Cytokine and Growth Factor Reviews 57 (2021) 85–92

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

IL-1 family and Cutaneous Leishmaniasis: A poorly understood relationship

Ester Alves da Silva Amorim [a,b,*], Áquila Alcântara de França [a,b], Valéria Rêgo Alves Pereira [b], Maria Carolina Accioly Brelaz-de-Castro [a,b]

[a] Federal University of Pernambuco (UFPE), Academic Center of Vitória (CAV), Rua do Alto do Reservatório s/n, Bela Vista, Vitória de Santo Antão, Pernambuco, PE, 55608-680, Brazil

[b] Oswaldo Cruz Pernambuco Foundation (Fiocruz/PE), Department of Immunology, Av. Moraes Rego, s/n - Cidade Universitária, 50670-420, Recife, Pernambuco, Brazil

ARTICLE INFO

Keywords:
IL-1 family
Cytokines
Cutaneous leishmaniasis
Inflammation
Immune response

ABSTRACT

The cytokines of the interleukin (IL) -1 family act in the initiation of an effective immune response in *Leishmania* infection, represented mainly by the T helper 1 (Th1) profile, in addition to being associated with disease exacerbation and controversial contributions in the Th2 responses. The family also includes members who self-regulate inflammation, such as antagonists and anti-inflammatory cytokines, most of which have not yet been studied in Cutaneous Leishmaniasis (CL) in humans. Here we summarize findings about what is known so far about the role of these cytokines in mice, the main study model, and in humans. We reinforce the importance of studies of these cytokines as new targets in the context of CL.

1. Introduction

Leishmaniasis is a tropical infectious disease that affects mainly low-income people. It does not receive necessary investments or attention in research and development of drugs, so it is considered neglected. This disease can occur in humans in three general clinical forms: visceral (VL), cutaneous (CL) and mucocutaneous (MCL), depending on the species of infectious *Leishmania*, with CL being the most prevalent clinical form worldwide [1]. With a distribution in 102 countries, the cases are mainly concentrated in poor countries in Southeast Asia, East Africa and Latin America, with around 350 million people at risk [2–4]. The drugs available for the treatment of the disease have several limitations, such as high cost and several side effects [5,6].

CL usually affects the skin and, in some cases, mucosal regions. An important association has been demonstrated between the immune response developed by the patient and the course of the infection. The progression and development of the disease occur due to the intense inflammatory condition that is generated in response to *Leishmania* infection in an attempt to eliminate the parasitic burden [7]. However, an exacerbated profile of proinflammatory response is not effective in eliminating parasites and can still leave consequences for the patient, which are the lesions and characteristic ulcers of the disease [7–9]. In this context, some studies highlight the cytokines of the interleukin (IL) -1 family because they act to propagate inflammation and are considered "triggers" for the expression of other proinflammatory cytokines. Their study can contribute strongly to a better understanding of the progress of the pathogenesis of *Leishmania* infection [10–12].

The IL-1 family includes 11 cytokines that participate in the immune responses against infections caused by pathogens, mediating the inflammatory response [13,14]. A certain heterogeneity in the roles of IL-1 familiy cytokines can be observed, including pro and anti-inflammatory agonists, as well as natural receptor antagonists that negatively regulate the inflammatory response [15,16]. Despite this, some stand out, such as IL-1α and IL-1β, which are the main agonists studied in several autoimmune and inflammatory contexts, including in CL [14]. In the literature, it is possible to observe some controversies regarding the role of some IL-1 cytokines in CL, represented by the dichotomy resistance and susceptibility to *Leishmania*. These divergences seem to be influenced, mainly, by the *Leishmania* species and the host's genetic background, as observed in studies with genetically modified mice. Few studies are observed in humans, and the extent to which these results can be extrapolated is something to be understood.

* Corresponding author at: Federal University of Pernambuco (UFPE), Academic Center of Vitória (CAV), Rua do Alto do Reservatório s/n, Bela Vista, Vitória de Santo Antão, Pernambuco, PE, 55608-680, Brazil.

E-mail addresses: esteralves1997@hotmail.com (E.A.S. Amorim), aquilaalcf@gmail.com (Á.A. de França), valeriaph@gmail.com (V.R.A. Pereira), carolina.brelaz@gmail.com (M.C.A. Brelaz-de-Castro).

https://doi.org/10.1016/j.cytogfr.2020.06.007
Received 19 May 2020; Accepted 4 June 2020
Available online 8 June 2020

2. Immune response in CL

The defense mechanism against *Leishmania* in humans involves several components of the innate and adaptive immune response, but these protozoa have developed strategies for escaping and modulating the immune response that guarantee their survival [17,18]. Much of what is known about resistance and susceptibility responses to *Leishmania* and disease severity comes from studies with different genetically modified murine models. They exhibit variations in disease severity and response to the pathogen, and there is a consensus regarding the characteristics of the developed immunological response in the CL observed among such models but not with humans. This response is discussed below, but despite this, it is important to be aware that the wide spectrum of clinical manifestations of CL in humans cannot be fully reproduced in the experimental model.

The efficiency of the innate immune response strategies performed by neutrophils depends on the species of infective *Leishmania*. Some studies show that leishmanias can survive inside neutrophils by inhibiting the formation of phagolysosome. For example, L. *major* and L. *braziliensis* may be resistant to the actions of Neutrophil Extracellular Traps (NETs) through digestion with endonucleases derived from both parasites and sandflies [19,20].

The development of subpopulations of T CD4+ lymphocytes can be directed in four main profiles: Th1, Th2, Th17 and Treg [14]. They all lead to different responses such as resistance and susceptibility to *Leishmania* and play important roles in the outcome of the disease [19]. The effective response against *Leishmania* is related to the development of the auxiliary profile 1 (Th1) and production of proinflammatory cytokines such as IL-12, IL-1, IFN-γ, TNF-α and IL-2 [14,21]. The susceptibility to infection is related to the development of a profile of helper T cells 2 (Th2) and production of cytokines such as IL-4, IL-5 and IL-13, resulting in the replication and persistence of the parasite [22].

In the resistance response, the Th1 lymphocytes induce the production of nitric oxide in macrophages that leads to the destruction of the parasite, in addition to host resistance [23]. The secretion of IL-12 by antigen presenting cells (APCs), macrophages and dendritic cells (DCs), promotes the differentiation of naïve T cells into IFNγ-secreting Th1 lymphocytes, through a major transcription factor which is the T-bet [22,24].

The Th1 profile in fact controls the multiplication and dissemination of the parasite in CL and MCL, but does not eradicate *Leishmania* infection and, when exacerbated, generates tissue damage. It is known that the excessive production of the Th1 response and proinflammatory cytokines are associated with severe immunopathology of the disease (Fig. 1). This is because, despite being factors necessary to kill *Leishmania*, IFN-γ, TNF and nitric oxide (NO) are also implicated in inflammation, leading to tissue damage [25]. In addition, asymptomatic individuals do not exhibit a stronger Th1 response than those with active disease, expressing low levels of IFN-γ and TNF and adequate levels of IL-10 [14,26,27].

Th17 cells also appear to contribute to the progression of CL in humans and mice. Boaventura et al. in 2010 [28] observed that IL-17 + cells are present in human mucosa lesions caused by *L. braziliensis*, mediating the infiltration of neutrophils. Bacellar et al. [29] also reported an increase in IL-17 expression in supernatants from peripheral blood mononuclear cell cultures after stimulation with *Leishmania* antigen, indicating that, despite having some role in defending against the pathogen [30], this cytokine contributes to the severity of the disease. In susceptible mice infected with L. *major*, IL-17 mediates the attraction of neutrophils and the release of proteinases that induce tissue damage and thus contributes to the progression of leishmaniasis [31].

