Journal of Research in Applied and Basic Medical Sciences 2022; 8(3): 161-168

Review Article

RABMS Journal of Research in Applied and Basic Medical Sciences

The Role of Surface Molecules in Host Responses of Leishmaniasis: Focus on Lipid Mediators

Ali Fattahi Bafghi*[1], Fatemeh Zare[2], Mostafa Gholamrezaei[3], Mahin Ghafourzadeh[4]

[1] *Professor, Parasitology and Mycology Department, Infectious Diseases Centers, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran*

[2] *Assistant Professor, Reproductive Immunology Research, Sadoughi University of Medical Sciences, Yazd, Iran*

[3] *Assistant Professor, Parasitology and Mycology Department, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran*

[4] *PhD student in Veterinary Parasitology Bahonar University of Kerman, Iran*

***Corresponding author:** Ali Fattahi Bafghi, **Address**: Parasitology and Mycology Department, school of medicine, Shahid Sadoughi University of medical sciences, P.O. Box No. 8915173134, Yazd, Iran, **Email**: a.fattahi@ssu.ac.ir
Tel: +9838203414

Abstract

Leishmaniasis is a neglected disease that affects more than 12 million people worldwide. After parasite inoculum by female blood-sucking insects, e.g. Phlebotomus, neutrophils quickly infiltrate and phagocytes Leishmania parasites. Macrophages are the second immune cells. They possess several pattern recognition receptors that respond to different surface molecules such as Lipophosphoglycan, glycoprotein 63 (GP63), PPG, GIPL, CP, and SAP. It was found that Leishmania GP63 cleaves several targets of infected macrophages, including the myristoylated alanine-rich C kinase substrate, p130CAS, PEST, NF-B, and AP-1. After activation of surface molecules, lipid metabolites of arachidonic acid, including leukotrienes and prostaglandins, are important mediators in Leishmaniasis. These lipid metabolites can be metabolized by different enzymes, including the cyclooxygenase and lipoxygenase.

***Keywords*:** Leishmaniasis; Glycoprotein 63; Surface Molecules

Received 01 June 2022; accepted for publication 16 September 2022

Introduction

Leishmaniasis is a neglected disease of tropical and subtropical areas that affects more than 12 million people worldwide (1). *Leishmaniasis* is transmitted by female blood-sucking insects of the genus *Phlebotomus* in the 'Old' World and by species of *Lutzomia* in the 'New' World. The parasite has two forms including Promastigote and Amastigote. Promastigotes have high mobility and is found in vector. Amastigote has no flagella and develops into phagocytic cells. It is fact that innate immune cells, including dermal dendritic Cells (DCs), Langerhans Cells (LCs) (2, 3), mast cells, T cells, and macrophages in the skin are the first line against *Leishmania* (4). After parasite inoculum, neutrophils quickly infiltrate and phagocytes *Leishmania* parasites (5-7). Macrophages are the second immune cells and are

the principal host cells for the *Leishmania* (8). Thus, neutrophils and macrophages play important roles in disease progression.

Surface molecules:

Surface molecules possess several Pattern Recognition Receptors (PRR) that respond to Pathogen-Associated Molecular Patterns (PAMPs) present in the *Leishmania* surface. Some of these molecules are Lipophosphoglycan (LPG), glycoprotein 63 (GP63), PPG, GIPL, CP, and SAP(9, 10) (Figure 1).

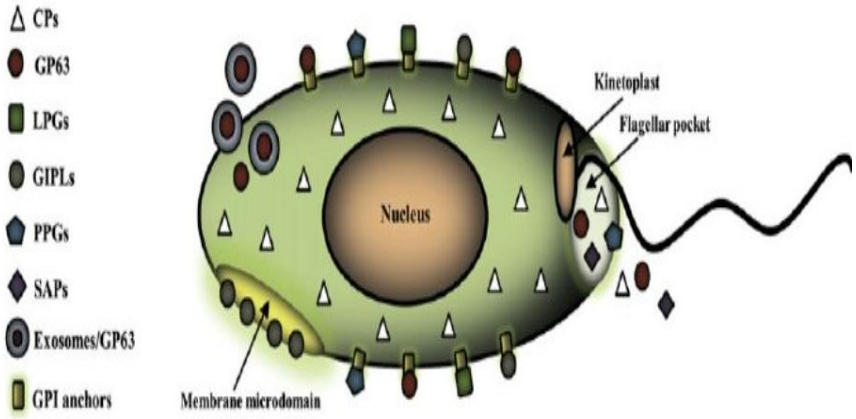

Fig 1. Leishmania virulence factors. This schematic shows surface molecules, including GP63, LPG, PPG, GIPL, CP, and SAP.

