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IMMUNOLOGY AND HOST-PARASITE INTERACTIONS - REVIEW

B-1 cell response in immunity against parasites

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Abstract

The peritoneal cavity has a microenvironment capable of promoting proliferation, differentiation, and activation of the resident cells and recruitment of blood cells through the capillary network involved in the peritoneum. Among the cells found in the peritoneal cavity, B-1 cells are a particular cell type that contains features that are not very well defined. These cells differ from conventional B lymphocytes (B-2) by phenotypic, functional, and molecular characteristics. B-1 cells can produce natural antibodies, migrate to the inflammatory focus, and have the ability to phagocytose pathogens. However, the role of B-1 cells in immunity against parasites is still not completely understood. Several experimental models have demonstrated that B-1 cells can affect the susceptibility or resistance to parasite infections depending on the model and species. Here, we review the literature to provide information on the peculiarities of B-1 lymphocytes as well as their interaction with parasites.

Keywords B-1 cells · Protozoan · Helminths · Immune response

An overview of the B-1 cell

The immune system is a complex, remarkably adaptive homeostatic system that has developed in vertebrates and includes functions such as protection against infectious microorganisms and tumor cells. This system includes innate, adaptive, and memory responses and has been adapted and refined to meet the challenge of eliminating pathogens more efficiently. In addition, the immune system must be tolerant and distinguish between self and non-self; thus, substances that are identified as non-self stimulates an immune response, while no harm is inflicted on the self. However, pathogenic microbes can evade the host response and generate different kinds of disease. Among the immunological cells mobilized against the presence of some pathogenic microorganisms, one cell type remains poorly described, B-1 cells.

Two B lymphocytes lines, designated B-1 and B-2, were identified based on their origins, anatomical distribution, cell surface markers, antibody subtypes produced, and self-renewing ability (Bao et al. 1998). In mice, B-1 cells are found in the peritoneal and pleural cavities, spleen, and at low detectable number in the lymph nodes (Table 1) (Hayakawa et al. 1983; Herzenberg et al. 1986a). Phenotypically, B-1 cells differ from B-2 cells because they have unusual surface marker expression; they are usually $CD19^{+}$, $CD43^{\pm}$, $CD23^{-}$, IgM^{high} and IgD^{low}, and $CD11b^{\pm}$ (Baumgarth 2011), but the CD11b expression is fluid on these cells, depending upon their migration status (Ghosn et al. 2008). These cells are still subdivided into B-1a ($CD5^{+}$) and B-1b ($CD5^{-}$) subsets (Herzenberg 2000; Hardy and Hayakawa 2001; Berland and Wortis 2002). Moreover, B-1 cells have a peculiar morphology when

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Table 1 Distribution and frequency of B-1 cells in mice tissues

Species	Site	Tissue site	Frequency (%)	References
Mouse	Immunological sites	Spleen	1–2	Yang et al. (2007)
		Bone marrow	0.1–0.2	Choi et al. (2012)
		Lymph nodes	0.1–0.3	Choi and Baumgarth (2008)
	Non-immunological sites	Peritoneal cavity	35–70[a]	Herzenberg (2000)
		Pleural cavity	35–70[a]	Review in Yenson and Baumgarth (2014)
		Intestinal lamina propria	< 50	Kroese et al. (1989)

[a] Frequency depends on the mice lineage, age, sex, and housing conditions

compared to B-2 cells when observed under the electron microscope (Abrahão et al. 2003). B-1 cells have been characterized as B lymphocytes due to their ability to rearrange immunoglobulin genes, synthesize IgM and IgD, and express characteristic B lymphocyte surface markers such as B220 and CD19 (Herzenberg et al. 1986b). Ontologically, B-1 cells originate during fetal development from precursors that are distinct from those of B-2 cells (Ghosn et al. 2011). Evidences suggest that during embryonic development and in the neonate B-1 cells arise in waves from several and distinct progenitors present in multiple tissues (Montecino-Rodrigue et al. 2016).

Comparing to B-2 cells, B-1 cells have a less diverse repertoire of immunoglobulins which are reflected by their ability to respond to antigens (Hardy et al. 1989). B-2 cells respond efficiently to protein antigens and, with the help of T lymphocytes, undergo affinity maturation and changes immunoglobulin heavy chain, leading to the formation of different antibody isotypes. In contrast, B-1 cells respond mainly to thymus-independent antigens, producing immunoglobulins that recognize molecules with repetitive epitopes such as in carbohydrates (Dorshkind and Montecino-Rodriguez 2007; Montecino-Rodrigue et al. 2016).

B-1 are unique cells in the immune response since they are able to produce immunoglobulins, phagocytose, present antigens to T lymphocytes, and produce immunomodulatory cytokines (Fig. 1) (Baumgarth 2017; Popi et al. 2016; Popi 2015). Thus, these functions may allow that B-1 cells to contribute to immunity against parasites. Parasitic infections remain one of the most important causes of morbidity and mortality worldwide (Cox 2002). Although many studies have focused on the pathogenesis and immune response against parasitic infections, few studies have been performed to better understand the role of B-1 cells in both protozoa and helminth infections. In this review, we aimed to summarize the major findings in the field of research on B-1 and parasitic diseases. Next, we describe and detail the functions of B-1 cells that may be relevant for parasite infection immunity.

Spontaneous and induced antibody production

B-1 cells play a role in the first line of defense established in mammals, a function that is attributed to the production of natural antibodies (Baumgarth et al. 2005). These antibodies are produced even in the absence of external antigenic stimuli, providing an initial protective barrier upon entry of certain pathogens and allowing enough time for B-2 cells to establish a more specific, long-lasting, complex, and larger response (Baumgarth et al. 2005). Among the antibodies produced by B-1 lymphocytes, many recognize self-antigens, such as Thy-1 (CD90) (Hayakawa et al. 2003), DNA (Casali et al. 1987), and phosphatidylcholine (Hayakawa et al. 1983). For this reason, it is believed that these antibodies recognize and remove senescent cells and antigens released by apoptotic cells, limiting the development of autoimmune diseases (Baumgarth et al. 2005).

B-1a cells produce low-affinity polyreactive natural IgM (nIgM) antibodies that bind to conserved epitopes. Thus, nIgM can also contribute to innate protection in the host (Briles et al. 1981; Masmoudi et al. 1990). Moreover, B-1b cells produce thymus-independent antibodies type 2 (TI-2) against polysaccharide antigens on the cell wall of certain bacteria and fungi (Haas et al. 2005; Rapaka et al. 2010). Natural IgM produced by B-1 cells provides a crucial barrier against the replication of microbes prior to the establishment of specific immune responses (Cole et al. 2009; Choi and Baumgarth 2008; Gil-Cruz et al. 2009). Despite their low general affinity and broad cross-reactivity, these preexisting antibodies directly neutralize and partially activate the classical pathway of the complement system (Baumgarth et al. 2000; Jayasekera et al. 2007), inhibiting the early replication of the microorganism (Baumgarth et al. 2000; Haas et al. 2005).