On the other hand, Th2 lymphocytes, which are involved in inducing the humoral response and eosinophilia, assume a role of susceptibility in CL by inducing the production of cytokines such as IL-4, IL-5, IL-6 and IL-13, leading to replication and persistence of the parasite [32]. In this profile, the inability of antigens to activate DCs to produce IL-12 results in a pathway of differentiation of naïve T lymphocytes into IL-4 secreting Th2, which activates STAT6 and consequently the transcription factor GATA3 [22]. Despite this, the production of anti-inflammatory cytokines, coming from the Th2 profile, at lower levels can contribute to the attenuation of inflammatory reactions and the repair of injuries [14,26].

3. IL-1 family

Members of the IL-1 family are known to be important proinflammatory cytokines and to be involved in disorders associated with inflammation. The family includes 11 cytokines, seven of which have

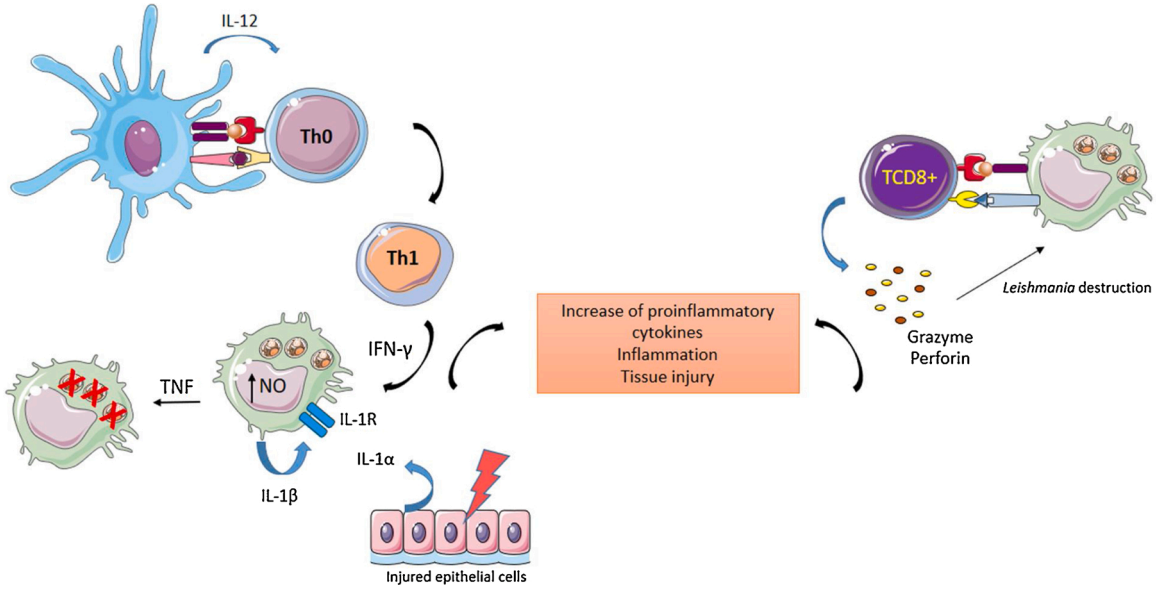

Fig. 1. Cellular immune response in CL. The death of the parasite during infection is an event that involves the action of immune cells and some major cytokines thatare crucial in activating response profiles associated with resistance. Despite this, the same response responsible for the clearance of parasites is implicated in theestablishment of a toxic microenvironment that leads to cell death. Components of this figure were created using modified templates from Servier Medical Art, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com.

proinflammatory and agonist activity (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β and IL-36γ), three act as receptor antagonists (IL-1Ra, IL-36Ra, IL-38) and one is considered anti-inflammatory (IL-37), and therefore, four down-regulate the inflammatory response (Fig. 2). In turn, the family of IL-1 receptors (IL-1R) consists of 10 members, including receptors and co-receptors, which are IL-1R1, IL-1R2, accessory proteins IL-1RAcP and IL-18Rβ, IL-18Rα, ST2 (or IL-33R), IL-36R, SIGIRR or TIR8, TIGIRR-2 or IL-1RAPLI and TIGIRR-1 or IL-1RAPL2 [15,16].

All of these cytokines have their genes located on chromosome 2, with the exception of IL-18 and IL-33, which are encoded on chromosomes 11 and 9 [33]. They are also considered "alarm cytokines" due to the role of initiating and spreading a network of proinflammatory mediators and inducing the expression of adhesion molecules in endothelial cells and leukocytes [12,34]. Among the cells that produce the IL-1 cytokines are neutrophils, monocytes, DCs, basophils, mast cells and macrophages, the latter being the main source from the immune system. The whole family is also secreted by epithelial cells [35,36].

Some cytokines from the IL-1 family, such as IL-1α and IL-1β, participate in the generation of IFN-γ-secreting T lymphocytes, thus polarizing a Th1 proinflammatory response that involves the production of TNF and NO and activation of macrophages [37,38], in addition to contributing to the activation of Th17 cells, a profile known to mediate the progression of leishmaniasis [29,39]. On the other hand, IL-33 has been associated with a type 2 [40] and a regulatory immune response [41], in addition to attenuating the development of type 1 immunity [42].

Another inflammatory cytokine is IL-18. The binding of IL-18 and IL-18Rβ to form the IL-18R complex leads to inflammatory signaling and Th1 responses. However, IL-18R can also bind to a co-receptor called TIR8 and allow signaling of IL-37, the only anti-inflammatory agonist in the family, thus leading to inhibition of inflammation [43]. Interestingly, the release of the mature forms of IL-1β, IL-18 and the IL-37b isoform requires processing by caspase-1 as a result of the activation of inflammasome complexes [43,44].

Another internal regulation of the IL-1 family on inflammation involves the action of IL-38, an antagonist that competes for binding to the IL-36R receptor with the other cytokines of the IL-36 subfamily (IL-36α, IL-36β and IL- 36γ), whose signaling involves the activation of nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways [45,46]. Thus, IL-38 has an anti-inflammatory function that still needs to be better understood, especially in humans and in leishmaniasis as a whole, since there are no studies that have evaluated it in this pathological context [47].

The IL-1 family cytokine signaling is intrinsically related to receptors that contain three extracellular immunoglobulin domains (with the exception of TIR8 or SIGIRR, which contains one) and a Toll / IL-1 receptor domain (Toll / interleukin-1 receptor / TIR) in the cytoplasmic portion (Fig. 2), which has a similarity shared with Toll-like receptors (TLR), mainly TLR4. This TIR domain participates in the signal transduction triggered by the ligand, signaling events such as pathogen detection, tissue damage and inflammation, allowing the recruitment of some molecules that intermediate the signaling pathway such as MyD88 and IRAK4 [16,36,43].

Most of the cytokines of the IL-1 family are produced in biologically inactive forms as precursors, which after a stimulus are cleaved in the mature form and capable of activating the receptor. Interestingly, some cytokines like IL-1α and IL-33 have their active precursor forms [43,48]. In addition to the natural antagonists of the family, another way of inhibiting the inflammatory response directed by IL-1 is the expression of decoy receptors such as IL-1R2, which are able to recognize and bind to the cytokine, but fail to form the receptor signaling complex and generate the response. IL-1R2 lacks the cytoplasmic TIR domain and captures the cytokine IL-1β more efficiently than IL-1α and IL-1Ra. Thus, the cytokine is not available to bind to its active receptor, neutralizing the action of IL-1β [43,49].