Several host immune receptors can bind *Leishmania* components, including Complement Receptor (11, 12), Mannose Receptor (MR) (13), Fc Gamma Receptors (FcγRs) (14), Fibronectin Receptors (FNRS) (9), and Toll-Like Receptors (TLR) (15). It was found that Leishmania GP63 cleaves several targets of infected macrophages, including the myristoylated alanine-rich C kinase substrate (MARKS), p130CAS, PEST, NF-B, and AP-1 (Figure 2).

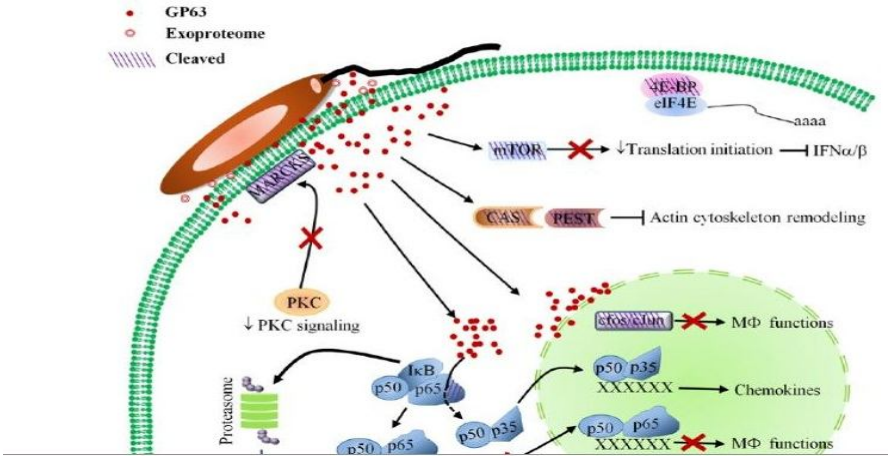

Fig 2. GP63-mediated degradation. Leishmania GP63 cleaves several targets of infected macrophages, including the myristoylated alanine-rich C kinase substrate (MARKS), p130CAS, PEST, NF-B, and AP-1.

Moreover, Leishmania GP63 cleaves and activates host PTPs (SHP-1, PTP1B, and TCPTP)

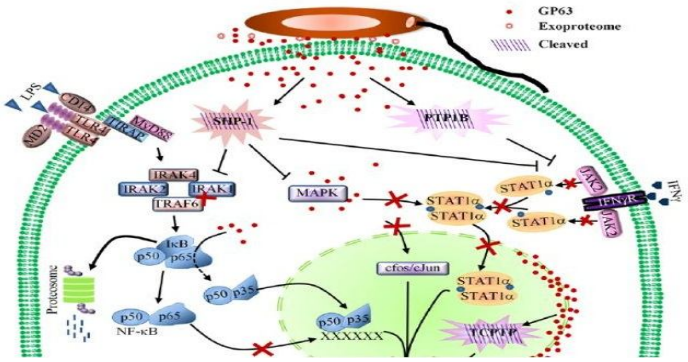

Fig 3. GP63- mediated PTP activation. Leishmania GP63 cleaves and activates host PTPs (SHP-1, PTP1B, and TCPTP).

Lipid mediators:

Lipid metabolites of Arachidonic Acid (AA), including Leukotrienes (LTs) and Prostaglandins (PGs), are important mediators in different physiological and pathophysiological functions, based on 5-Lipoxygenase-Activating Protein (FLAP) pathway (**Figure 4**).

