Leishmaniasis comprises a group of parasitic diseases caused by several species of the *Leishmania* genus. Depending on the combination of the parasite species and yet unknown factors of the host, the disease can manifest itself as a single cutaneous ulcer, multiple lesions throughout the body or even visceral infection which, when untreated, is often lethal [1]. The disease is transmitted by infected females of sand flies of the Phlebotominae family during blood feeding [2] and affects approximately 300,000 people worldwide annually, mainly in the tropical and subtropical areas [3].

The immune response against the parasite is dependent both on the innate as well as the adaptive responses (for recent reviews, see [4–7]). In this review we will focus primarily on the innate aspects of the immune response and the role of the purinergic signaling in the modulation of such response.
Innate response to *Leishmania*

During blood feeding of infected phlebotomine females, neutrophils rapidly migrate to the site of infection and phagocytize metacyclic promastigotes that are injected together with the insect saliva [8,9]. The role of neutrophils during infection is contradictory. These cells have been reported to help eliminate the parasite via the production of ROS and the induction of extracellular traps [10,11]. However, they also may play a role in inhibiting macrophage activation, due to their death by apoptosis after infection by the parasite [12]. Neutrophils also secrete chemokines that recruit monocytes/macrophages as well as dendritic cells to the site of infection [4,13].

Dendritic cells (DC) are antigen presenting cells capable of producing IL-12 upon infection with some *Leishmania* species such as *Leishmania major* [14]. This production of IL-12 is crucial to the development of a specific Th1 response that is protective to the host [15,16]. However, *Leishmania amazonensis*, which causes a severe form of cutaneous leishmaniasis (diffuse cutaneous leishmaniasis) characterized by the lack of specific immune response in patients [17], inhibits DC activation and interfere with antigen presentation and development of T cell response [18] thus evading the immune response both in humans and in the mouse model [17–21].

Even though *Leishmania* can infect neutrophils and DC, macrophages are the cells in which these parasites live and multiply within the infected mammalian host. *Leishmania* gain access to macrophages via phagocytosis mediated by complement fragments that are deposited and inactivated on the surface of the parasite, due to the action of proteases present on the surface of the infective promastigote [22–25]. The entry of the parasite via complement receptor (CR3)-mediated phagocytosis interferes with macrophage activation allowing the parasite to prevent the initial respiratory burst that, otherwise, would destroy the parasite [26]. However, upon activation by IFN-γ [27,28], produced by both NK [29] and T cells (both CD4 [30] and CD8 [31]), macrophages are activated to produce ROS and NO which are the main effector mechanisms for parasite killing within these cells [32].

In spite of the potential ability of the host to control parasite growth, several mechanisms contribute to evasion of the immune response by *Leishmania*. These mechanisms include, in addition to those already mentioned above, escape from complement activation [26,33], inhibition of macrophage activation by apoptotic neutrophil [12], production of inhibitory cytokines such as IL-10 and TGF-β by macrophages and DC, and the induction of regulatory T cells capable of controlling the immune response [4,19,21]. Although these inhibitory mechanisms have been extensively studied, the evasion of the immune response by some parasite species, in special *L. amazonensis*, is not restricted to these mechanisms. For example, IL-10 deficient mice infected with *L. amazonensis* still develop lesions in spite of an increased Th1 response [34]. Thus, it is conceivable that other mechanisms of immune evasion are present during *Leishmania* infection and modulation of the immune response via purinergic signaling may be one of such mechanisms.

Purinergic signaling and inflammation

During infection or cell injury, ATP can be released to the extracellular milieu and has been described as a danger signal, alerting the immune system to alterations in cellular integrity [35–38]. ATP can also be released by intact cells through connexin and panexin channels and also via the P2X<sub>7</sub> receptor [39].

Extracellular ATP is a potent inducer of inflammation characterized by macrophage and DC activation and increased production of IL-12 and TNF-α by these cells [40–45]. ATP exerts its effects by binding to P2 receptors which are divided in two subtypes: P2X receptors, that are associated to ionic channels and protein G coupled-P2Y [46–48]. In immune cells, P2X<sub>7</sub> is the main ATP receptor and its activation accounts for most of the inflammatory effects of extracellular ATP [49–51].

