amebas can be found in immunocompetent individuals (Marciano-Cabral and Cabral 2003; Modica et al. 2018; Muzzi et al. 2018) The presence of T and B cells, in addition to microglia, macrophages, multinucleated giant cells, and polymorphonuclear cells, in granulomas observed in immunocompetent individuals and healthy mice infected with *Acanthamoeba* (Fig. 1a) in opposition to rare granulomas observed in AIDS patients with GAE and mice immunosuppressed and infected with ameba (Martínez 1982; Visvesvara et al. 2007) supports the notion that the concerted action of immune cells within granulomas results in sequestration of amebas and is instrumental in slowing or controlling the progression of GAE (Janitschke et al. 1996; Harrison et al. 2010).

Recently, with the evaluation of more clinical cases, it has become apparent that classification of GAE is not as clear-cut as previously thought. Modica et al. (2018) described an unusual case of non-granulomatous *Acanthamoeba* cerebellitis in an immunocompetent adult with abrupt onset of neurological impairment and histopathological findings of excised cerebellar mass of necrosis, inflammation, and trophozoites, but without granulomas, while Guarner et al. (2007) reported that histopathology of *Balamuthia* infections showed a wider spectrum of inflammatory reactions, from acute inflammation only to mixed inflammation with or without granulomas. Currently, it also become clear that an early development of type IV hypersensitivity reaction (dependent of Th1 lymphocyte activation and pro-inflammatory cytokines) tends to develop during amebic encephalitis; in cases in which this immune reaction is not sufficient to control infection, granuloma may develop and wall off the amebas and injured tissue (Baig 2015; Guarner et al. 2007).

Since GAE is not a chronic disease, no role can be attributed to the granuloma in the persistence of the parasite. In addition, the amebas involved in GAE have the external environment as their natural habitat and only eventually infect humans. Furthermore, they do not depend on the host for transmission. If we are faced with amebas in the transition to the parasitic way of life, then the role of granuloma in the transmission can be evaluated in the future.

Future studies done by using in vivo imaging, real-time markers for granuloma cells, cytokines, and ameba developed through novel probes and transgenic technology should provide a detailed and complete picture of granuloma development and activity during GAE.

Toxoplasmosis

Toxoplasma gondii is an obligate intracellular protozoan in which felines are the definitive hosts and mammals and birds are the intermediate hosts. In humans *T. gondii* infection occurs through the ingestion of tissue cysts (containing bradyzoites) from undercooked meat, consumption of food or drink contaminated with oocysts, or ingestion of oocysts from the environment (Dubey 2008). In immunocompetent

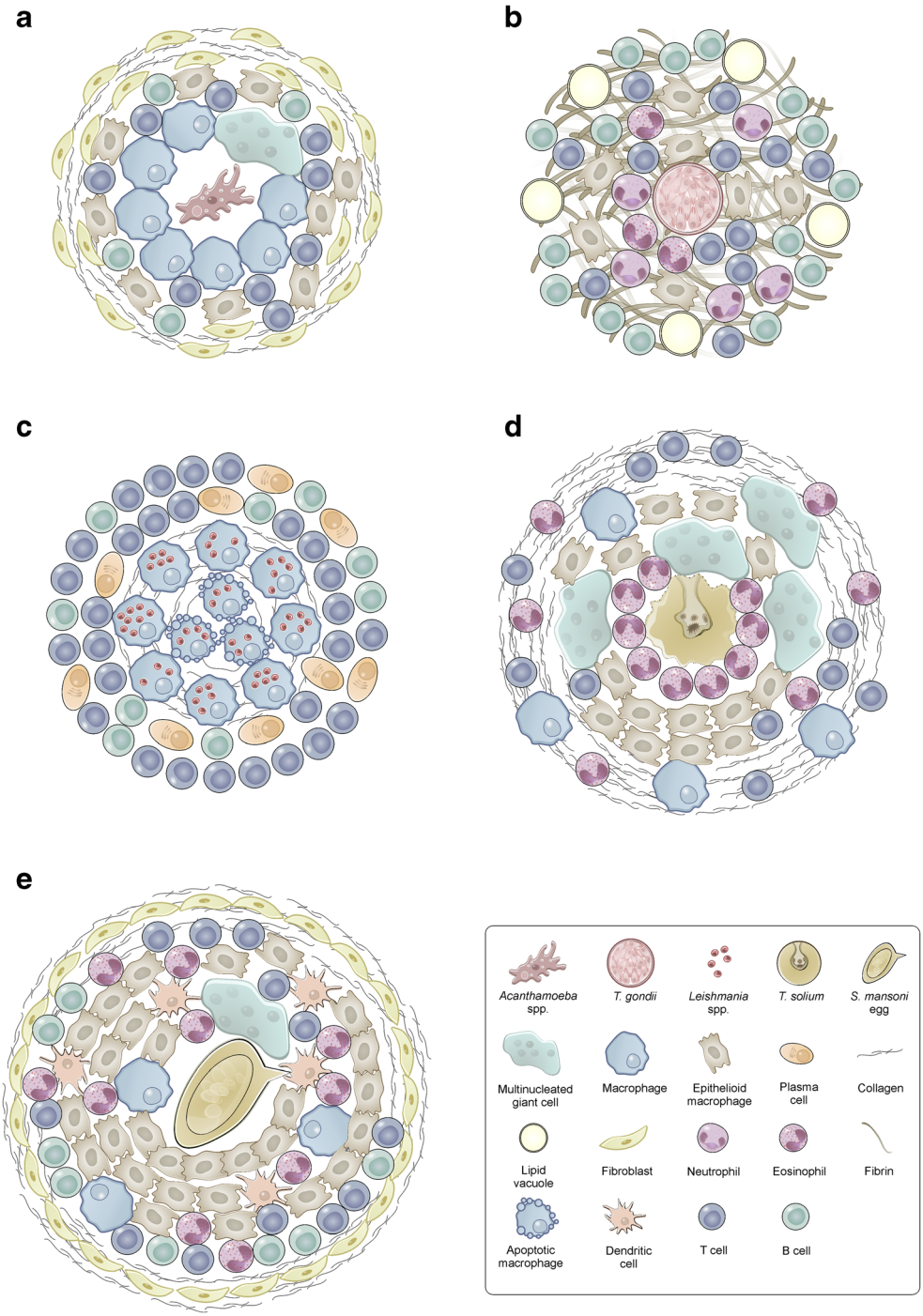

Fig. 1 The granuloma composition in some parasitic diseases. **a** GAE well-developed granuloma with ameba surrounded by multinucleated giant cell, epithelioid macrophages, macrophages, T and B cells, fibroblasts, and peripheral collagen fibers. **b** Toxoplasmosis less organized granuloma with parasites, macrophages, T and B cells, neutrophils, eosinophils, and lipid vacuoles surrounded by fibrin. **c** Leishmaniasis granuloma with focal dying infected macrophages, collagen fibers surrounded by infected macrophages, plasma cells, and T cells. **d** NCC granuloma with a dying *T. solium* cysticercus surrounded by eosinophils, multinucleated giant cells, epithelioid macrophages, macrophages, T cells, and collagen fibers. **e** Schistosomiasis mansoni granuloma with egg surrounded by macrophages, eosinophils, dendritic cells, and T and B cells. Fibroblasts and collagen fibers in the periphery present as signs of fibrosis

humans, toxoplasmosis is asymptomatic; however, nonspecific flu-like symptoms, lymphadenopathy, and some rare complications might be associated with primary infection (Saadatnia and Golkar 2002; Dubey 2008). *T. gondii* infection during pregnancy may be harmful or even fatal to the fetus (Saadatnia and Golkar 2002). Ocular toxoplasmosis or toxoplasmic retinochoroiditis results from both congenital and acquired parasite infections (Commodaro et al. 2009; Schlüter and Barragan 2019). Toxoplasmosis is also an opportunistic infection, particularly in immunodeficiency conditions such as HIV/AIDS or organ transplants; in these patients, reactivation of a latent infection might result in toxoplasmic encephalitis, which is potentially fatal if not treated properly (Saadatnia and Golkar 2002; Commodaro and Barragan 2009).

Toxoplasmosis is classified as a granulomatous disorder (Zumla and James 1996; Shah et al. 2016). Guarner (2012) characterized granulomas induced by *T. gondii* as

"granulomas with a vacuole surrounded by fibrin" composed by macrophages, multinucleated cells, lymphocytes, neutrophils, and lipid vacuoles surrounded by fibrin, but did not discriminate organ localization (Fig. 1b). Shah et al. (2016) associated toxoplasmosis with non-necrotizing granulomas observed in the lung, lymph nodes, and liver. In fact, there are reports of granulomas in the liver and also the bone marrow of immunocompetent and immunodeficient patients (Bertoli et al. 1995; Abdulla and Jemshad 2017). Histologically, ocular toxoplasmosis typically presents extensive granulomatous inflammatory infiltration of the choroid and areas of necrosis (Montoya and Liensenfeld 2004; Belfort et al. 2010). In toxoplasmic lymphadenitis in immunocompetent individuals, reactive follicular hyperplasia, irregular clusters of epithelioid histiocytes encroaching on and blurring the margins of the germinal centers, and focal distension of sinuses with monocytoid cells are commonly seen, while Langhans giant cells, granulomas, microabscesses, foci of necrosis, and parasites (or their DNA) are not typically detected (Montoya and Liensenfeld 2004). In ocular toxoplasmosis, granulomatous inflammation of the choroid is commonly seen (Montoya and Liensenfeld 2004). In cerebral toxoplasmosis in AIDS patients, analyses of brain tissue in surgical biopsies and autopsies vary; moderate to severe inflammation, predominance of neutrophils, and frequent fibrous encapsulation are important histological findings (Falangola et al. 1994).

In other hosts infected with *T. gondii*, the presence of granuloma was reported. For example, brain lesions found in rabbits were characterized by inflammation, edema, necrosis, and the presence of granuloma surrounded by cells with pyknotic nucleus and large cells with epithelioid appearance (De Lima et al. 2016). Brain granulomas were also observed in cats suffering from toxoplasmosis (Pfohl and Dewey 2005; Falzone et al. 2008).

