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Review Article

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Th17 Cell and Inflammatory Infiltrate Interactions in Cutaneous Leishmaniasis: Unraveling Immunopathogenic Mechanisms

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ABSTRACT

The inflammatory response during cutaneous leishmaniasis (CL) involves immune and non-immune cell cooperation to contain and eliminate *Leishmania* parasites. The orchestration of these responses is coordinated primarily by $CD4^+$ T cells; however, the disease outcome depends on the Th cell predominant phenotype. Although Th1 and Th2 phenotypes are the most addressed as steers for the resolution or perpetuation of the disease, Th17 cell activities, especially IL-17 release, are recognized to be vital during CL development. Th17 cells perform vital functions during both acute and chronic phases of CL. Overall, Th17 cells induce the migration of phagocytes (neutrophils, macrophages) to the infection site and $CD8^+$ T cells and NK cell activation. They also provoke granzyme and perforin secretion from $CD8^+$ T cells, macrophage differentiation towards an M2 phenotype, and expansion of B and Treg cells. Likewise, immune cells from the inflammatory infiltrate have modulatory activities over Th17 cells involving their differentiation from naive $CD4^+$ T cells and further expansion by generating a microenvironment rich in optimal cytokines such as IL-1β, TGF-β, IL-6, and IL-21. Th17 cell activities and synergies are crucial for the resistance of the infection during the early and acute stages; however, if unchecked, Th17 cells might lead to a chronic stage. This review discusses the synergies between Th17 cells and the inflammatory infiltrate and how these interactions might destine the course of CL.

Keywords: Th17 cells; Cutaneous leishmaniasis; Host-pathogen interactions; Immune response; Immunomodulation

INTRODUCTION

Cutaneous leishmaniasis (CL) is a worldwide spread vector-borne parasitic disease caused by various members of the *Leishmania* genus and transmitted by sand flies (1). The World Health Organization estimates 600,000 to 1 million new cases worldwide, occurring mainly in the Americas, Middle East, and Central Asia; however, some factors such as rapid

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Conflict of Interest

The authors declare no potential conflicts of interest.

Abbreviations

APC, antigen-presenting cell; CL, cutaneous leishmaniasis; DC, dendritic cell; DCL, disseminated cutaneous leishmaniasis; GC, germinal center; iNOS, inducible nitric oxide synthase; KO, knockout; LC, Langerhans cell; LCL, localized cutaneous leishmaniasis; LPG, lipophosphoglycan; MC, mast cell; MCET, mast cells release extracellular trap; ML, mucocutaneous leishmaniasis; NET, neutrophil extracellular trap; PAMP, pathogen-associated molecular pattern; PTX3, pentraxin 3; PV, parasitophorous vacuole; RORγt, retinoid-acid-receptor-related orphan nuclear receptor gamma; SNP, single nucleotide polymorphism; WT, wild-type.

Author Contributions

Conceptualization: Zamora-Chimal J, Morales-Primo AU, Pedraza-Zamora CP; Data curation: Zamora-Chimal J, Morales-Primo AU; Formal analysis: Morales-Primo AU; Investigation: Morales-Primo AU; Methodology: Zamora-Chimal J, Morales-Primo AU; Supervision: Zamora-Chimal J, Pedraza-Zamora CP; Visualization: Zamora-Chimal J, Morales-Primo AU, Becker I, Pedraza-Zamora CP; Writing - original draft: Zamora-Chimal J, Morales-Primo AU, Pedraza-Zamora CP; Writing - review & editing: Zamora-Chimal J, Becker I, Pedraza-Zamora CP.

urbanization, human migration, and climate change lead to the risk of transmission and emergence of CL in non-endemic zones (2). This disease manifests in multiple clinical forms, influenced by both the pathogen species and the host's immune response. Among these clinical manifestations are localized and disseminated cutaneous leishmaniasis (LCL and DCL, respectively) and other severe outcomes like mucocutaneous leishmaniasis (ML) and post-kala-azar dermal leishmaniasis (1,3). The clinical features of CL range from the LCL single skin papule that may or may not ulcerate and is occasionally self-healing, to DCL, characterized by dozen to thousands of polymorphic skin lesions to the more severe mucocutaneous involving tissue destruction and local deformities (3,4).

Leishmania life cycle is characterized by 2 stages: promastigote and amastigote. The cycle begins when the motile promastigote stage is transferred from the female sand fly to the mammalian host during a blood meal. Once inside the host, the immune system deploys monocytes and neutrophils to phagocyte promastigotes. Inside the phagocytes, promastigotes transform into non-motile amastigotes and reproduce through binary fission. Eventually, amastigotes burst from the phagocytes to infect new cells. The cycle is completed when a sand fly ingests phagocytes infected with amastigotes, which then transform into promastigotes in the sand fly's gut (1,5).

The outcome of the disease is shaped by interactions between the host immune components, encompassing both adaptive and innate systems, and the parasite. Th1 response confers resistance against *Leishmania* infection by activating macrophages through IFN-γ. However, an excessive Th1 response can result in tissue destruction (5,6). Conversely, the Th2 response has been associated with an increased parasite load, rendering the host susceptible to the infection (7). It is important to note that the interactions within the immune system during *Leishmania* infection are intricate, especially when considering the inherent diversity stemming from study models (whether human or rodent), and the presence of multiple Th responses.

Th17 are a subset of Th cells mostly known for their production of IL-17, a critical molecule involved in recruiting neutrophils (8). Recent studies have reported contributions of the Th17 response during cutaneous *Leishmania* infection (9). However, the effects of Th17 activities on the inflammatory infiltrate and adjacent tissues in the cutaneous lesions remain unclear. In this review, we further analyze this subject to gain a better understanding.

Th17 IMMUNOBIOLOGY

Th17 cells are a specific subset of $CD4^+$ T cells first identified by Harrington *et al.* (10) in 2005. They reported in their seminal work the existence of a novel lineage of $CD4^+$ T cells characterized by their production of IL-17 (10). Th17 cells were generated in response to IL-23 stimulation in naïve $CD4^+$ cells and showed a new developmental program different from those of Th1 and Th2 cells. Notably, the differentiation of the Th17 phenotype was inhibited when naive $CD4^+$ cells were exposed to IFN-γ and IL-4, both critical cytokines in Th1 and Th2 responses, respectively (10).

However, Th17 differentiation cannot be achieved by IL-23 alone. Instead, it requires the presence of other molecules, such as IL-6, IL-1β, IL-21 and TGF-β (10,11). These cytokines induce the expression of the retinoid-acid-receptor-related orphan nuclear receptor gamma

(RORγt) in naive T cells, ultimately leading to their polarization, with IL-23 stabilizing the differentiation process (12).

Dendritic cells (DCs) play a pivotal role in Th17 differentiation, and their functions are closely linked to the tissue in which they reside and the prevailing inflammatory environment (13). For instance, DCs stimulated with infected apoptotic cells release TGF-β, IL-6 and IL-23. This combined release triggers the secretion of IL-17 and upregulation of *Rorc*, the gene encoding RORγt in naive $CD4^+$ cells, leading to the induction of the Th17 phenotype (14). Inflammatory monocyte-derived DCs have a specialized role in driving Th17 cell development by secreting IL-1β, IL-6, IL-23 and likely TGF-β (15).

Additionally, Ag-presenting T cells have the ability to trigger Th17 differentiation. T cells acquire MHC receptors from Ag-presenting cells (APCs) during the immunological synapse through a process called trogocytosis. Subsequently, through T-T Ag presentation, the presenting T cell interacts with a naive T $CD4^+$ cells, promoting their differentiation into the Th17 cell subset (16). However, specific conditions are required for this Th17 differentiation, including high T cell to APC ratios and low Ag concentrations (16). Interestingly, the presenting T cell differentiates into a pro-tolerogenic Treg, as evidenced by their expression of Foxp3, the Treg cell master regulator (16).