In order to regulate the extracellular effects of ATP, its concentration is controlled by the action of extracellular enzymes of which the main players in immune cells are the ecto-5’-nucleotidase (CD39) that hydrolyses ATP to ADP and subsequently to AMP and the ecto-5’-nucleotidase (CD73) that removes the phosphate group of AMP leading to the production of adenosine. Adenosine is, then, deaminated to inosine by adenosine deaminase [52,53]. In addition, adenosine concentrations inside and outside the cell are kept relatively constant (between 30 and 300 nM) by the action of bidirectional nucleoside transporters. However, in pathophysiological conditions such as hypoxia, ischemia and cell injury, adenosine extracellular concentrations can peak at 10 μM [54–56].

By acting on P1 receptors, in particular A2A and A2B, adenosine counteracts the inflammatory effects of ATP [57]. Thus adenosine inhibits the production of inflammatory cytokines by macrophages and DC and the production of microbial effectors by neutrophils and macrophages. In addition, adenosine stimulates the synthesis of IL-10, one of the major regulatory cytokines [47,58–63].

Thus, the balance between extracellular ATP and adenosine can contribute to the control of inflammation by, respectively, stimulating or inhibiting the cells involved in the immune response. Next, we present data from the recent literature that show that the purinergic system may interfere with the establishment of infection by *Leishmania*.

The role of saliva

As mentioned above, *Leishmania* promastigotes are transmitted by the bite of an infected phlebotomine. During blood feeding, the insect regurgitates a portion of saliva is inoculated in the host dermis. In order to facilitate the blood meal, phlebotomine saliva is endowed with several substances that prevent blood clotting formation. Thus, saliva from phlebotomine sand flies (Phlebotomus papatasii and *Phlebotomus argenteipes*) is rich in adenosine and AMP [64–66]. In addition, transcriptome analysis indicated the presence of apyrase and S’-nucleotidases in the saliva of *Lutzomyia longipalpis* [67], *Phlebotomus perniciosus*, *P. argenteipes*, *Phlebotomus ariasi* [68] and *Phlebotomus duboscqi* [69]. AMP and adenosine...
inhibit platelet aggregation [70]. The presence of nucleotidases in the saliva contributes to the hydrolysis of extracellular ATP, preventing platelet aggregation and blood clot formation [71].

In addition to prevention of blood clotting, the presence of adenosine, AMP and ectonucleotidases may also influence the host immune response and facilitate the establishment of the infection. It has been demonstrated that addition of salivary gland extract together with the parasite exacerbates lesion development in the murine model of leishmaniasis [72–75]. Recent studies by Carregaro and colleagues [76] demonstrated that adenosine and AMP present in the saliva of *P. papatasi* exacerbate lesion development in *L. amazonensis* infected mice, probably due to increased IL-10 production and induction of tolerogenic dendritic cells and regulatory T cells. These effects seem to be mediated by the A2A adenosine receptor. Corroborating the role of nucleotides and nucleosides of the insect saliva in the immunomodulation of the host response Katz and colleagues [64] demonstrated that *P. papatasi* saliva decreases NO production by activated macrophages. The same was not observed when the saliva of *L. longipalpis* is used. Interestingly, the levels of AMP are smaller in the saliva of *L. longipalpis* than in the saliva of *P. papatasi*. In addition, adenosine deaminase activity has been observed in the saliva of *L. longipalpis* [77] and *P. duboscqi* [78], but not in the saliva of *P. papatasi* [78]. The presence of adenosine deaminase could contribute to a decrease in adenosine concentration at the bite site thus inhibiting the modulatory effect of the saliva.

Altogether, these results indicate a strong involvement of the purinergic signaling pathway during the first moments of the inoculation of the parasite in the host dermis.

**Leishmania ectonucleotidases**

In addition to the effects promoted by the insect saliva, ectoenzymes present on the surface of the promastigote may also contribute to the establishment of the infection by Leishmania.

Leishmania and other trypanosomatids are incapable of de novo synthesis of the purine ring and thus depend on salvage pathways to synthesize purine nucleotides [79,80]. In order to obtain nucleosides from the external medium these parasites express ectonucleotidases thus enabling the external hydrolysis of nucleotides to the respective nucleosides.

Amongst the several ectonucleotidases the ecto-nucleoside triphosphate diphosphohydrolase (E-NTPDase – EC 3.6.1.5) and the ecto-5' -nucleotidase (EC 3.1.3.5) have been shown to exert important roles in the infection by Leishmania. E-NTPDase has been reported on Leishmania tropica [81] and *L. amazonensis* [82,83]. In addition to E-NTPDase, we also demonstrated that *L. amazonensis* presents ecto-5’-nucleotidase activity [84].