Despite these histopathological studies, the mechanism and dynamics of granuloma development have been *little studied*. The murine model of toxoplasmosis has been used to study immune response disease (Denkers and Gazzinelli 1998). Mice develop fatal acute infection in which the liver, spleen, and lymph nodes are affected, while granulomas containing parasites are seen in the liver (Corrêa et al. 2017) and chronic progressive diseases characterized by cyst burden and granuloma are detected in the brain (Schaeffer et al. 2009), depending on both the parasite and mouse strains. In an elegant study, Schaeffer et al. (2009) aiming to examine T cell–*T. gondii* interactions in the brains of chronic infected mice through time-lapse and two-photon imaging, structures composed of balls of static monocyte myeloid cells enclosing parasites and that are surrounded by T cells were described. Interestingly, time-lapse imaging revealed that granulomas accumulated parasite-specific T cells and individual parasites and not cysts. In this scenario, it is possible that antigen recognition in macrophages by T cells, stimulation of T cell effector responses, and macrophage activation by T cells take place in granulomas. The authors suggest that the physical "walling of" parasites within granuloma could provide a means of controlling parasite spread while avoiding a more potentially damaging effector mechanism. This is likely, since cell recruitment and containment are seen in granuloma development (Schaeffer et al. 2009).

On the other hand, different *T. gondii* strains differ in their capacities to induce pathology; type 1 strains are more virulent and lethal than type 2 strains, and type 3 parasites are the least virulent strains resulting in lower cyst burden and less brain inflammation (Suzuki et al. 1993; Saeij et al. 2005). The tachyzoites long-distance migratory capacity and shorter doubling time of division, and decreased conversion to the bradyzoites, observed in type 1 strains as well as the high levels of the inflammatory cytokines causing pathology by type 2 strains, are directly involved in the outcome of toxoplasmosis (Saeij et al. 2005). Recently, Chen et al. (2020) proposed a parasite strategy that modulates the M2 macrophage phenotype, which could provide a refuge for *T. gondii* replication. Using a type 3 strain *T. gondii*–expressing Cre recombinant rhoptries, they demonstrated that the parasites inject rhoptry proteins into infected macrophages and non-infected macrophages, activating STAT3 and STAT6 transcription factors and inducing M2 macrophages with limited actimicrobial activities. Whether this phenomenon is occurring within granuloma containing viable parasites is not yet known, but it could be one of the mechanisms involved in the long time span *T. gondii* remains in their hosts.

The presence of granulomas seems to be important for the persistence (latency and chronicity) of the *T. gondii*, since viable parasites and cysts are surrounded by granulomas, and studies point out that healthy mice have chronic toxoplasmosis and the presence of granulomas (168 days), while immunodeficient and athymic mice have an acute phase and die after 3 days (Schlüter et al. 1991). Consequently, granulomas should play a positive role in the transmission of *T. gondii*, since intermediate hosts such as rodents and rabbits have granulomas in their tissues, and the parasite spreads to a definitive host field, largely through a predator–prey system.

Finally, in the case of *T. gondii* granuloma, understanding *histopathological* pattern assessment and the review of granulomas in different tissues of natural *T. gondii* infections is necessary, as well as mechanistic studies of granulomas using different approaches, such as single-cell analysis and laser microdissection.

Leishmaniasis

Species of genus *Leishmania* are protozoan belonging to the order Kinetoplastida and family Trypanosomatidae, which are transmitted by phlebotominae sandfly vectors. There are two

life cycle stages amastigotes, found in vertebrate hosts, mainly in mononuclear phagocytes, and extracellular promastigotes, found in sandflies. *Leishmania* is divided into old and new world variants. There are more than 20 species which may produce clinical diseases in humans, most inducing a spectrum of clinical responses ranging from self-healing cutaneous lesions (CL) to nonhealing cutaneous and mucosal lesions (ML), and visceral disease (Burza et al. 2019).

Leishmaniasis is considered granulomatous infections (Zumla and James 1996; Guarner 2012; Shah et al. 2016). The granuloma induced during leishmaniasis is classified as epithelioid with minimal or no necrosis (Fig. 1c), and, as we will see below, granulomas in the case of leishmaniasis are associated with the curative phase of infection (Kaye and Beattie 2016).

The CL present complex histopathological patterns in both the old and new worlds, making a simple classification difficult. Authors reported two histological patterns: early lesions (less than 1 year) with diffuse macrophage infiltrates and amastigotes, and late lesions (more than 1 year) with organized granulomas (Mansour et al. 1993; Kurban et al. 1996). Ridley (1980) classified CL histopathology findings into five types: diffuse macrophage involvement without necrosis, diffuse macrophage necrosis, focal macrophage necrosis, early reactive tuberculoid granuloma, and tuberculoid granuloma. The intact macrophage granuloma without necrosis, macrophage lyses with necrosis, and macrophage activation with granuloma formation are host responses against *Leishmania* (Ridley and Ridley 1986; Venkataram et al. 2001; Arruda et al. 2002). Recent studies reinforce these previous analyses and add relevant information to understand the importance of granuloma for parasite control during CL. For example, Safaei et al. (2002) analyzed PCR for *Leishmania* and histopathological findings of skin biopsies of self-healing CL cases in old world countries and showed that despite the detection of parasite DNA in the majority of skin tissues, visualization of amastigotes was associated only with the presence of unorganized granuloma (called by authors immature granuloma), and the parasite itself was not visualized in mature granulomas. In another study, a surprisingly high number of caseating granulomas were found in CL cases in the old world (Aoun et al. 2014). The authors showed that patients with these granulomas had slower healing processes than patients with tuberculoid granulomas (Aoun et al. 2014). In the new world, the species of *Leishmania* subgenus, *L. amazonensis*, induces CL with macrophagic granuloma characterized by a dense infiltrate of vacuolated macrophages and lymphocytes, and species of *Viannia* subgenus, *Leishmania braziliensis*, induces ulcerated CL containing epithelioid granulomas with lymphocytes, plasma cells, and very few macrophages and amastigotes (Silveira et al. 2004). To better understand the sequential events of granuloma development during CL, Teva et al. (2003) infected *Macaca mulata*, a macaque model of infection, with *L. braziliensis*, and found that up to 72 h after parasite inoculation, there was recruitment of polymorphonuclear leukocytes, mast cells, and macrophages. After 2–3 weeks, the dermis showed an infiltrate containing macrophages and some macrophages contained amastigotes. In the late stages of CL, more differentiated macrophages evolved to form tuberculoid-type granulomas consisting of epithelioid cells, Langhans-type multinucleated giant cells, lymphocytes, and plasma cells surrounded by macrophages and fibroblasts. In the cutaneous scars, fibroblasts proliferated and invaded the granulomas with fibrotic substitution (Teva et al. 2003). It should be noted that some *Leishmania* species have been known to infect fibroblasts (Corte-Real et al. 1995; Elshoura et al. 1996; Bogdan et al. 2000). Whether they are a safe target for parasites and account for the persistence of parasites after the resolution of lesions is currently *unknown* (Corte-Real et al. 1995; Bogdan et al. 2000). Teva et al. (2003) also showed that IFN-γ- and/or TNF-α-producing CD4+ and CD8+ T cells are present in the granulomatous lesions of *M. mulata*, suggesting that the scenario established in mice and in vitro models, in which macrophages are activated by IFN-γ and TNF-α produced by T cells for the elimination of intracellular parasites via the triggering of microbicidal molecules, such as reactive oxygen species and reactive nitrogen species, occurs during the granuloma stage. Another relevant molecule, the TLR9 (Toll-like receptor), was shown to be present in the dermis of patients with CL. TLR9 expression is intense and restricted to granuloma containing giant cells; it is likely that the amastigotes within the granuloma present protozoan DNA (CpG motifs) that stimulates TLR9 expression, granuloma formation, and parasite control (Tuon et al. 2010).

In the case of ML, most patients exhibit earlier self-healing CL induced by *L. braziliensis*. The parasite can persist in healing lesions and tends to metastasize, resulting in recurrent lesions with the potential for mucosal involvement (Mendonça et al. 2004). In ML, necrosis of the nasopharyngeal mucous tissue is associated with the presence of abundant infiltrates of lymphocytes and plasma cells, with very few histiocytes, macrophages, and parasites (Mendonça et al. 2004). In some studies with ML patients, a tuberculoid granulomatous reaction associated with the Th1 response pattern (CD4 T cells, INF, and TNF production) was detected; in other studies, a mixture of Th1 and Th2 responses (IL-4, IL-5, IL-10 production) was detected in ML patients (Cáceres-Dittmar et al. 1993; Pirmez et al. 1993). Using the *M. mulata* model of *L. braziliensis* infection, Souza-Lemos et al. (2008) analyzed an individual with ML; the mucosal lesion showed an exudative cellular reaction associated with focal tissue necrosis, followed by poorly organized granuloma. Further investigation with a larger number of ML patients and the development of animal models of ML are

necessary to elucidate the immunopathology and granulomatous responses during ML.

Visceral leishmaniasis (VL) caused by *Leishmania infantum* in the new world and *Leishmania donovani* in the old world manifests by splenomegaly accompanied or not by hepatomegaly; bone marrow and lymph nodes are parasitized, and anemia, thrombocytopenia, and neutropenia are frequent (Rodrigues et al. 2016). Although only a small proportion of infected individuals manifests clinical disease, *VL is fatal* when *not treated* (Sing et al. 2014). The splenic histopathology changes frequently associated with VL are hyperplastic reactive lymphoid follicles, no clear distinction between white and red pulps, a large reduction of normal resident cell populations and/or replacement by plasma cells, hyperplasia and hypertrophy of macrophages where parasites proliferate, and failure of granulomatous response (Veress et al. 1983; Goto and Prianti 2009; Hermida et al. 2018). In the liver, hypertrophy and hyperplasia of Kupffer cells with variable parasitism, foamy macrophage aggregates, infected macrophages forming small nodules or loosely formed granulomas, pericellular fibrosis, and failure to develop organized granulomas are characteristics of VL (Hermida et al. 2018). Although scarce data are available concerning asymptomatic patients, Pampiglione et al. (1974) biopsied the livers of asymptomatic patients with positive delayed type hypersensitivity for *Leishmania* and observed granulomas consisting of epithelioid macrophages, histiocytes, lymphocytes, and plasma cells. Taken together, these results suggest a causal relation between granuloma and resistance to VL.