Some examples of the importance of these nIgMs in the initial response to infectious diseases have been shown using experimental models. It was demonstrated that nIgM from B-1 cells contributes to initial protection against influenza virus

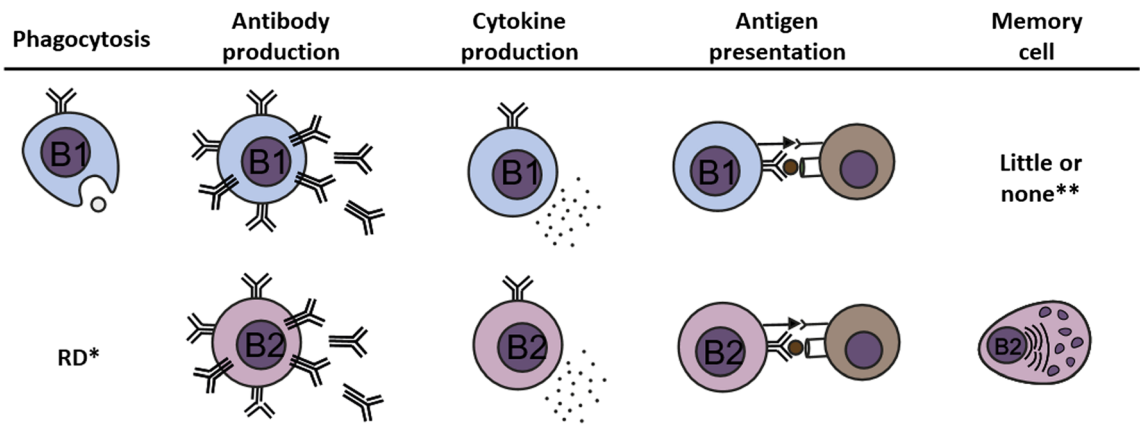

Fig. 1 Immune functions of B-1 and B-2 cells. B-1 cells are able to phagocytose, but recent studies (RD*) have shown that B-2 cells also have the ability to phagocytose. As B-2 lymphocytes, B-1 cells produce and secrete antibodies, but IgM is the major secreted isotype. Both B-1 and B-2 cells produce cytokines, but B-1 cells spontaneously release IL-10. As B-2 cells, B-1 cells may present antigen to T lymphocytes. The activation of B-2 lymphocytes can induce production of memory cells, but few studies demonstrated such properties in B-1 cells

(Baumgarth et al. 2000). Mice that lacked IgM produced by B-1 cells had increased mortality after challenge with influenza virus, demonstrating the role of these antibodies in the initial protection to the virus (Baumgarth et al. 2000). Interestingly, B-1 cells are also able to produce natural antibodies against galactose terminal resides (anti-α gal antibodies) (Ohdan et al. 2000). These anti-α gal antibodies can contribute to malaria defense because they target *Plasmodium sporozoites* and induce complement-mediated cytotoxicity (Yilmaz et al. 2014), control transmission, but their role in blood stage is not completely understood (Yilmaz et al. 2014). Anti-alpha gal antibodies also recognize epitopes present in *T. cruzi* and *Leishmania* (Avila et al. 1989). In Chagas disease these antibodies appear to be related with extensive localized "autoimmune-like" inflammatory reactions (Travassos and Almeida 1993), but the importance of anti-alpha gal antibodies released by B-1 cells on the Chagas disease is still unclear.

Depending on the site of infection, B-1 cells will have different fate (Baumgarth 2011). Infections of mucosal surfaces lead to the redistribution of B-1a cells to regional lymph nodes which differentiate into IgM-secreting cells in a polyclonal response, independent of the B cell receptor (BCR) (Choi and Baumgarth 2008). Already systemically inoculated antigens induce the migration of B-1 cells from the body cavities to the spleen or to the lamina propria where they differ in IgM- or IgA-secreting cells (Martin et al. 2001; Yang et al. 2007; Ohdan et al. 2000). On the other hand, B-1b cells appear to undergo clonal expansion in response to antigen exposure and produce increased amounts of specific antibodies, although the tissue where this production occurs is still controversial.

The role of antibodies produced by B-1 cells was evaluated in few models of parasite infections. BALB/c mice intraperitoneally infected with *Trypanosoma cruzi* showed a decrease in the percentage of peritoneal B-1 cells after 15 days of infection (highest parasitemia period) (Merino et al. 2010). In this model, the reduced number of peritoneal B-1 cells was associated with an increase in their differentiation in antibody-secreting plasmocytes induced by components produced by the parasite (Merino et al. 2010). Thus, B-1 differentiation in antibody-producing plasmocytes appears to be linked to an increased susceptibility of BALB/c animals to *T. cruzi* infection. B-1 cells showed to be involved in the pathogenesis of toxoplasmosis in an experimental model, but their role remains controversial (Chen et al. 2000). In response to infection with the parasite, B-1 cells from BALB/c and C57BL/6 mice produced IL-10 and antibodies against heat shock protein 70 (HSP70), which regulates susceptibility to infection by *Toxoplasma gondii* (Chen et al. 2003a). In contrast, the transfer of primed B-1, but not naïve B-1, to B cell-deficient mice (muMT) protected these animals after challenge with *T. gondii* (Chen et al. 2003a; Chen et al. 2003b). Therefore, in this model, B-1 cells showed a protective role during infection.

Besides the production of IgM, IgG, and IgA, few reports have shown IgE production by B1 cells (Takatsu et al. 1992; Vink et al. 1999; Perona-Wright et al. 2008; Savage and Baumgarth 2015). A recent work demonstrated that B-1 cells produced poly-specific IgE during infection with the nematode parasites *Nippostrongylus brasiliensis* and *Heligmosomoides polygyrus bakeri* (Martin et al. 2018). The B-1 cell-derived IgE reduced mastocyte cell degranulation by a probably mechanism of IgE saturation of FcεRI, leading to a decrease in helminth clearance (Martin et al. 2018). This work proposes a regulatory mechanism to IgE produced by B1 cells. Although several works have demonstrated the antibodies production by B-1 cells, few studies have shown the induction of memory cells (Cole et al. 2009; Yang et al. 2012).

Thus, the natural and inducible antibodies produced by B-1 cells can affect immunity against the parasites by the classical

complement activation, antibody-dependent cell-mediated cytotoxicity (ADCC), regulatory mechanisms, and phagocytosis. Further studies using other protozoa and helminths models are necessary to better understand the pathophysiology of natural and induced antibodies secreted by B-1 cells.

Cytokine production

B-1 cells spontaneously produce IL-10 (O'Garra et al. 1992; Griffin and Rothstein 2012), a cytokine with anti-inflammatory properties (Mosser and Zhang 2008). This cytokine shows pleiotropic effects on immune system since it inhibits antigen presentation, T cell proliferation, acts regulating the production of inflammatory cytokines, among other functions (Mosser and Zhang 2008). Several studies have demonstrated that natural and induced production of IL-10 by B-1 cells can contribute to modulate the immune response in some experimental infections (Barbeiro et al. 2011; Gonzaga et al. 2015; Gonzaga et al. 2017). In visceral leishmaniasis, IL-10-knockout mice (IL-10KO) mice that receive adoptive transfer of B-1 cells from wild-type were more susceptible to *Leishmania chagasi* infection than IL-10KO mice (Gonzaga et al. 2015), suggesting that IL-10 produced by B-1 cells contribute to the susceptibility to parasite infection. In addition, B-1 cells from IL-10KO mice were more resistance to *Leishmania major* infection than B-1 cells from wild-type (Arcanjo et al. 2015). Thus, it is possible to speculate that IL-10 from B-1 can participate in the immunoregulation, allowing the parasite growth and contributing to disease progression.

