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MORPHOLOGY, LIFE CYCLE, PATHOGENESIS AND VIRULENCE FACTORS OF GENUS *LEISHMANIA* : A REVIEW

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Abstract

Leishmania spp. are intracellular protozoan parasites that spent part of their life cycle in a sand fly midgut and the other is completed in mammalian tissues. The parasite is responsible for a group of human diseases called Leishmaniasis and the place of stability of the parasite is Macrophages where it doubles and remains alive inside it using some defense mechanisms against the acidity and oxidative stresses which produce within the macrophages. In addition, production of (heat shock proteins) to regulate response to heat shock. Moreover, the promastigote contains a glycocalyx which is important to colonize on gut wall of sand fly and complete it life cycle. So that there are many virulence factors that responsible of parasite pathogenicity. As for the clinical symptoms, their appearance depends on Leishmania species and host immunity, which may either be restricted to the skin as in the case of cutaneous leishmaniasis or extend to internal organs and cause death in untreated cases.

Key words: Leishmaniasis, *Leishmania* spp., virulence factors, pathogenicity

Introduction

Leishmania spp. has a life cycle that is completed in 2 hosts, one of which is an invertebrate host, the sand fly, in which it is present in the Promastigotes phase, and the other is the vertebral host in which it is present in the amastigotes phase. Amastigotes are also called as Leishman Donovan (L-D) bodies (Geraled and Larry, 2005).

The main vertebrate hosts for *Leishmania* spp. are mammals include human, dogs and several species of rodents. The parasite causes a group of human diseases called leishmaniasis. Species that infect human beings are worldwide distributed in Africa, Asia, Europe, The Americas, and the Mediterranean region. According to studies, the new annual injuries range from 1.5 to 2 injuries, with the potential of 350 million people at risk of infection, while the number of deaths is estimated at about 70,000 annually. *Leishmania* species is responsible for the different symptoms, as part of it heals itself and part of it is fatal if not treated, as in visceral leishmaniasis (Hoyos *et al.,* 2016).

The main species of *Leishmania* include, the causative agent of cutaneous leishmaniasis are *Leishmania tropica* and *Leishmania major* produced cutaneous ulcers also Known as oriental sore, Delhi boil, whereas *Leishmania donovani* cause visceral leishmaniasis or Kala-azar, Dum-Dum fever and *Leishmania brazieliensis* cause mucocutaneous leishmaniosis or Espundia (Levinson and Jawetz, 1994).

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Morphology and Life Cycle

The life cycle involves the sand fly of genus *Phlebotomus* is the intermediate host and vector.

A female sand fly is the main carrier of the disease. When a blood meal is taken from an infected person, the blood contains an amastigote that turns into a promastigote, doubles in the midgut, and moves to the pharynx to be ready to transfer to another host. The life cycle within a sand fly is approximately 10 days (Sadlova and Volf, 2003).

Next, the sand fly containing the infective stage, which is Promastigote, is injected into an uninfected host while feeding it. The macrophages cells devour the promastigote and convert it into an amastigote that multiplies inside the macrophages and causes its bursting to release phases that infect other cells. In this way, the life cycle of the parasite inside the person continues and is complete when another sand fly comes and takes the blood meal from the infected person (Bates and Rogers,

2004).

All amastigotes in mammalian tissues are similar, they are spheroid to avoid, usually range between 2.5µm to 5.0 µm. Because of the similarity of amastigotes in all tissues and the difficulty in differentiating between species, so the attempts to solve this problem done by PCR to amplify kinetoplast DNA from samples (Cupolillo *et al.,* 2003).

Leishmania stages survival in macrophages

The promastigote is coated with glycocalyx which protects these stages from host hydrolases and component of serum in bloodstream and digestive tract in insects.

The main component of glycocalyx is a complex consist of lipophosphoglycan (LPG). LPG include a long phosphoglycan chain (made of oligosaccharide–phosphate repeat units) that is establish to the plasma membrane via a GPI (glycosylphosphatidylinositol) anchor (Nadeer and McConville, 2008). *Leishmania* mutants lacking LPG do not have the ability to colonize on their vector. primarily because they cannot bind to the gut wall of the digestive tract. Studies investigated that *L. donovani* that lacked LPG is less virulent in BALB/c mice. In addition, there are other functions for LPG such as binding for macrophage receptors, inhibition of phagolysosome maturation (Spath *et al.,* 2003) so LPG is important virulence factor in pathogenesis of leishmaniasis. Remarkably, the surface glycocalyx of LPG is completely lost after promastigote differentiation to amastigotes, suggesting that LPG is not necessary for amastigote virulence (McConville and Blackwell, 1991).

After sand fly injected metacyclic promastigotes into the skin of mammalian then promastigotes are highly resistant to serum component and engulfed by macrophage then transform to amastigotes.

Macrophages are responsible for persisting infection inside human bodies. Studies reveals that *Leishmania* parasites reside and replicate within phagolysosome components. Amastigote has the ability to withstand the surrounding environment which is rich in hydrolytic enzymes. As a result of its presence inside the macrophage, it interferes with endosome and lysosome and acquires the characteristics of lysosomes (Lodge, 2006).

The amastigote also resists the acidic environment p H (4.7-5.2) present inside the gap that contains it and the reason for this acidity is due to the activity of the H + ATPase enzyme and it will go through all its metabolic processes despite these processes performed by promastigote in an environment with a neutral pH.