Several studies have associated the presence of E-NTPDase and ecto-5’-nucleotidase activities to the virulence of different *Leishmania* species [82,84–86]. Thus, parasites with increased ectonucleotidase activity are more capable of infecting macrophages [87] and induce larger lesions in mice [84,86]. Furthermore, we have demonstrated a positive correlation between the ATP, ADP and AMP hydrolytic activity in *Leishmania braziliensis* isolates and their ability to control the establishment of the immune response in mice. More importantly, a positive correlation between the nucleotide hydrolytic activity and the severity of the clinical manifestation was also observed [85]. Similarly, *L. amazonensis* isolates with different ectonucleotidase activity show distinct capacity to survive in infected macrophages and to down-modulate nitric oxide production [87]. Interestingly, the association of ectonucleotidase activity and parasite virulence seems not to be restricted to Leishmania, given that it has been reported also in *Trypanosoma cruzi* [88], *Toxoplasma gondii* [89] and *Legionella pneumophila* [90]. These studies suggest that the hydrolysis of extracellular ATP to adenosine, in addition to fuel the parasite’s salvage pathways to synthetize purine nucleotides [78,79]. In order to obtain nucleosides from the external medium these parasites express ectonucleotidases thus enabling the external hydrolysis of nucleotides to the respective nucleosides.

**Purinergic signaling and immune response**

Once inoculated in the dermis of the host *Leishmania* promastigotes are phagocytized by cells present at the site of infection. Although the macrophage is the cell in which the parasite proliferates and persist to establish the infection, it has been demonstrated that Leishmania are also phagocytized by neutrophils and dendritic cells and this interaction can modulate the immune response to the parasite.

Neutrophils rapidly infiltrate the site of infection and phagocytize the inoculated promastigotes [8,9]. It has been proposed that interaction of the parasite with these cells induces neutrophil apoptosis. The interaction of the apoptotic neutrophil loaded [12] or not [8] with the parasite would then deactivate the macrophage, favoring parasite survival within the phagolysosome. As mentioned above, *Leishmania* also induces the release of NET (neutrophil extracellular traps) by neutrophils and may also degrade the nucleic acids present in
this structure via the action of a 3’-nucleotidase [10,93]. Although no direct proof has been yet provided, it is conceivable that nucleic acid hydrolysis may release adenosine which, by acting on the adenosine receptors A2A and/or A2B, could modulate the host immune response.

Dendritic cells have also been shown to be infected by Leishmania promastigotes [94]. This infection is capable of modulating the dendritic cell ability to present antigen to T cells thus affecting the establishment of the adaptive immune response [18,95–98]. Our group has shown that, at least part of the modulatory effect of the infection on the activation of dendritic cells (expression of CD40) is dependent on the activation of the A2B adenosine receptor, mediated by the production of extracellular adenosine originated by the increased ectonucleotidase expression (CD39 and CD73) on the surface of infected cells [18]. In addition, this study also shows that inhibition of dendritic cell activation interferes with T cell proliferation which can be reverted by the blockade of the A2B adenosine receptor.

Infection of macrophages by Leishmania is dependent on the phagocytosis of the parasite. Interestingly, an increased expression of P2X7 receptors is observed in infected macrophages [99,100]. Due to the upregulation of the P2X7 receptors, addition of extracellular ATP to infected macrophage cultures reduces the percentage of infected macrophages, suggesting a possible role of these receptors in the control of the parasite. The control of parasite growth by activated P2X7 receptors seems to be mediated by the production of LTβ4 [101].

In spite of the expression of P2X7 receptor by infected macrophages and the ability of added extracellular ATP to control parasite proliferation, Leishmania survives within these cells, indicating that other purinergic signaling mechanisms may exist in the infected macrophage. In fact, we have observed that macrophages infected by L. amazonensis express high levels of CD39 and CD73 and that inhibition of the A2B adenosine receptor during infection favors the survival of the parasite (unpublished observations). Furthermore, we have demonstrated that activation of the adenosine A2B receptor inhibits the production of NO and IL-12 by infected macrophages even in the presence of activating stimuli such as IFN-γamma and LPS [87], allowing for the enhanced survival of the parasite. Corroborating these findings, a recent study also shows that inhibition of dendritic cell activation interferes with T cell proliferation which can be reverted by the blockade of the A2B adenosine receptor.