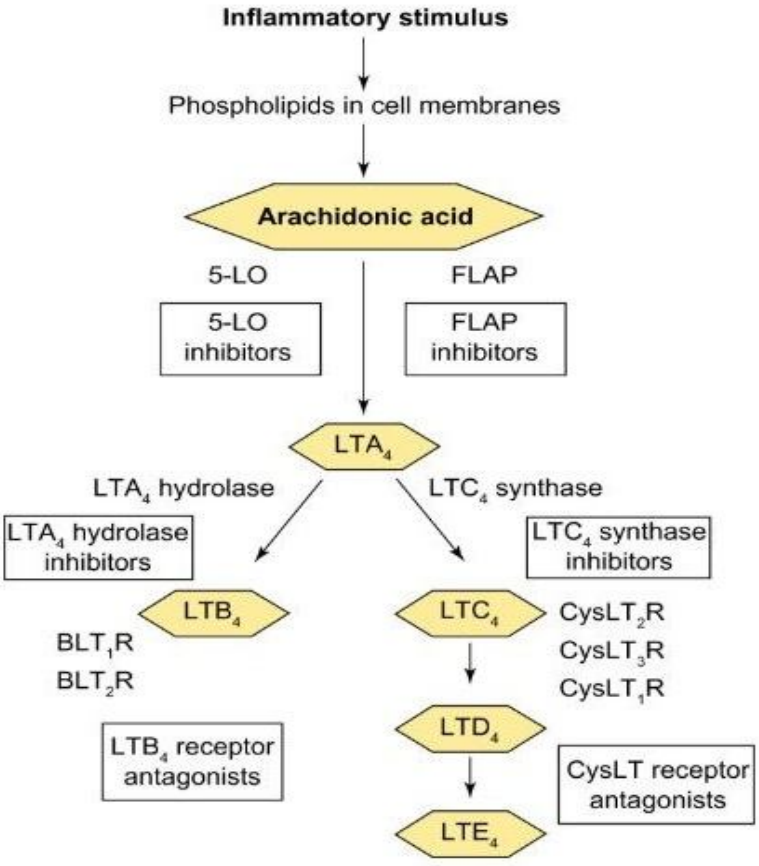

Fig 4. 5-Lipoxygenase Activating Protein (FLAP) pathway.

They are released by cytosolic phospholipase A_2. These lipid metabolites can be metabolized by different enzymes, including cyclooxygenase (COX) and 5-lipoxygenase (5-LO). The activation of $cPLA_2$ and 5-LO involves an increase of intracellular Ca^{2+} and subsequently activation of certain protein kinases (16). The AA is presented to 5-LO by an essential accessory protein called 5-lipoxygenase (5-LO) activating protein (FLAP). LTA_4 can be conjugated with reduced glutathione by LTC_4 synthase (LTC_4S) to form LTC_4, or be hydrolyzed by LTA_4 hydrolase (LTA_4H) to form LTB_4 (17). LTC_4 is rapidly converted to LTD_4 by the glutamyl leukotrienase removing glutamic acid molecule of LTC_4, and LTD_4 can be further converted to LTE_4 by a dipeptidase which removes a glycine residue of LTD_4 molecule (18). PGs are formed when AA is metabolized by sequential actions of cyclooxygenase (19). COX has both cyclooxygenase (COX) and peroxidase activity. There are three COX isoforms, COX-1, COX-2, and COX-3 (20). COX-1 and COX-3 are constitutively expressed while COX-2 is induced by inflammatory stimuli (21, 22). Moreover, four bioactive PGs are found, PGE_2, PGI_2, PGD_2, and PGF_2 (19). Importantly, they possess potential anti-inflammatory effects (23).

These effects can be used by parasites to evade the immune system. The most effective mechanism against *Leishmania* is the production of reactive oxygen species (ROS) and nitric oxide (NO) (24). An effective response against infection by *Leishmania* is given by the induction of T_h1 and T_h17 responses (25, 26), while T_h2 response promotes susceptibility (26). Elimination of *Leishmania amazonensis* by P2X7 receptor depends on the production of LTB_4 and leukotrienes B_4 receptor 1 (BLT1) (27). Other studies have shown the production of LTB_4 in resistance to *Leishmania amazonensis* and *Leishmania braziliensis* (28, 29). This resistance is due to the production of ROS and NO; it may be produced after P2X7 receptor activation (30, 31) (Figure 5).