Th17 and Treg cells both depend on TGF-β as a crucial cytokine for their differentiation, as it triggers the expression of RORγT for Th17 cells and Foxp3 for T reg cells. However, these 2 cell subsets are governed by different main transcription factors and serve distinct roles (17). Nonetheless, during inflammatory events, Th17 and Treg cells are interconnected, not only due to their initial signals, but also because of their roles in regulating inflammation. Molecules such as hypoxia-inducible factor 1, mTOR and cytokines like IL-6 and IL-21 play crucial roles in maintaining the balance between Th17 and Treg cells (18-20). Disruption of this balance have severe consequences. For instance, during a Th17-driven autoimmune response, Treg cell populations may decrease, impairing the self-tolerance and the control of autoreactive T cells, thereby promoting helping disease development (19).

The IL-17 family of cytokines comprises several members, with IL-17A being the signature cytokine of Th17 cells, and it ranges from IL-17A to IL-17F (21). IL-17A, often referred to simply as IL-17, is a pleiotropic pro-inflammatory cytokine with both beneficial and detrimental effects. It plays a role in the progression of various autoimmune diseases and the clearance of infections (21). IL-17, including IL-17F, another cytokine secreted by Th17 cells, has the ability to activate innate and tissue-resident cells, leading to the production of various cytokines, chemokines, matrix metalloproteinases, and antimicrobial peptides (22). Additionally, IL-17 promotes the recruitment and activation of neutrophils, leading to the release of extracellular traps (neutrophil extracellular traps [NETs]) (23).

Another notable feature of IL-17 feature is its capacity to amplify ongoing inflammatory responses rather than initiating them *de novo* (24). Instead, IL-17 synergizes with other molecules like TNF and IFN-γ to sustain the inflammatory environment (25). For instance, the synergy between IL-17 and TNF enhances the chemoattraction and rolling of neutrophil by activating the endothelial cells, leading to the expression of cellular adhesion molecules like P- and E-selectin, as well as and chemokines such as CXCL1, CXCL2, CXCL5 and CXCL8 (25,26).

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Additionally, Th17 cells also produce IL-21 and IL-22 (27). IL-21 is a cytokine involved in the differentiation, function, and regulation of both innate and adaptive immune cells (28). In contrast, IL-22 primarily targets non-hematopoietic cells such as epithelial cells and fibroblasts. It plays a role in tissue regeneration by inhibiting apoptosis in epithelial cells and promoting their proliferation (29).

Th17 AND CL

The presence and impact of IL-17 and Th17 responses have been extensively investigated across various *Leishmania* species. As mentioned earlier, Th17 cells play a crucial role in host defense against pathogens, including bacteria and intracellular parasites (30-32). Indeed, reports indicate that Th17/IL-17 responses confer resistance against different *Leishmania* species, both in visceral and cutaneous clinical manifestations (32,33).

Regarding the beneficial role of Th17 cells during a *Leishmania* infection, studies have shown that early expansion of Th17 cells, along with $CD4^+$ cells producing IFN-γ and IL-10, correlates with self-healing of wounds in B6 mice infected with *Leishmania braziliensis* (34). As the infection progresses, the number of these cells tends to diminish, likely to aid in parasite clearance (34), and mitigate the risk of an excessive pro-inflammatory response. Additionally, research has revealed the presence of cytokines associated with the differentiation, maintenance, and activity of Th17 cells in lesions of human patients infected with *Leishmania panamensis* (33). Furthermore, also, it was suggested that Th17 cell activity contributes to parasite control, possibly through the production of IL-17 and the activation of the NLRP3 inflammasome (33). Although solid evidence supporting this phenomenon is lacking, the correlations observed between parasite burden and $IL\text{-}17^+$ cell density indicate a potential beneficial effect (33). However, since the $IL\text{-}17^+$ cell density exceeded that of $ROR\gamma t^+$ cells, it is possible that other mechanisms, such as Th1 $IL\text{-}17^+$ cells (35), also play a role in parasite clearance. Conversely, patients with subclinical *L. braziliensis* infections exhibit an atypical type 1 immune response. Instead, innate immune responses, aided by IL-17 producing cells, are responsible for rapid parasite control (36).

Pentraxin 3 (PTX3) is an innate pattern recognition molecule that plays a multifaceted role in host defense against pathogens, as well as in the regulation of inflammation and tissue remodeling (37). PTX3 is expressed in various cell types including epithelial and endothelial cells, fibroblasts, and myeloid lineage cells, such as monocytes and neutrophils. It has been associated with the regulation of Th17 cells and the production of IL-17 (38). Studies have shown that PTX3 is overexpressed in inflamed sites of mice infected with *Leishmania major* (39). Moreover, infected PTX3-deficient ($PTX3^{-/-}$) mice exhibited smaller lesion sizes compared to their wild-type (WT) counterparts, which correlated with a lower parasite load at 10 wk post-infection (39). Furthermore, the infected $PTX3^{-/-}$ mice showed higher concentration of $IL\text{-}17A^+CD4^+$ T cells, which were consistent with *in vitro* production of IL-17A from splenocytes isolated from the knockout (KO) mice and stimulated with soluble *Leishmania* Ag (39). Additionally, PTX3 was found to negatively regulate Th17 transcription factors, such as RORγt and STAT3 and inhibit the production of IL-17 transcripts (39). These findings suggest that PTX3 suppresses IL-17 responses, and its absence leads to increased Th17 activity and resistance against CL caused by *L. major*. These observations show the complex interplay between PTX3, Th17 cells and IL-17 in *Leishmania* infections and their impact on disease outcomes.

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However, despite their potentially beneficial role, Th17 cells can also exacerbate pro-inflammatory responses to the point of disease progression and worsening (40). Th17 cells can enhance and sustain pro-inflammatory responses by recruiting neutrophils, which may lead to parasite spread and host susceptibility (40,41). For instance, ear wounds in *L. major*-infected IL-17$^{-/-}$ BALB/c mice had fewer neutrophils due to the absence of chemokines like CXCL1, CXCL2, and CXCL5, which were recovered by injecting IL-17, consequently increasing neutrophil recruitment (40). Interestingly, the wounds in IL-17$^{-/-}$ mice did not develop necrosis, in contrast to the control, demonstrating that IL-17 is a molecule required for the progression of the disease (40). Moreover, we demonstrated that the chronicity of *Leishmania mexicana* infection is associated with a concomitant increase in Th17 cells and neutrophils in the inflamed sites, using both the susceptible BALB/c and the semi-resistant C57BL/6 mouse models (41). The mouse models BALB/c and C57BL/6 have been used for studying leishmaniasis due to their different genetic backgrounds (42). After 90 days of infection, Th17 and neutrophil infiltration, as well as lesion size, were greater in the BALB/c model compared to the C57BL/6 model, indicating that BALB/c susceptibility is likely due to an uncontrolled inflammatory response that facilitates parasite spreading (41).

ML represents the most severe clinical outcome of dermal infections, characterized by an uncontrolled immune response directed against a low number of parasites. This immune response leads to the formation of ulcer lesions and subsequent destruction of mucosal and cartilaginous tissues (43). Boaventura *et al.* (44) demonstrated the presence of IL-17 in the tissue samples of ML patients. Interestingly, IL-17 was found to be secreted not only by Th17 cells but also by CD8^{+} and CD14^{+} cells. Crucial cytokines and markers associated with Th17 differentiation, such as IL-23, TGF-β and RORγt, were also detected in these samples (44). Furthermore, IL-17 acted as a chemotactic molecule for neutrophils, which, in turn, secreted various enzymes like neutrophil elastase, myeloperoxidase and metalloproteinase 9, contributing to tissue damage (44).