Conflict of interest

The authors declare that they have no competing interests.

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References

[1] Herwaldt BL. Leishmaniasis. Lancet 1999;354:1191–9.
[2] Kamhawi S. Phlebotomine sand flies and Leishmania parasites: friends or foes? Trends Parasitol 2006;22:439–45.
[3] Alvar J, Velez ID, Bern C, Herrero M, Desjeux P, Cano J, et al. Leishmaniasis worldwide and global estimates of its incidence. PLoS One 2012;7:e35671.
[4] Kaye P, Scott P. Leishmaniasis: complexity at the host-pathogen interface. Nat Rev Microbiol 2011;9:604–15.
[5] Cecilio P, Perez-Cabezas B, Santarem N, Maciel J, Rodrigues V, Cordeiro da Silva A. Deception and manipulation: the arms of Leishmania, a successful parasite. Front Immunol 2014;5:480.
[6] Gollob KJ, Viana AG, DutraWO. Immuno-regulation in human American leishmaniasis: balancing pathology and protection. Parasite Immunol 2014;36:367–76.
[7] Gurung P, Kanneganti TD. Innate immunity against Leishmania infections. Cell Microbiol 2015;17:1286–94.
[8] Peters NC, Egen JS, Secundino N, Debrabant A, Kimblin N, Kamhawi S, et al. In vivo imaging reveals an essential role for neutrophils in leishmaniasis transmitted by sand flies. Science 2008;321:970–4.
[9] Thalhofer CJ, Chen Y, Sudan B, Love-Homan L, Wilson ME. Leucocytes infiltrate the skin and draining lymph nodes in response to the protozoan Leishmania infantum chagasi. Infect Immun 2011;79:108–17.
[10] Guimarães-Costa AB, Nascimento MT, Froment GS, Soares RP, Morgado FN, Conceição-Silva F, et al. Leishmania amazonensis promastigotes induce and are killed by neutrophil extracellular traps. Proc Natl Acad Sci USA 2009;106:6748–53.
[11] Novais FO, Santiago RC, Bañica A, Khouri R, Afonso L, Borges VM, et al. Neutrophils and macrophages cooperate in host resistance against Leishmania braziliensis infection. J Immunol 2009;183:8088–98.
[12] Laskay T, van ZG, Solbach W. Neutrophil granulocytes as host cells and transport vehicles for intracellular pathogens: apoptosis as infection-promoting factor. Immunobiology 2008;213:183–91.
[13] Charmoy M, Brunner-Agten S, Aebischer D, Auderset F, Lauinois F, Milon G, et al. Neutrophil-derived CCL3 is essential for the rapid recruitment of dendritic cells to the site of Leishmania major inoculation in resistant mice. PLoS Pathog 2010;6:e1000755.
[14] Berberich C, Ramirez-Pineda JR, Hambrecht C, Alber G, Skeiky YA, Moll H. Dendritic cell (DC)-based protection against an intracellular pathogen is dependent upon DC-derived IL-12 and can be induced by molecularly defined antigens. J Immunol 2003;170:3171–9.
Afonso LCC, Scharton TM, Vieira LO, Wysocka M, Trinchieri G, Scott P. The adjuvant effect of Interleukin-12 in a vaccine against Leishmania major. Science 1994;263:235–7.

Heinzel FP, Schoenhaut DS, Rerko RM, Rosser LE, Gately MK. Recombinant Interleukin 12 cures mice infected with Leishmania major. J Exp Med 1993;177:1505–9.

Silveira FT, Lainson R, Corbett CE. Clinical and immunopathological spectrum of American cutaneous leishmaniasis with special reference to the disease in Amazonian Brazil: a review. Mem Inst Oswaldo Cruz 2004;99:239–51.

Figueiredo AB, Serafim TD, Marques-da-Silva EA, Meyer-Silveira FT, Lainson R, Corbett CE. Clinical and immunopathological spectrum of American cutaneous leishmaniasis with special reference to the disease in Amazonian Brazil: a review. Mem Inst Oswaldo Cruz 2004;99:239–51.

Olivier M, Gregory DJ, Forget G. Subversion mechanisms by which Leishmania parasites can escape the host immune response: a signaling point of view. Clin Microbiol Rev 2005;18:293–305.