Dogs are also *L. infantum* hosts; amastigotes can be found in macrophages of the bone marrow, lymph nodes, liver, and spleen; the commonest clinical signs of canine leishmaniasis (CanL) are lymphadenomegaly, alopecia, onychogryphosis, exfoliative dermatitis, atrophic myositis of masticatory muscles, glomerulonephritis, polyarthritis, and uveitis (Maia and Campino 2018). The findings reported in dogs with CanL reinforce the notion that granuloma is associated with the resistance phase of *Leishmania* infection. For example, in a clinical–histopathological study carried out in Venezuela, the livers of asymptomatic dogs showed well-organized granulomas walling off parasites, macrophages, T cells, and dendritic cells (Sanchez et al. 2004). In contrast, livers from symptomatic dogs showed unorganized infiltrate composed of T cells and heavily parasited Kupffer cells; in the spleens, a similar histologic pattern was observed in CanL (Sanchez et al. 2004). A histological description of intralobular hepatic granulomas of mongrel dogs naturally infected with *L. infantum* with defined clinical status from two Brazilian endemic areas also indicated a higher number of granulomas constituted by parasitized or non-parasitized macrophages, epithelioid cells, lymphocytes, plasma cells, and neutrophils in asymptomatic dogs as compared with the livers of oligosymptomatic and symptomatic CanL animals from both geographical regions (Sant'Ana et al. 2007). Interestingly, in a recent paper, Lima and co-workers studied semi-domiciled and street dogs with differing clinical manifestations of CanL in an endemic area in the State of Bahia, Brazil, and found that the frequency and morphological characteristics of granulomas bore no relation to clinical manifestations in the dogs, nor was there any association with the control of parasitism and the well-organized granulomas containing many amastigotes in their interior (Lima et al. 2019). The authors proposed, based on similar findings of some experimental models of leishmaniasis as well as in tuberculosis studies, that granulomas in dogs may also be permissive or non-permissive to *Leishmania*, i.e., can either eliminate parasites or favor their survival (Murray 2001; Lima et al. 2014; Lin et al. 2016; Lima et al. 2019).

The mouse models of leishmaniasis has helped a great deal in understanding the immune mechanisms, as well as providing insight into details of granulomas; some reviews on both subjects have been published in recent years (Nieto et al. 2011; Kaye et al. 2004; Rodrigues et al. 2016). Below is a brief summary of important investigations and their conclusions related to granulomas in mouse models of leishmaniasis.

Mice strains, such as C57Bl/6, infected with *L. amazonensis* or *Leishmania major* have a controlled disease associated with a Th1 response; histologically, lesions show a mononuclear infiltration, few infected macrophages, granuloma formation, and necrosis that are not seen in the lesions of susceptible mice strains. In the susceptible mice (Balb/c), the Th2 response is dominant and the lesions displayed a monomorphic appearance with massive numbers of vacuolated and heavily parasitized macrophages, and no granulomas were seen (Almeida et al. 1996; Giorgio et al. 1998). In some mice strains infected with *L. donovani* or *L. infantum*, the liver infection is self-resolving, depending on the Th1 immune response, and induces granulomas, while in the spleen, parasites persist and granulomas fail to form, resulting in a life-long chronic infection (Kaye et al. 2004; Salguero et al. 2018). The use of a combination of approaches including intravital microscopy, confocal microscopy, adoptive cell transfer, and gene-targeted mice has allowed the examination of the spatial–temporal development of granulomas within the mouse liver during VL. During the first hours after the phagocytosis of amastigotes by Kupffer cells, the granuloma begins with mononuclear cell recruitment and infected Kupffer cell fusion to form multinucleate cells and aggregates (Kaye and Scott 2011). As the infection proceeds, chemokines such as CCL2, CCL3, and CXCL10 produced by Kupffer cells are detected and more inflammatory cells are recruited (Kaye et al. 2004; Kaye and Scott 2011). The CD4 and CD8 T cells (antigen-specific and non-specific T cells) and invariant NKT (iNKT, see below) are recruited to the granuloma and move freely into and out of granulomas. The long-term contact between CD4 T cells and APC (antigen-presenting cells) was not widely observed, although Kupffer cells laden with

amastigotes form long-lasting antigen-specific interactions with $CD8^+$ T cells within the granuloma (Kaye and Scott 2011; Beattie et al. 2010). The predominance of *Th1-type inflammatory cytokines* in hepatic tissue during experimental VL has been extensively demonstrated (Salguero et al. 2018). For example, IFN-γ produced by lymphoid cells including CD4 T cells and NKT cells, which activates microcidal functions of Kupffer cells; IL-12 produced by Kupffer cells; and TNF-α were detected at significantly higher levels in the liver and were involved in cell recruitment to granuloma (Murray et al. 1992; Cotterell et al. 1999; Saunders and Cooper 2000; Beattie et al. 2010; Robert-Gangneaux et al. 2012). Using the same experimental approaches, the Bousso group studying the mouse model of CL induced by *L. major* showed heterogeneity in the level of parasitic specific CD4 T cell infiltration in different areas of dermal lesional tissue (i.e., granulomas and stromal microenvironment). They also showed that both stable and labile contacts between infected cells and CD4 T cells in the lesional tissue occur. This should result in an efficient activation of microbial mechanisms in infected macrophages by IFN-γ produced by T cells and maintenance of niches (Filipe-Santos et al. 2009; Müller et al. 2012; Heyde et al. 2018). These niches are not detrimental to *L. major*, since a high parasite burden represents a source of non-self-antigens. A similar conclusion can be made for experiments discussed below, using a murine VL model.

With the aim to understand the granuloma dynamics in VL and the regulatory mechanisms operating to limit excessive granuloma formation that can lead to pathological consequences, Moyo et al. (2018) used transcriptomics, agent-based modeling. The in vivo experiments with a mouse model of VL showed that granuloma formation proceeds asynchronously, i.e., granulomas are found side by side with granuloma-free scattered infected Kupffer cells (outside of granulomas) in the *hepatic tissue at the same time*. The data also demonstrated that in addition to the infected Kupffer cells, non-infected Kupffer cells also produce various chemokines (Cxcl1, Cxcl2, Cxcl3, Ccl3, Ccl4, Cxcl5, Cxcl8, Ccl9, and Cxcl10), some of them are able to attract the iNKT cells, a subtype of NKT cell, which participate in the establishment of a sustained cytokine synthesis network, including the production of large amounts of INF-γ involved in cell attraction and parasite clearance within liver granulomas. The authors *hypothesized* that both infected and non-infected Kupffer cells producing chemokines will compete with each other to attract NKT cells, affecting the formation of granulomas (Moyo et al. 2018), i.e., ultimately inhibiting the extent of the granuloma and leaving infected cells isolated and non-engaged in granulomas in the liver tissue.

In addition to the host genotype that shapes the immune response against the parasite and granuloma formation, *Leishmania* intraspecific differences also shape the outcome of the infection. For example, a *L. major* strain isolated from a patient with nonhealing CL induces resistant C57Bl/6 chronic and nonhealing lesions. The Sacks group showed that these mice mounted a strong Th1 response, but had lesional IL10 and dermal infected M2 macrophages (Anderson et al. 2005, Lee et al. 2018). The parasite induction of suppressor cells and cytokines in the inflammatory site might be an evasive strategy to render Th1 response relatively ineffective and prevent the parasite clearance, and it should occur through distinct mannose-containing glycoconjugates expressed in nonhealing *L. major* strain (Lee et al. 2018).

Leishmaniasis is a spectrum of zoonotic diseases, which makes it difficult to draw general conclusions. However, we suggest that the granulomatous responses in leishmaniasis, in general, are host-protective and are not host-deleterious structures. The various observations of the presence of non-permissive granulomas for amastigotes in tissues of hosts (rodents, dogs, and humans) and niches containing infected cells that are non-engaged in granulomas, during CL and VL, suggest that the granuloma environment can "protect" some amastigotes from death. Leishmaniasis is a disease transmitted by insect vector, which the infected reservoirs are necessary for the transmission of the parasite. The importance of reservoirs can be appreciated by the wide variety of classes infected with *Leishmania*, seven mammal orders—Marsupialia, Cingulata, Pilosa, Rodentia, Primate, Carnivora, and Chiroptera (Roque and Jansen 2014).

The granuloma is host-protective in leishmaniasis but also seems to be important in maintaining the life cycle of this parasite, and many aspects of the dynamics of granuloma organization during leishmaniasis have been understood in recent years. However, there are many interesting facets of the subject yet to be explored, such as the importance of these structures in immunological memory, the determination of parasitic antigenic stimuli for granuloma formation, differences at the level of individual granulomas, and the immunometabolic features of these structures, a research area, which is developing, particularly in the case of granulomas in tuberculosis (Wilson et al. 2019), as well as the studies of granulomatosis lesions in natural and wild animal reservoirs of *Leishmania*.

Neurocysticercosis

Taenia solium is a *cestode* parasite whose life cycle includes the adult stage, the eggs, or oncospheres, and the larval stage, or cysticercus. Humans are definitive hosts when infected by cysticercus by ingestion of raw or semi-cooked pork, and pigs are intermediate hosts when they ingest feces with proglotes containing eggs (García et al. 2003). Humans can also become infected with *T. solium* when they ingest water or vegetables contaminated with eggs. The cysticercus develops in nervous tissues, and the disease is referred to as neurocysticercosis (NCC). As in other larval taeniid infections, granulomatous

responses are observed in NCC, and the development of the immune tissue responses against various larval taeniids infections has been reviewed (Fleury et al. 2016; García et al. 2018).