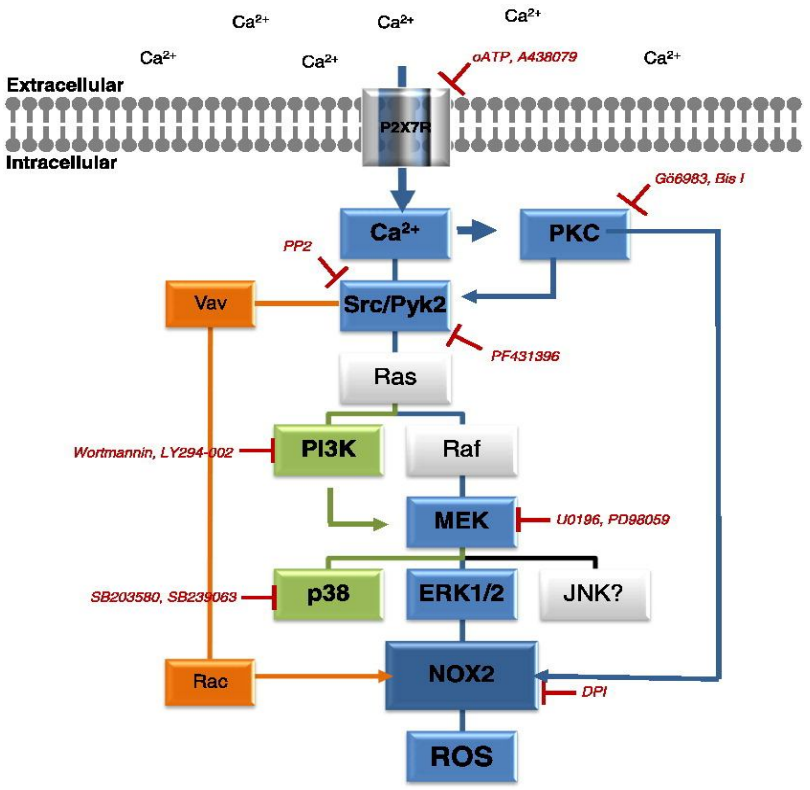

Fig 5. Oxidative stress induced by P2X7 receptor stimulation in murine macrophages is mediated by c- Src/Pyk2 and ERK1/2.

The P2X7 receptor activation and LTB_4 release have been implicated in the polarization of T_h1 and T_h17 responses (32-34). It is known that PGE_2 possesses anti-inflammatory activity, facilitating *Leishmania* infection in macrophages and suppressing inflammatory response in both cutaneous and visceral *Leishmaniasis* (35, 36). Several *Leishmania* species possess lipid corpuscles as organelles and are able to produce PGs such as $PGF_{2\alpha}$ (37). PGE_2 inhibits NO production (38) and T_h1 and T_h17 development (39, 40) but stimulates T_h2 response, favoring infection (40). *Leishmania* has developed methods to subvert microbial mechanisms and immune responses against itself. For example, *Leishmania amazonensis* infection increases ecto-nucleotidase expression in DC (41). It is found that the blocking of the A_{2B} receptors increases production of NO and decreases parasite survival, suggesting participation of Adenosine (Ado) in this process (42). Ado increases COX-2 expression and PGE_2 production in neutrophils (43, 44). This corroborates the fact that both Ado and PGE_2 stimulate the release of anti-inflammatory cytokines such as interleukin (IL)-10 in macrophages (45), while inhibiting the release of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and IL-12 in DCs and macrophages (46). Ado decreases production and release of LTB_4 (47, 48), which modulates Microbicidal mechanisms. *Leishmania amazonensis* is capable to negatively modulate the production of LTB_4 via P2X7 receptor activation (27). However, in other species of *Leishmania*, such as *Leishmania braziliensis*, the neutrophils are important for parasite elimination (49). *Lutzomyia longipalpis* saliva also contains high levels of Ado, modulating the inflammatory micro-environment, causing NO inhibition, and macrophage inactivation, which in turn increases the parasitic load in macrophages and neutrophils (50). It was shown that exosomes are co-inoculated with *Leishmania* into mammalian hosts (51). It is tempting to correlate it with a burst of ATP secretion, local Ado generation and PGE_2 production. *Lutzomyia longipalpis* saliva triggers the production and release of PGE_2 and decreases LTB_4 (52) (Figure 6).