The host's genetic background is another variable that determines the outcome of leishmaniasis. Single nucleotide polymorphisms (SNPs) in the IL-17 gene have been associated with autoimmune and infection diseases (45,46). One such SNP, r2275913, leads to the substitution of guanine for adenine in the promoter region of the human *IL17A* gene (47). This SNP affects the binding motif of the NFAT, a crucial regulator of *IL17A* expression (48). In patients with CL infected with *L. braziliensis* who carry the r2275913 SNP, there were fewer Th17 cells, resulting in reduced IL-17 production and a greater parasite burden compared to individuals without the SNP (47). While this mutation was not directly linked to susceptibility in patients with CL, researchers did not rule out its possible association with the acquisition and development of CL outcomes.

Conversely, *Leishmania* parasites possess the ability to modulate the host immune response to their advantage. Exosomes are vesicles formed within the cell's multivesicular bodies that are expelled into the extracellular space (49). These vesicles carry various cargos, including lipids, proteins, and genetic material, which, upon uptake by other cells, can reprogram the recipient cells (50). When footpad-lesions in *L. major*-infected mice were inoculated with isolated parasite exosomes, the lesions exhibited a larger volume and a higher parasite burden compared to those inoculated with parasites alone (51). Additionally, *L. major* exosomes exacerbated lesion development by favoring parasite replication and promoting the production of IL-17, suggesting a potential involvement of Th17 cells in this process (51). Notably, these exosomes were found in the sand fly's gut, implying that the contents of

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exosomes inoculated by the sand fly during its blood meal, could influence early events in the infection process (51).

Th17 EFFECTS ON THE INFLAMMATORY INFILTRATE OF CL

Multiple factors determine the intensity of the immune response against *Leishmania*, including the species of the parasite, the components injected by the sand fly's saliva, and the genetic and inflammatory background of the host. Furthermore, interactions among immune cells and resident tissues during the infection are also key factors in leading to either a proper or detrimental inflammatory response. In general, the inflammatory infiltrate in CL is characterized by the presence of neutrophils, macrophages, $CD4^+$, $CD8^+$, IL-17^+ T cells, NK cells, B cells, plasma cells, and DCs (52-55). However, the proportions and activities of these cells vary depending on the study model, the clinical manifestation, and the stages of the infection (41,56,57).

Furthermore, both inflammatory and non-inflammatory skin resident cells participate in the responses against *Leishmania* and are also targets of Th17 cytokines (22,57,58). Here, we will discuss the modulation and potential scenarios arising from Th17 interactions with the cells in the inflammatory infiltrate in CL.

Neutrophils

Neutrophils belong to the myeloid lineage of innate immune cells and are known to be one of the first lines of defense against pathogens. They possess an extensive array of weaponry and cellular mechanisms, including phagocytosis, respiratory burst, and the release of molecular components (granules containing metalloproteinases, antimicrobial peptides, cytokines, and NETs (59). Due to these activities, neutrophils have been recognized as crucial for controlling *Leishmania* infection. Neutrophils are rapidly and massively recruited to the site of infection following the inoculation of *Leishmania* parasites (60,61). However, the functional role of neutrophils can be either beneficial or detrimental to the host depending on the species of the parasite and its stage (62).

It was reported that neutrophils aid in the early elimination of *L. major* (63), *L. braziliensis* (64) and *Leishmania amazonensis* (65). In contrast, experiments involving neutrophil-depleted mice have shown fewer parasite loads, smaller lesion sizes and an overall better resolution of infection, suggesting a harmful role of neutrophils (60,66). Additionally, some *Leishmania* parasites have developed countermeasures against neutrophil microbicidal mechanisms to the point of using the neutrophils as vehicles for infecting other cells (62). This phenomenon, described as the "Trojan horse" model, was first reported in 2003 and outlines a scenario in which *Leishmania* hijacks neutrophils, inhibits their effector mechanisms, proliferates within them, and then infects macrophages (67,68).

Th17 cells and neutrophils have an intimate relationship due to the ability of IL-17 to induce the recruitment of neutrophils (69). IL-17 synergizes with TNF to trigger the secretion of chemokines, such as CXCL1, CXCL5 and CXCL8, from endothelial and epithelial cells (26,70). These chemokines are just a few examples of those that attract neutrophils are attracted (**Figs. 1** and **2**) (71). Furthermore, Pelletier *et al.* (72) demonstrated that activated Th17 cells can also produce CXCL8, therefore inducing neutrophil migration. Interestingly, neutrophils secrete CCL2 and CCL20, which are chemokines for Th1 and Th17 cells, illustrating a reciprocal system

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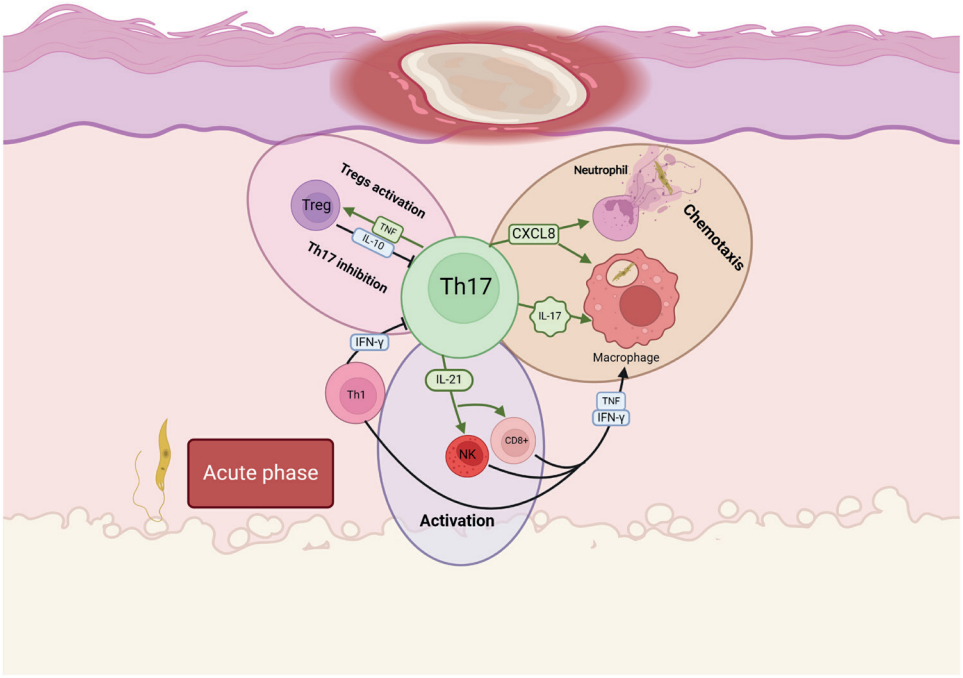

Figure 1. Th17 cell's main activities during acute leishmaniasis. We distinguish 3 Th17 cell main activities: 1) Chemotaxis of phagocytes such as neutrophils and macrophages via CXCL8 and IL-17. 2) Activation of cytotoxic cells, namely NK and CD8+ cells, and pro-inflammatory-cytokine secretion. 3) Negative feedback between the activation of Tregs cells via TNF and Th17 cells inhibition via IL-10.