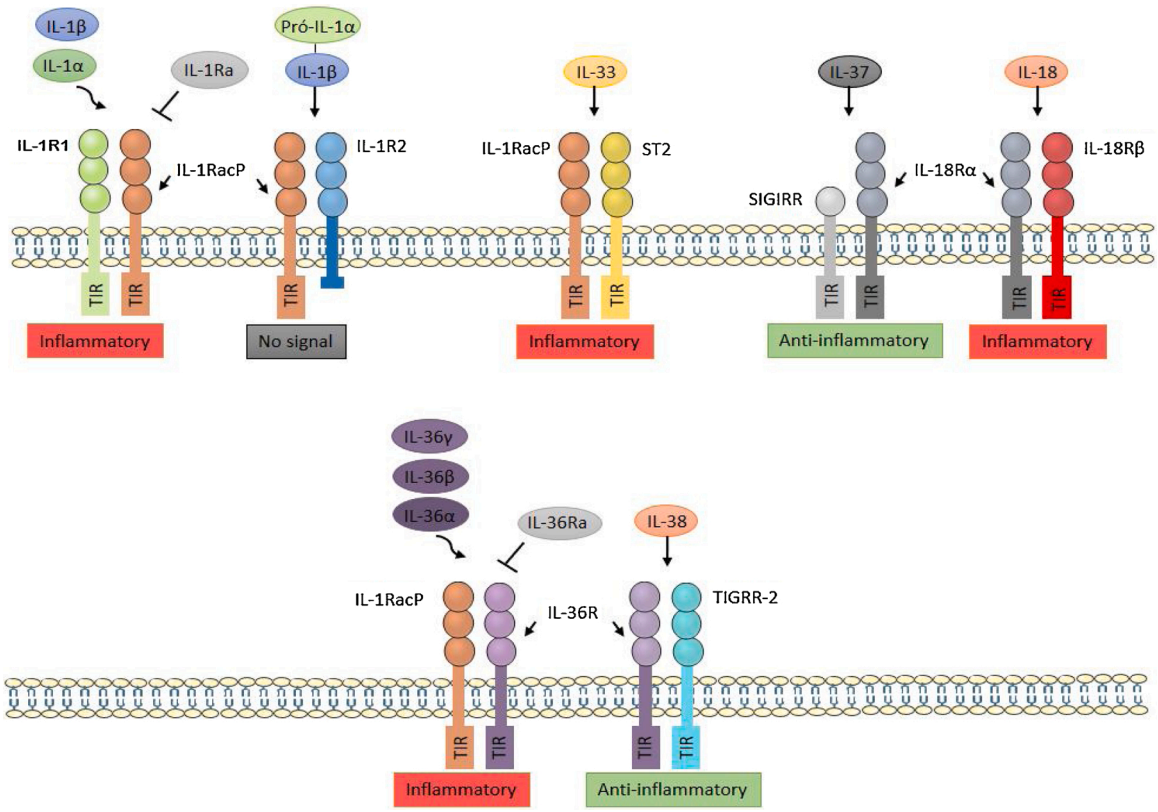

Fig. 2. Family of cytokines IL-1 and its main receptors and co-receptors. Components of this figure were created using modified templates from Servier Medical Art, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com.

4. Role of IL-1 in cutaneous leishmaniasis

Currently, few studies associate the role of this family in the context of leishmaniasis in patients, but there are many indications that it contributes to the pathogenesis in humans [11,38,50]. They participate directly in the activation of the immune response against pathogens; so, the performance of these cytokines becomes crucial for an effector and resistance mechanism against *Leishmania*. The balance of this response is also necessary for the tissue healing process to occur and result in the clinical cure of cutaneous leishmaniasis. In addition, understanding the role of anti-inflammatory IL-1 cytokines, which modulate the response of agonists themselves, can contribute to therapeutic strategies. To better understand what we have so far and considering the different study models, we have grouped the main information in the table below (Table 1). The table emphasizes and how much this family still needs to be studied in CL.

4.1. Mice as the main study model in cutaneous Leishmania infections

The role of IL-1 cytokines in susceptibility and resistance to *Leishmania* is still a subject of controversy, even in studies with murine models. Due to its contribution in the activation and differentiation of T CD4+ lymphocytes and the development of the Th1 response, some studies have highlighted IL-1α as a participant in the induction of the resistance response to *L. major* observed in resistant C57BL/6 mice. On the other hand, lower levels of expression of this cytokine are observed by DCs of susceptible BALB/c mice, known to succumb to leishmaniasis due developing strong Th2 responses [37,51,52]. In this sense, another study showed that infection by L. *major* in macrophages of BALB/c mice induces the gene expression of IL-1α through a MyD88-dependent signaling pathway, although no protein secretion has been detected, indicating post-transcriptional regulatory mechanisms to inhibit cytokine production [53].

Even so, the performance of IL-1 also appears to be associated with dysregulation of the immune response [29]. Within this context, one study showed that IL-1α-deficient BALB/c mice had a less severe disease, with the development of a significantly reduced number of nodules [12], while another described the detrimental effect of long-term exposure of IL-1α for disease progression by inducing a Th2 response profile in the later stage of infection [37].

The knockout of IL-1Ra in BALB/c mice also leads to an exacerbated activation of IL-1α/β, making them develop pathological conditions such as autoimmunity and arthritis, the latter also due to excessive induction of IL-17, in addition to impaired production of IL-12 and IFN-γ [54]. Despite this, the knockout of this antagonist was also described causing a decrease in the parasitic burden in susceptible mice, and its use in the attenuation of IL-1 resulted in a lower progression of leishmaniasis [12].

IL-1β is secreted by hematopoietic cells, mainly macrophages and monocytes, and has a more systemic circulation, in contrast to IL-1α which has a more localized action [16,36]. Although IL-1β induces the differentiation of effector T CD4+ lymphocytes, which at the beginning of the infection protect against *Leishmania*, the continuation of its high production during the chronic phase of the infection also leads to the progression of the disease [36]. In addition, even though IL-1β signaling via MyD88 is important in the recognition and response to *Leishmania* infection in mice because it induces NO production by macrophages, its role does not seem to be crucial in the resistance observed in C57BL/6 mice, but in BALB/c [54,55]. This may be because the already differentiated Th1 cells do not express receptors for IL-1, and therefore the cytokine has no effect on them [56]. In both VL and CL, for example, during infections by *L. donovani* and *L. guyanensis*, the activation of the inflammasome complex is impaired, and consequently the processing of IL-1. This interference has consequences in the clearance of parasites [57,58].

As with IL-1β, the cytokine IL-18 is initially produced as a precursor that is cleaved by caspase-1. A peculiar characteristic of IL-18 is that this cytokine can be of the Th1 or Th2 type, depending on the presence of other cytokines in the microenvironment [49,59]. Controversial results regarding its contribution to CL are observed depending on the *Leishmania* species and the host's genetic background. The deletion of IL-18 in resistant C57BL/6 mice infected with *L. major* resulted in increased lesions, but there was no change in the levels of IFN-γ and in the ability to generate the Th1 response, thus the mice were still capable of resolving the disease [60]. However, another study showed that this same knockout mouse model infected with *L. amazonensis* developed smaller lesions and parasitic load, indicating that IL-18 would be involved in susceptibility to infection by this pathogen [61]. Anyway, the absence of IL-18 in mice seems to be associated with the induction of the Th2 phenotype and a decrease in the Th1 cell response, having a role in the imbalance of Th1/Th2 responses whose exacerbated alteration is ahead of the intense tissue inflammation/injury or *Leishmania* persistence, respectively [62,63].

The polarization of the Th2 response, which is also associated with the diffuse and visceral forms of leishmaniasis [64], may also be influenced by IL-33, a cytokine of the IL-1 family that contributes to susceptibility in VL, negatively modulating the Th1 response and the recruitment of immune cells in the liver [42,65]. In CL, there are some studies that focus on evaluating the expression of its receptor (ST2) in mouse Th2 cells, initially identified as an orphan receptor and whose signaling was associated with the IL-33 ligand only in 2005 [66–68]. Although the performance of IL-33 does not seem to be crucial in the differentiation of Th2 cells and the production of cytokines in this profile, the suppression of its signaling with monoclonal anti-ST2 antibodies in BALB/c mice, during infection with *L. major,* lead to a stronger Th1 response, thus it seems to play a role in susceptibility to the parasite

Table 1
Summary of the main functions of ligands of the IL-1 family in CL.