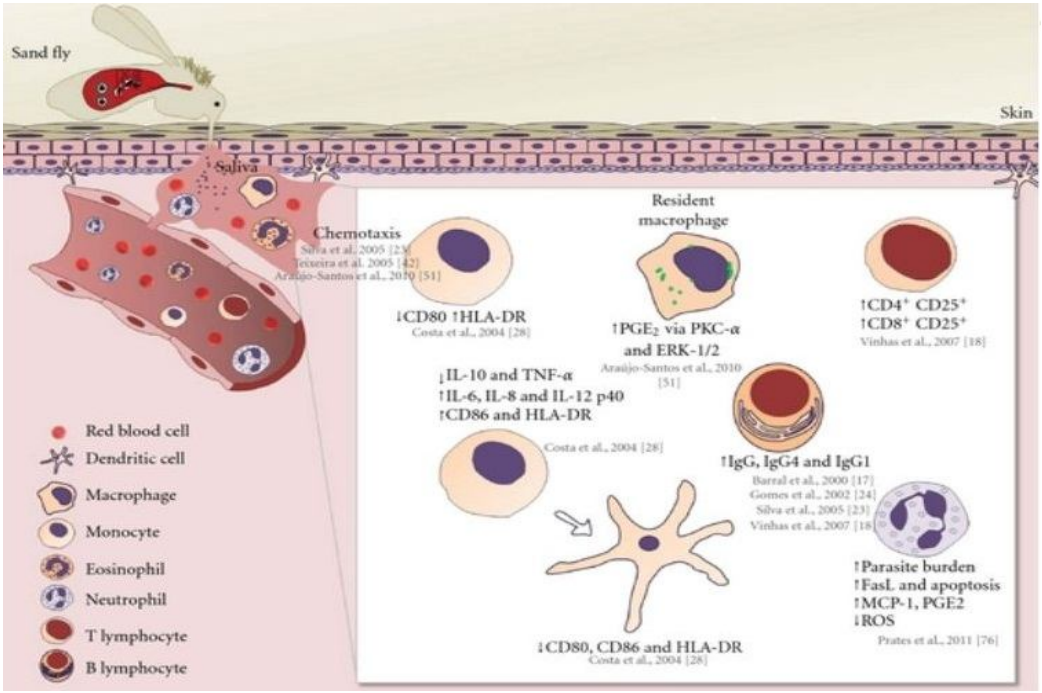

Fig 6. Roles of *Lutzomyia longipalpis* saliva in the host immune response cell. After injection, a set of events can be triggered in the host immune response.

Conclusion

They possess several pattern recognition receptors that respond to different surface molecules, such as Lipophosphoglycan, glycoprotein 63 (GP63), PPG, GIPL, CP, and SAP. It was found that Leishmania GP63 cleaves several targets of infected macrophages, including the myristoylated alanine-rich C kinase substrate, p130CAS, PEST, NF-B, and AP-1**.** After activation of surface molecules, lipid metabolites of arachidonic acid, including leukotrienes and prostaglandins, are important mediators in *Leishmaniasis*. These lipid metabolites can be metabolized by different enzymes, including the cyclooxygenase and lipoxygenase.

Acknowledgments There is no acknowledgment to declare

Conflict of interest

The authors have no conflict of interest in this study.