However, other cytokine types are also produced by B-1 cells. Mice intraperitoneally treated with *Propionibacterium acnes* had an increase in the number of B-1b cells that were positive for IL-4, IL-5, and IL-12 (Mussalem et al. 2012). The soluble polysaccharide from bacteria increased B-1b cell expression of IL-10 and IL-12 cytokines (Mussalem et al. 2012). The cytokine expression was also altered in B-1 cells from mice intraperitoneally infected with *Leishmania amazonensis*. After 24 h of infection, peritoneal B-1 cells increase the expression of both IL-10 and TNF-α cytokines (Geraldo et al. 2016). These studies support the hypothesis that these cells are plastic and respond differently depending on the stimulus. A better understanding of the activation profiles of this cell, as well as the mechanisms by which B-1 cells are activated, can uncover the role of these cells in infectious and parasitic diseases.

Phagocytic function

Consistent with the expression of surface markers characteristic of macrophages, some authors have described the ability of B-1 cells to differentiate into phagocytic cells (Gao et al. 2012; Almeida et al. 2001). Borrello and Phipps (1995) were the first authors to demonstrate that the populations of $CD5^+$ splenic B cells from the spleen, co-cultured with fibroblasts, expressed macrophages markers, such as F4/80 and Mac-1, and exhibited phagocytic capacity (Borrello and Phipps 1995, 1996). It has been shown that during the differentiation of B-1 cells to phagocytes, the gene expression was altered with reduced expression of genes related to the lymphoid lineage and a concomitant increase in the expression of genes related to the myeloid lineage (Popi et al. 2009), clearly showing that these cells have the molecular mechanisms to change their phenotype.

Corroborating the differentiation capacity of B-1 cells in phagocytes, Almeida et al. (2001) demonstrated that peritoneal B-1 cells spontaneously differentiate into macrophage-like cells capable of phagocytizing sheep red blood cells and zymosan. The ability of B-1 cells to phagocytose opsonized latex beads and microbes by using classical phagocytic receptors were also reported (Gao et al. 2012; Ghosn et al. 2006). In vivo, these cells also differentiated into cells with macrophage phenotypes (Popi et al. 2012; Gambero et al. 2016) and phagocytosed apoptotic blebs, *Escherichia coli* and *Leishmania amazonensis* (Gao et al. 2012; Novaes et al. 2010; Geraldo et al. 2016). The phagocytose ability of B-1 cells is well documented in the literature but recent works have demonstrated that B-2 lymphocytes can also phagocytose bacteria and latex beads (Zhu et al. 2016; Martínez-Riaño et al. 2018).

The in vitro models have contributed to better clarifying the role of B-1 cells in differentiated into phagocytes in the response to *Leishmania*. Arcanjo et al. (2015) demonstrated that B-1 cells phagocyzed promastigotes of *L. major* in an IL-10 production-dependent process. Our group demonstrated that these cells were more permissive to infection in vitro with *L. amazonensis* promastigotes than peritoneal macrophages. B-1 cells had a significantly higher phagocytic index compared with peritoneal or medullar macrophages at 16 and 24 h (Geraldo et al. 2016). Recently, Arcanjo et al. (2017a) showed that B-1 cells promoted the growth of *L. major* amastigotes inside peritoneal murine macrophages due to elevated levels of PGE2 and IL-10 produced by these cells. Understanding the complex interactions of B-1 cells perform with other cells of the immune system during the course of *Leishmania* infection and other parasites may help to better determine the roles of these cells in the pathogenesis of the leishmaniasis as well as other infection diseases.

Antigen-presenting cell function

Several studies demonstrated that B-1 cells express MHC class II, CD40, CD80, and CD86, and therefore, it has been

proposed that these cells could have the ability to present antigens (Vigna et al. 2002; Gambero et al. 2016;Tumang et al. 2004). Corroborating this hypothesis, Zhong et al. (2007) demonstrated that peritoneal B-1 cells were able to present OVA peptide to OVA-responsive transgenic T cells since their promoted proliferation of these $CD4^+$ T cells. In addition, Margry et al. (2013) showed that peritoneal B-1a cells present antigen to $CD4^+$ T cells in vivo. However, there are few reports showing B-1 cells acting as antigen-presenting cells (APCs) (Margry et al. 2013; Sato et al. 2004; Vigna et al. 2002; Wang and Rothstein 2012; Popi et al. 2016).

Besides these antigen-presenting capacities, B-1 cells induce the differentiation of T cells. Peritoneal B-1a cells stimulated the increase in vitro of IL-10, IL-4, and IFN-γ-producing $CD4^+$ T cells, suggesting that these cells have ability to induce peripheral adaptive immune responses (Margry et al. 2013). On the other hand, in vitro peritoneal B-1 cells stimulated T cell to express IL-17 and IFN- γ in the presence of TGF-β and IL-2, thus leading these cells to differentiation in Th17 and Th1 profiles, respectively (Zhong et al. 2007; Wang and Rothstein 2012). However, further studies are necessary to investigate the role of B-1 cells in inducing T cell differentiation in the context of parasite infections. Although speculative, the possibility that the B1 cell-mediated generation of Th1/Th17 cells may have a role in inducing inflammatory reactions and immune responses against parasites cannot be ruled out.

In vivo models to study B-1 cells in parasite infections

To better assess the role of B-1 cells in homeostasia and immunity, some studies have used X-linked immune-deficient mice (XIDs) that are genetically devoid of the Bruton enzyme tyrosine kinase (Btk). This defect leads to impairments in the development of B cells (Khan et al. 1995; Rawlings et al. 1993), especially in the subset of B-1 cells which shows significant reduction in the peritoneal cavities of XID mice (Hayakawa et al. 1983).

Using this model, B-1 cells showed a protective role in experimental infection with *Giardia muris* and *Encephalitozoon cuniculi* (Snider et al. 1988; Langanke Dos Santos et al. 2018). XID mice developed prolonged infections and produced lower levels of serum IgG anti-*G. muris* compared with background controls. The inability to elicit an appropriate humoral immune response probably contributed to the inability to eliminate the parasite in XID animals (Snider et al. 1988). The protection related with the presence of B-1 cells was also demonstrated in infection with the microsporidia *Encephalitozoon cuniculi.* XID mice were more susceptible to infection with the parasite than the background BALB/c (Langanke Dos Santos et al. 2018).

On the other hand, XID mice infected with *Trypanosoma cruzi* exhibited low levels of specific and non-specific immunoglobulins in serum, and were able to control parasitemia in comparison to the control (Minoprio et al. 1993). Analysis of mRNA transcripts in the spleen of infected animals showed that XID mice produced high mRNA levels of mRNA for IFN-γ, IL-2, and IL-4, and low mRNA levels of IL-10 after 4 days of infection. The administration of anti-IFN-γ in XID led to an increase in parasitemia, demonstrating the important role of IFN-γ in these animals as one of the factors associated with parasite resistance (Minoprio et al. 1993).