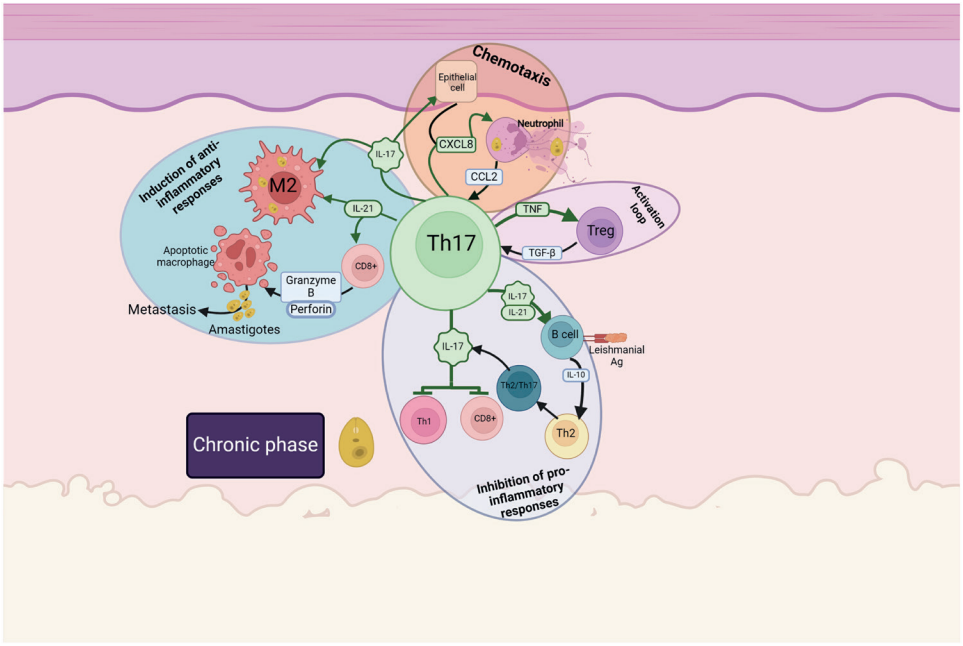

Figure 2. Th17 cell's main activities during chronic leishmaniasis. We sort Th17 cell main activities into 4 categories. 1) Chemotaxis feedback between neutrophils and Th17 cells via CCL2 and CXCL8, respectively. 2) Activation loop between Treg and Th17 cells via TGF-β and TNF, respectively. 3) Inhibition of pro-inflammatory responses through IL-17 and IL-21 release targeting Th1 and CD8+ cells. This inhibition mechanism is sustained by the differentiation of Th2 cells to Th2/Th17 cells via IL-10 from activated B cells. 4) Induction of anti-inflammatory responses through differentiating macrophages towards an M2 phenotype via IL-17 and IL-21. Additionally, these cytokines activate CD8+ cells, which lyse infected macrophages, liberating the amastigotes and perpetuating the infection.

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of chemoattraction between neutrophils and Th17 cells (**Fig. 2**) (72). These findings, along with our report of a concomitant increase in both neutrophils and Th17 cells (41), suggest a positive feedback loop that intensifies over time, potentially leading to chronicity of the disease.

NETs are composed of microbicidal proteins bound to decondensed chromatin fibers and are released by neutrophils. Despite their beneficial role against pathogens, NETs have also been implicated in the development of various autoimmune diseases (73). *Leishmania* parasites have been reported to stimulate the release of NETs release; however, some *Leishmania* species have developed evasive mechanisms that allow them to survive the toxic effects of NETs (62). Supernatants from the culture of IL-17-stimulated KPC cells (an epithelial lineage), have been shown to enhance the *ex vivo* PAD4-dependant release of NETs compared to the direct addition of recombinant IL-17 (23). This evidence underscores the essential role of IL-17 in stimulating epithelial cells to modulate neutrophil activities and NETs release, potentially augmenting the pro-inflammatory response against *Leishmania*. Surprisingly, cathelicidin (LL-37), an antimicrobial peptide released from neutrophils during degranulation and NETs liberation, enhances the expression of RORγT and IL-17 on $CD4^+$ T cells, inducing their differentiation toward a Th17 phenotype in a TGF-β-dependent manner (74). Altogether, the Th17/neutrophil axis represents a close relationship where both cell types reciprocate stimuli for activation, migration and proliferation. In the context of CL, this relationship may initially seem beneficial but potentially becomes detrimental over longer time frames (**Figs. 1** and **2**).

Macrophages

Macrophages play an indispensable role in the *Leishmania* life cycle. Once engulfed by the macrophages, *Leishmania* parasites are capable of surviving within the phagolysosome by converting it into a parasitophorous vacuole (PV) (75). The PV nurtures the parasite, allowing it to differentiate into an amastigote and to proliferate. When the macrophage becomes overwhelmed by the parasites, it may either burst or undergo apoptosis, leading to the clearance of the parasites and debris by newly recruited immune cells, thereby infecting other cells (75). However, in the presence of IFN-γ and TNF, macrophages activate their leishmanicidal activities by producing of nitric oxide (76). Conversely, alternative activated macrophages, via IL-4 and IL-13 (considered the regulatory phenotype), favors the parasite survival and growth (77).

IL-17 is a cytokine with the potential to induce various effects on macrophages. First, IL-17 exerts a chemotactic role on macrophages as they express IL-17RA, the IL-17 receptor (78,79). Furthermore, IL-17 induces the alternative activation of macrophages (M2) (80). THP-1 derived-macrophages treated with IL-17 overexpress characteristic markers and cytokines of the M2 phenotype, such as CD163 and CD206, TGF-β, VEGF and IL-10 (80). IL-17 also elicits the phosphorylation of IkBα, suggesting this alternative activation is mediated via the NF-κB pathway (80). M2 macrophages have been associated with the diffuse clinical form of CL. Wounds from DCL patients show greater concentrations of molecules related to the activity of M2 macrophages, such as IL-10, TGF-β, prostaglandin E_2 and arginase-1 (81,82). Infected M2 macrophages enzymatically produce polyamines via arginase-1 activity, which, in turn, promotes the intramacrophagic proliferation and survival of *Leishmania* parasites (83). Additionally, IL-21, another cytokine released by the Th17 cells, plays a role in macrophage polarization towards an M2 phenotype (**Fig. 2**) (84). THP-1derived macrophages stimulated with IL-21 during the M2-polarization process, overexpress markers such as CD86, CD163 and IL-10 (84). Based on these reports, we can hypothesize that an uncontrolled Th17 response during the late stage of the *Leishmania* infection will provoke the recruitment of macrophages

and the subsequent polarization into an M2 phenotype. Later, these M2 macrophages, along with neighboring neutrophils, will become infected, sustain the infection, and most likely, contribute to its spread, leading to the chronic phase.

DCs

DCs are a group of immune cells responsible for orchestrating the immune response by linking and modulating the innate and adaptive systems. As members of the professional APCs family, DCs have the ability to phagocytose particles and present them for priming T cells activities (85). DCs exist in 2 different states: immature and mature, with the mature state being the only one capable of activating T cells. DCs' activation and maturation are elicited through the presence of extracellular signals such as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns, which stimulate DCs' pattern-recognition receptors, leading to changes in the expression of surface costimulatory proteins (CD40, CD80, CD83, CD86 and MHC II), chemokines receptors, metabolic activity and cytokine secretion (85,86).

Multiple reports have addressed DCs as important players in the modulation of the immune response during *Leishmania* infection (87). DCs participate in parasite uptake, Ag presentation and the priming of $CD4^+$ cells (54,77). DCs secrete IL-12, a vital cytokine for initiation of Th1 responses and clearing *Leishmania* parasites (88). IL-12 induces IFN-γ secretion by $CD4^+$, $CD8^+$ T cells and NK cells, which, in turn, activates the leishmanicidal mechanisms in phagocytes, killing the parasite (88,89).

However, *Leishmania* parasites have mechanisms for neutralizing and subverting DC activities in their favor. GP63, a *Leishmania* surface protease, helps the parasite to evade elimination in the phagolysosome by cleaving and modulating host signaling molecules (90,91). Indeed, GP63 cleaves VAMP8, a protein of the SNARE group, hindering the assembly of the NADPH oxidase complex (92), promoting parasite survival. As a result, T cell activation is reduced due to an impaired cross-presentation (92).