References

1. Desjeux P. Leishmaniasis: current situation and new perspectives. Comp Immunol Microbiol Infect Dis 2004;27(5):305-18.
2. Merad M, Ginhoux F, Collin M. Origin, homeostasis and function of Langerhans cells and other langerin-expressing dendritic cells. Nat Rev Immunol 2008;8(12):935-47.
3. Nestle FO, Di Meglio P, Qin J-Z, Nickoloff BJ. Skin immune sentinels in health and disease. Nat Rev Immunol 2009;9(10):679-91.
4. Solbach W, Laskay T. The host response to Leishmania infection. Adv Immunol 1999;74:275-317.
5. Beil W, Meinardus-Hager G, Neugebauer D, Sorg C. Differences in the onset of the inflammatory response to cutaneous leishmaniasis in resistant and susceptible mice. J Leukoc Biol 1992;52(2):135-42.
6. Peters NC, Egen JG, 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(5891):970-4.
7. Ribeiro-Gomes F, Sacks D. The influence of early neutrophil-Leishmania interactions on the host immune response to infection. Front Cell Infect Microbiol 2012;2:59.
8. Ribeiro-Gomes FL, Otero AC, Gomes NA, Moniz-de-Souza MCA, Cysne-Finkelstein L, Arnholdt AC, et al. Macrophage interactions with neutrophils regulate Leishmania major infection. J Immunol 2004;172(7):4454-62.
9. Brittingham A, Chen G, McGwire BS, Chang K-P, Mosser DM. Interaction of Leishmania gp63 with cellular receptors for fibronectin. Infect Immun 1999;67(9):4477-84.
10. Vargas-Inchaustegui DA, Tai W, Xin L, Hogg AE, Corry DB, Soong L. Distinct roles for MyD88 and Toll-like receptor 2 during Leishmania braziliensis infection in mice. Infect Immun 2009;77(7):2948-56.
11. Peters C, Aebischer T, Stierhof Y-D, Fuchs M, Overath P. The role of macrophage receptors in adhesion and uptake of Leishmania mexicana amastigotes. J Cell Sci 1995;108(12):3715-24.
12. Kedzierski L, Montgomery J, Bullen D, Curtis J, Gardiner E, Jimenez-Ruiz A, et al. A leucine-rich repeat motif of Leishmania parasite surface antigen 2 binds to macrophages through the complement receptor 3. J Immunol 2004;172(8):4902-6.
13. Blackwell JM, Ezekowitz R, Roberts MB, Channon JY, Sim RB, Gordon S. Macrophage complement and lectin-like receptors bind Leishmania in the absence of serum. J Exp Med 1985;162(1):324-31.
14. Kima PE, Constant SL, Hannum L, Colmenares M, Lee KS, Haberman AM, et al. Internalization of Leishmania mexicana complex amastigotes via the Fc receptor is required to sustain infection in murine cutaneous leishmaniasis. J Exp Med 2000;191(6):1063-8.
15. Kropf P, Freudenberg N, Kalis C, Modolell M, Herath S, Galanos C, et al. Infection of C57BL/10ScCr and C57BL/10ScNCr mice with Leishmania major reveals a role for Toll-like receptor 4 in the control of parasite replication. J Leukoc Biol 2004;76(1):48-57.
16. Peters-Golden M, Brock T. 5-lipoxygenase and FLAP. Prostaglandins Leukot Essent Fatty Acids 2003;69(2):99-109.