Cytokine	Receptors and co-receptor	Role in CL	Cell or model type	References
IL-1α	IL-1R1, IL-1R2, IL-1RAcP	Participates in the differentiation of Th0 lymphocytes into type 1; excess and long-term levels can exacerbate the disease	BALB/c mice	[12,37]
IL-1β	IL-1R1, IL-1R2, IL-1RAcP	May be associated with disease progression	RAG mice, human biopsies and PBMCs	[11,75]
IL-1Ra	IL-1R1	Important mitigation of lesion development	BALB/c and RAG mice	[11,12, 54]
IL-18	IL-18Rα, IL-18Rβ	It seems to depend on the species of *Leishmania* and the genetic profile of the host, despite contributing to the susceptibility	C57BL/6 and BALB/c mice	[61,85, 86]
IL-33	ST2, IL-1RAcP	Associated with Th2 responses, although it is not crucial for its development. Negatively regulates Th1 response and IFN-γ production	BALB/c mice	[65,87]
IL-36α, β, γ and IL-36Ra	IL-36R, IL-1RAcP	n/a	n/a	–
IL-37	IL-18Rα, TIR8 (SIGIRR)	n/a	n/a	–
IL-38	IL-36R, TIGIRR-2	n/a	n/a	–

PBMC-peripheral blood mononuclear cells, n/a – not analyzed.

[65].

4.2. What is known in humans and what are the gaps to fill?

There are few studies that correlate the IL-1 family and CL in humans, and the use of mice as the main study model can raise problems of extrapolating results due to some variables of the infection model itself [22]. This lead to several gaps regarding the molecular immune response developed during human infection by *Leishmania* parasites. In order to build a panoramic view on this subject, in this topic we have gathered the findings available in the literature and then indicate the spaces to be filled.

Only three IL-1 cytokines have been studied so far in humans, including the main inflammatory IL-1α and IL-1β, and the dual IL-18. A survey of patients infected with *L. mexicana* with localized lesions allowed the visualization of IL-1α, with a significant increase in lesions older than 4 months when compared to those of 2 months in duration. The authors justify the increase and the correlation with other cytokines when considering the elevation of infiltrated T lymphocytes in the lesion [69]. In fact, an increase in cytokines may be linked to the duration of the lesion [70], however, more studies need to be done seeking to better elucidate the relationship of disease duration, number of T cells and the expression of this cytokine. No other studies were found that brought IL-1α in the context of the disease, which draws attention due to the fact that this cytokine is constitutively present in epithelial cells, so it is important to understand its contribution to pathogenesis in the context of this cutaneous disease.

IL-1β, unlike IL-1α, is best described. In the infection by *L. mexicana*, researchers demonstrated a possible association of a polymorphism located in the promoter region of the IL-1β gene and the worsening of CL related to the induction of the cytokine expression due to the mutation [50]. Therefore, the increase in IL-1β production favors the establishment of inflammation and can induce the spread of the parasite, which, as is well known, uses immune cells as hosts. The same authors reported levels of IL-1β directly proportional to the parasitic burden, in addition to a much greater distribution of this cytokine in lesions cells of patients with diffuse cutaneous leishmaniasis (DCL) [50].

With regard to the distribution of IL-1β, high levels in patients with DCL and in a few with the localized form allowed this cytokine to be correlated with the severity of the disease and inflammation [50]. Caceres-Dittmar et al. (1993) [71] showed that the mRNA responsible for the production of this cytokine was less expressed in DCL, a form of leishmaniasis characterized by an important Th2 deviation from the immune response and failures in the activation of Th1 lymphocytes [72]. In *L. tropica* infection, IL-1β was found at high levels in almost all biopsies analyzed [73]. In the case of *L. major* infection, a study showed that, although the stimulus significantly induced the expression of IL-1β, there was no significant difference in the levels observed between healed patients, asymptomatic individuals and controls [74].

During the infection by *L. braziliensis*, IL-1β also showed correlations with the appearance of ulcers, the duration of lesions and areas of necrosis [75,76]. Infection with *L. braziliensis* is known for the development of a more severe form of CL and MCL, characterized by strong Th1 deviations and exacerbated inflammation, showing that this parasite has a strong immunogenicity. When infected macrophages were investigated with and without IL-1β blocked by neutralizing antigens, it was seen that it had no role in the elimination of parasites. Thus, in patients who are not at risk of increased parasitic load, blocking this cytokine becomes an efficient alternative to fight the disease [75]. Although it is not clear how this cytokine directs the progression of CL, together these findings show that *L. braziliensis* seems to cause a modulation that guides patients to a more inflammatory response.

The current treatment for cases of CL is based on the use of pentavalent antimonial, that have a high degree of toxicity. The action of these drugs includes mainly the induction of leishmanicidal activity of macrophages [77] and immunomodulation based on CD4 + and CD8 + T cells, but the detailed mechanism is still not well understood [78]. Considering this, two studies showed the effect of the pentavalent antimonials on plasma levels of IL-1β. The first, carried out by Kocyigit et al. [79], observed a three-fold increase in IL-1β levels in patients after 21 days of treatment with Glucantime® compared to the before treatment group. The second study [70] showed high levels of IL-1β in infected patients during use antimonial (Pentostam®) compared to healthy individuals, that significantly decreased after treatment and clinical cure. Due to methodological divergences, further studies are needed correlating the treatment based on pentavalent antimonials and the levels of cytokines participating in the course of *Leishmania* infection through different routes of administration.

Divergent results are also presented regarding IL-18 during *Leishmania* infection. In 2013, Shahi et al. [80] found higher levels of IL-18 production in supernatants from PBMC culture stimulated with *L. major* antigens from patients with chronic CL lesions compared to cured individuals. This indicated a much more susceptible and aggravating role of this cytokine in the pathology than disease resistance. IL-18 was also significantly increased in lesions of patients with *L. tropica* in the acute and chronic conditions of CL, compared to the production of that same cytokine in healthy skin cells of the same individuals [81].

On the other hand, a study made a survey of all transcripts produced by human macrophages derived from the U937 cell line after infection of *L. braziliensis* for 72 h, and within the group of negatively regulated genes was *IL-18*. This may indicate the modulation that *Leishmania* exerts on the host's defense machinery in an attempt to stabilize the infection, as this investigation time may simulate a later stage of infection by the parasite [82]. Stimulation of PBMC cells from healthy individuals with *L. major* does not seem to be able to induce IL-18, but rather IL-1β, both cytokines matured by the imflamasome [74]. This reinforces the idea of IL-18's flexible role, regulated by the microenvironment and the presence of other cytokines such as IL-12 [83], emphasizing the need to further study its and synergism with other cytokines.

In addition to the IL-1 type 1 receptor antagonist, other cytokines in the family have a suppressive effect on inflammation induced by the inflammatory agonists themselves, such as IL-37, IL-38 and IL-36Ra, and can become potential therapeutic targets. Although IL-36 has been associated with chronic inflammatory diseases [84] and responses mediated by Th17 cells [45], known to contribute to tissue damage and progression of leishmaniasis in mouse strains susceptible to *L. major* [26] and patients with American cutaneous leishmaniasis [27], we do not know what their role is in leishmaniasis.

5. Conclusion

Although quite heterogeneous, we observed that the IL-1 cytokine family plays a central role in the recognition of pathogens and in directing an immune response from different profiles, whether Th1, Th2 or Th17, all of which are important in the context of CL. Some paradoxes in animal studies involve the action of the main inflammatory cytokines IL-1α/β, as there seems to be a fine line between their importance in resistance, as an effector mechanism against *Leishmania* and their contribution to the exacerbation of the inflammation responsible for the pathology. However, there seems to be a consensus that in the later stages of infection, such cytokines play a role in susceptibility and aggravates the progression of CL.