NCC may be symptomless (high percentage of infected individuals) or associated with a variable clinical spectrum such as seizures and epilepsy, through headaches, focal signs, and cognitive deficits (García et al. 2018). Histological and radiological data from parenchymal NCC in humans indicate an initial stage (vesicular stage) of the infection in which viable parasite and scanty inflammatory reaction are seen in the brain, with no symptoms exist (Nash et al 2018; Carpio et al. 2018). Currently, it is accepted that cysts can survive in the human brain for a long time, likely protected by the blood–brain barrier and by promoting a suppressive inflammatory environment (García et al. 2010; Adalid-Peralta et al. 2013; Del Brutto 2014). In vitro studies have demonstrated that a metacestode factor (MF) is derived from viable cysticerci of *T. solium*–inhibited lymphocyte proliferation and production of IL-2 and INF-γ in murine spleen cells and TNF-α by macrophages, and that human dendritic cells promote regulatory T cell differentiation in the presence of viable *T. solium* cysticerci (Molinari et al. 1990; Tato et al. 1995; Arechavaleta et al. 1998; Adalid-Peralta et al. 2013).

The colloidal stage occurs when eventually the cyst dies and, consequently, cannot promote an inflammatory suppressive environment. On the contrary, antigens released from disintegrated or dead parasites elicit a local and inflammatory Th1 reaction that initiates with stimulated microglial cells and resident macrophages producing and secreting chemokines such as CCL2, CXCL8, and CCL3 that cause transendothelial migration of peripheral monocytes and neutrophils, a prerequisite for granuloma development (granular stage). These granulomas are mainly composed of degenerative parasite surrounded by macrophages, epithelioid cells, multinucleated giant cells, neutrophils, B cells, T cells, and plasma cells as well as layers of types I and III collagen (Fig. 1d) with prevalent Th1 cytokines such as INF-γ and IL-18, whereas the Th2 profile included IL-13 (Restrepo et al. 2001; García et al. 2010; Fleury et al. 2016).

The colloidal and granular stages are seen in symptomatic NCC patients, and it has been hypothesized from the findings in human brain biopsies, mice models of NCC, and in vitro studies that neuroinflammation and granuloma in NCC are a "double-edged sword," i.e., granulomas formed in response to dying parasites are required to act as a barrier between antigens and disintegrating parasites and adjacent CNS tissue, but potentially cause an increase in symptomatology and clinical complications (Carpio et al. 2018). For example, recently, Robinson et al. (2012) showed that brain biopsies from NCC patients contained the substance P, a neuropeptide produced by neurons, endothelial cells, and immunocytes, and involved in the pathogenesis of seizures; in addition extracts of granulomas from NCC mice caused seizures when injected into the hippocampus of wild type mice, but not when injected into transgenic mice deficient SP receptor, suggesting that seizures are the result of the granulomatous host response rather than mediators produced by the parasite itself.

Once the parasite debris is cleared from the tissue, the granuloma resolves. In the calcified phase, the granulation tissue is replaced by collagenous structures and calcification (Escobar 1983; White 2000; Robinson et al. 2012), and the calcified lesions with the surrounding edema have been associated with episodic seizure activity, leading researchers to speculate that substance P within the inflammatory response leading to edema around calcified cysts causes seizures in this setting as well (Stringer et al. 2003; Robinson et al. 2012).

However, there is evidence to suggest that *T. solium* has developed mechanisms to delay granulomatous response. Cysts cysteine proteinase, which induces lymphocyte apoptosis (Mkupasi et al. 2013), a small RNA peptide which reduces size and cellularity of murine granuloma (Tato et al. 1995) and parasite mature micro RNA, which suppress inflammatory cytokine production in macrophages (Landa et al. 2019), should be a role in the downregulation of granulomatous response.

Humans as an intermediate hosts are dead-end host of *T. solium*. Pigs, a *T. solium*–preferred species as intermediate hosts, have chronic cysticercosis which is characterized by the simultaneous presence of intact cysts surrounded by stable fibrous capsules, and degenerative cysts surrounded by Th1-type inflammatory granulomas in heart and skeletal muscles (Alvarez et al. 2002; Londoño et al. 2002). The parasite persistence in these tissues guarantees that the definitive host become infected, since the *T. solium* life cycle involves a predator–prey system.

Although many aspects of immunopathology of NCC are known, several questions remain unanswered. Some of these are related to granulomas: the identification of antigens responsible for immunomodulation and granuloma development, the role of different cells in the control of disease and the pathology of NCC, and the mechanisms associated with the resolution of granuloma and calcified *T. solium* development.

Schistosomiasis mansoni

Schistosoma is digenetic flatworms that belong to the Plathelminthes phylum and Trematodea class. In the mammalian definitive hosts, the male and female adults reside within the mesenteric veins of the intestine (*S. mansoni*), mate, and produce eggs. The eggs are deposited in the venules, move toward the *lumen* of the intestine, and are excreted with *feces*; in fresh water, the now miracidia penetrate the snail host and transform into *cercarias*. These larvae are released from the snail into water; can penetrate the dermis of mammalian hosts;

and develop, during a complex migration in the host body, into adult worms (Pearce 2005).

There are many pathogenic *Schistosoma* species, such as *S. mansoni*, *S. haematobium*, *S. japonicum*, and *S. mekongi*. In this review, we focus on schistosomiasis mansoni, since the periovular granuloma induced during the infection is one of the most studied granulomatous responses. Indeed, schistosomiasis is a disease caused predominantly by the host's immune response to schistosome eggs and the granulomatous reaction they evoke (Burke et al. 2009).

There is acute and chronic schistosomiasis. The acute disease is uncommon in residents of endemic areas and is characterized by myalgia, abdominal pain, diarrhea, fatigue, malaise, and fever. Most patients recover spontaneously, whereas some develop more serious disease, diarrhea, diffuse abdominal pain, and hepatomegaly, as a consequence of the worm maturation and initiation of egg deposition (McManus et al. 2018). Reviewing the studies of outbreaks of acute schistosomiasis mansoni in Brazil, Lambertucci (2010) demonstrated that there are usually necrotic–exudative periovular granulomas with dense eosinophilic infiltrate on the serosal surface of the liver tissue obtained by needle biopsy and in the intestine of patients with well-defined clinical pictures. Data of the immune responses of some patients with acute disease showed that their peripheral blood mononuclear cells stimulated with adult worm antigen produced mixed Th1 and Th2 cytokines (Williams et al. 1994; Abath et al. 2006). De Jesus et al. (2002) showed that patients with acute schistosomiasis produced more INF-γ than chronically infected patients, but fewer patients with acute disease produced IL-10 in response to soluble egg antigen (Abath et al. 2006). Unfortunately, these results were not related to the presence of granulomas in the tissues.

In chronic schistosomiasis, the intestinal form causes nonspecific abdominal pain, diarrhea with or without blood, and anemia, and is associated with the deposition and retention of eggs produced by the female worm in the intestinal mesenteries (mainly of the colon and terminal ileum) (Burke et al. 2009; Weerakoon et al. 2015; Costain et al. 2018). A subsequent granulomatous response is observed around the eggs if they are not voided and form large non-malignant masses, pseudopolyposis, and microulceration (Burke et al. 2009; Betson et al. 2010); in other colonic biopsies, mild inflammatory infiltrates were observed in chronic schistosomal patients, but also sub-mucosal fibrosis and granulomas around the eggs, composed of eosinophils, lymphocytes, macrophages, and plasma cells (Mohamed et al. 1990; Cao et al. 2010; Swe et al. 2016).

The hepatosplenic disease is the severe form of schistosomiasis mansoni which *occurs in about 10%* of infected individuals (Lambertucci et al. 2000; Voieta et al. 2010). The disease is associated with enlargement of the liver and spleen, as well as periportal fibrosis that leads to portal hypertension, portacaval shunting, ascites, and gastrointestinal varices which can result in fatal upper gastrointestinal bleeding (Strickland 1994; De Cook 1986; Burke et al. 2009; Colley et al. 2014). There is some variability in the histological findings of liver fragments from patients; variable degrees of fibrosis with the absence or presence of periovular granulomas, sometimes with calcified egg, were reported (Voieta et al. 2010; Hegade et al. 2012). The granuloma can contain egg or remnants inside an area of eosinophilic necrosis, or engulfed in multinucleated giant cells present in the center, surrounded by epithelioid cells, lymphocytes, plasma cells, eosinophils, and histiocytes (Fig. 1e); the older granulomas contain fibroblasts, fibrocytes, and collagen fibers (Kubasta et al. 1965). Since this hepatosplenic disease is chronic, with slow progression of infection and host defense, patients can present mild, moderate to severe fibrosis, as well as active or gradual decrease of granulomatous reaction, which could explain the variability of histological pattern and dynamic of granuloma formation and pathology reported in the literature (Kubasta et al. 1965; Andrade 2009; Colley et al. 2014).

The idea that granuloma is a host-protective structure that serves to "wall off" the egg and also destroy the egg and the miracidium inside is logical. Although there is some controversy, it has been suggested that abundance of eosinophils within granulomas and their cytotoxic granules is involved in egg destruction (Andrade 1987; Schwartz and Fallon 2018). In addition to granulomas ensuring egg containment, they sequester egg-secreted products and antigens that can be hepatotoxic, such as omega-1 and IPSE/alpha-1 or inductors of exaggerated immune response against the parasite (Wilson et al. 2007; Abdulla et al. 2011; Schwartz and Fallon 2018). Granulomas also serve to preserve gut integrity and prevent subsequent bacterial invasion during schistosome infection (Chuah et al. 2014). In addition, intestinal granulomatous inflammation facilitates egg translocation into the lumen and excretion in the feces, indicating that granuloma could be a beneficial structure for the parasite (Schwartz and Fallon 2018)

The granulomas are also deleterious to the host. Several substances such as lysozyme, β-glucuronidase, prostaglandins, leukotrienes, and free radicals produced by cell populations within the granuloma are potentially destructive to the surrounding tissue (Chuah et al. 2014). The fibrosis triggered by granulomas is the main cause of the pathology associated with schistosomiasis mansoni (see above). As noted by Wilson et al. (2007), granuloma formation therefore seems to be a compromise, which allows the host to live with the infection for many years, and presumably, the chronic detrimental effects associated with granulomas (fibrosis, portal hypertension) represent a better alternative for host and parasite, than that of the host dying soon after parasite egg production.

The more significant findings related to granuloma development and associated immune responses during schistosomiasis mansoni were obtained from mouse models; the essential points are *briefly* summarized *below*.