17. Ago H, Kanaoka Y, Irikura D, Lam BK, Shimamura T, Austen KF, et al. Crystal structure of a human membrane protein involved in cysteinyl leukotriene biosynthesis. Nature 2007;448(7153):609-12.
18. Murphy RC, Gijón MA. Biosynthesis and metabolism of leukotrienes. Biochem J 2007;405(3):379-95.
19. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. Arterioscler Thromb Vasc Biol 2011;31(5):986-1000.
20. Smith T, McCracken J, Shin Y-K, DeWitt D. Arachidonic acid and nonsteroidal anti-inflammatory drugs induce conformational changes in the human prostaglandin endoperoxide H2 synthase-2 (cyclooxygenase-2). J Biol Chem 2000;275(51):40407-15.
21. Dubois RN, Abramson SB, Crofford L, Gupta RA, Simon LS, Van De Putte LB, et al. Cyclooxygenase in biology and disease. FASEB J 1998;12(12):1063-73.
22. Chandrasekharan N, Dai H, Roos KLT, Evanson NK, Tomsik J, Elton TS, et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. Proc Natl Acad Sci 2002;99(21):13926-31.
23. Scher JU, Pillinger MH. The anti-inflammatory effects of prostaglandins. J Invest Med 2009;57(6):703-8.
24. Mukbel RM, PATTEN C, Gibson K, Ghosh M, Petersen C, Jones DE. Macrophage killing of Leishmania amazonensis amastigotes requires both nitric oxide and superoxide. Am J Trop Med Hyg 2007;76(4):669-75.
25. Miralles GD, Stoeckle M, McDermott D, Finkelman F, Murray H. Th1 and Th2 cell-associated cytokines in experimental visceral leishmaniasis. Infec Immun 1994;62(3):1058-63.
26. Dey R, Majumder N, Majumdar SB, Bhattacharjee S, Banerjee S, Roy S, et al. Induction of Host Protective Th1 Immune Response by Chemokines in Leishmania donovani-infected BALB/c Mice. Scand J Immunol 2007;66(6):671-83.
27. Chaves MM, Marques-da-Silva C, Monteiro APT, Canetti C, Coutinho-Silva R. Leukotriene B4 Modulates P2X7 Receptor–Mediated Leishmania amazonensis Elimination in Murine Macrophages. J Immunol 2014;192(10):4765-73.
28. Serezani CH, Perrela JH, Russo M, Peters-Golden M, Jancar S. Leukotrienes are essential for the control of Leishmania amazonensis infection and contribute to strain variation in susceptibility. J Immunol 2006;177(5):3201-8.
29. Morato CI, da Silva IA, Borges AF, Dorta ML, Oliveira MA, Jancar S, et al. Essential role of leukotriene B 4 on Leishmania (Viannia) braziliensis killing by human macrophages. Microbes Infect 2014;16(11):945-53.
30. Hu Y, Fisette PL, Denlinger LC, Guadarrama AG, Sommer JA, Proctor RA, et al. Purinergic receptor modulation of lipopolysaccharide signaling and inducible nitric-oxide synthase expression in RAW 264.7 macrophages. J Biol Chem 1998;273(42):27170-5.
31. Martel-Gallegos G, Casas-Pruneda G, Ortega-Ortega F, Sánchez-Armass S, Olivares-Reyes JA, Diebold B, et al. Oxidative stress induced by P2X7 receptor stimulation in murine macrophages is mediated by c-Src/Pyk2 and ERK1/2. Biochim Biophys Acta Gen Subj 2013;1830(10):4650-9.
32. Lee W, Kim HS, Lee GR. Leukotrienes induce the migration of Th17 cells. Immun Cell Biol 2015;93(5):472-9.
33. Sacramento LA, Cunha FQ, de Almeida RP, da Silva JS, Carregaro V. Protective role of 5-lipoxigenase during Leishmania infantum infection is associated with Th17 subset. BioMed Res Int 2014;2014.
34. Toda A, Terawaki K, Yamazaki S, Saeki K, Shimizu T, Yokomizo T. Attenuated Th1 induction by dendritic cells from mice deficient in the leukotriene B4 receptor 1. Biochimie 2010;92(6):682-91.
35. Lonardoni M, Barbieri C, Russo M, Jancar S. Modulation of Leishmania (L.) amazonensis growth in cultured mouse macrophages by prostaglandins and platelet activating factor. Mediators Inflamm 1994;3(2):137-41.
36. Barreto-de-Souza V, Pacheco GJ, Silva AR, Castro-Faria-Neto HC, Bozza PT, Saraiva EM, et al. Increased Leishmania replication in HIV-1–infected macrophages is mediated by tat protein through cyclooxygenase-2 expression and prostaglandin E2 synthesis. J Infect Dis 2006;194(6):846-54.
37. Kabututu Z, Martin SK, Nozaki T, Kawazu S-i, Okada T, Munday CJ, et al. Prostaglandin production from

arachidonic acid and evidence for a 9, 11-endoperoxide prostaglandin H 2 reductase in Leishmania. Int J Parasitol 2003;33(2):221-8.

