



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

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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

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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).

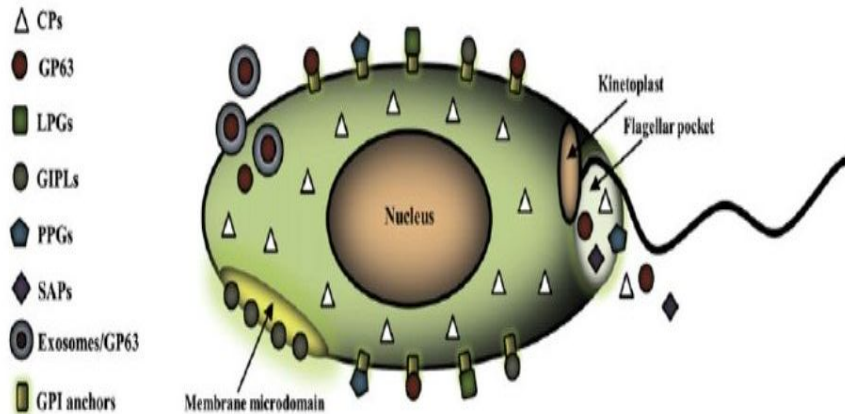


Fig 1. *Leishmania* virulence factors. This schematic shows surface molecules, including GP63, LPG, PPG, GIPL, CP, and SAP.

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).

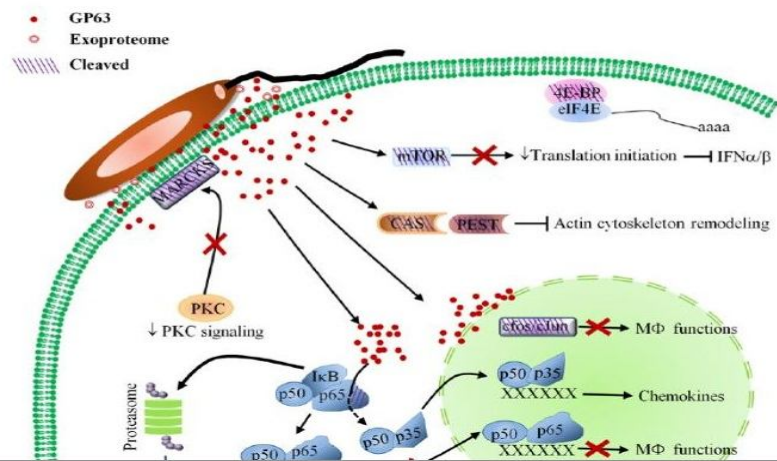


Fig 2. GP63-mediated degradation. *Leishmania* GP63 cleaves several targets of infected macrophages, including the myristoylated alanine-rich C kinase substrate (MARKS), p130CAS, PEST, NF-B, and AP-1.

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

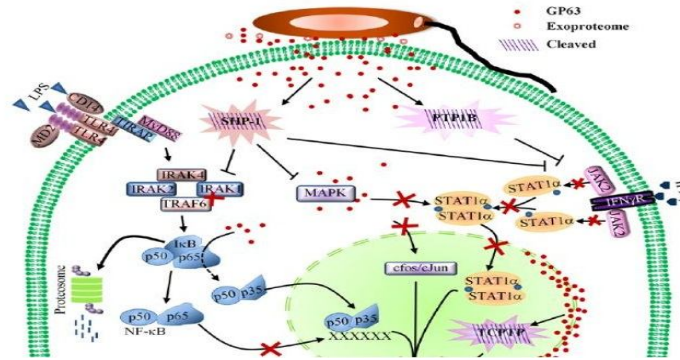


Fig 3. GP63- mediated PTP activation. Leishmania GP63 cleaves and activates host PTPs (SHP-1, PTP1B, and TCPTP).

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).