The reports indicating that T cell–deprived, nude, and severe combined immunodeficiency diseased mice being unable to mount granulomatous responses against *Schistosoma* and all dying earlier than comparably infected immunologically healthy mice strongly suggest that the process of the *granuloma* formation is T cell–dependent and that granuloma *protects* the host (Wilson et al. 2007). Schistosomiasis mansoni induces a Th2-type prevailing immune response, but also an initial Th1 pro-inflammatory cytokine release when the host is exposed to a migrating immature parasite (Hams et al. 2013). Following this initial phase, the CD4 Th cells enter the lesion and release IL-12 and INF-γ, which facilitate the hepatic granuloma formation with monocyte, mast cell, dendritic cell, and lymphocyte influx. The SEA (soluble egg antigens) and ω-1 antigen (see below for more details) are taken up by dendritic cells which stimulate Th2 cell expansion as well as IL-4, IL-5, and IL-13 production, leading to lymphocytes and eosinophils infiltration, and the enlargement of the granuloma (Lundy and Lukacs 2013). The peak of this Th2 response is closely associated with the magnitude of granulomatous inflammation surrounding the egg. After this stage, the schistosome egg becomes degenerated and disintegrated, and a Th2-type reaction accompanied by a change of cellularity of the granuloma, with influx of eosinophils, fibroblasts, and the accumulation of M2 macrophages, is detected in the hepatic tissue (Lundy and Lukacs 2013). The M2 macrophage phenotype is acquired through IL-4 and IL-13 mediating IL4Rα signaling and is associated with arginase-1 expression, an enzyme converting L-arginine to L-orthinine, which is further converted to proline, a critical amino acid for the production of collagen and therefore the development of fibrosis (Lundy and Lukacs 2013; Schwartz and Fallon 2018). The IL-13 also signals fibroblasts to produce collagen by similar mechanism (Schwartz and Fallon 2018). Innumerous studies have identified various subtypes of lymphocytes in the granulomas such as B cells, Th17 cells, and T reg cell; cytokines such as alarmins, IL-33, and IL-25; chemokines such as the macrophage inflammatory proteins (MIP-1β and MIP-2); and vascular endothelial factor and hypoxia-inducible factor (Park et al. 2001; Aráujo et al. 2010; Hams et al. 2013). All these cells and biomolecules should be players in Schistosoma granuloma. It is noted that, in contrast to the eggs deposited in the liver, the eggs in the intestine are shed, which could explain the differences in the granuloma cellularity and composition: intestinal granulomas, harboring more macrophages and less eosinophils, T and B cells, and a tendency to be more organized with fewer circumferal collagen fibers (Amaral et al. 2017; Schwartz and Fallon 2018).

The larval form housed in the egg is the responsible for the production and release of SEA, a complex mixture of stimulatory antigens. Initial experiments, suggesting the importance of these antigens, demonstrated that SEA-specific antibodies downmodulate granuloma formation, due to neutralization and sequestration of the antigens by antibodies (Jankovic et al. 1997). Now, we know that the SEA antigens α-1 and ω-1 (T2 ribonuclease) and lact-N-fucopentaose III, through binding and internalization on DC and macrophages, lead to polarization of these cells toward M2–Th2 responses, increase lymphocyte and eosinophil infiltration, and induce the enlargement of granulomas (Lundy and Lukacs 2013). More recently, the genetic manipulation by lentivirus transduction demonstrated that ω-1 knockdown eggs impair granuloma expansion by diminishing the area, as well as macrophage, B cell, and CD4 T cell infiltration (Hagen et al. 2014). These data demonstrated the impact of egg antigens on granuloma formation, reflecting on the host immune system and, in a broader sense, in overcoming the disease.

Many aspects of granuloma formation during schistosomiasis have *already been* revealed, allowing this chronic parasitic disease to be an example of the triple role of granulomas. These structures are shaping the host–parasite interaction as structure host-protective (walling "off" and destructing eggs), as well as host-deleterious (fibrosis) and parasite beneficial (facilitating egg translocation into the lumen and excretion in the feces). This excellent model of a granulomatous parasitic disease will continue to help understand the mechanistic and functional aspects of infectious granulomas.

Conclusions and perspective

The chronic aspect of many parasitic diseases with long-term host/parasite survival is the result of a combination of a host immune response which did not work properly worked, while parasite escape systems worked well. Thus, the appearance of granulomas during various parasitic diseases is frequent, since these structures will only form when individual immune cells do not control the invading agent. In this review, we referred to some parasitic granulomatous diseases, and it became clear that while in some of them the host-protective mechanisms of granulomas are described, as in GAE, toxoplasmosis, and leishmaniasis, in NCC and schistosomiasis mansoni, granuloma is a "double-edged sword." The diversity of granulomatous responses during these parasitic diseases has also became evident, despite the restricted variety of cell types found in granulomas (Fig. 1).

It is difficult to generalize the future directions for research in the area of granulomatous response in the diseases discussed in this review. What we can bet on is that the importance of granuloma in disease outcome will be further discussed in the following years, as well as the mechanistic

aspects, such as the spatio-temporal localization of immune transcripts and protein localization, cellular metabolism, and micronutrient availability within granulomas. The granuloma is a complex structure, and deciphering all its details will be a great step in understanding and controlling the host–parasite interaction.

Acknowledgments We thank the unknown referee for constructive review of the paper, Noili Demaman for English language editing, and Ana Carolina Andrade Vitor Kayano for artwork.

Funding information This work was supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, and Fundação de Amparo à Pesquisa do Estado de São Paulo, Brazil.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Abath FGC, Morais CNL, Montenegro CE, Wynn TA, Montenegro SM (2006) Immunopathogenic mechanisms in schistosomiasis: what can be learnt from human studies? Trends Parasitol 22:85–91

Abdulla MC, Jemshad A (2017) Bone marrow granuloma due to toxoplasmosis presenting as isolated thrombocytopenia in na immunocompetent patient. Egypt J Haematol 42:78–79

Abdulla MH, Lim KC, McKerrow JH, James H, Caffrey CR (2011) Proteomic identification of IPSE/alpha-1 as a major hepatotoxin secreted by *Schistosoma mansoni* eggs. PLoS Negl Trop Dis 5: e1368–e1377

Adalid-Peralta L, Arce-Sillas A, Fragoso G, Cárdenas G, Rosetti M, Casanova-Hernández D, Rangel-Escareno C, Uribe-Figueroa L, Fleury A, Sciutto E (2013) Cysticerci drive dendritic cells to promote *in vitro* and *in vivo* Tregs differentiation. Clin Dev Immunol 2013:981468

Adams DO (1976) The granulomatous inflammatory response. Am J Pathol 84:164–192

Almeida RP, Barral-Netto M, Jesus AMR, Freitas LAR, Carvalho EM, Barral A (1996) Biological behavior of Leishmania amazonensis isolated from humans with cutaneous, mucosal or visceral leishmaniasis in Balb/c mice. Am J Trop Med Htg 54:178–184

Alvarez JI, Londoño DP, Alvarez AL, Trujillo J, Jamarillo MM, Restrepo BI (2002) Granuloma formation and parasite disintegration in porcine cysticercosis: comparison with human neurocysticercosis. J Comp Pathol 127:186–193

Amaral KB, Silva TP, Dias FF, Malta KK, Rosa FM, Costa-Neto SF, Gentile R, Melo RCN (2017) Histological assessment of granulomas in natural and experimental *Schistosoma mansoni* infections using whole slide imaging. PLoS One 12:e0184696–e0184715

Anderson CF, Mendez S, Sacks DL (2005) Nonhealing infection despite Th1 polarization produced by a strain of *Leishmania major* in C57BL/6 mice. J Immunol 174:2934–2941

Andrade ZA (1987) Pathology of human schistosomiasis. Mem Inst Oswaldo Cruz 82:17–23

Andrade ZA (2009) Schistosomiasis and liver fibrosis. Parasite Immunol 31:656–663

Aoun J, Habib R, Charaffeddine K, Taraif S, Loya A, Khalifeh I (2014) Caseating granulomas in cutaneous leishmaniasis. PLoS Negl Trop Dis 8:e325

Aráujo AP, Frezza TF, Alegretti SM, Giorgio S (2010) Hypoxia, hypoxia-inducible factor 1a and vascular endothelial growth factor in a murine model of *Schistosoma mansoni* infection. Exp Mol Pathol 89: 327–333

Arechavaleta F, Molinari JL, Tato P (1998) A *Taenia solium* metacestode factor nonspecifically inhibits cytokine production. Parasitol Res 84: 117–122

Arruda MSP, Nogueira MES, Bordon AP (2002) Histological evaluation of the lesion induced by inoculation of *Leishmania mexicana* in the cheek pouch of the hamster. Ver Soc Bras Med Trop 35:293–297

Baig AM (2015) Pathogenesis of amoebic encephalitis: are the amoebae being credited to an 'inside job' done by the host immune response? Acta Trop 148:72–76

Beattie L, Peltan A, Maroof A (2010) Dynamic imaging of experimental *Leishmania donovani*-induced hepatic granulomas detects Kupffer cell-restricted antigen presentation to antigen-specific CD8+ T Cells. PLoS Pathog 6:e1000805

Belfort RN, Rasmussen S, Kherani A, Lodha N, Williams J, Fernandes BF, Burnier MN Jr (2010) Bilateral progressive necrotizing retinochoroiditis in an immunocompromised patient: histopathological diagnosis. Acta Ophthalmol 88:614–615

Bertoli F, Espino M, Arosemena JR, Fishback JL, Frenkel JK (1995) A spectrum in the pathology of toxoplasmosis in patients with acquired immunodeficiency syndrome. Arch Pathol Lab Med 119:214–224

Betson M, Sousa-Figueiredo JC, Rowell C, Kabatereine N, Stothard JR (2010) Intestinal schistosomiasis in mothers and young children in Uganda: investigation of field-applicable markers of bowel morbidity. Am J Trop Med Hyg 83:1048–1055

Bogdan C, Donhauser N, Döring R, Rollinghoff M, Diefenbach A, Ritig MG (2000) Fibroblasts as host cells in latent leishmaniosis. J Exp Med 191:2121–2130

Boros LD (1986) Experimental granulomatosis. Clin Dermatol 4:10–12

Burke ML, Jones MK, Gobert GN (2009) Immunopathogenesis of human schistosomiasis. Parasite Immunol 31:163–176