For leishmaniasis, the role of B-1 cells is still unclear. XID mice infected with *Leishmania major* (one of the species responsible for the cutaneous form of the disease) presented a higher parasitic load in lymphatic organs (Hoerauf et al. 1994). In contrast, animals depleted of B-1 cells and infected with *L. major* developed similar disease as compared to the control mice (Babai et al. 1999). Our group has been studying the role of B-1 cells in experimental leishmaniasis, and we demonstrated that XID mice infected with *L. chagasi* showed a significantly reduced parasite load in the spleen compared with control animals (Gonzaga et al. 2015). The transfer of B-1 cells to XID mice restored susceptibility, suggesting that such cells may be related to susceptibility to infection (Gonzaga et al. 2015). The putative mechanisms involved in the susceptibility seem to be linked to IL-10 since the adoptive transfer of B-1 cells from wild-type animals to IL-10KO mice led to increased susceptibility of recipients (Gonzaga et al. 2015). Corroborating these findings, Arcanjo et al. (2017b) showed that B-1-deficient mice infected with *L. chagasi* developed reduced splenomegaly with diminished splenic parasite burden and lower levels of IL-10 secretion of splenocytes at 30 days post-infection (Arcanjo et al. 2017a). In contrast, XID were more susceptible to *L. amazonensis* infection (etiological agent of the cutaneous form of leishmaniasis) than background control mice (Gonzaga et al. 2017), suggesting that B-1 cells can contribute to improving the control of cutaneous infection caused by *L. amazonensis* (Gonzaga et al. 2017). Thus, the participation of B-1 cells in leishmaniasis depends on the causal species of disease.

To helminth infections, the B-1 cells generally contribute positively to defense against these parasites. XID mice have demonstrated a reduced ability to control infections by *Brugia pahangi* (Paciorkowski et al. 2000), *Brugia malayi* (Paciorkowski et al. 2000), *Strongyloides stercoralis* (Herbert et al. 2002), and *Schistosoma mansoni* (Gaubert et al. 1999). Mechanisms of B cell-mediated protection have already been identified and include antibody production, antigen presentation, and cytokine secretion.

Studies involving experimental infections with *Brugia malayi* and *Brugia pahangi* in B lymphocyte-deficient mice demonstrated that these animals were permissive to infection by the genus *Brugia* while the immunocompetent mice were

resistant (Paciorkowski et al. 2000). In addition, XID animals were as permissive as those that did not have all B cells, suggesting that B-1 cells should be responsible for the host protection (Paciorkowski et al. 2000). The reconstitution of (Rag)-$1^{-/-}$ mice with B-1b cells conferred resistance against *Brugia* infection, proposing that B1-b cells are required to mediate host resistance to this parasite (Paciorkowski et al. 2000). The same profile was observed in animals infected with the pathogenic filariae *Litomosoides sigmodontis.* XID mice showed significantly more adult worms compared to the background control. The susceptibility observed in XID mice can be explained by lower antibody production in response to dominant parasite antigen and by diminished B cell-derived IL-10, which led to deficient parasite-driven Th2 cytokine production (Al-Qaoud et al. 1998). Corroborating these findings, in vitro studies have demonstrated that ES-62 antigen (a protein from *Acanthocheilonema viteae*, a filarial nematode of rodents that share well-conserved epitopes with *B. malayi* and *Onchocerca volvulus*) activated peritoneal B-1 cells, leading to an increase in cell proliferation and IL-10 secretion (Wilson et al. 2003).

The importance of B-1 cells has also been investigated in XID mice immunized with *Strongyloides stercoralis* larvae stage 3 (L3) (another helminth nemathelminthe) (Herbert et al. 2002). The immunization led to insignificant levels of IgM and a significant IgG response, which was approximately half the level detected in immunized wild-type mice. The authors purposed that B-1 cells could participate in immunity against *Strongyloides stercoralis* infection, not as a source of immunoregulatory molecules but by producing parasite-specific antibodies (Herbert et al. 2002).

Infection of XID mice with the plathelminthe *Schistosoma mansoni* showed that, compared with the background control, B-1 cell-deficient mice had more susceptibility to parasite infection, as demonstrated by an increase in the number of eggs found in tissues, significant mortality, and an increase in the densities of granulomas (Gaubert et al. 1999). The immune responses in infected XID mice demonstrated high levels of IFN-gamma and IL-4 and low quantities of IL-10. The antibody profile was also altered in XID mice, suggesting that the absence of B-1 cells interfered with the quality of the protective immune response against *S. mansoni* (Gaubert et al. 1999). In addition, peritoneal B-1 cells proliferated and secreted large amounts of IL-10 after stimulation with carbohydrate antigens from *S. mansoni* egg, but the mechanisms and the receptors involved in these responses are not yet clear (Velupillai et al. 1997).

Table 2 Contribution of B-1 cells in immunity to different parasites

Parasites	Species	Contribution of B-1 cells in immunity	Effector mechanism (*speculative)	References
Helminth	*Brugia malayi* and *Brugia pahangi*	Resistance	Humoral response, raise of IL-10 and Th2 response*	Paciorkowski et al. (2000)
	Litomosoides sigmodontis	Resistance	Production of IL-10 and antibodies, Th2 response*	Al-Qaoud et al. (1998)
	Nippostrongylus brasiliensis and *Heligmosomoides polygyrus bakeri*	Susceptibility	Production of IgE by B-1 cells	Martin et al. (2018)
	Schistosoma mansoni	Resistance	Production of IL-10 and antibodies*	Gaubert et al. (1999)
	Strongyloides stercoralis	Resistance	Antibody production*	Herbert et al. (2002)
Protozoa	*Encephalitozoon cuniculi*	Resistance	Production or stimulation of production of pro-inflammatory cytokines (IFN-γ, IL-6, TNF-α)	Langanke Dos Santos et al. (2018)
	Giardia muris	Resistance	Humoral response*	Snider et al. (1988)
	Leishmania amazonensis	Resistance	Production of IL-10 and TNF-α	Geraldo et al. (2016)) and Gonzaga et al. (2017)
	Leishmania chagasi	Susceptibility	Production of IL-10	Gonzaga et al. (2015) and Arcanjo et al. (2017a)
	Leishmania major	Resistance/no effect	Production of IL-10/PGE2	Hoerauf et al. (1994), Arcanjo et al. (2015)/Babai et al. (1999)
	Toxoplasma gondii	Susceptibility/resistance	Production of IL-10 and antibodies/production or stimulation of high expression of both Th1 and Th2-type cytokines and a high level of NO	Chen et al. (2000), Chen et al. (2003a))/Chen et al. (2003b)
	Trypanosoma cruzi	Susceptibility	Production of cytokines* and differentiation into plamocytes	Minoprio et al. (1993) and Merino et al. (2010)

Table 3 B-1 cells properties versus future advances in the context of parasitic diseases