38. Griffon B, Cillard J, Chevanne M, Morel I, Cillard P, Sergent O. Macrophage-induced inhibition of nitric oxide production in primary rat hepatocyte cultures via prostaglandin E2 release. Hepatology 1998;28(5):1300-8.
39. Betz M, Fox B. Prostaglandin E2 inhibits production of Th1 lymphokines but not of Th2 lymphokines. J Immunol 1991;146(1):108-13.
40. Snijdewint F, Kaliński P, Wierenga E, Bos J, Kapsenberg M. Prostaglandin E2 differentially modulates cytokine secretion profiles of human T helper lymphocytes. J Immunol 1993;150(12):5321-9.
41. Figueiredo AB, Serafim TD, Marques-da-Silva EA, Meyer-Fernandes JR, Afonso LC. Leishmania amazonensis impairs DC function by inhibiting CD40 expression via A2B adenosine receptor activation. Eur J Immunol 2012;42(5):1203-15.
42. Gomes RS, de Carvalho LCF, de Souza Vasconcellos R, Fietto JLR, Afonso LCC. E-NTPDase (ecto-nucleoside triphosphate diphosphohydrolase) of Leishmania amazonensis inhibits macrophage activation. Microbes Infect 2015;17(4):295-303.
43. Cadieux J-S, Leclerc P, St-Onge M, Dussault A-A, Laflamme C, Picard S, et al. Potentiation of neutrophil cyclooxygenase-2 by adenosine: an early anti-inflammatory signal. Journal Cell Sci 2005;118(7):1437-47.
44. Pouliot M, Fiset M-É, Massé M, Naccache PH, Borgeat P. Adenosine up-regulates cyclooxygenase-2 in human granulocytes: impact on the balance of eicosanoid generation. J Immunol 2002;169(9):5279-86.
45. MacKenzie KF, Clark K, Naqvi S, McGuire VA, Nöehren G, Kristariyanto Y, et al. PGE2 induces macrophage IL-10 production and a regulatory-like phenotype via a protein kinase A–SIK–CRTC3 pathway. J Immunol 2013;190(2):565-77.
46. Haskó G, Kuhel DG, Chen J-F, Schwarzschild MA, Deitch EA, Mabley JG, et al. Adenosine inhibits IL-12 and TNF-α production via adenosine A2a receptor-dependent and independent mechanisms. FASEB J 2000;14(13):2065-74.
47. Flamand N, Boudreault S, Picard S, Austin M, Surette ME, Plante H, et al. Adenosine, a potent natural suppressor of arachidonic acid release and leukotriene biosynthesis in human neutrophils. Am J Respir Crit Care Med 2000;161:S88-S94.
48. Krump E, Picard S, Mancini J, Borgeat P. Suppression of leukotriene B4 biosynthesis by endogenous adenosine in ligand-activated human neutrophils. J Exp Med 1997;186(8):1401-6.
49. Novais FO, Santiago RC, Báfica A, Khouri R, Afonso L, Borges VM, et al. Neutrophils and macrophages cooperate in host resistance against Leishmania braziliensis infection. J Immunol 2009;183(12):8088-98.
50. De Moura TR, Oliveira F, Rodrigues GC, Carneiro MW, Fukutani KF, Novais FO, et al. Immunity to Lutzomyia intermedia saliva modulates the inflammatory environment induced by Leishmania braziliensis. PLoS Negl Trop Dis 2010;4(6):e712.
51. Atayde VD, Aslan H, Townsend S, Hassani K, Kamhawi S, Olivier M. Exosome secretion by the parasitic protozoan Leishmania within the sand fly midgut. Cell Rep 2015;13(5):957-67.
52. Araújo-Santos T, Prates DB, Andrade BB, Nascimento DO, Clarêncio J, Entringer PF, et al. Lutzomyia longipalpis saliva triggers lipid body formation and prostaglandin E 2 production in murine macrophages. PLoS Negl Trop Dis 2010;4(11):e873.