In humans, how these cytokines behave during *Leishmania* infection is poorly understood, especially how antimonial treatment modulates such molecules and the involved mechanism of the inflammatory response exacerbation. Currently there is strong evidence that such cytokines contribute to tissue degradation. The clarification of the role of the IL-1 family further contributes to elucidating the adaptive success of this parasite, which exerts a strong modulation on the host's immune response. Thus, we reinforce how crucial it is to understand its dynamics in CL forthe discovery of new therapeutic targets.

Funding

AMORIM, E. A. S is the recipient of a MSc fellowship from FACEPE. FRANCA, A. A. is the recipient of a BSc fellowship from PIBIC/UFPE. This work was supported by FACEPE (APQ 0820-2.11.2017).

Declarations of Competing Interest

None.

References

[1] H.J.C. de Vries, S.H. Reedijk, H.D.F.H. Schallig, Cutaneous Leishmaniasis: recent developments in diagnosis and management, Am. J. Clin. Dermatol. 16 (2015) 99–109, https://doi.org/10.1007/s40257-015-0114-z.
[2] J. Alvar, I.D. Vélez, C. Bern, M. Herrero, P. Desjeux, J. Cano, J. Jannin, M. de Boer, Leishmaniasis worldwide and global estimates of its incidence, PLoS One 7 (2012) 1–6, https://doi.org/10.1371/journal.pone.0035671.
[3] Pan American Health Organization, Manual of Procedures for Surveillance and Control of Leishmaniasis in the Americas, PAHO/WHO, 2019.
[4] D. Pace, Leishmaniasis, J. Infect. 69 (2014) S10–S18, https://doi.org/10.1016/j.jinf.2014.07.016.
[5] R.P. Ribeiro-Romão, A.F. Saavedra, A.M. Da-Cruz, E.F. Pinto, O.C. Moreira, Development of real-time PCR assays for evaluation of immune response and parasite load in golden hamster (Mesocricetus auratus) infected by Leishmania (Viannia) braziliensis, Parasit. Vectors 9 (2016), https://doi.org/10.1186/s13071-016-1647-6.
[6] L.S. Sangenito, V. da Silva Santos, C.M. d'Avila-Levy, M.H. Branquinha, A.L. Souza dos Santos, S.S.C. de Oliveira, Leishmaniasis and chagas disease – neglected tropical diseases: treatment updates, Curr. Top. Med. Chem. 19 (2019) 174–177, https://doi.org/10.2174/1568026619031903282155136.
[7] A. Giudice, C. Vendrame, C. Bezerra, L.P. Carvalho, T. Delavechia, E.M. Carvalho, O. Bacellar, Macrophages participate in host protection and the disease pathology associated with Leishmania braziliensis infection, BMC Infect. Dis. 12 (2012) 75, https://doi.org/10.1186/1471-2334-12-75.
[8] L.P. Carvalho, S. Passos, A. Schriefer, E.M. Carvalho, Protective and pathologic immune responses in human tegumentary leishmaniasis, Front. Immunol. 3 (2012) 301, https://doi.org/10.3389/fimmu.2012.00301.
[9] T.M. Campos, R. Costa, S. Passos, L.P. Carvalho, Cytotoxic activity in cutaneous leishmaniasis, Mem. Inst. Oswaldo Cruz 112 (2017) 733–740, https://doi.org/10.1590/0074-02760170109.
[10] J.R. Lukens, J.M. Gross, T.D. Kanneganti, IL-1 family cytokines trigger sterile inflammatory disease, Front. Immunol. 3 (2012) 315, https://doi.org/10.3389/fimmu.2012.00315.
[11] F.O. Novais, A.M. Carvalho, M.L. Clark, L.P. Carvalho, D.P. Beiting, I.E. Brodsky, E. M. Carvalho, P. Scott, CD8+ T cell cytotoxicity mediates pathology in the skin by inflammasome activation and IL-1β production, PLoS Pathog. 13 (2017) e1006196, https://doi.org/10.1371/journal.ppat.1006196.
[12] E. Voronov, S. Dotan, L. Gayvoronsky, R.M. White, I. Cohen, Y. Krelin, F. Benchetrit, M. Elkabets, M. Huszar, J. El-On, R.N. Apte, IL-1-induced inflammation promotes development of leishmaniasis in susceptible BALB/c mice, Int. Immunol. 22 (2010) 245–257, https://doi.org/10.1093/intimm/dxq006.
[13] M. Charmoy, B.P. Hurrell, A. Romano, S.H. Lee, F. Ribeiro-Gomes, N. Riteau, K. Mayer-Barber, F. Tacchini-Cottier, D.L. Sacks, The Nlrp3 inflammasome, IL-1β, and neutrophil recruitment are required for susceptibility to a nonhealing strain of Leishmania major in C57BL/6 mice, Eur. J. Immunol. 46 (2016) 897–911, https://doi.org/10.1002/eji.201546015.
[14] N. Maspi, A. Abdoli, F. Ghaffarifar, Pro- and anti-inflammatory cytokines in cutaneous leishmaniasis: a review, Pathog. Glob. Health 110 (2016) 247–260, https://doi.org/10.1080/20477724.2016.1232042.
[15] L.A. Borthwick, The IL-1 cytokine family and its role in inflammation and fibrosis in the lung, Semin. Immunopathol. 38 (2016) 517–534, https://doi.org/10.1007/s00281-016-0559-z.
[16] C. Garlanda, C.A. Dinarello, A. Mantovani, The Interleukin-1 family: back to the future, Immunity 39 (2013) 1003–1018, https://doi.org/10.1016/j.immuni.2013.11.010.
[17] P.R.L. Machado, L. Carvalho, M.I.A.S. Araújo, E.M. Carvalho, Immune response mechanisms to infections, An. Bras. Derm. Sifilogr. 79 (2004) 647–664, https://doi.org/10.1590/S0365-05962004000600002.
[18] M. Rossi, N. Fasel, How to master the host immune system? Leishmania parasites have the solutions!, Int. Immunol. 30 (2018) 103–111, https://doi.org/10.1093/intimm/dxx075.
[19] F. Bahrami, A.M. Harandi, S. Rafati, Biomarkers of cutaneous leishmaniasis, Front. Cell. Infect. Microbiol. 8 (2018) 222, https://doi.org/10.3389/fcimb.2018.00222.
[20] I.B. Regli, K. Passelli, B.P. Hurrell, F. Tacchini-Cottier, Survival mechanisms used by some Leishmania species to escape neutrophil killing, Front. Immunol. 8 (2017) 1558, https://doi.org/10.3389/fimmu.2017.01558.
[21] B.M. Scorza, E.M. Carvalho, M.E. Wilson, Cutaneous manifestations of human and murine leishmaniasis, Int. J. Mol. Sci. 18 (2017), https://doi.org/10.3390/ijms18061296.
[22] D. Sacks, N. Noben-Trauth, The immunology of susceptibility and resistance to Leishmania major in mice, Nat. Rev. Immunol. 2 (2002) 845–858, https://doi.org/10.1038/nri933.
[23] G. Gupta, S. Oghumu, A.R. Satoskar, Mechanisms of immune evasion in leishmaniasis. Adv. Appl. Microbiol., Academic Press Inc, 2013, pp. 155–184, https://doi.org/10.1016/B978-0-12-407679-2.00005-3.
[24] J. Alexander, F. Brombacher, T helper1/T helper2 cells and resistance/susceptibility to Leishmania infection: is this paradigm still relevant? Front. Immunol. 3 (2012) 80, https://doi.org/10.3389/fimmu.2012.00080.
[25] O. Bacellar, H. Lessa, A. Schriefer, P. Machado, A.R. De Jesus, W.O. Dutra, K. J. Gollob, E.M. Carvalho, Up-regulation of Th1-type responses in mucosal leishmaniasis patients, Infect. Immun. 70 (2002) 6734–6740, https://doi.org/10.1128/IAI.70.12.6734-6740.2002.
[26] J.E. Allen, T.A. Wynn, Evolution of Th2 immunity: a rapid repair response to tissue destructive pathogens, PLoS Pathog. 7 (2011) e1002003, https://doi.org/10.1371/journal.ppat.1002003.
[27] R.C. Bittar, R.S. Nogueira, R. Vieira-Gonçalves, V. Pinho-Ribeiro, M.S. Mattos, M. P. Oliveira-Neto, S.G. Coutinho, A.M. Da-Cruz, T-cell responses associated with resistance to Leishmania infection in individuals from endemic areas for Leishmania (Viannia) braziliensis, Mem. Inst. Oswaldo Cruz 102 (2007) 625–630, https://doi.org/10.1590/s0074-02762007005000069.
[28] V.S. Boaventura, C.S. Santos, C.R. Cardoso, J. De Andrade, W.L.C. Dos Santos, J. Clarêncio, J.S. Silva, V.M. Borges, M. Barral-Netto, C.I. Brodskyn, A. Barral, Human mucosal leishmaniasis: neutrophils infiltrate areas of tissue damage that express high levels of Th17-related cytokines, Eur. J. Immunol. 40 (2010) 2830–2836, https://doi.org/10.1002/eji.200940115.
[29] O. Bacellar, D. Faria, M. Nascimento, T.M. Cardoso, K.J. Gollob, W.O. Dutra, P. Scott, E.M. Carvalho, Interleukin 17 production among patients with american cutaneous leishmaniasis, J. Infect. Dis. 200 (2009) 75–78, https://doi.org/10.1086/599380.
[30] A.F. Almeida, Avaliação da produção de citocinas Th17, Th1 e Th2 por linfócitos T em pacientes com Leishmaniose Tegumentar Americana (Master's thesis), Retrieved from, Oswaldo Cruz Foundation, Recife, Brazil, 2013, https://www.arca.fiocruz.br/handle/icict/14498.
[31] S. Lopez Kostka, S. Dinges, K. Griewank, Y. Iwakura, M.C. Udey, E. von Stebut, IL-17 promotes progression of cutaneous leishmaniasis in susceptible mice, J. Immunol. 182 (2009) 3039–3046, https://doi.org/10.4049/jimmunol.0713598.
[32] R.O. Pinheiro, Leishmaniose tegumentar americana: mecanismos imunológicos, tratamento e profilaxia, Infarma-Ciências Farmacêuticas 16 (2004) 79–82 (Accessed 23 April 2020), http://revistas.cff.org.br/?journal=infarma&page=article&op=view&path%5B%5D=318.
[33] A. Malik, T.D. Kanneganti, Function and regulation of IL-1α in inflammatory diseases and cancer, Immunol. Rev. 281 (2018) 124–137, https://doi.org/10.1111/imr.12615.
[34] P. Rider, Y. Carmi, O. Guttman, A. Braiman, I. Cohen, E. Voronov, M.R. White, C. A. Dinarello, R.N. Apte, IL-1α and IL-1β recruit different myeloid cells and promote different stages of sterile inflammation, J. Immunol. 187 (2011) 4835–4843, https://doi.org/10.4049/jimmunol.1102048.
[35] R.N. Apte, E. Voronov, Is interleukin-1 a good or bad "guy" in tumor immunobiology and immunotherapy? Immunol. Rev. 222 (2008) 222–241, https://doi.org/10.1111/j.1600-065X.2008.00615.x.
[36] J.E. Sims, D.E. Smith, The IL-1 family: regulators of immunity, Nat. Rev. Immunol. 10 (2010) 89–102, https://doi.org/10.1038/nri2691.
[37] S.L. Kostka, J. Knop, A. Konur, M.C. Udey, E. Von Stebut, Distinct roles for IL-1 receptor type I signaling in early versus established Leishmania major infections, J. Invest. Dermatol. 126 (2006) 1582–1589, https://doi.org/10.1038/sj.jid.5700309.
[38] P. Scott, F.O. Novais, Cutaneous leishmaniasis: immune responses in protection and pathogenesis, (n.d.). https://doi.org/10.1038/nri.2016.72.
[39] Y. Chung, S.H. Chang, G.J. Martinez, X.O. Yang, R. Nurieva, H.S. Kang, L. Ma, S. S. Watowich, A.M. Jetten, Q. Tian, C. Dong, Critical regulation of early Th17 cell differentiation by interleukin-1 signaling, Immunity 30 (2009) 576–587, https://doi.org/10.1016/j.immuni.2009.02.007.
[40] C. Cayrol, J.P. Girard, IL-33: an alarmin cytokine with crucial roles in innate immunity, inflammation and allergy, Curr. Opin. Immunol. 31 (2014) 31–37, https://doi.org/10.1016/j.coi.2014.09.004.
[41] A.B. Molofsky, A.K. Savage, R.M. Locksley, Interleukin-33 in tissue homeostasis, injury, and inflammation, Immunity 42 (2015) 1005–1019, https://doi.org/10.1016/j.immuni.2015.06.006.
[42] O. Rostan, J.P. Gangneux, C. Piquet-Pellorce, C. Manuel, A.N.J. McKenzie, C. Guiguen, M. Samson, F. Robert-Gangneux, The IL-33/ST2 axis is associated with human visceral leishmaniasis and suppresses Th1 responses in the livers of BALB/c mice infected with Leishmania donovani, MBio 4 (2013), https://doi.org/10.1128/mBio.00383-13.
[43] D. Boraschi, P. Italiani, S. Weil, M.U. Martin, The family of the interleukin-1 receptors, Immunol. Rev. 281 (2018) 197–232, https://doi.org/10.1111/imr.12606.
[44] M.F. Nold, C.A. Nold-Petry, J.A. Zepp, B.E. Palmer, P. Bufler, C.A. Dinarello, IL-37 is a fundamental inhibitor of innate immunity, Nat. Immunol. 11 (2010) 1014–1022, https://doi.org/10.1038/ni.1944.
[45] F.L. Van De Veerdonk, A.K. Stoeckman, G. Wu, A.N. Boeckermann, T. Azam, M. G. Netea, L.A.B. Joosten, J.W.M. Van Der Meer, R. Hao, V. Kalabokis, C. A. Dinarello, IL-38 binds to the IL-36 receptor and has biological effects on immune cells similar to IL-36 receptor antagonist, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 3001–3005, https://doi.org/10.1073/pnas.1121534109.