Furthermore, DCs have demonstrated the potential to induce the differentiation of Th17 cells (15,93). Human inflammatory DCs, $CD11c^+HLA\text{-}DR^+BDCA^+CD16^-$, secrete Th17-polarizing cytokines, such as IL-1β, IL-6 and IL-23, inducing the production of IL-17 in memory $CD4^+$ T cells and the expression of RORγT in naive $CD4^+$ T cells (15). Regarding leishmaniasis, Dietze-Schwonberg *et al.* (93) reported that DCs play a key role in the induction of Th17 cells through the secretion of IL-23p19. $IL\text{-}23p19^{-/-}$BALB/c and $IL\text{-}17A^{-/-}$BALB/c mice presented smaller wound sizes and lower parasite burdens during the first 14 wk post-infection, along with reduced levels of IL-17A (93). This evidence reinforces the theory that Th17 cells activities are responsible for the progression of leishmaniasis; however, other cells like DCs might induce the polarization of this phenotype, which, in turn, is triggered by the influence of *Leishmania* parasites or other immune cells. Indeed, IL-17A treatment reduced the production of IL-12, TNF-α, or IL-6 by DCs (94).

Epidermal DCs, also known as Langerhans cells (LCs), are a specialized subset of DC that reside in the outer layer of the skin, where they survey for Ags by forming cellular networks (95). LCs express surface markers such as CD45, CD11b and c, MHC-II, CD1a, E-cadherin and CD207 (C-type lectin langerin) (95,96). Langerin is not only found in the membrane of LCs, but is also associated with specialized organelles called Birbeck granules, where it acts as an endocytic receptor (97).

Given that CL is a skin disease, it is feasible to consider LCs as a vital component of the defense against *Leishmania* through parasite uptake, Ag presentation and T cell activation (98). Indeed, LCs, but no other APCs, have the ability to internalize *L. major* parasites and rapidly transporting them to the nearest lymph node, where they induce the proliferation of *L. major*-primed T cells (99). Notably, LCs from *L. major*-sensitized mice were able to induce delayed-type hypersensitivity when transferred to naive recipient mice, demonstrating their stimulatory effect on T cells *in situ* (99). On the contrary, depletion of Langerin$^+$ DCs, specifically LCs, led to smaller wounds and a reduced parasite burden caused by *L. major* in Langerin-DTR C57BL/6 mice (100). LCs depletion also resulted in a reduction of Treg cells, which are implicated in the suppression of resistant Th1 responses (100). However, C5B7L/6 mice self-healed their wounds whether they had LCs or not, showing that LCs alone are insufficient to drive susceptibility to leishmaniasis in this strain (100). Ultimately, *Leishmania* amastigotes can acquire CD1a molecules upon exiting LCs via exocytosis (101). Although this phenomenon has not been functionally characterized, various *Leishmania* species have been reported to possess the CD1a marker (102).

Since LCs derive from DCs, they share some modulatory roles over Th17 cells. Aliahmadi *et al.* (103) reported the secretion of Th17-polarizing cytokines such as IL-6, IL-1β, TGF-β and IL-23 from TLR2-activated LCs. Additionally, TLR2-activated CD1c$^+$/langerin$^+$ monocyte-derived LC-like cells induces the expression of RORγT and IL-17 from CD3/CD28 co-stimulated CD4$^+$ T cells (103).

Lipophosphoglycan (LPG) is the most prominent molecule on the *Leishmania* surface and plays a critical role in its survival and infectivity (104). LPG activates phagocytes through TLR2, leading to the production of pro-inflammatory cytokines for parasite resistance (105). Notably, LCs secret not only Th17 cytokines upon TLR2 stimulation but also IL-12, making them another source for inducing a Th1 response (106).

Altogether, infection with *Leishmania* parasites might lead to the activation of LCs through TLR2 upon LPG stimulation, resulting in the secretion of beneficial pro-inflammatory cytokines. However, an imbalance in this response, might lead to the induction of the Th17 phenotype and the perpetuation of a pro-inflammatory environment.

Mast cells (MCs)

MCs are sentinel skin-resident cells that play a role in host defense by modulating the immune response through a plethora of receptors and secretory mediators (107). Their effector mechanisms include the production of pro-inflammatory cytokines, degranulation of various molecules such as histamine, heparin and chondroitin sulfate, and the release of extracellular traps (108,109). MCs are mainly activated through the binding of an Ag to their surface protein complex, comprised of IgE and FcεRI. However, MCs can also be activated through other stimuli, such as chemokines, cytokines, IgA, IgG, adenosine, C3a and PAMPs (108). They release cytokines associated with both Th1 responses (TNF, IFN-γ and IL-12) and Th2 responses (IL-4, IL-5, IL-10 and TGF-β) (110). Nevertheless, MCs' activation has the potential to become harmful to the host, leading to chronic inflammation, tissue remodeling or even death (107).

The role of MCs role during leishmaniasis has not reached a consensus; while some reports show MCs to play a protective role for the host, others suggest they may have negative or neutral (111). Since MCs are among the first lines of defense, their activities might bias

the immune response during the inoculation of *Leishmania* promastigotes (112). Studies supporting the protective role of MCs have reported MC-deficient mice have larger skin lesions with greater parasite loads when infected with *L. major* (113). Granuloma formation during leishmaniasis is linked to parasite containment for subsequent elimination, and MC-deficient mice failed to form granulomas, leading to the dissemination of *L. major* parasites and systemic disease (113). MCs also promote the recruitment of neutrophils, macrophages and DCs, so their absence causes an impairment in the phagocyte activities (113). Consequently, *L. major*-T cell priming is impaired, and the IFN-γ/IL-4 ratio is skewed towards a Th2 response, revealing the importance of MCs for a resistant response against *L. major* (113). In another study, it was shown that MCs release extracellular traps (MCETs), when co-cultured with *Leishmania tropica* promastigotes, and these MCETs contain histones and tryptase that reduce parasite viability (114). However, Romão *et al.* (115) demonstrated that non-degranulated MCs favor susceptibility to leishmaniasis. BALB/c and C57BL/6 mice pretreated with 48/80—a compound that triggers MCs degranulation—, and infected with *L. major* promastigotes, had smaller lesion sizes and lower parasite loads compared with their control counterparts (115). Moreover, 48/80 pretreated BALB/c mice had an augmented production of IFN-γ and up-regulated CCL5, CCL2 and inducible nitric oxide synthase (iNOS), shifting their typical Th2 response toward a Th1 (115).

MCs activities have the potential to activate Th17 cells both directly and indirectly. MC-DC binding and cross-talk lead to the maturation of immature DCs, as evidenced by the expression of surface markers such as CD80, CD86 and CD40, crucial molecules for T cell activation (116). Furthermore, MC-primed DCs promote the polarization of $CD4^+$ T cells toward both Th1 and Th17 phenotypes, as evidenced by the secretion of IFN-γ and IL-17, respectively (116). The Th17 profile is also induced upon TLR/FcεRI triggering and inflammasome-independent IL-1β production from MCs (117). Altogether, the ambivalent potential of MCs' activities during leishmaniasis may lead to a favorable outcome of the infection, although it is more likely to drive Th17 differentiation, thereby fostering the infection.

Th1 and Th2 cells

As previously mentioned, numerous studies have extensively investigated the effects of Th1 and Th2 polarization on leishmaniasis by employing BALB/c and C57BL/6 mice as susceptibility and resistance models, respectively. BALB/c mice are characterized by an anti-inflammatory Th2 response, distinguished by the production of cytokines such as IL-4, IL-5 and IL-13. In contrast, C57BL/6 mice exhibit a resistant pro-inflammatory profile in which cytokines such as IFN-γ, TNF, and IL-12 trigger leishmanicidal mechanisms in phagocytes (42,118). However, in humans, this relationship is more complex due to the variations in the patients' immune response and *Leishmania* species. Moreover, new Th profiles have been discovered, further complicating our understanding of the role of T $CD4^+$ cells in leishmaniasis. Yet for the sake practicality, we will only focus on both Th1 and Th2 profiles.

It is worth noting that Th1 and Th2 responses are correlated with the severity of certain clinical outcomes in CL. Th2 profile is involved in the progression of DCL due to the production of anti-inflammatory cytokines that lead to an unresponsive immune response (118). Interestingly, while the Th1 profile is associated with clearing the infection, it is also related to an exacerbation of pro-inflammatory responses that can give rise to ML (118).