Burza S, Croft SL, Boelaert M (2019) Leishmaniasis. Lancet 393:951–970

Cáceres-Dittmar G, Tapia FJ, Sanchez MA, Yamamura M, Uyemura K, Modlin RL, Bloom BR, Convit J (1993) Determination of the cytokine profile in American cutaneous leishmaniasis using the polymerase chain reaction. Clin Exp Immunol *91*:500–505

Cao J, Liu WJ, Xu XY, Zou XP (2010) Endoscopic findings and clinicopathologic characteristics of colonic schistosomiasis: a report of 46 cases. World J Gastroenterol 16:723–727

Carpio A, Fleury A, Romo ML, Abraham R (2018) Neurocysticercosis: the good, the bad, and the missing. Expert Ver Neurother 18:289–301

Chen L, Christian DA, Kochanowsky JA, Phan AT, Clark JT, Wang S, Berry C, Oh J, Chen X, Roos DS, Beiting DP, Koshy AA, Hunter CA (2020) The *Toxoplasma gondii* virulence factor ROP16 acts in cis and trans, and suppresses T cell responses. J Exp Med 217: e20181757

Chensue SW (2013) Chemokines in innate and adaptative granuloma formation. Front Immunol 4:43. Chuah C, Jones MK, Burke ML, McManus DP, Gobert GN (2014) Cellular and chemokine-mediated regulation in schistosome-induced hepatic pathology. Trends Parasitol 30:141–150

Chuah C, Jones MK, Burke ML, McManus DP, Gobert GN (2014) Cellular and chemokine-mediated regulation in schistosome-induce hepatic pathology. Trends Parasitol 30:141–150

Colley DG, Bustinduy AL, Secor WE, King C (2014) Human schistosomiasis. Lancet 383:2253–2264

Commodaro AG, Belfort RN, Rizzo LV, Muccioli C, Silveira C, Burnier MM Jr, Belfort R Jr (2009) Ocular toxoplasmosis–an update and review of the literature. Mem Inst Oswaldo Cruz 104:345–350

Corrêa G, Lindenberg CA, Moreira-Souza ACA, Savio LEB, Takiya CM, Marques-da-Silva C, Vommaro RC, Coutinho-Silva R (2017) Inflammatory early events associated to the role of P2X7 receptor in acute murine. Immunobiology 222:676–683

Corte-Real S, Santos CB, Meirelles MN (1995) Differential expression of the plasma membrane Mg2+ ATPase and Ca2+ ATPase activity during adhesion and interiorization of *Leishmania amazonensis* in fibroblasts in vitro. J Submicrosc Cytol Pathol 27:359–366

Costain AH, MacDonald AS, Smits HH (2018) Schistosome egg migration: mechanisms, pathogenesis and host immune responses. Front Immunol 9:3042–3057

Cotterell SEJ, Engwerda CR, Kaye PM (1999) *Leishmania donovani* infection initiates T cell-independent chemokine responses, which are subsequently amplified in a T cell-dependent manner. Eur J Immunol *29*:203–214

De Cook KM (1986) Hepatosplenic schistosomiasis: a clinical review. Gut 27:734–745

De Jesus AR, Silva A, Santana LB, Magalhães A, Jesus AM, Almeida RP, Rêgo MAV, Burattini MN, Pearce EJ, Carvalho EM (2002) Clinical and immunologic evaluation of 31 patients with acute schistosomiasis mansoni. J Infect Dis 185:98–105

De Lima DCV, Santos AS, Da Silva LTR, Melo RPB, Silva AG, Pinheiro JW Jr, Mota RA (2016) Occurrence of *Toxoplasma gondii* in domestic rabbits of Northeastern Brazil. Acta Parasitol 61:500–507

Del Brutto OH (2014) Neurocysticercosis. Neurohospitalist 4:205–212

Denkers EY, Gazzinelli RT (1998) Regulation and function of T-cell-mediated immunity during *Toxoplasma gondii* infection. Clin Microbiol Ver 4:569–588

Díaz A, Sagasti C, Casaravilla C (2017) Granulomatous responses in larval taeniid infectious. Parasite Immunol 40(5):e12523

Dubey JP (2008) The history of *Toxoplasma gondii*-the first 100 years. J Eukaryot Microbiol 55:467–475

Duggal SD, Rongpharpi SR, Duggal AS, Kumas A, Biswal I (2017) Role of *Acanthamoeba* in granulomatous encephalitis: a review. J Infect Dis Immune Ther 1:1. https://doi.org/10.4172/JIDITH.1000103 Corpus ID: 56064175

El-shoura SM, Tallab T, Bahamdan K (1996) Human cutaneous leishmaniasis: ultrastructural interactions between the inflammatory cells and Leishman bodies in the skin lesions. Parasite J 3:229–236

Escobar A (1983) The pathology of neurocysticercosis. In: Palacios E, Rodriguez-Carbajal, Taveras J, editors. Cysticercosis of the central nervous system. Springfield 27-54.

Falangola MF, Reichler BS, Petito CK (1994) Histopathology of cerebral toxoplasmosis in human immunodeficiency virus infection: a comparison between patients with early-onset and late-onset acquired immunodeficiency syndrome. Hum Pathol 25:1091–1097

Falzone C, Baroni M, De Lorenzi D, Mandara MT (2008) *Toxoplasma gondii* brain granuloma in a cat: diagnosis using cytology from na intraoperative sample and sequential magnetic resonance imaging. J Small Anim Pract 49:95–99

Filipe-Santos O, Pescher P, Breart B, Lippuner C, Aebischer T, Glaichenhaus N, Späth GF, Bousso P (2009) A dynamic map of antigen recognition by CD4 T Cells at the site of *Leishmania major* infection. Cell Host Microbe 6:23–33

Fleury A, Cardenas G, Adalid-Peralta L, Fragoso G, Sciutto E (2016) Immunopathology in *Taenia solium* neurocysticercosis. Parasite Immunol 38:147–157

García HH, Gonzalez A, Evans CAW, Gilman RH (2003) *Taenia solium* cysticercosis. Lancet 362:547–556

García HH, Gonzalez AE, Rodriguez S, Tsang VCW, Pretell EJ, Gozales I, Gilman RH, Cysticercosis Working Group in Peru (2010) Neurocysticercosis. Unraveling the nature of the single cysticercal granuloma. Neurology 75:654–658

García HH, O'Neal SE, Noh J, Handali S, Cysticercosis Working Group in Peru (2018) Laboratory diagnosis of neurocysticercosis (*Taenia solium*). J Clin Microbiol 56:e00424–e00418

Ghoname SI, Mohamed AH, El-Dafrawy SM (2017) Immune response of stimulated *Biomphalaria alexandrina* snails with *Schistosoma mansoni* infection. J Egypt Soc Parasitol 47:219–225

Giorgio S, Linares E, Ischiropoulos H, Von Zuben FJ, Yamada A, Augusto O (1998) In vivo formation of electron paramagnetic resonance-detectable nitric oxide and nitrotyrosine is not impaired during murine leishmaniasis. Infect Immun 66:807–814

Goto H, Prianti MG (2009) Immunoactivation and immunopathogeny during active visceral leishmaniasis. Rev Inst Med Trop S Paulo 5: 241–246

Guarner J (2012) Detection of microorganisms in granulomas that have been formalin-fixed: review of the literature regarding use of molecular methods. Scientifica 2012: -16

Guarner J, Bartlett J, Shieh W-J, Paddock CD, Visvesvara GS, Zaki SR (2007) Histopathological spectrum and immunohistochemical diagnosis of amebic meningoencephalitis. *Mod Pathol* 20:1230–1237

Guiraldo E, Schlesinger LS (2013) Modeling the *Mycobacterium tuberculosis* granuloma–the critical battlefield in host immunity and disease. Front Immunol 4:98. https://doi.org/10.3389/fimmu.2013.00098

Hagen J, Young ND, Every AL, Pagel CN, Schnoeller C, Scheerlinck JP, Gasser RB, Kalinna BH (2014) Omega-1 knockdown in *Schistosoma mansoni* eggs by lentivirus transduction reduces granuloma size in vivo. Nat Commun 5:5375

Hams E, Aviello G, Fallon PG (2013) The *Schistosoma* granuloma: friend or foe? Front Immunol 4:1–7

Harrison JL, Ferreira GA, Raborn ES, Lafrenaye D, Marciano-Cabral F, Cabral GA (2010) *Acanthamoeba culbertsoni* elicits soluble factors that exert anti-microglial cell activity. Infect Immun 78:4001–4011

Hegade VS, Armstrong MJ, Smithson JAJ (2012) Hepatic schistosomiasis. QJMed 105:87

Helming L, Gordon S (2008) The molecular basis of macrophage fusion. Immunobiology 212:85–93

Hermida MD, Melo CVB, Lima IDS, Oliveira GGS, Dos-Santos WLC (2018) Histological disorganization of spleen compartments and severe leishmaniasis. Front Cell Infect Microbiol 8:1–10

Heyde S, Philipsen L, Formaglio P, Fu Y, Baars I, Höbbel G, Kleinholz CL, Seiß EA, Stettin J, Gintschel P, Dudeck A, Bousso P, Schraven B, Müller AJ (2018) CD11c-expressing Ly6C+CCR2+ monocytes constitute a reservoir for efficient *Leishmania* proliferation and cell-to-cell transmission. PLoS Pathog 14:e1007374

Ito T, Connett JM, Kunkel SL, Matsukawa A (2013) The linkage of innate and adaptive immune response during granulomatous development. Front Immunol 4:1–8

James DG (2000) A clinicopathological classification of granulomatous disorders. J Postgrad Med 76:457–465

Jankovic D, Kullberg MC, Dombrowicz D, Barbieri S, Caspar P, Wynn TA, Paul WE, Cheever AW, Kinet JP, Sher A (1997) Fc epsilonRI-deficient mice infected with *Schistosoma mansoni* mount normal Th2-type responses while displaying enhanced liver pathology. J Immunol 159:1868–1875