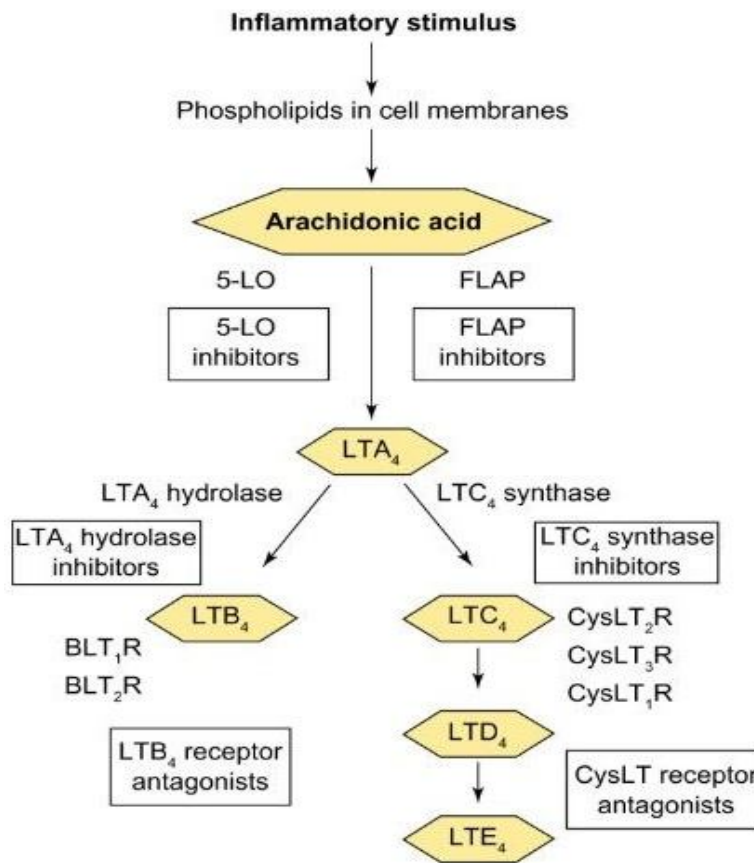


Fig 4. 5-Lipoxygenase Activating Protein (FLAP) pathway.

They are released by cytosolic phospholipase A₂. These lipid metabolites can be metabolized by different enzymes, including cyclooxygenase (COX) and 5-lipoxygenase (5-LO). The activation of cPLA₂ and 5-LO involves an increase of intracellular Ca²⁺ 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). LTA₄ can be conjugated with reduced glutathione by LTC₄ synthase (LTC₄S) to form LTC₄, or be hydrolyzed by LTA₄ hydrolase (LTA₄H) to form LTB₄ (17). LTC₄ is rapidly converted to LTD₄ by the glutamyl leukotriene removing glutamic acid molecule of LTC₄, and LTD₄ can be further converted to LTE₄ by a dipeptidase which removes a glycine residue of LTD₄ 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, PGE₂, PGI₂, PGD₂, and PGF₂ (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 LTB₄ and leukotrienes B₄ receptor 1 (BLT1) (27). Other studies have shown the production of LTB₄ 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).