B-1 cell properties	Effector mechanisms	Future advances
Natural and/or inducible antibody production	Classical complement activation, antibody-dependent cell-mediated cytotoxicity (ADCC), regulatory mechanisms, and phagocytosis	To evaluate the effector mechanisms of natural and induced antibodies produced by B-1 cells on helminths and/or protozoa infections
Releasing of pro- and/or anti-inflammatory cytokines	Depend on the cytokine produced	To understand the activation of B-1 cells in the context of parasitic infections
Phagocytosis	Engulfing, activation, and killing of parasites (protozoa)	To better understand the molecular mechanisms of B-1 cell differentiation in phagocytic cells
Antigen presentation and inducing of T cell differentiation	Differentiation of T lymphocytes into effector cells (Th1, Th2, Th17)	To evaluate the induction of Th subtypes by B-1 cells in immunity against parasites

Although the use of XID mice to study B-1 cells is somewhat limited, since defects in other B cell populations are also found in these animals, several studies using the adoptive transfer of B-1 cells to these animals corroborated the findings in XID animals. The effects caused by the absence of these cells were total or partial reversed after the adoptive transfer of B-1 cell to XID mice. Thus, the studies with XID animals showed that B-1 cells can contribute to resistance or susceptibility depend on the protozoa infection. On the other hand, to helminth infections, these cells seem to be linked to protection since the IL-10 and the antibodies produced by B-1 cells, especially IgM, can also directly contribute to defense against helminthes. Table 2 summarizes the role of B-1 cells in the parasite infections.

Human B-1 cells

Studies to characterize human B-1 cells in the peripheral blood have shown that populations expressing CD20+, CD27+, and CD43+ share some characteristics with mouse B-1 cells, especially those involved with production of natural antibodies and secretion of antibodies with autoreactive features (Rothstein et al. 2013; Quách et al. 2016). However, this issue is still under debate in the literature. The better characterization of human B-1 cells and their impact on the outcome of infections could bring more understanding of the importance of these cells in protection against parasitic infections and homeostasis.

Concluding remarks

Parasites are widely distributed in the world and are responsible for several important diseases that affect millions of people, especially in countries with a low index of human development. To ensure survival and dissemination, parasitic protozoans have developed the ability to subvert host immune responses (Lopes et al. 2012). The adopted strategy depends on the organism since protozoans are highly variable in terms of life cycle, tissue tropism, and other features.

After infection B-1 cells and their products can influence the outcome of a parasite infection by producing different kind of anti-inflammatory and inflammatory cytokines, secreting natural and specific antibodies against parasite antigens, presenting antigen and phagocytosing pathogens (Table 3). The versatility of B-1 cells makes them unique in the context of the immune response. The abilities to phagocytose, present antigen, and produce natural antibodies link these cells with the innate immune response, but the ability to produce specific antibodies includes B-1 cells in adaptive response. The role of B-1 cells in protozoan infection is still not clear because it is dependent on the model, parasite, and life stage of the parasites. However, during helminthic infections, the presence of B-1 cells in most models is associated with appropriate defense and the development of a protective response. A deeper understanding of the biological properties of B-1 cells will be key to determining how these cells operate and how to modulate their responses to contribute to improved treatment of parasite diseases.

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Compliance with ethical standards

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

References

Abrahão TB, Freymüller E, Mortara RA, Lopes JD, Mariano M (2003) Morphological characterization of mouse B-1 cells. Immunobiology 208:401–411. https://doi.org/10.1078/0171-2985-00287

Al-Qaoud KM, Fleischer B, Hoerauf A (1998) The Xid defect imparts susceptibility to experimental murine filariosis—association with a lack of antibody and IL-10 production by B cells in response to phosphorylcholine. Int Immunol 10:17–25

Almeida SR, Aroeira LS, Frymuller E, Dias MA, Bogsan CS, Lopes JD, Mariano M (2001) Mouse B-1 cell-derived mononuclear phagocyte, a novel cellular component of acute non-specific inflammatory exudate. Int Immunol 13:1193–1201

Arcanjo AF, LaRocque-de-Freitas IF, Rocha JD, Zamith D, Costa-da-Silva AC, Nunes MP, Mesquita-Santos FP, Morrot A, Filardy AA, Mariano M, Bandeira-Melo C, DosReis GA, Decote-Ricardo D, Freire-de-Lima CG (2015) The PGE2/IL-10 Axis determines susceptibility of B-1 cell-derived phagocytes (B-1CDP) to *Leishmania major* infection. PLoS One 10:e0124888. https://doi.org/10.1371/journal.pone.0124888

Arcanjo AF, Nico D, de Castro GMM, da Silva Fontes Y, Saltarelli P, Decote-Ricardo D, Nunes MP, Ferreira-Pereira A, Palatnik-de-Sousa CB, Freire-de-Lima CG, Morrot A (2017a) Dependency of B-1 cells in the maintenance of splenic Interleukin-10 producing cells and impairment of macrophage resistance in visceral Leishmaniasis. Front Microbiol 8:978. https://doi.org/10.3389/fmicb.2017.00978

Arcanjo AF, Nunes MP, Silva-Junior EB, Leandro M, da Rocha JDB, Morrot A, Decote-Ricardo D, Freire-de-Lima CG (2017b) B-1 cells modulate the murine macrophage response to *Leishmania major* infection. World J Biol Chem 8:151–162. https://doi.org/10.4331/wjbc.v8.i2.151

Avila J, Rojas LM, Galili U (1989) Immunogenic gal alpha 1——3Gal carbohydrate epitopes are present on pathogenic American *Trypanosoma* and *Leishmania*. J Immunol 142:2828–2834

Babai B, Louzir H, Cazenave PA, Dellagi K (1999) Depletion of peritoneal CD5+ B cells has no effect on the course of *Leishmania major* infection in susceptible and resistant mice. Clin Exp Immunol 117:123–129

Bao S, Beagley KW, Murray AM, Caristo V, Matthaei KI, Young IG, Husband AJ (1998) Intestinal IgA plasma cells of the B1 lineage are IL-5 dependent. Immunology 94:181–188. https://doi.org/10.1046/j.1365-2567.1998.00512.x

Barbeiro DF, Barbeiro HV, Faintuch J, Ariga SK, Mariano M, Popi AF, de Souza HP, Velasco IT, Soriano FG (2011) B-1 cells temper endotoxemic inflammatory responses. Immunobiology 216:302–308. https://doi.org/10.1016/j.imbio.2010.08.002

Baumgarth N (2011) The double life of a B-1 cell: self-reactivity selects for protective effector functions. Nat Rev Immunol 11:34–46. https://doi.org/10.1038/nri2901

Baumgarth N (2017) A hard(y) look at B-1 cell development and function. J Immunol 199:3387–3394. https://doi.org/10.4049/jimmunol.1700943

Baumgarth N, Herman OC, Jager GC, Brown LE, Herzenberg LA, Chen J (2000) B-1 and B-2 cell-derived immunoglobulin M antibodies are nonredundant components of the protective response to influenza virus infection. J Exp Med 192:271–280

Baumgarth N, Tung JW, Herzenberg LA (2005) Inherent specificities in natural antibodies: a key to immune defense against pathogen invasion. Springer Semin Immunopathol 26:347–362. https://doi.org/10.1007/s00281-004-0182-2