[46] X. Yuan, X. Peng, Y. Li, M. Li, Role of IL-38 and its related cytokines in inflammation, Mediators Inflamm. 2015 (2015) 807976, https://doi.org/10.1155/2015/807976.
[47] T. Garraud, M. Harel, M.A. Boutet, B. Le Goff, F. Blanchard, The enigmatic role of IL-38 in inflammatory diseases, Cytokine Growth Factor Rev. 39 (2018) 26–35, https://doi.org/10.1016/j.cytogfr.2018.01.001.
[48] C.A. Dinarello, The IL-1 family of cytokines and receptors in rheumatic diseases, Nat. Rev. Rheumatol. 15 (2019) 612–632, https://doi.org/10.1038/s41584-019-0277-8.
[49] C.A. Dinarello, Immunological and inflammatory functions of the Interleukin-1 family, Annu. Rev. Immunol. 27 (2009) 519–550, https://doi.org/10.1146/annurev.immunol.021908.132612.
[50] E.A. Fernández-Figueroa, C. Rangel-Escareño, V. Espinosa-Mateos, K. Carrillo-Sánchez, N. Salaiza-Suazo, G. Carrada-Figueroa, S. March-Mifsut, I. Becker, Disease severity in patients infected with Leishmania mexicana relates to IL-1β, PLoS Negl. Trop. Dis. 6 (2012) e1533, https://doi.org/10.1371/journal.pntd.0001533.
[51] A. Iwasaki, The importance of CD11b+ dendritic cells in CD4+ T cell activation in vivo: with help from interleukin 1, J. Exp. Med. 198 (2003) 185–190, https://doi.org/10.1084/jem.20030737.
[52] E. Von Stebut, J.M. Ehrchen, Y. Belkaid, S.L. Kostka, K. Mölle, J. Knop, C. Sunderkötter, M.C. Udey, Interleukin 1α promotes TH1 differentiation and inhibits disease progression in Leishmania major-susceptible BALB/c mice, J. Exp. Med. 198 (2003) 191–199, https://doi.org/10.1084/jem.20030159.
[53] T.R. Hawn, A. Ozinsky, D.M. Underhill, F.S. Buckner, S. Akira, A. Aderem, Leishmania major activates IL-1 alpha expression in macrophages through a MyD88-dependent pathway, Microbes Infect. 4 (2002) 763–771, https://doi.org/10.1016/s1286-4579(02)01596-4.
[54] K. Kautz-Neu, S.L. Kostka, S. Dinges, Y. Iwakura, M.C. Udey, E. Von Stebut, A role for leukocyte-derived IL-1RA in DC homeostasis revealed by increased susceptibility of IL-1RA-deficient mice to cutaneous leishmaniasis, J. Invest. Dermatol. 131 (2011) 1650–1659, https://doi.org/10.1038/jid.2011.99.
[55] D.S. Lima-Junior, D.L. Costa, V. Carregaro, L.D. Cunha, A.L.N. Silva, T.W.P. Mineo, F.R.S. Gutierrez, M. Bellio, K.R. Bortoluci, R.A. Flavell, M.T. Bozza, J.S. Silva, D. S. Zamboni, Inflammasome-derived IL-1β production induces nitric oxide-mediated resistance to Leishmania, Nat. Med. 19 (2013) 909–915, https://doi.org/10.1038/nm.3221.
[56] K. Shibuya, D. Robinson, F. Zonin, S.B. Hartley, S.E. Macatonia, C. Somoza, C. A. Hunter, K.M. Murphy, A. O'Garra, IL-1 alpha and TNF-alpha are required for IL-12-induced development of Th1 cells producing high levels of IFN-gamma in BALB/c but not C57BL/6 mice, J. Immunol. 160 (1998) 1708–1716 (Accessed 23 April 2020), http://www.ncbi.nlm.nih.gov/pubmed/9469428.
[57] A.K. Gupta, K. Ghosh, S. Palit, J. Barua, P.K. Das, A. Ukil, Leishmania donovani inhibits inflammasome-dependent macrophage activation by exploiting the negative regulatory proteins A20 and UCP2, FASEB J. 31 (2017) 5087–5101, https://doi.org/10.1096/fj.201700407R.
[58] M.A. Hartley, R.O. Eren, M. Rossi, F. Prevel, P. Castiglioni, N. Isorce, C. Desponds, L.F. Lye, S.M. Beverley, S.K. Drexler, N. Fasel, Leishmania guyanensis parasites block the activation of the inflammasome by inhibiting maturation of IL-1β, Microb. Cell 5 (2018) 137–149, https://doi.org/10.15698/mic2018.03.619.
[59] J.H. Lee, D.H. Cho, H.J. Park, IL-18 and cutaneous inflammatory diseases, Int. J. Mol. Sci. 16 (2015) 29357–29369, https://doi.org/10.3390/ijms161226172.
[60] G.M. Monteforte, K. Takeda, M. Rodriguez-Sosa, S. Akira, J.R. David, A. R. Satoskar, Genetically resistant mice lacking IL-18 gene develop Th1 response and control cutaneous leishmania major infection, J. Immunol. 164 (2000) 5890–5893, https://doi.org/10.4049/jimmunol.164.11.5890.
[61] L.M.A. Sousa, M.B.H. Carneiro, L.M. dos Santos, C.C. Natale, M.E. Resende, D. M. Mosser, L.Q. Vieira, IL-18 contributes to susceptibility to Leishmania amazonensis infection by macrophage-independent mechanisms, Cytokine 74 (2015) 327–330, https://doi.org/10.1016/j.cyto.2015.01.021.
[62] A. Dayakar, S. Chandrasekaran, S.V. Kuchipudi, S.K. Kalangi, Cytokines: Key determinants of resistance or disease progression in visceral leishmaniasis: Opportunities for novel diagnostics and immunotherapy, Front. Immunol. 10 (2019) 670, https://doi.org/10.3389/fimmu.2019.00670.
[63] X.Q. Wei, B.P. Leung, W. Niedbala, D. Piedrafita, G.J. Feng, M. Sweet, L. Dobbie, A. J. Smith, F.Y. Liew, Altered immune responses and susceptibility to Leishmania major and Staphylococcus aureus infection in IL-18-deficient mice, J. Immunol. 163 (1999) 2821–2828 (Accessed 23 April 2020), http://www.ncbi.nlm.nih.gov/pubmed/10453027.
[64] L.R. Castellano, D.C. Filho, L. Argiro, H. Dessein, A. Prata, A. Dessein, V. Rodrigues, Th1/Th2 immune responses are associated with active cutaneous leishmaniasis and clinical cure is associated with strong interferon-γ production, Hum. Immunol. 70 (2009) 383–390, https://doi.org/10.1016/j.humimm.2009.01.007.
[65] P. Kropf, S. Herath, R. Klemenz, I. Müller, Signaling through the T1/ST2 molecule is not necessary for Th2 differentiation but is important for the regulation of type 1 responses in nonhealing Leishmania major infection, Infect. Immun. 71 (2003) 1961–1971, https://doi.org/10.1128/iai.71.4.1961-1971.2003.
[66] R. Kakkar, R.T. Lee, The IL-33/ST2 pathway: therapeutic target and novel biomarker, Nat. Rev. Drug Discov. 7 (2008) 827–840, https://doi.org/10.1038/nrd2660.