Amastigote also avoids free radicals generated by macrophages through specific mechanisms such as heme analysis and prevent the NADPH oxidase pool (Pham *et al.,* 2005).

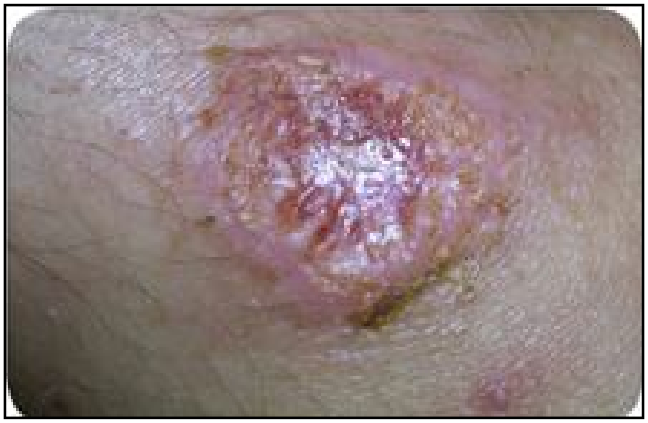
Regulation response to heat shock

Leishmania tolerance to temperature is very important for survival at (33–37°C) in mammalian bodies. Both Highly temperature and acidity induce promastigote differentiation to amastigotes in vitro (Alcolea *et al.,* 2010). Recent studies have suggested that HSPs (heat shock proteins) responsible of regulating heat shock responses. The major HSP families of *Leishmania*, including HSP70, HSP90 and STI1 (stress inducible protein 1)/HOP (HSP organizer protein), are essentially expressed in both life cycle stages but exceptional up regulated during heat shock (Morales *et al.,* 2010).

Prevention the effect of oxidative stress

Amastigotes within macrophage are exposed to oxidative and nitrosative (NOS) stresses as a result of ROS and NOS production by the macrophage. In addition, the metabolic processes within the parasite, such as mitochondrial respiration, also lead to oxidative stress. So that partial or complete deletion of any of the oxidative defense mechanisms of *Leishmania* leads to a loss of virulence. For example, trypanothione, that composed of two glutathione molecules linked by the polyamine spermidine. Trypanothione is linked to many processes performed by glutathione in other organisms, such as the metabolism of peroxides, although enzymes involved in the synthesis and recycling of oxidized trypanothione are essential, *Leishmania* mutants if loss single allele deletions in trypanothione reductase also loss their virulence in macrophages. So that, this enzyme is the main target of confront line in anti leishmanial drugs, such as trivalent and pentavalent antimony (Wyllie *et al.,* 2004).

Finally, these observations suggest that the oxidative

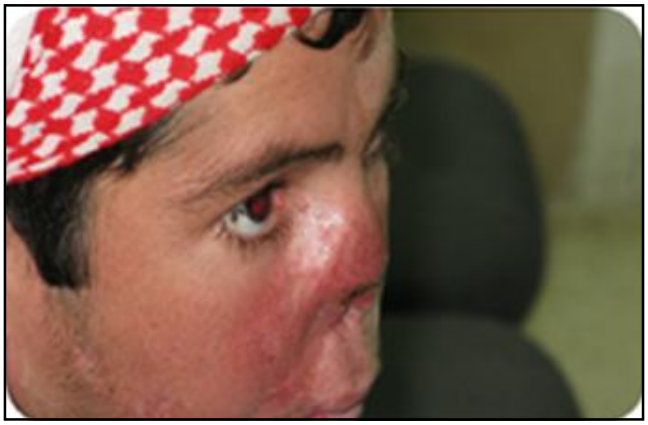


Clinical forms of cutaneous leishmaniasis (WHO, 2015)

defense mechanisms of *Leishmania* is very important in virulence and pathogenicity of parasite.

Pathogenesis

In cutaneous leishmaniasis, the period between a sand fly bite and the onset of symptoms ranges from a few days to many months and lesions are restricted to the skin, red color may disappear but in most cases they turn into crusts under them ulcers and these lesions can unite with each other and turn into a sorely area accompanying bacterial secondary infection (Vargas-Martínez *et al.,* 2013).



Clinical forms of mucocutaneous leishmaniasis (WHO, 2015)

Clinical forms of visceral leishmaniasis (WHO, 2015).

In mucocutaneous leishmaniasis, the parasite moves from the location of the sand fly bite to the mucous membranes of the mouth, nasal passage and ears, and causes tissue and cartilage damage in the affected areas with a secondary infection of the bacterium, necrosis causing major deformities, and the parasite may invade the larynx and trachea and lead to voice loss (Reithinger *et al.,* 2007).

In visceral leishmaniasis, the parasite infects the internal organs of the reticuloendothelial system and the infection progresses without symptoms to severe and develops into what is called Kala-azar. After a sand fly bite, symptoms begin to appear between 10 days to a year, but most often appear from 2-4 months in the form of anemia, Hepatic and spleen enlargement, decreased bone marrow efficiency, accompanied by a secondary infection with bacteria due to weak body immunity and decreased production of white blood cells in addition to bleeding from the mucous membranes due to low blood platelet production and death (Murray *et al.,* 2005).

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