Berland R, Wortis HH (2002) Origins and functions of B-1 cells with notes on the role of CD5. Annu Rev Immunol 20:253–300. https://doi.org/10.1146/annurev.immunol.20.100301.064833

Borrello MA, Phipps RP (1995) Fibroblasts support outgrowth of splenocytes simultaneously expressing B lymphocyte and macrophage characteristics. J Immunol 155:4155–4161

Borrello MA, Phipps RP (1996) The B/macrophage cell: an elusive link between CD5+ B lymphocytes and macrophages. Immunol Today 17(10):471–475

Briles DE, Nahm M, Schroer K, Davie J, Baker P, Kearney J, Barletta R (1981) Antiphosphocholine antibodies found in normal mouse serum are protective against intravenous infection with type 3 streptococcus pneumoniae. J Exp Med 153:694–705

Casali P, Burastero SE, Nakamura M, Inghirami G, Notkins AL (1987) Human lymphocytes making rheumatoid factor and antibody to ssDNA belong to Leu-1+ B-cell subset. Science 236(4797):77–81

Chen M, Aosai F, Mun HS, Norose K, Hata H, Yano A (2000) Anti-HSP70 autoantibody formation by B-1 cells in *Toxoplasma gondii*-infected mice. Infect Immun 68(9):4893–4899

Chen M, Aosai F, Norose K, Mun HS, Yano A (2003a) The role of anti-HSP70 autoantibody-forming V(H)1-J(H)1 B-1 cells in *Toxoplasma gondii*-infected mice. Int Immunol 15(1):39–47

Chen M, Mun HS, Piao LX, Aosai F, Norose K, Mohamed RM, Belal US, Fang H, Ahmed AK, Kang HK, Matsuzaki G, Kitamura D, Yano A (2003b) Induction of protective immunity by primed B-1 cells in *Toxoplasma gondi* -infected B cell-deficient mice. Microbiol Immunol 47:997–1003

Choi YS, Baumgarth N (2008) Dual role for B-1a cells in immunity to influenza virus infection. J Exp Med 205:3053–3064. https://doi.org/10.1084/jem.20080979

Choi YS, Dieter JA, Rothaeusler K, Luo Z, Baumgarth N (2012) B-1 cells in the bone marrow are a signifi cant source of natural IgM. Eur J Immunol 42:120–129

Cole LE, Yang Y, Elkins KL, Fernandez ET, Qureshi N, Shlomchik MJ, Herzenberg LA, Vogel SN (2009) Antigen-specific B-1a antibodies induced by *Francisella tularensis* LPS provide long-term protection against F. Tularensis LVS challenge. Proc Natl Acad Sci U S A 106:4343–4348. https://doi.org/10.1073/pnas.0813411106

Cox FE (2002) History of human parasitology. Clin Microbiol Rev 15:595–612

Dorshkind K, Montecino-Rodriguez E (2007) Fetal B-cell lymphopoiesis and the emergence of B-1-cell potential. Nat Rev Immunol 7:213–219. https://doi.org/10.1038/nri2019

Gambero M, Teixeira D, Butin L, Ishimura ME, Mariano M, Popi AF, Longo-Maugéri IM (2016) *Propionibacterium acnes* induces an adjuvant effect in B-1 cells and affects their phagocyte differentiation via a TLR2-mediated mechanism. Immunobiology 221:1001–1011. https://doi.org/10.1016/j.imbio.2016.03.003

Gao J, Ma X, Gu W, Fu M, An J, Xing Y, Gao T, Li W, Liu Y (2012) Novel functions of murine B1 cells: active phagocytic and microbicidal abilities. Eur J Immunol 42:982–992. https://doi.org/10.1002/eji.201141519

Gaubert S, Viana da Costa A, Maurage CA, Lima EC, Fontaine J, Lafitte S, Minoprio P, Capron A, Grzych JM (1999) X-linked immunodeficiency affects the outcome of *Schistosoma mansoni* infection in the murine model. Parasite Immunol 21:89–101

Geraldo MM, Costa CR, Barbosa FM, Vivanco BC, Gonzaga WF, Novaes E, Brito RR, Popi AF, Lopes JD, Xander P (2016) *In vivo* and *in vitro* phagocytosis of *Leishmania (Leishmania) amazonensis* promastigotes by B-1 cells. *Parasite Immunol* 38(6):365–376. https://doi.org/10.1111/pim.12324

Ghosn EE, Russo M, Almeida SR (2006) Nitric oxide-dependent killing of *Cryptococcus neoformans* by B-1-derived mononuclear phagocyte. J Leukoc Biol 80:36–44. https://doi.org/10.1189/jlb.1005603

Ghosn EE, Sadate-Ngatchou P, Yang Y, Herzenberg LA (2011) Distinct progenitors for B-1 and B-2 cells are present in adult mouse spleen. Proc Natl Acad Sci U S A 108:2879–2884. https://doi.org/10.1073/pnas.1019764108

Ghosn EE, Yang Y, Tung J, Herzenberg LA (2008) CD11b expression distinguishes sequential stages of peritoneal B-1 development. Proc Natl Acad Sci U S A 105:5195–5200. https://doi.org/10.1073/pnas.0712350105

Gil-Cruz C, Bobat S, Marshall JL, Kingsley RA, Ross EA, Henderson IR, Leyton DL, Coughlan RE, Khan M, Jensen KT, Buckley CD, Dougan G, MacLennan IC, López-Macías C, Cunningham AF (2009) The porin OmpD from nontyphoidal Salmonella is a key target for a protective B1b cell antibody response. Proc Natl Acad Sci U S A 106:9803–9808. https://doi.org/10.1073/pnas.0812431106

Gonzaga WFKM, Geraldo MM, Vivanco BC, Popi AF, Mariano M, Batista WL, Xander P (2017) Evaluation of experimental infection with *L. (L.) Amazonensis* in X-linked Immunodeficient mice. J Parasitol 103:708–717. https://doi.org/10.1645/16-145

Gonzaga WF, Xavier V, Vivanco BC, Lopes JD, Xander P (2015) B-1 cells contribute to susceptibility in experimental infection with *Leishmania (Leishmania) chagasi*. Parasitology 142:1506–1515. https://doi.org/10.1017/S0031182015000943

Griffin DO, Rothstein TL (2012) Human "orchestrator" CD11b(+) B1 cells spontaneously secrete interleukin-10 and regulate T-cell activity. Mol Med 18:1003–1008. https://doi.org/10.2119/molmed.2012.00203.