Janitschke K, Martínez AJ, Visvesvara GS, Schuster F (1996) Animal model *Balamuthia mandrillaris* CNS infection: contrast and comparison in immunodeficient and immunocompetent mice: a murine model of "Granulomatous" amebic encephalitis. J Neuropathol Exp Neurol 55:815–821

Kalra SK, Sharma P, Shyam K, Tejan N, Ghoshal U (2020) *Acanthamoeba* and its pathogenic role in granulomatous amebic encephalitis. Exp Parasitol 208:107788

Kaye P, Scott P (2011) Leishmaniasis: complexity at the host–pathogen interface. Nat Rev Microbiol 9:604–615

Kaye P, Svensson M, Ato M, Maroof A, Polley R, Stager S, Zubairi S, Engwerda CR (2004) The immunopathology of experimental visceral leishmaniasis. Immunol Rev 201:239–253

Kaye PM, Beattie L (2016) Lessons from other diseases: granulomatous inflammation in leishmaniasis. Semin Imunopathol 38:249–260

Khan NA (2003) Pathogenesis of *Acanthamoeba* infections. Microb Pathog 34:277–285

Kinard BE, Magliocca KR, Guarner J, Delille CA, Roser SM (2016) Longstanding suppurative granulomatous inflammation of the infratemporal fossa. Oral Maxillofac Surg Cases 2:14–17

Klippe JH, Kirsten D, Andrée C (2004) Rudolf Virchow (1821-1902) and the origin of the term "granuloma". Pneumonologie 58:449–454

Kubasta M, Dusek J, Kubastová B, Kodousek R (1965) Needle biopsy of the liver in schistosomiasis mansoni. Comparison of examination of fresh tissue and sections. Gastroenterology 49:280–286

Kurban AK, Malak JA, Farah FS, Chaglassian HT (1996) Histopathology of cutaneous leishmaniasis. Arch Dermatol 93:396–401

Lambertucci JR (2010) Acute schistosomiasis mansoni: revisited and reconsidered. Mem Inst Oswaldo Cruz 105:422–435

Lambertucci JR, Serufo JC, Gerspacher-Lara R, Rayes AA, Teixeira R, Nobre V, Antunes CM (2000) *Schistosoma mansoni*: assessment of morbidity before and after control. Acta Trop 77:101–108

Landa A, Navarro L, Ochoa-Sánchez A, Jiménez L (2019) *Taenia solium* and *Taenia crassiceps*: miRNomes of the larvae and effects of miR-10-5p and let-7-5p on murine peritoneal macrophages. Biosci Rep 39:BSR20190152

Lee SH, Charmoy M, Romano A, Paun A, Chaves MM, Cope FO, Ralph DA, Sacks DL (2018) Mannose receptor high, M2 dermal macrophages mediate nonhealing *Leishmania major* infection in a Th1 immune environment. J Exp Med 215:357–375

Lima IS, Silva JS, Almeida VA, Leal FG, Souza PA, Larageira DF, Moura-Neto JP, Fraga DBM, Freitas LAR, Dos-Santos WLC (2014) Severe clinical presentation of visceral leishmaniasis in naturally infected dogs with disruption of the splenic white pulp. *PLoS One* 9:e87742

Lima IS, Solcá MS, Tafuri WL, Freitas LAR, Dos-Santos WLC (2019) Assessment of histological liver alterations in dogs naturally infected with *Leishmania infantum*. Parasit Vectors 12:487

Lin PL, Maiello P, Gideon P, Coleman T, Cadena AM, Rodgers MA, Gregg R, O'Malley M, Tomko J, Fillmore D, Frye J, Rutledge T, DiFazio RM, Janssen C, Klein E, Andersen PL, Fortune SM, Flynn JL (2016) PET CT identifies reactivation risk in cynomolgus macaques with latent *M. tuberculosis*. PLoS Pathog 12:e1005739

Londoño DP, Alvarez JI, Trujillo J, Jaramillo MM, Restrepo BI (2002) The inflammatory cell infiltrates in porcine cysticercosis: immunohistochemical analysis during various stages of infection. Vet Parasitol 109:249–259

Lundy SK, Lukacs NW (2013) Chronic schistosome infection leads to modulation of granuloma formation and systemic immune suppression. Front Immunol 4:1–17

Maia C, Campino L (2018) Biomarkers associated with *Leishmania infantum* exposure, infection, and disease in dogs. Front Cell Infect Microbiol 8:302

Mansour L, el-Marhoumy SM, Eid MM, Gawish K (1993) A histopathological study of different clinical forms of cutaneous leishmaniasis. J Egypt Soc Parasitol 23:591–597

Marciano-Cabral F, Cabral G (2003) *Acanthamoeba* spp. as agents of disease in humans. Clin Microbiol Rev 16:273–307

Mariano M (1995) The experimental granuloma. A hypothesis to explain the persistence of the lesion. Rev Inst Med Trop São Paulo 37:161–176

Martínez AJ (1982) Acanthamoebiasis and immunosuppression: case report. J Neuropathol Exp Neurol 45:548–557

McManus DP, Dunne DW, Sacko M, Utzinger J, Vennervald BJ, Zhou X-N (2018) Schistosomiasis. Nat Rev Dis Primers 4(1):13. https://doi.org/10.1038/s41572-018-0013-8

Meir M, Grosfeld T, Barkan D (2018) Establishment and validation of *Galleria mellonella* as a novel organism to study *Mycobacterium abscessus* infection, pathogenesis and treatment. Antimicrob Agents Chemother 62:02539–02547

Mendonça MG, Brito MEF, Rodrigues HEG, Bandeira V, Jardim ML, Abath FGC (2004) Persistence of Leishmania parasites in scars after clinical cure of American cutaneous leishmaniasis: is there a sterile cure? J Infect Dis 189:1018–1023

Modica S, Miracco C, Cusi MG, Tordini G, Muzii VF, Iacoangeli F, Nocentini C, Ali IKM, Roy S, Cerase A, Zanelli G, De Luca A, Montagnani F (2018) Non-granulomatous cerebellar infection by *Acanthamoeba* spp. in an immunocompetent host. Infection 46(6): 885–889

Mkupasi EM, Sikasunge CS, Ngowi HA, Leifsson PS, Johansen MV (2013) Detection of cysteine protease in *Taenia solium*-induced brain granulomas in naturally infected pigs. Vet Parasitol 197:360–363

Muzii VF, Iacoangeli F, Karin MAI NC, Roy S, Cerase A, Zanelli G, De Luca A, Montagnani F (2018) Non-granulomatous cerebellar infection by *Acanthamoeba* spp. in an immunocompetent host. Infection 46:885–889

Mohamed ARES, Karawi MAA, Yasawy MI (1990) Schistosomal colonic disease. Gut 31:439–442

Molinari JL, Tato P, Reynoso AO, Cázares JM (1990) Depressive effect of a *Taenia solium* cysticercus factor on cultured human lymphocytes stimulated with phytohaemagglutinin. Ann Trop Med Parasitol 84:205–208

Montoya JG, Liensenfeld O (2004) Toxoplasmosis. Lancet 363:1965–1976

Moore JWJ, Moyo D, Beattie L, Andrews PS, Timmis J, Kaye PM (2013) Functional complexity of the *Leishmania* granuloma and the potential of *in silico* modeling. Front Immunol 4:1–7

Moyo D, Beattie L, Andrews PS (2018) Macrophage transactivation for chemokine production identified as a negative regulator of granulomatous inflammation using agent-based modeling. Front Immunol 9:637

Müller AJ, Filipe-Santos O, Eberl G, Aebischer T, Späth GF, Bousso P (2012) CD4+ T cells rely on a cytokine gradient to control intracellular pathogens beyond sites of antigen presentation. Immunity 37: 147–157

Murray HW (2001) Tissue granuloma structure-function in experimental visceral leishmaniasis. Int J Exp Pathol 82:249–267

Murray HW, Squires KE, Miralles CD, Stockle MY, Granger AM, Granelli-Piperno A, Bogdan C (1992) Acquired resistance and granuloma formation in experimental visceral leishmaniasis. Differential T cell and lymphokine roles in initial versus established immunity. J Immunol 148:1858–1863

Nash TE, Pretell EJ, Lescano AG, Bustos JA, Gilman RH, Gonzalez E, Garcia HH, Cysticercosis Working Group (2018) Seizure activity in patients with calcified neurocysticercosis: a prospective cohort and nested case-control study. Lancet Neurol 7:1099–1105

Nathan C (2016) Macrophages' choice: take it in or keep it out. Immunity 45:710–711

Nieto A, Domínguez-Bernal G, Orden JA, Fuente RD, Madrid-Elena N, Carrión J (2011) Mechanisms of resistance and susceptibility to experimental visceral leishmaniosis: BALB/c mouse versus Syrian hamster model. Vet Res 42:39

Págan AJ, Ramakrishnan L (2018) The formation and function of granulomas. Annu Rev Immunol 36:23–27

Pampiglione S, Manson-Bahr PEC, Giungi F, Giungi G, Parenti A, Trotti CG (1974) Studies on Mediterranean leishmaniasis. 2. Asymptomatic cases of visceral leishmaniasis. Trans R Soc Trop Med Hyg 68:447–453

Park MK, Hoffmann KF, Cheever AW, Amichay D, Wynn TA, Farber JM (2001) Patterns of chemokine expression in models of *Schistosoma mansoni* inflammation and infection reveal relationships between

type 1 and type 2 responses and chemokines *in vivo*. Infect Immun 69:6755–6768

Pearce EJ (2005) Priming of the immune response by schistosome eggs. Parasite Immunol 27:265–270

Perez MT, Bush LM (2007) Fatal amebic encephalitis caused by *Balamuthia mandrillaris* in an immunocompetent host. A clinicopathological review of pathogenic free-living amebae in human hosts. Case Report. Ann Diagn Pathol 11:440–447

Pettit DAD, Williamson J, Cabral GA, Marciano-Cabral F (1996) In vitro destruction of nerve cell cultures by *Acanthamoeba* spp.: a transmission and scanning electron microscopy study. J Parasitol 82:769–777

Pfohl JC, Dewey CW (2005) Intracranial *Toxoplasma gondii* granuloma in a cat. J Feline Med Surg 7:369–374