[67] P. Kropf, L.R. Schopf, C.L. Chung, D. Xu, F.Y. Liew, J.P. Sypek, I. Müller, Expression of Th2 cytokines and the stable Th2 marker ST2L in the absence of IL-4 during Leishmania major infection, Eur. J. Immunol. 29 (1999) 3621–3628, https://doi.org/10.1002/(SICI)1521-4141(199911)29:11<3621::AID-IMMU3621>3.0.CO;2-Z.
[68] J. Schmitz, A. Owyang, E. Oldham, Y. Song, E. Murphy, T.K. McClanahan, G. Zurawski, M. Moshrefi, J. Qin, X. Li, D.M. Gorman, J.F. Bazan, R.A. Kastelein, IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines, Immunity 23 (2005) 479–490, https://doi.org/10.1016/j.immuni.2005.09.015.
[69] P.C. Melby, F.J. Andrade-Narvaez, B.J. Darnell, G. Valencia-Pacheco, V.V. Tryon, A. Palomo-Cetina, Increased expression of proinflammatory cytokines in chronic lesions of human cutaneous leishmaniasis, Infect. Immun. 62 (1994) 837–842, https://doi.org/10.1128/iai.62.3.837-842.1994.
[70] I.K. Al-Aubaidi, Serum cytokine production in patients with Cutaneous Leishmaniasis before and after treatment, Iraqi J. Med. Sci. 9 (2011) 55–60.
[71] G. Caceres-dittmar, F.J. Tapia, M.A. Sánchez, M. Yamamura, K. Uyemura, R. L. Modlin, B.R. Bloom, J. Convit, Determination of the cytokine profile in American cutaneous leishmaniasis using the polymerase chain reaction, Clin. Exp. Immunol. 91 (2008) 500–505, https://doi.org/10.1111/j.1365-2249.1993.tb05931.x.
[72] F.T. Silveira, R. Lainson, C.E.P. Corbett, Clinical and immunopathological spectrum of american cutaneous leishmaniasis with special reference to the disease in Amazonian Brazil – a review, Mem. Inst. Oswaldo Cruz 99 (2004) 239–251, https://doi.org/10.1590/S0074-02762004000300001.
[73] G.K. Katara, A. Raj, R. Kumar, K. Avishek, H. Kaushal, N.A. Ansari, R.A. Bumb, P. Salotra, Analysis of localized immune responses reveals presence of Th17 and Treg cells in cutaneous leishmaniasis due to Leishmania tropica, BMC Immunol. 14 (2013), https://doi.org/10.1186/1471-2172-14-52.
[74] W. Kammoun-rebai, I. Naouar, V. Libri, M. Albert, H. Louzir, Protein biomarkers discriminate Leishmania major -infected and non-infected individuals in areas endemic for cutaneous leishmaniasis, BMC Infect. Dis. (2016) 1–10, https://doi.org/10.1186/s12879-016-1458-6.
[75] D. Santos, T.M. Campos, M. Saldanha, S.C. Oliveira, M. Nascimento, D.S. Zamboni, P.R. Machado, S. Arruda, P. Scott, E.M. Carvalho, L.P. Carvalho, IL-1β production by intermediate monocytes is associated with immunopathology in cutaneous leishmaniasis, J. Invest. Dermatol. 138 (2018) 1107–1115, https://doi.org/10.1016/j.jid.2017.11.029.
[76] J.C. dos Santos, B. Heinhuis, R.S. Gomes, M.S.M.A. Damen, F. Real, R.A. Mortara, S.T. Keating, C.A. Dinarello, L.A.B. Joosten, F. Ribeiro-Dias, Cytokines and microbicidal molecules regulated by IL-32 in THP-1-derived human macrophages infected with New World Leishmania species, PLoS Negl. Trop. Dis. 11 (2017), https://doi.org/10.1371/journal.pntd.0005413.
[77] B.S. McGwire, A.R. Satoskar, Leishmaniasis: clinical syndromes and treatment, QJM 107 (2014) 7–14, https://doi.org/10.1093/qjmed/hct116.
[78] I. Lakhal-Naouar, B.M. Slike, N.E. Aronson, M.A. Marovich, The immunology of a healing response in cutaneous leishmaniasis treated with localized heat or systemic antimonial therapy, PLoS Negl. Trop. Dis. 9 (2015) e0004178, https://doi.org/10.1371/journal.pntd.0004178.
[79] A. Kocyigit, S. Gur, M.S. Gurel, V. Bulut, M. Ulukanligil, Antimonial therapy induces circulating proinflammatory cytokines in patients with cutaneous leishmaniasis, Infect. Immun. 70 (2002) 6589–6591, https://doi.org/10.1128/IAI.70.12.6589-6591.2002.
[80] M. Shahi, M. Mohajery, S.A.A. Shamsian, H. Nahrevanian, S.M.J. Yazdanpanah, Comparison of Th1 and Th2 responses in non-healing and healing patients with cutaneous leishmaniasis, Rep. Biochem. Mol. Biol. 1 (2013) 43–48 (Accessed 23 April 2020), http://www.ncbi.nlm.nih.gov/pubmed/26989708.
[81] Y. Taslimi, C. Agbajogu, S.F. Brynjolfsson, N. Masoudzadeh, V. Mashayekhi, S. Gharibzadeh, M. Östensson, S.S. Nakka, A. Mizbani, S. Rafati, A.M. Harandi, Profiling inflammatory response in lesions of cutaneous leishmaniasis patients using a non-invasive sampling method combined with a high-throughput protein detection assay, Cytokine 130 (2020) 155056, https://doi.org/10.1016/j.cyto.2020.155056.
[82] C. Ovalle-Bracho, C. Franco-Muñoz, D. Londoño-Barbosa, D. Restrepo-Montoya, C. Clavijo-Ramírez, Changes in macrophage gene expression associated with leishmania (Viannia) braziliensis infection, PLoS One 10 (2015) e0128934, https://doi.org/10.1371/journal.pone.0128934.
[83] K. Nakanishi, T. Yoshimoto, H. Tsutsui, H. Okamura, Interleukin -18 regulates both Th1 and Th2 responses, Annu. Rev. Immunol. 19 (2001) 423–474, https://doi.org/10.1146/annurev.immunol.19.1.423.
[84] Z.C. Yuan, W.D. Xu, X.Y. Liu, X.Y. Liu, A.F. Huang, L.C. Su, Biology of il-36 signaling and its role in systemic inflammatory diseases, Front. Immunol. 10 (2019), https://doi.org/10.3389/fimmu.2019.02532.
[85] K.J. Bryson, X.Q. Wei, J. Alexander, Interleukin-18 enhances a Th2 biased response and susceptibility to Leishmania mexicana in BALB/c mice, Microbes Infect. 10 (2008) 834–839, https://doi.org/10.1016/j.micinf.2008.03.009.
[86] X.Q. Wei, W. Niedbala, D. Xu, Z.X. Luo, K.G.J. Pollock, J.M. Brewer, Host genetic background determines whether IL-18 deficiency results in increased susceptibility or resistance to murine Leishmania major infection, Immunol. Lett. 94 (2004) 35–37, https://doi.org/10.1016/j.imlet.2004.04.001.
[87] K. Oboki, T. Ohno, N. Kajiwara, H. Saito, S. Nakae, IL-33 and IL-33 receptors in host defense and diseases, Allergol. Int. 59 (2010) 143–160, https://doi.org/10.2332/allergolint.10-RAI-0186.