Perrella Balestieri FM, Pires Queiroz AR, Scavone C, Assis CV, Barral-Netto M, Abrahamsson IA. Leishmania (L.) amazonensis-induced inhibition of nitric oxide synthesis in host macrophages. Microb Infect 2002;4:23–9.

Rodrigues V, Cordeiro-da-Silva A, Laforge M, Ouaissi A, Akhard K, Silvestre R, et al. Impairment of T cell function in parasitic infections. PLoS Negl Trop Dis 2014;8.

Mosser DM, Edelson PJ. The mouse macrophage receptor for C3bi (CR3) is a major mechanism in the phagocytosis of Leishmania promastigotes. J Immunol 1985;135:2785–9.

Mosser DM, Springer TA, Diamond MS. Leishmania promastigotes require opsonic complement to bind to the human leukocyte integrin Mac-1 (CD11b/CD18). J Cell Biol 1992;116:511–20.

Peters C, Aebischer T, Stierhof YD, Fuchs M, Overath P. The role of macrophage receptors in adhesion and uptake of Leishmania mexicana amastigotes. J Cell Sci 1995;108(Pt 12):3715–24.

Wozencraft AO, Sayers G, Blackwell JM. Macrophage type 3 complement receptors mediate serum-independent binding of Leishmania donovani. Detection of macrophage-derived complement on the parasite surface by immunoelectron microscopy. J Exp Med 1986;164:1332–7.

Mosser DM, Edelson PJ. The third component of complement (C3) is responsible for the intracellular survival of Leishmania major. Nature 1987;327:329–31.

Green SJ, Crawford RM, Hockmeyer JT, Metzler MS, Nacy CA. Leishmania major amastigotes initiate the L-arginine-dependent killing mechanism in IFN-g-stimulated macrophages by induction of tumor necrosis factor. J Immunol 1990;145:4290–7.

Mougneau E, Bihi F, Glancienh N. Cell biology and immunology of Leishmania. Immunol Rev 2011;240:286–96.

Scharton-Kersten T, Scott P. The role of the innate immune response in Th1 cell development following Leishmania major infection. J Leukoc Biol 1995;57:515–22.

Scott P. IFN-γ modulates the early development of Th1 and Th2 responses in a murine model of cutaneous leishmaniasis. J Immunol 1991;147:3149–55.

Belkaid Y, von Stebut E, Mendez S, Lira R, Caler E, Bertholet S, et al. CD8+ T cells are required for primary immunity in C57BL/6 mice following low-dose, intradermal challenge with Leishmania major. J Immunol 2002;168:3892–4000.