Pirmez C, Yamamura M, Uyemura K, Paes-Oliveira M, Conceição-Silva F, Modlin RL (1993) Cytokine patterns in the pathogenesis of human leishmaniasis. J Clin Invest 91:1390–1395

Pisarski K (2019) The global burden of diseases of zoonotic parasitic diseases: top 5 contenders for priority consideration. Trop Med Infect Dis 4:44–52

Ramakrishnan L (2012) Revisiting the role of the granuloma in tuberculosis. Nat Rev Immunol 12:352–366

Restrepo BI, Alvarez JI, Castaño JA, Arias LF, Restrepo M, Trujillo J, Colegial CH, Teale JM (2001) Brain granulomas in neurocysticercosis patients are associated with a Th1 and Th2 profile. Infect Immun 69:4554–4560

Ridley DS (1980) A histological classification of cutaneous leishmaniasis and its geographical expression. Trans R Soc Trop Med Hyg 74: 515–521

Ridley MJ, Ridley DS (1986) Monocyte recruitment, antigen degradation and localization in cutaneous leishmaniasis. Br J Exp Pathol 67: 209–218

Robert-Gangneaux F, Drogoul AS, Rostan O (2012) Invariant NKT cells drive hepatic cytokinic microenvironment favoring efficient granuloma formation and early control of *Leishmania donovani* infection. PLoS One 7:e33413

Robinson P, Garza A, Weinstock J, Serpa JA, Goodman JC, Eckols KT, Firogary B, Tweardy DJ (2012) Substance P causes seizures in neurocysticercosis. PLoS Pathog 8:e1002489–e1002499

Rodrigues V, Cordeiro-da-Silva A, Laforge M, Silvestre R, Estaquier J (2016) Regulation of immunity during visceral *Leishmani*a infection. Parasit Vectors 9:118

Roque AL, Jansen AM (2014) Wild and synanthropic reservoirs of Leishmania species in the Americas. Int J Parasitol Parasites Wildl 3:251–262

Saadatnia G, Golkar M (2002) A review on human toxoplasmosis. Scand J Infect Dis 44:805–814

Saeij JP, Boyle JP, Boothroyd JC (2005) Differences among the three major strains of *Toxoplasma gondii* and their specific interactions with the infected host. Trends Parasitol 21:476–481

Safaei A, Motazedian MH, Vasei M (2002) Polymerase chain reaction for diagnosis of cutaneous leishmaniasis in histologically positive, suspicious and negative skin biopsies. Dermatol 205:18–24

Salguero FJ, Garcia-Jimenez L, Lima I, Seifert K (2018) Histopathological and immunohistochemical characterisation of hepatic granulomas in *Leishmania donovani*-infected BALB/c mice: a time course study. Parasit Vectors 11:73

Sanchez MA, Diaz NL, Zerpa O, Negron E, Convit J, Tapia FJ (2004) Organ-specific immunity in canine visceral leishmaniasis: analysis of symptomatic and asymptomatic dogs naturally infected with *Leishmania chagasi*. Am J Trop Med Hyg 70:618–624

Sant'Ana JAP, Lima WG, Oliveira MR, Simões LA, Michalick MSM, Melo MN, Tafuri WL, Tafuri WL (2007) Hepatic granulomas in canine visceral leishmaniasis and clinical status. Arq Bras Med Vet Zootec 59:1137–1144

Saunders BM, Cooper AM (2000) Restraining mycobacteria role of granulomas in mycobacterial infections. Immunol Cell Biol 78:334–341

Schaeffer M, Han SJ, Chtanova T, Dooren GG, Herzmark P, Chen Y, Roysam B, Striepen B, Robey EA (2009) Dynamic imaging of T cell-parasite interactions in the brains of mice chronically infected with *Toxoplasma gondii*. J Immunol 182:6379–6393

Schlüter D, Löhler J, Deckert M, Hof H, Schwendemann G (1991) Toxoplasma encephalitis of immunocompetent and nude mice: immunohistochemical characterisation of *Toxoplasma* antigen, infiltrates and major histocompatibility complex gene products. J Neuroimmunol 31:185–198

Schlüter D, Barragan A (2019) Advances and challenges in understanding cerebral toxoplasmosis. Front Immunol 10:242–257

Schwartz C, Fallon PG (2018) Schistosoma "eggs-iting" the host: granuloma formation and egg excretion. Front Immunol 9:2492–2507

Seitzer U, Haas H, Gerdes J (2001) A human *in vitro* granuloma model for the investigation of multinucleated giant cell and granuloma formation. Histol Histopathol 16:645–653

Shah KK, Pritt BS, Alexander MP (2016) Histopathologic review of granulomatous inflammation. J Clin Tuberc Other Mycobact Dis 7:1–12

Silveira FT, Lainson R, Corbett CEP (2004) Clinical and immunopathological spectrum of American cutaneous leishmaniasis with special reference to the disease in Amazonian Brazil-a review. Mem Inst Oswaldo Cruz 99:239–2351

Sing OP, Hasker E, Sacks D, Boelaert M, Sundar S (2014) Asymptomatic leishmania infection: a new challenge for *Leishmania* control. Clin Infect Dis 58:1424–1429

Souza-Lemos C, Campos SN, Teva A, Côrte-Real S, Fonseca EC, Porrozzi R, Grimaldi G Jr (2008) Dynamics of immune granuloma formation in a *Leishmania braziliensis*-induced self-limiting cutaneous infection in the primate *Macaca mulatta*. J Pathol 216:375–386

Strickland GT (1994) Gastrointestinal manifestations of schistosomiasis. Gut 35:1334–1337

Stringer JL, Marks LM, White AC Jr, Robinson P (2003) Epileptogenic activity of granulomas associated with murine cysticercosis. Exp Neurol 183:532–536

Suzuki Y, Orellana MA, Wong S, Conley FK, Remington JS (1993) Susceptibility of chronic infection with *Toxoplasma gondii* does not correlate with susceptibility to acute infection in mice. Infect Immun 61:2284–2288

Swe T, Baqui A, Naimg AT, Baqui T, Sherigar J, Mansour M (2016) Non-necrotizing colonic granuloma induced by schistosomiasis. J Community Hosp Intern Med Perspect 6:33114–33116

Tato P, Castro AM, Soto R, Arechavaleta F, Molinari JL (1995) Suppression of murine lymphocyte proliferation induced by a small RNA purified from the *Taenia solium* metacestode. Parasitol Res 81:181–187

Tenor JL, Oehlers SH, Yang JL, Tobin DM, Prefect JR (2015) Live imaging of host-parasite interactions in a zebrafish infection model reveals cryptococcal determinants of virulence and central nervous system invasion. mBio 6:e01425–e01415

Teva A, Porrozi R, Cupolillo E, Pirmez C, Oliveira-Neeto MP, Grimaldi G Jr (2003) *Leishmania* (Viannia) *braziliensis*-induced chronic granulomatous cutaneous lesions affecting the nasal mucosa in the Rhesus Monkey (*Macaca Mulatta*) model. Parasitology 127:437–447

Thomas M, Rao R, Kumar GN (2018) An overview of suppurative granuloma. Indian J Dermatopathol Diagn Dermatol 5:19–26

Tuon FF, Fernandes RR, Pagliari DMIS, Amato VS (2010) The expression of TLR9 in human cutaneous leishmaniasis is associated with granuloma. Parasite Immunol 32:769–772

Turk JL (1998) Encyclopedia of immunology. 2nd ed. Roitt & Delves, London, pp 1023–1026

Van den Bossche J, Laoui D, Naessens T, Smits HH, Hokke CH, Stijlemans B, Grooten J, Baetselier P, Ginderachter JAV (2015) E-

cadherin expression in macrophages dampens their inflammatory responsiveness *in vitro*, but does not modulate M2-regulated pathologies in vivo. Sci Rep 5:12599–12610

Venkataram M, Moosa M, Devi L (2001) Histopathological spectrum in cutaneous leishmaniasis: a study in Oman. Indian J Dermatol Venereol Leprol 67:294–298

Veress B, Abdalla RE, El Hassan AM (1983) Visceral spreading depletion of thymus-dependent regions and amyloidosis in mice and hamsters infected intradermally with *Leishmania* isolated from Sudanese cutaneous leishmaniasis. Br J Exp Pathol 64:505–514

Visvesvara GS, Moura H, Schuster FL (2007) Pathogenic and opportunistic free-living amoebae: *Acanthamoeba* spp., *Balamuthia mandrillaris*, *Naegleria fowleri*, and *Sappinia diploidea*. FEMS Immunol Med Microbiol 50:1–26

Voieta I, Queiroz LC, Andrade LM, Silva LCS, Fontes VF, Barbosa A Jr, Resende V, Petroianu A, Andrade Z, Antunes CM, Lambertucci JR (2010) Imaging techniques and histology in the evaluation of liver fibrosis in hepatosplenic schistosomiasis mansoni in Brazil: a comparative study. Mem Inst Oswaldo Cruz 105:414–421

Weerakoon KGAD, Gobert GN, Cai P, McManus DP (2015) Advances in the diagnosis of human schistosomiasis. Clin Microbiol Ver 28:939–967

White AC Jr (2000) Neurocysticercosis: updates on epidemiology, pathogenesis, diagnosis, and management. Annu Ver Med 51:187–206

Williams GT, Williams WJ (1983) Granulomatous inflammation-a review. J Clin Pathol 36:723–733

Williams ME, Montenegro S, Domingues AL (1994) Leucocytes of patients with *Schistosoma mansoni* respond with a Th2 pattern of cytokine production to mitogen or egg antigens but with a Th) pattern to worm antigens. J Infect Dis 170: 946-954.

Wilson JL, Mayr HK, Weichhart T (2019) Metabolic programming of macrophages: implications in the pathogenesis of granulomatous disease. Front Immunol 10:2265

Wilson MS, Mentink-Kane MM, Pesce JT, Ramalingam TR, Thompson R, Wynn TA (2007) Immunopathology of schistosomiasis. Immunol Cell Biol 85:148–154

Yadav D, Ramam M (2018) Epithelioid cell granuloma. Indian J Dermatopathol Diagn Dermatol 5:7–18

Zumla A, James DG (1996) Granulomatous infections: etiology and classification. Clin Infect Dis 23:146–158