Haas KM, Poe JC, Steeber DA, Tedder TF (2005) B-1a and B-1b cells exhibit distinct developmental requirements and have unique functional roles in innate and adaptive immunity to *S. pneumoniae*. Immunity 23:7–18. https://doi.org/10.1016/j.immuni.2005.04.011

Hardy RR, Carmack CE, Shinton SA, Riblet RJ, Hayakawa K (1989) A single VH gene is utilized predominantly in anti-BrMRBC hybridomas derived from purified Ly-1 B cells Definition of the VH11 family. *J Immunol* 142:3643–3651

Hardy RR, Hayakawa K (2001) B cell developmental pathways. Annu Rev Immunol 19:595–621. https://doi.org/10.1146/annurev.immunol.19.1.595

Hayakawa K, Asano M, Shinton SA, Gui M, Wen LJ, Dashoff J, Hardy RR (2003) Positive selection of anti-thy-1 autoreactive B-1 cells and natural serum autoantibody production independent from bone marrow B cell development. J Exp Med 197:87–99

Hayakawa K, Hardy RR, Parks DR, Herzenberg LA (1983) The "Ly-1 B" cell subpopulation in normal immunodefective, and autoimmune mice. J Exp Med 157:202–218

Herbert DR, Nolan TJ, Schad GA, Abraham D (2002) The role of B cells in immunity against larval *Strongyloides stercoralis* in mice. Parasite Immunol 24:95–101

Herzenberg LA (2000) B-1 cells: the lineage question revisited. Immunol Rev 175:9–22

Herzenberg LA, Stall AM, Lalor PA, Sidman C, Moore WA, Parks DR (1986a) The Ly-1 B cell lineage. Immunol Rev 93:81–102

Herzenberg LA, Stall AM, Lalor PA, Sidman C, Moore WA, Parks DR, Herzenberg LA (1986b) The LY-1B cell lineage. Immunol Rev 93:81–102. https://doi.org/10.1111/j.1600-065X.1986.tb01503.x

Hoerauf A, Solbach W, Lohoff M, Rollinghoff M (1994) The Xid defect determines an improved clinical course of murine leishmaniasis in susceptible mice. Int Immunol 6:1117–1124

Jayasekera JP, Moseman EA, Carroll MC (2007) Natural antibody and complement mediate neutralization of influenza virus in the absence of prior immunity. J Virol 81:3487–3494. https://doi.org/10.1128/JVI.02128-06

Khan WN, Alt FW, Gerstein RM, Malynn BA, Larsson I, Rathbun G, Davidson L, Müller S, Kantor AB, Herzenberg LA (1995) Defective B cell development and function in Btk-deficient mice. Immunity 3:283–299

Kroese FG, Butcher EC, Stall AM, Lalor PA, Adams S, Herzenberg LA (1989) Many of the IgA producing plasma cells in murine gut are derived from self-replenishing precursors in the peritoneal cavity. Int Immunol 1:75–84

Langanke Dos Santos D, Alvares-Saraiva AM, Xavier JG, Spadacci-Morena DD, Peres GB, Dell'Armelina Rocha PR, Perez EC, Lallo MA (2018) B-1 cells upregulate CD8 T lymphocytes and increase proinflammatory cytokines serum levels in oral encephalitozoonosis. Microbes Infect 20:196–204. https://doi.org/10.1016/j.micinf.2017.11.004

Lopes MF, Zamboni DS, Lujan HD, Rodrigues MM (2012) Immunity to protozoan parasites. J Parasitol Res 2012:250793. https://doi.org/10.1155/2012/250793

Margry B, Wieland WH, van Kooten PJ, van Eden W, Broere F (2013) Peritoneal cavity B-1a cells promote peripheral $CD4^+$ T-cell activation. Eur J Immunol 43(9):2317–2326. https://doi.org/10.1002/eji.201343418

Martin F, Oliver AM, Kearney JF (2001) Marginal zone and B1 B cells unite in the early response against T-independent blood-borne particulate antigens. Immunity 14:617–629

Martin RK, Damle SR, Valentine YA, Zellner MP, James BN, Lownik JC, Luker AJ, Davis EH, DeMeules MM, Khandjian LM, Finkelman FD, Urban JF, Conrad DH (2018) B1 cell IgE impedes mast cell-mediated enhancement of parasite expulsion through B2 IgE blockade. Cell Rep 22:1824–1834. https://doi.org/10.1016/j.celrep.2018.01.048

Martínez-Riaño A, Bovolenta ER, Mendoza P, Oeste CL, Martín-Bermejo MJ, Bovolenta P, Turner M, Martínez-Martín N, Alarcón B (2018) Antigen phagocytosis by B cells is required for a potent humoral response. EMBO Rep 19(9):e46016. https://doi.org/10.15252/embr.201846016

Masmoudi H, Mota-Santos T, Huetz F, Coutinho A, Cazenave PA (1990) All T15 id-positive antibodies (but not the majority of VHT15+ antibodies) are produced by peritoneal CD5+ B lymphocytes. Int Immunol 2:515–520

Merino MC, Montes CL, Acosta-Rodriguez EV, Bermejo DA, Amezcua-Vesely MC, Gruppi A (2010) Peritoneum from *Trypanosoma cruzi*-infected mice is a homing site of Syndecan-1 neg plasma cells which mainly provide non-parasite-specific antibodies. Int Immunol 22:399–410. https://doi.org/10.1093/intimm/dxq019

Minoprio P, el Cheikh MC, Murphy E, Hontebeyrie-Joskowicz M, Coffman R, Coutinho A, O'Garra A (1993) Xid-associated resistance to experimental Chagas' disease is IFN-gamma dependent. J Immunol 151:4200–4208

Montecino-Rodrigue E, Fice M, Casero D, Berent-Maoz B, Barber CL, Dorshkind K (2016) Distinct genetic networks orchestrate the emergence of specific waves of fetal and adult B-1 and B-2 development. Immunity 45(3):527–539. https://doi.org/10.1016/j.immuni.2016.07.012

Mosser DM, Zhang X (2008) Interleukin-10: new perspectives on an old cytokine. Immunol Rev 226:205–218. https://doi.org/10.1111/j.1600-065X.2008.00706.x

Mussalem JS, Squaiella-Baptistão CC, Teixeira D, Yendo TM, Thies FG, Popi AF, Mariano M, Longo-Maugéri I (2012) Adjuvant effect of killed *Propionibacterium acnes* on mouse peritoneal B-1 lymphocytes and their early phagocyte differentiation. PLoS One 7(3):e33955. https://doi.org/10.1371/journal.pone.0033955

Novaes E, Brito RR, Cortez BA, Machado-Santelli GM, Xander P, De Lorenzo BH, Oliveira HC, Thies FG, Kioshima ES, Maricato JT, Lopes JD, Mariano M (2010, 2010) *In Vitro* and *In Vivo* Phagocytic Ability of Mouse B-1 Cells. Immunol Immunogen Insights:231–239. https://doi.org/10.4137/III.S6156

O'Garra A, Chang R, Go N, Hastings R, Haughton G, Howard M (1992) Ly-1 B (B-1) cells are the main source of B cell-derived interleukin 10. Eur J Immunol 22:711–717. https://doi.org/10.1002/eji.1830220314

Ohdan H, Swenson KG, Kruger Gray HS, Yang YG, Xu Y, Thall AD, Sykes M (2000) Mac-1-negative B-1b phenotype of natural antibody-producing cells, including those responding to gal alpha 1,3Gal epitopes in alpha 1,3-galactosyltransferase-deficient mice. J Immunol 165:5518–5529

Paciorkowski N, Porte P, Shultz LD, Rajan TV (2000) B1 B lymphocytes play a critical role in host protection against lymphatic filarial parasites. J Exp Med 191:731–736