Th17 cells share a close relationship with both Th1 and Th2 $CD4^+$ T cells. Some evidence suggests that Th1 and Th17 cells may have a regulatory role on each other. In experimental

autoimmune uveitis, Th17 cells from IFN-γ KO mice immunized with interphotoreceptor retinoid-binding protein infiltrated the eye and produced significant amounts of IL-17, contributing to disease susceptibility (119). However, blocking IL-17 at any stage of the disease reversed the inflammatory response, providing protection. Conversely, when Th17 cells were absent, Th1 cells played a central pathogenic role by producing IL-22, IFN-γ, IL-6 and IL-1α (119). This suggests that mediators from each cell type inhibit the development of the other. Indeed, IFN-γ has been shown to have inhibitory effects on Th17 differentiation, while IL-17A does the same to Th1 cells (120,121). This same phenomenon occurs in leishmaniasis. In an *L. major* infection mice model with the absence of IL-10, IFN-γ produced by Th1 cells inhibits the differentiation of Th17 cells and subsequent neutrophil recruitment, ultimately controlling the infection (122).

Th2 cells are commonly known for deploying suppressive signals through the production of cytokines such as IL-4, IL-5, IL-9 and IL-13, even though they also play an active role in helminth infections by activating eosinophils (123). In CL, Th2 responses are associated with non-healing wounds as they counteract beneficial activities of Th1 cells (124,125). Susceptible BALB/c mice lacking IL-4$^{-/-}$, IL-13$^{-/-}$ and IL-4Rα$^{-/-}$ have been shown to delay or even control the progression of the disease (126). However, the premise that Th2 cells antagonize resistance against leishmaniasis remains unclear, and other approaches are reviewed elsewhere (124). Nevertheless, the microenvironment created by the Th2 cells can modulate Th17 activities, and vice versa. In asthma patients with varying severity, 2 mutually exclusive clusters were detected based on their Th2 and Th17 signatures with a broad range of severity (127). Blockade of Th2 cytokines, IL-4 and IL-13 in an asthma mice model led increased production of IL-17A (127). Conversely, blocking IL-17A resulted in overexpression of Th2 cytokines, indicating mutual regulation between these cell subsets (127). In fact, IL-4 has been found to inhibit Th17 differentiation by preventing STAT3 from binding to the *IL17A* promoter, mediated by STAT6 (128). On the contrary, IL-17A$^{-/-}$ BALB/c mice infected with *L. major* exhibited smaller lesions and fewer parasites compared to WT mice, even though the BALB/c mice maintained their Th2 response (40). Interestingly, Th2 activated cells can transdifferentiate into a Th2/Th17 phenotype characterized by the expression of GATA3 and Foxp3 along with their signature cytokines of both T cell subtypes (129). These cells were generated after stimulation with IL-1β, IL-6 and IL-21 cytokines (129). These pieces of evidence suggest that Th2 and Th17 cells counteract each other; however, it appears in leishmaniasis, having both responses may increase the likelihood of an unfavorable outcome, possibly due to the presence of Th2/Th17 cells (**Fig. 2**).

Tregs

Tregs comprise a subset of Th cells essential for regulation and suppression of the immune response by producing anti-inflammatory cytokines such as IL-10 and TGF-β (17,130,131). Tregs and Th17 cells share the common differentiation factor TGF-β. However, the absence of pro-inflammatory cytokines in the microenvironment promotes the up-regulation of the transcription factor Foxp3, dictating the fate of a Treg program (17). Tregs can be generated in the thymus or extrathymically at peripheral sites, being called tTregs and pTregs, respectively (132). However, there is a third type of Tregs induced with the stimuli of TGF-β and IL-2 (17). Tregs participate in tolerance towards favorable microbiota and as immune response modulators (130). Nonetheless, they are also able to inhibit beneficial activities during an infection or sterile immunity (131,133). Tregs are also able to suppress Th17 cytokine production via IL-10, not only from Th17 cells but also from other immune cells (134).

Tregs role during CL have been associated with wound-healing and prevention of exacerbated inflammatory responses. Ablation of Tregs through inhibition of indoleamine-2,3-deoxygenase demonstrated that mice infected with *L. panamensis* manifest intense pro and anti-inflammatory cytokine productions consisting of IFN-γ, IL-13 and IL-17, along with larger lesion sizes and higher parasite concentrations (135). Moreover, transfer of Tregs from healthy to infected mice ameliorated their established lesions and reduced the production of the before-mentioned pro and anti-inflammatory cytokines (135). Conversely, persistence of *L. major* after healing of C57BL/6 mice is related to IL-10 production in Tregs (136). *L. major*-infected RAG$^{-/-}$ mice failed to resolve the infection when transferred with CD4^{+}CD25^{+} Treg cells from WT mice (136). Surprisingly, a similar outcome was observed in IL-10$^{-/-}$ mice that were healed from *L. major* infection and then reinfected (136). Thus, Tregs modulate the immune response through IL-10 dependent and independent mechanisms, leading to persistence of infection (136).

Despite their contradictory activities, there is evidence of the cooperation between Tregs and Th17 cells (137). TGF-β secreted from Tregs induces the differentiation of naive CD4^{+} T cells into Th17 cells (as evidenced by their production of IL-17), when they are in the presence of IL-6 secreted by LPS-stimulated DCs (138). Furthermore, immunization and depletion of Treg cells in *Foxp3*.luciDTR4 mice, lead to a reduction in the proportion of IL-17^{+} cells compared with their non-depleted counterpart (139). Additionally, Th17 cell development was recovered after the transfer of Tregs into RAG-deficient hosts (139). Interestingly, TGF-β from Tregs was not necessary for Th17 cells development. Tregs regulate IL-2 availability, which modulates Th17 induction, either by inhibiting its production from other cells or consuming it (139). On the other hand, Th17 cells provide advantageous cytokines for Tregs development. When RAG-deficient mice were co-transferred with Tregs and other Th subsets (Th0, Th1, Th2, Th17), the Treg/Th17 pair was the one with the highest Foxp3 expression, revealing that Th17 cells promote the expansion of Tregs via TNF (137). Regarding leishmaniasis, and supported by the present evidence, we hypothesized that the reciprocal stimulation between Tregs and Th17 might be linked to the persistence of the infection and an exacerbated activity of Th17 cells. Indeed, lesions from CL patients infected with *L. tropica* exhibited high levels of RORγt, Foxp3, IL-10, and IL-17 mRNA, which correlated with the state of the infection (140).

CD8^{+} T cells

CD8^{+} T cells, also known as CTLs, conform another branch of the adaptive immune response endowed with the task of the Ag-specific cell-mediated lysis. This mechanism is achieved through the recognition of an Ag presented by MHC-I on target cells via the TCR-CD8 receptor for a subsequent release of peptidases, such as, perforin and granzyme (141). To achieve this, APCs must prime CD8^{+} T cells in secondary lymphoid organs from where they subsequently proliferate and migrate to infection sites or tumors (141,142). For their differentiation, CD8^{+} T cells require cytokines, such as IFN-α and prominently IL-2 and IL-12, that in turn, will activate the regulator Blimp-1 and differentiation factor T-bet, respectively (143). Furthermore, the uptake and processing of peptides in the cytosol are essential for MHC-I Ag presentation. However, *Leishmania* parasites are instead harbored in PVs. Thus, 2 hypotheses for *Leishmania* Ag presentation were proposed: 1) *Leishmania* peptide leakage from the vacuole to the cytosol and, 2) Ag presentation by the phagolysosome, although no concrete evidence supports either (144). Nevertheless, CD8^{+} T cells are able to recognize *Leishmania* Ags and drive different immune responses. CD8^{+} T cells specifically targeted for the leishmanial Ag GP46/M-2 induced the lysis of GP46/M-2-transfected cells and, more importantly, of macrophages infected with *L. amazonensis* (145). This event is averted

with the addition of cytosolic proteasome inhibitors, proving that leishmanial Ags can be classically presented through MHC-I (145). Also, IFN-γ–producing $CD8^+$ T cells are involved in immunity during *Leishmania* reinfection. After 5 days after reinfection with *L. major*, parasite-specific high IFN-γ–producing $CD8^+$ T cells expand in lymph nodes and spleen, and recirculate in the bloodstream of BALB/c mice (146). Additionally, immune BALB/c mice presented smaller footpad swellings and lower parasite burdens, showing the effectiveness of the $CD8^+$ T cell memory respon*se against L. major* (146).