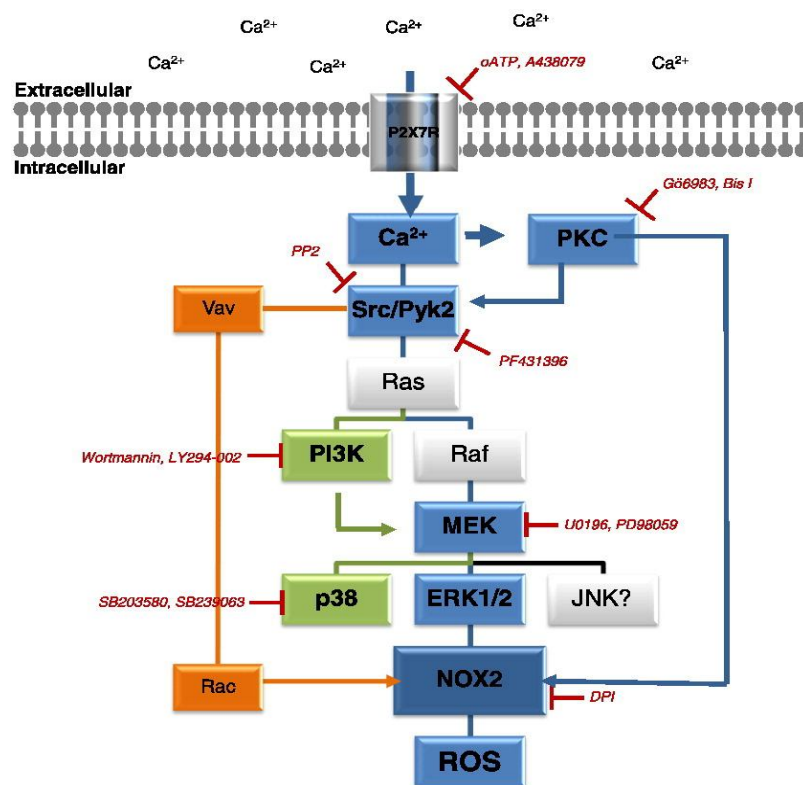


Fig 5. Oxidative stress induced by P2X7 receptor stimulation in murine macrophages is mediated by c- Src/Pyk2 and ERK1/2.

The P2X7 receptor activation and LTB₄ release have been implicated in the polarization of T_H1 and T_H17 responses (32-34). It is known that PGE₂ 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_{2α} (37). PGE₂ 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 PGE₂ production in neutrophils (43, 44). This corroborates the fact that both Ado and PGE₂ 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 LTB₄ (47, 48), which modulates Microbicidal mechanisms. *Leishmania amazonensis* is capable to negatively modulate the production of LTB₄ 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 PGE₂ production. *Lutzomyia longipalpis* saliva triggers the production and release of PGE₂ and decreases LTB₄ (52) (Figure 6).

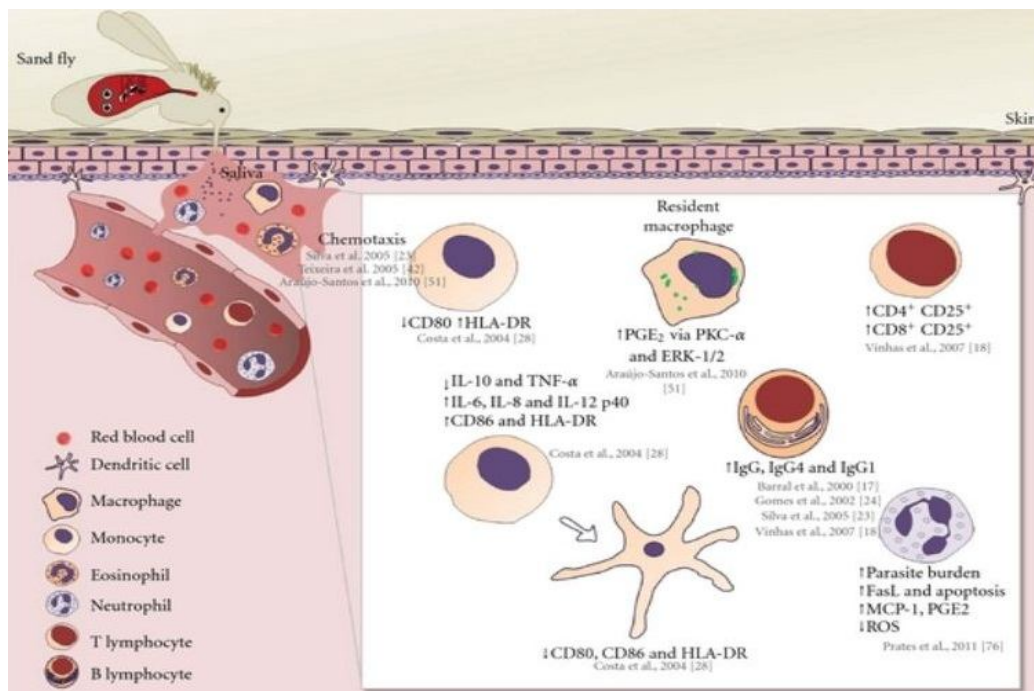


Fig 6. Roles of *Lutzomyia longipalpis* saliva in the host immune response cell. After injection, a set of events can be triggered in the host immune response.

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.

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Conflict of interest

The authors have no conflict of interest in this study.

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