Perona-Wright G, Mohrs K, Taylor J, Zaph C, Artis D, Pearce EJ, Mohrs M (2008) Cutting edge: helminth infection induces IgE in the absence of mu- or delta-chain expression. J Immunol 181(10):6697–6701

Popi AF (2015) B-1 phagocytes: the myeloid face of B-1 cells. Ann N Y Acad Sci 1362:86–97. https://doi.org/10.1111/nyas.12814

Popi AF, Longo-Maugéri IM, Mariano M (2016) An overview of B-1 cells as antigen-presenting cells. Front Immunol 7:138. https://doi.org/10.3389/fimmu.2016.00138

Popi AF, Motta FL, Mortara RA, Schenkman S, Lopes JD, Mariano M (2009) Co-ordinated expression of lymphoid and myeloid specific transcription factors during B-1b cell differentiation into mononuclear phagocytes in vitro. Immunology 126:114–122. https://doi.org/10.1111/j.1365-2567.2008.02883.x

Popi AF, Osugui L, Perez KR, Longo-Maugeri IM, Mariano M (2012) Could a B-1 cell derived phagocyte "be one" of the peritoneal macrophages during LPS-driven inflammation? PLoS One 7(3):e34570. https://doi.org/10.1371/journal.pone.0034570

Quách TD, Rodríguez-Zhurbenko N, Hopkins TJ, Guo X, Hernández AM, Li W, Rothstein TL (2016) Distinctions among circulating antibody-secreting cell populations, including B-1 cells, in human adult peripheral blood. J Immunol 196(3):1060–1069. https://doi.org/10.4049/jimmunol.1501843

Rapaka RR, Ricks DM, Alcorn JF, Chen K, Khader SA, Zheng M, Plevy S, Bengtén E, Kolls JK (2010) Conserved natural IgM antibodies mediate innate and adaptive immunity against the opportunistic fungus pneumocystis murina. J Exp Med 207:2907–2919. https://doi.org/10.1084/jem.20100034

Rawlings DJ, Saffran DC, Tsukada S, Largaespada DA, Grimaldi JC, Cohen L, Mohr RN, Bazan JF, Howard M, Copeland NG, Jenkins NA, Witte ON (1993) Mutation of unique region of Bruton's tyrosine kinase in immunodeficient XID mice. Science 261:358–361

Rothstein TL, Griffin DO, Holodick NE, Quach TD, Kaku H (2013) Human B-1 cells take the stage. Ann N Y Acad Sci 1285:97–114. https://doi.org/10.1111/nyas.12137

Sato T, Ishikawa S, Akadegawa K, Ito T, Yurino H, Kitabatake M, Yoneyama H, Matsushima K (2004) Aberrant B1 cell migration into the thymus results in activation of CD4 T cells through its potent antigen-presenting activity in the development of murine lupus. Eur J Immunol 34(12):3346–3358. https://doi.org/10.1002/eji.200425373

Savage HP, Baumgarth N (2015) Characteristics of natural antibody-secreting cells. Ann N Y Acad Sci 1362:132–142. https://doi.org/10.1111/nyas.12799

Snider DP, Skea D, Underdown BJ (1988) Chronic giardiasis in B-cell-deficient mice expressing the xid gene. Infect Immun 56(11):2838–2842

Takatsu K, Takaki S, Hitoshi Y, Mita S, Katoh S, Yamaguchi N, Tominaga A (1992) Cytokine receptors on Ly-1 B cells. IL-5 and its receptor system. Ann N Y Acad Sci 651:241–258

Travassos LR, Almeida IC (1993) Carbohydrate immunity in American trypanosomiasis. Springer Semin Immunopathol 15(2–3):183–204

Tumang JR, Hastings WD, Bai C, Rothstein TL (2004) Peritoneal and splenic B-1 cells are separable by phenotypic, functional, and transcriptomic characteristics. Eur J Immunol 34(8):2158–2167. https://doi.org/10.1002/eji.200424819

Velupillai P, Secor WE, Horauf AM, Harn DA (1997) B-1 cell (CD5+ B220+) outgrowth in murine schistosomiasis is genetically restricted and is largely due to activation by polylactosamine sugars. J Immunol 158(1):338–344

Vigna AF, Godoy LC, Almeida SR, Mariano M, Lopes JD (2002) Characterization of B-1b cells as antigen presenting cells in the immune response to gp43 from *Paracoccidioides brasiliensis in vitro*. Immunol Lett 83(1):61–66

Vink A, Warnier G, Brombacher F, Renauld JC (1999) Interleukin 9-induced in vivo expansion of the B-1 lymphocyte population. J Exp Med 189(9):1413–1423

Wang Y, Rothstein TL (2012) Induction of Th17 cell differentiation by B-1 cells. Front Immunol 3:281. https://doi.org/10.3389/fimmu.2012.00281

Wilson EH, Katz E, Goodridge HS, Harnett MM, Harnett W (2003) *In vivo* activation of murine peritoneal B1 cells by the filarial nematode phosphorylcholine-containing glycoprotein ES-62. Parasite Immunol 25(8–9):463–466

Yang Y, Ghosn EE, Cole LE, Obukhanych TV, Sadate-Ngatchou P, Vogel SN, Herzenberg LA, Herzenberg LA (2012) Antigen-specific memory in B-1a and its relationship to natural immunity. Proc Natl Acad Sci U S A 109(14):5388–5393. https://doi.org/10.1073/pnas.1121627109

Yang Y, Tung JW, Ghosn EE, Herzenberg LA (2007) Division and differentiation of natural antibody-producing cells in mouse spleen. Proc Natl Acad Sci U S A 104(11):4542–4546. https://doi.org/10.1073/pnas.0700001104

Yenson V, Baumgarth N (2014) Purification and immune phenotyping of B-1 cells from body cavities of mice. Methods Mol Biol 1190:17–34. https://doi.org/10.1007/978-1-4939-1161-5_2

Yilmaz B, Portugal S, Tran TM, Gozzelino R, Ramos S, Gomes J, Regalado A, Cowan PJ, d'Apice AJ, Chong AS, Doumbo OK, Traore B, Crompton PD, Silveira H, Soares MP (2014) Gut microbiota elicits a protective immune response against malaria transmission. Cell 159(6):1277–1289. https://doi.org/10.1016/j.cell.2014.10.053

Zhong X, Gao W, Degauque N, Bai C, Lu Y, Kenny J, Oukka M, Strom TB, Rothstein TL (2007) Reciprocal generation of Th1/Th17 and T(reg) cells by B1 and B2 B cells. Eur J Immunol 37(9):2400–2404. https://doi.org/10.1002/eji.200737296

Zhu Q, Zhang M, Shi M, Liu Y, Zhao Q, Wang W, Zhang G, Yang L, Zhi J, Zhang L, Hu G, Chen P, Yang Y, Dai W, Liu T, He Y, Feng G, Zhao G (2016) Human B cells have an active phagocytic capability and undergo immune activation upon phagocytosis of Mycobacterium tuberculosis. Immunobiology 221(4):558–567. https://doi.org/10.1016/j.imbio.2015.12.003