Ester Amorim is a biologist graduated from the Federal University of Pernambuco in 2018. During graduation, she started her scientific initiation in 2016 at Aggeu Magalhães Institute (IAM/FIOCRUZ/PE) were she studied polymorphisms and epigenetic regulations in inflammation caused by atherosclerotic diseases. Now she is a mater student at the Federal University of Pernambuco and focus on the gene regulation of IL-1 cytokines in leishmaniasis.

Áquila Alcantara de França is a nursing student at the Federal University of Pernambuco. He works as a scientific initiation student in the areas of immunology and parasitology, focusing on studying the IL-1 family on cutaneous leishmaniasis. He works together with master students at the Federal University of Pernambuco and at the Aggeu Magalhães Institute (IAM/FIOCRUZ/PE).

Valéria Rêgo Alves Pereira has a PhD in Cellular and Molecular Biology from the Oswaldo Cruz Foundation (2003). Currently she is a Senior Technologist in Public Health and responsible for the Flow Cytometry Core unit at Aggeu Magalhães Institute (IAM/FIOCRUZ/PE). She is part of the Ethics Committee in Human Research of IAM and a professor on the Post-Graduation programs of Therapeutic Innovation (UFPE) and Health Biosciences and Biotechnology (IAM). She leads the research group of Immunology of Infectious and Parasitic Diseases, has expertise in Immunology with emphasis in Immunoparasitology, acting mainly on the studies of the cellular and humoral responses of individuals who are susceptible to infectious and parasitic diseases in different stages of the pathological process, mainly with leishmaniasis.

Maria Carolina Accioly Brelaz-de-Castro graduated in Biomedicine from the Federal University of Pernambuco (UFPE), has a master's degree in Sciences from the Aggeu Magalhães Institute (IAM) and a doctorate (2013) and postdoctorate (2015) in Therapeutic Innovation from UFPE. She is currently a professor at UFPE and at the postgraduate program in Therapeutic Innovation, from the same University. She is a collaborator of IAM and a member of their flow cytometry core unit. She has experience in the fields of Immunology and Parasitology and her research group is focused on the development of immunological biomarkers and vaccines for infectious and parasitic diseases, mainly working with leishmaniasis.