Liese J, Schleicher U, Bogdan C. The innate immune response against Leishmania parasites. Immunobiology 2008;213:377–87.
relationships and pathophysiologic significance. Purinergic Signal 2006;2:209–30.
[53] Zimmermann H. Extracellular metabolism of ATP and other nucleotides. Naunyn Schmiedeber Arch Pharmacol 2000;362:299–309.
[54] Hagberg H, Andersson P, Lacarewicz J, Jacobson I, Butcher S, Sandberg M. Extracellular adenosine, inosine, hypoxanthine, and xanthine in relation to tissue nucleotides and purines in rat striatum during transient ischemia. J Neurochem 1987;49:227–31.
[55] Schulte G, Fredholm BB. Signalling from adenosine receptors to mitogen-activated protein kinases. Cell Signal 2003;15:813–27.
[56] Zetterstrom T, Vernet L, Ungerstedt U, Tossman U, Zetterstrom R, Ylikoski R. Adenosine, AMP, hypoxanthine, and xanthine in relation to tissue nucleotides and purines in rat striatum during transient ischemia. J Neurochem 1987;49:227–31.
[57] Fredholm BB, Ijzerman AP, Jacobson KA, Klotz KN, Linden J. Purinergic regulation of the immune system. Natute Rev Immunol 2016;16:177–92.
[58] Cekic C, Linden J. Purinergic regulation of the immune system. Natute Rev Immunol 2016;16:177–92.
[59] Cekic C, Linden J. Purinergic regulation of the immune system. Natute Rev Immunol 2016;16:177–92.
[60] Hasko G, Kuhel DG, Chen JF, Schwarzschild MA, Deitch EA, Haerter PJ, Mrowietz U, et al. Expression and function of the A2B adenosine receptor impairs the maturation and immunogenicity of dendritic cells. J Immunol 1996;64:5442–7.
[61] Sandberg M. Extracellular adenosine, inosine, hypoxanthine, and xanthine in relation to tissue nucleotides and purines in rat striatum during transient ischemia. J Neurochem 1987;49:227–31.
[62] Cekic C, Linden J. Purinergic regulation of the immune system. Natute Rev Immunol 2016;16:177–92.
[63] Kato H, Jochim RC, Lawyer PG, Valenzuela JG. Identification and characterization of a salivary adenosine deaminase from the sand fly Lutzomyia longipalpis. Proc Natl Acad Sci USA 1999;96:15155–60.
[64] Lima HC, Titus RG. Effects of sand fly vector saliva on development of cutaneous lesions and the immune response to Leishmania braziliensis in BALB/c mice. Infect Immun 1996;64:5442–5.
[65] Morrisey RV, Shoemaker CB, David JR, Lanzaro GC, Titus SG. Sandfly maxadilan exacerbates infection with Leishmania major and vaccinating against it protects against L. major infection. J Immunol 2001;167:5226–30.
[66] Norowsky NB, Sun J, Elnaem D, Lanzaro G, Soong L. Sand fly saliva enhances Leishmania amazonensis infection by modulating interleukin-10 production. Infect Immun 2004;72:1240–7.
[67] Carregaro V, Ribeiro JM, Valenzuela JG, Souza-Junior DL, Costa DL, Oliveira CJ, et al. Nucleosides present on phlebotomine saliva induce immunosuppression and promote the infection establishment. PLoS Negl Trop Dis 2015;9:e0003600.
[68] Charlub R, Rowton ED, Ribeiro JM. The salivary adenosine deaminase from the sand fly Lutzomyia longipalpis. Exp Parasitol 2000;95:45–53.
[69] Kato H, Jochim RC, Lawyer PG, Valenzuela JG. Identification and characterization of a salivary adenosine deaminase from the sand fly Lutzomyia longipalpis. Exp Parasitol 2000;95:45–53.
[70] Panter E, Idzeko M, Heroy Y, Rheinen H, Gebicke-Haerter PJ, Mrowietz U, et al. Expression and function of adenosine receptors in human dendritic cells. FASEB J 2001;15:1963–70.
[71] Panter E, Idzeko M, Heroy Y, Rheinen H, Gebicke-Haerter PJ, Mrowietz U, et al. Expression and function of adenosine receptors in human dendritic cells. FASEB J 2001;15:1963–70.
[72] Wilson JM, Ross WG, Agbai ON, Frazier R, Figler RA, Rieger J, et al. The A2B adenosine receptor impairs the maturation and immunogenicity of dendritic cells. J Immunol 2009;182:4616–23.
[73] Katz O, Walitumbi JN, Zer R, Warburg A. Adenosine, AMP, and protein phosphatase activity in sandfly saliva. Am J Trop Med Hyg 2000;62:145–50.
[74] Ribeiro JM, Katz O, Pannell LK, Walitumbi J, Warburg A. Salivary glands of the sand fly Phlebotomus papatasi contain pharmacologically active amounts of adenosine and 5′-AMP. J Exp Biol 1999;202:1515–9.
[75] Ribeiro JM, Modi G. The salivary adenosine/AMP content of Phlebotomus argentipes Anandale and Brunetti, the main vector of human kala-azar. J Parasitol 2001;87:915–7.
[76] Valenzuela JC, Garfeld M, Rowton ED, Pham VM. Identification of the most abundant secreted proteins from the salivary glands of the sand fly Lutzomyia longipalpis, vector of Leishmania chagasi. J Exp Biol 2004;207:3717–29.
[77] Anderson JM, Oliveira F, Kamhawi S, Mans Bj, Reynoso D, Seitz AE, et al. Comparative salivary gland transcriptomics of sandfly vectors of visceral leishmaniasis. BMC Genomics 2006;7:52.
[78] Hamaaki K, Kato H, Terayama Y, Iwata H, Valenzuela JC. Functional characterization of a salivary apyrase from the sand fly, Phlebotomus duboscqi, a vector of Leishmania major. J Insect Physiol 2009;55:1044–9.
[79] Vial C, Rolf MG, Mahaut-Smith MP, Evans RJ. A study of P2X1 receptor function in murine megakaryocytes and human platelets reveals synergy with P2Y receptors. Br J Pharmacol 2002;135:363–72.
on *Leishmania amazonensis* infection and immune response in C57B/6 mice. Acta Trop 2010;115:262–9.