Yet, $CD8^+$ T cell have also been related to detrimental activities in CL. In a differential study of inflammatory profiles in the early and late stages of *L. amazonensis* infections, a higher proportion of granzyme A^+ $CD8^+$ T cells were found in lesions from late stages compared with the early stages (147). Furthermore, a positive correlation was found between the number of granzyme A^+ $CD8^+$ T cells and the intensity of the inflammatory infiltrate in lesions from late stages, suggesting that granzyme A might be involved in tissue destruction, leading to ulceration of the lesions (147). Another study reported that skin and circulating CD8 T^+ cells overexpressed cytolytic molecules such as perforin, granzyme A, granzyme B, granulysin and the degranulating marker CD107a in patients infected with *L. braziliensis* (148). Interestingly, *L. braziliensis*-infected $RAG^{-/-}$ BALB/c mice transferred with WT CD8 T cells showed uncontrolled lesions, as seen with the destruction of the tissue and parasite spread, confirming the metastasis of the infection (148). This last report inspired Novais and Scott (144) to propose a model in which cytolysis of *Leishmania*-infected phagocytes by CTLs is probably responsible for the liberation and further metastasis of the parasites. Additionally, IL-21 upregulates the expression and production of granzyme B and perforin in $CD8^+$ T cells (**Fig. 2**) (149). Overall, functions of CTLs can be both augmented and diminished by Th17 cells. While IL-17 inhibits the migration of CTLs to the site of infection, those $CD8^+$ T cells that are already present, perform their cytolytic mechanisms enhanced by IL-21, provoking the dissemination of the parasites and leading to a chronic state of the disease.

Cytokines of Th17 cells induce multiple responses on $CD8^+$ T cells. IL-2 secreted from DC-activated Th17 cells stimulates the proliferation and cytotoxic activity, mediated by perforin, of $CD8^+$ T cells (150). Surprisingly, these effects were mediated by the peptide MHC I (pMHC I), which Th17 cells acquired during their early interaction with DCs, likely via trogocytosis (150). In contrast, in another study, $CD8^+$ T cells treated with IL-17A, notably down-regulated the expression of chemokine receptor CXCR3 (151). This study group concluded that Th17 cells are the primary source of IL-17A and that the STAT3 signaling pathway is responsible for the down-regulation of CXCR3, thereby inhibiting the migration capabilities of $CD8^+$ T cells (151). These reports demonstrate that interaction of $CD8^+$ T cells with Th17 cells through MHC-I is beneficial for the expansion and activation of $CD8^+$ T cells, whereas IL-17A alone mitigates their activities. Unfortunately, there is no report about pMHC I-TCR interaction between Th17 and $CD8^+$ cells during CL, so we can only hypothesize that the interaction between these 2 cell types through the pMHC I-TCR complex, drives the activation of CTLs and possibly exacerbates the immune response.

B cells

B cells are a cornerstone for the well-functioning of the adaptive immunity, mainly by producing antibodies, but they also modulate various immune responses. One of their immunomodulating functions during infections includes the activation of DCs and T-cell subsets, through the release of both cytokines and chemokines, as well as acting as APCs (152,153). The specific roles of B cells during viral, bacterial and protozoan infections are

discussed elsewhere (152,154,155). In CL, outcome of B cells activities depends on factors such as the *Leishmania* species or strain, reinfection and the specific B cell subset involved. They are often regarded as key cells in the susceptibility of infection. Anti-IgM-treated BALB/c mice, which lack B cells, are able to control their cutaneous lesions when infected with *L. major* (156). Furthermore, BALB/c μMT, another B cell-lacking mouse, showed resistance when infected with the *L. major* strain, LV39 (157). These mice displayed a Th1 response that resulted from the adaptive transfer of B cells specific for leishmanial Ags (157), where direct presentation of leishmanial Ags from B cells led to susceptibility towards infection with *L. major* (157).

B1 cells comprise a subset of innate-like B cells with various functions, such as, constitutive IgM secretion, Ag presentation and IL-10 production (158,159). In mice, B1 cells are divided into 2 subsets, depending on the expression of the surface marker CD5: B1a ($CD5^+$) and B1b ($CD5^-$) cells (160). In addition to expressing CD5, human B1 cells also express $CD27^+CD43^+$ (159). Although, depletion of IL-10-producing B1 cells did not contribute to susceptibility to the infection with *L. major*, IL-10 secreted from $CD1d^+CD5^+$ regulatory B cells is crucial for developing Th2 cell response, and therefore, contributes to the susceptibility against *L. major* in BALB/c mice (161,162). *L. major*-infected BALB/c μMT mice reconstituted with $IL\text{-}10^{-/-}$ B cells, developed lesion sizes and parasite burdens comparable to their non-transferred counterparts (162). Additionally, IL-10 produced either through an autocrine pathway or through a secreted pathway by B cells, inhibits the production of IL-12 from *L. major*-stimulated bone marrow DCs, showing that this cytokine is responsible for the Th2 polarization most likely through the down-regulation of IL-12 (162). On the other hand, B cells have beneficial roles against *L. braziliensis*, contrary to what happens during *L. major* infection. *L. major*-infected C3HeB/FeJ mice exhibit resistance when challenged with *L. amazonensis* promastigotes, leading to a the decrease in parasite load and wound healing after 10 wk of infection (163). Noteworthy, C3HeB/FeJ mice display resistance against *L. major* infection but show susceptibility to *L. amazonensis*. Furthermore, antibodies from $MHC\text{-}II^+/CD11b^-$ B cells of lymph nodes and other soluble factors derived from $CD4^+$ T cells isolated from *L. major*-infected mice trigger activation of *L. amazonensis*-infected bone marrow derived-macrophages, thus killing the parasites (164). Interestingly, LPS-stimulated macrophages activated via IgG-FcγR and IFN-γ, induce the production of ROS, such as superoxide and nitric oxide, which are well-known leishmanicidal mechanisms (165).

The role of Th17 cells, and therefore of IL-17, in the support and maintenance of B cells has been a controversial topic. Co-culture of B cells and Th17 cells led to an increase in proliferation of B cells, as well as to an antibody isotype switch to IgG1, IgG2a, IgG2b, and IgG3 (166). Moreover, Th17-recipient TCRα KO mice showed an augmented formation of germinal centers (GCs) in their lymph nodes and spleen after 7 days of immunization (166). Transfer of Th17 cells to IL17R KO and IL21R KO mice led to fewer and smaller GCs or a total absence of GCs, respectively, confirming that Th17 cytokines, IL-17 and IL-21, must synergize in order to activate various effects on B cells (**Fig. 2**) (166). In another similar study, mice that received Th17 cells presented a higher number and percentage of GCs, indicating that Th17 cells promote B cell clonal expansion along with the enhanced production of Ag-specific Abs (167). Furthermore, these Th17 cells were localized at close proximity of follicles in lymph nodes during the early development of the humoral immune response (167). In contrast, Shibui *et al.* (168) demonstrated that IL-17a, IL-17F, IL-21, or IL-25 had little to no effect on B cell antibody production or isotype switching *in vitro*. It is difficult to infer the outcome of Th17 activities over B cells in leishmaniasis with the previous reports alone, so further exploration of this topic is required for designing new therapeutic targets or vaccines.

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Lastly, B cells also produce IL-17, which has been associated with autoimmune diseases and parasitic infections (169,170). In Chagas disease caused by *Trypanosoma cruzi*, B cells are the major source of IL-17 (171). IL-17 from B cells is secreted through a pathway different from the canonical RORγT-Th17 program. Interestingly, IL-17 $^{+}$B cells outnumbered Th17 cells, providing a protective role during the acute stage of the *T. cruzi* infection (171). Although the infectious mechanisms of both parasites are different, we can hypothesize that IL-17^{+}B cells can play a beneficial role, similar to Th17 cells, during the early stages of Leishmaniasis. Yet, if they are not properly regulated, they can also lead to a chronic phenotype, similar to Th17 cells.

NK cells

NK cells are lymphoid cells that mediate responses against tumors, viral infected-cells and other pathogens, such as bacteria and parasites. These responses mainly encompass the secretion of pro-inflammatory cytokines such as TNF and IFN-γ and the lysis of targeted cells (172). Cellular lysis is achieved through the balance between activating and inhibitory signaling receptors in the membrane surface of NK cells and their ligands on the target cell. Once NK cells are activated, cytoskeleton rearrangements take place. Later, the lytic granules are transported to the membrane, releasing cytolytic molecules such as perforin 1 and granzyme B, thus causing apoptosis in the target cell (172). For this to occur, an immunological lytic synapse between the NK cell and the target cell needs to be formed (173).

The role of NK cells in CL has been described in several reports. Human NK cells incubated with purified LPG from metacyclic *L. major*, exhibited a nuclear translocation of NF-κB, and overexpression of TLR2, IFN-γ and TNF (174). In summary, NK cells activation resulting from the recognition of LPG from *L. major* is beneficial for the host, because the release of pro-inflammatory cytokines is essential for controlling the infection (174,175). However, the cytolytic activity of NK cells appears to be impaired during leishmaniasis. Mononuclear phagocytic cells were resistant to NK cell cytotoxicity, both when they were infected with *L. major* or with *L. infantum* amastigotes, either *in vivo* or *in vitro* (176). Incubation of mononuclear phagocytic with *L. major* promastigotes did not alter the expression of activating nor inhibitory ligands, turning NK cells unresponsive for a cytolytic attack (176). Nonetheless, cytokine-activated NK cells triggered leishmanicidal mechanisms (NO_2 production) on *L. infantum*-infected macrophages through the secretion of IFN-γ, TNF and the activation of iNOS (176). Although *L. infantum* is known for causing visceral leishmaniasis, there have been cases where it was isolated from cutaneous lesions (177). The activation of macrophages does not require contact with NK cells. Yet a direct contact between NK cells and *L. major* and *L. aethiopica* promastigotes has been reported, with a probable exchange of cytoplasm (178). Surprisingly, this direct contact did not kill the parasites but instead killed NK cells (178). NK cells were only able to eliminate *L. aethiopica* promastigotes in a 5:1 ratio or a ratio superior to that (176,178). It is noteworthy that *L. major* promastigotes impaired the cytotoxic activity of NK cells against susceptible cell lines (178). These NK cells had been activated in an IL-12-independent way, even though IL-12 is essential for their activation, along with the formation of a synapse between NK cells and mature DCs (179). Remarkably, leishmanial zinc metalloprotease gp63, which plays a role during the infection of macrophages and also modulates the complement system (180), reduces the expression of CD16, CD56, and NKp30 and impairs the proliferation of NK cells (181).

The activities of NK cells vary depending on the clinical manifestation of leishmaniasis. Thus, patients with LCL, infected with *L. mexicana*, showed a higher number of NK cells in peripheral blood and lesions compared to patients with DCL (182). Additionally, NK cells from DCL

patients showed a down-regulation of TLR1, TLR2 and TLR6, (all of which bind to LPG) and a diminished production of IFN-γ and TNF, which renders these NK cells unable to exert leishmanicidal mechanisms on infected macrophages, thus contributing to disease progression (182). Thus, the role of NK cells in leishmaniasis is not always beneficial for the host, since parasites have developed multiple means to interfere with their activities. Furthermore, cytotoxic molecules from NK cells have been linked with progression of leishmaniasis, which was evidenced in lesions of CL patients infected with *L. braziliensis*, that showed a high concentration of cytotoxic NK cells and extracellular granzyme B in the lesions (183).

NK cells and Th17 cells are able to modulate each other through multiple signals and mediators. Incubation of NK cells with IL-17a leads to an increase in the number of NK cells, yet their expression of killer Ig-like receptors, remained unchanged (184,185). Furthermore, stimulation of NK cells with IL-17A, D and F only leads to a slight increase in the cytokine production and to a moderate cytotoxic activity (184). In contrast, stimulation of NK cells with IL-21 activates them through the IL-21R, triggering the production of IFN-γ and TNF, and enhancing their cytolytic activity (**Fig. 1**) (186). Interestingly, IL-21 also promotes the differentiation of Th1 cells to a Th17 phenotype, as evidenced by their expression of RORγt and IL-17A (186). Hence, during CL, IL-21 produced by Th17 cells is likely to induce the activation and differentiation of NK and Th17 cells, respectively. Although the role of IL-21 during leishmaniasis remains controversial, some evidence shows that they can be detrimental for the host (187). During pregnancy, $CD56^{bright}CD27^{+}$NK cells abrogate the inflammation mediated by Th17 cells through the secretion of IFN-γ at the maternal-fetal interface, yet this is reverted when the numbers of Th17 cells are elevated (188).

Th17 cells and NK cells are also capable of expressing each other's key molecules. Thus, NK cells are an alternative source of IL-17, which has been linked to the progression of asthma in experimental mouse models (189). Similarly, the danger and stress sensor NKG2D, commonly expressed in NK cells but also in $CD4^{+}$ T cells and in T-bet^{+}Th17 cells, modulates the behavior of Th17 cells, enhancing their production of pro-inflammatory cytokines such as IFN-γ and GM-CSF (190).

Taken together, NK and Th17 cells interact with each other through multiple signals that can counteract, synergize or replace their responses. During leishmaniasis, the activation of NK cells triggered by Th17 cells possibly favors the resolution of the infection, yet a finely tuned control system is needed, to avoid an exacerbated pro-inflammatory response.

Concluding remarks and perspectives

Th17 cells are a subset of T cells that have been related to an exacerbated pro-inflammatory response. This can lead to the progression of various autoimmune diseases but also to the protection against pathogens. The main contribution of Th17 cells during leishmaniasis involves the immunomodulation of the inflammatory infiltrate via the release of pro-inflammatory cytokines (primarily but not exclusively IL-17A). Several cells of the inflammatory infiltrate are capable of regulating the activities of Th17 cells and their interplay affects the disease outcome. Resident skin cells, such as epithelial cells from all substrates, endothelial cells, keratinocytes and fibroblasts, among others, are also affected by the Th17 cells and can influence the inflammatory infiltrate. Current evidence points to Th17 cells as ambivalent cells, depending on the stage of infection: in the early stages they are beneficial, since they recruit and activate neutrophils and macrophages in the infection site, favoring the uptake and elimination of parasites (**Fig. 1**), yet they can also be harmful, if

this pro-inflammatory response is not correctly regulated, which leads to the chronic stage of the infection (**Fig. 2**). This regulation is influenced by different cells of the inflammatory infiltrate, many of which can trigger the differentiation towards a Th17 phenotype, thus sustaining a detrimental pro-inflammatory environment.

Altogether, Th17 cells are likely to play a key role in leishmaniasis, steering the disease evolution from an acute to a chronic phase of the infection, by modulating molecular signals and cellular interactions. The molecular and cellular players that influence the disease progression in CL remain a complex field of research that needs to address the cellular network and interactions to allow for a more complete understanding of this disease.

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