[87] Gomes RS, de Carvalho LC, de Souza Vasconcellos R, Fietto JL, Afonso LC. E-NTPDase (ecto-nucleoside triphosphate diphosphohydrolase) of *Leishmania amazonensis* inhibits macrophage activation. Microbes Infect 2015;17:295–303.

[88] Santos RF, Possa MA, Bastos MS, Guedes PM, Almeida MR, DeMarco R, et al. Influence of ecto-nucleoside triphosphate diphosphohydrolase activity on trypanosoma cruzi infectivity and virulence. PLoS Negl Trop Dis 2009;3:e387.

[89] Asai T, Miura S, Sibley LD, Okabayashi H, Takeuchi T. Biochemical and molecular characterization of nucleoside triphosphate hydrolase isozymes from the parasitic protozoan *Toxoplasma gondii*. J Biol Chem 1995;270:11391–7.

[90] Sansom FM, Newton HJ, Crikis S, Cianciotto NP, Cowan PJ, d’Apice AJ, et al. A bacterial ecto-triphosphate diphosphohydrolase similar to human CD39 is essential for intracellular multiplication of *Legionella pneumophila*. Cell Microbiol 2007;9:1922–35.

[91] Paletta-Silva R, Meyer-Fernandes JR. Adenosine and immune imbalance in visceral leishmaniasis: the possible role of ectonucleotidases. J Trop Med 2012;2012:590874.

[92] Vasconcellos Rde S, Mariotti-Moura C, Gomes RS, Serafim TD, Firmino Rde C, Silva EBM, et al. *Leishmania infantum* ecto-nucleoside triphosphate diphosphohydrolase-2 is an apyrase involved in macrophage infection and expressed in infected dogs. PLoS Negl Trop Dis 2014;8:e3309.

[93] Guimaraes-Costa AB, Desouza-Vieira TS, Paletta-Silva R, Freitas-Mesquita AL, Meyer-Fernandes JR, Saraiva EM. 3’-Nucleotidase/nuclease activity allows *Leishmania* parasites to escape killing by neutrophil extracellular traps. Infect Immun 2014;82:1732–40.

[94] Brandonisio O, Spinelli R, Pepe M. Dendritic cells in *Leishmania* infection. Microb Infect 2004;6:1402–9.

[95] Prina E, Abdi SZ, Lebastard M, Perret E, Winter N, Antoine JC. Dendritic cells as host cells for the promastigote and amastigote stages of *Leishmania amazonensis*: the role of opsonins in parasite uptake and dendritic cell maturation. J Cell Sci 2004;117:315–25.

[96] Qi H, Popov V, Soong L. *Leishmania amazonensis*-dendritic cell interactions in vitro and the priming of parasite-specific CD4⁺ T cells in vivo. J Immunol 2001;167:4534–42.

[97] Vasquez RE, Xin L, Soong L. Effects of CXCL10 on dendritic cell and CD4⁺ T-cell functions during *Leishmania amazonensis* infection. Infect Immun 2008;76:161–9.

[98] Xin L, Li K, Soong L. Down-regulation of dendritic cell signaling pathways by *Leishmania amazonensis* amastigotes. Mol Immunol 2008;45:3371–82.

[99] Chaves SP, Torres-Santos EC, Marques C, Figliuolo VR, Persechini PM, Coutinho-Silva R, et al. Modulation of P2X(7) purinergic receptor in macrophages by *Leishmania amazonensis* and its role in parasite elimination. Microb Infect 2009;11:842–9.

[100] Coutinho-Silva R, Correa G, Sater AA, Ojcius DM. The P2X-receptor and intracellular pathogens: a continuing struggle. Purinergic Signal 2009;5:197–204.

[101] Chaves MM, Marques-da-Silva C, Monteiro AP, Canetti C, Coutinho-Silva R. Leukotriene B4 modulates P2X7 receptor-mediated *Leishmania amazonensis* elimination in murine macrophages. J Immunol 2014;192:4765–73.

[102] Vijayamahantesh, Amit A, Kumar S, Dikhit MR, Jha PK, Singh AK, et al. Up regulation of A2B adenosine receptor on monocytes are crucially required for immune pathogenicity in Indian patients exposed to *Leishmania donovani*. Cytokine 2016;79:38–44.