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Leishmaniasis disease: Causes, Types & Symptoms, Diagnosis and Current Treatment

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Abstract

Leishmania protozoan parasites, causative agent of various disease range from mild cutaneous to fatal visceral leishmaniasis affecting millions of people worldwide.leishmaniasis is transmitted by the bite of an infected female sand fly.Approximately 1.5-2.0 million cases are reported in the world annually from this disease and the death toll is estimated to be 57,000. Along with Brazil, Sudan and Bangladesh, India contributes to 90 per cent of the global burden of visceral leishmaniasis (VL). Currently available drugs are insufficient and associated with several side effects.In this review, we try to featuring an overview of leishmaniasis disease that how it transmit, different types and symptoms, diagnostic methods of the disease and finally we discuss the current treatment and potential drug target of *Leishmania.*

Key-Words: Leishmaniasis; *Leishmania*;Treatment; Drug Target

Introduction

Obligate protozoan parasite *Leishmania*belonging to the family of trypanosomatidscausative agent of Leishmaniasisdisease. These parasites are transmitted through 30 different species of *Phlebotomines*and fly in old world and *Leutzomia* in new world as extracellular, flagellated promastigotes and replicate as intracellular, aflagellateamastigotes in mononuclear phagocytes in mammalian hosts.[1,2]. The *Leishmania*genome contains about 8,000 genes, and the functions of most genes (hypothetical proteins) are still unknown [32].Leishmaniasisis responsible for many diseases whose symptoms range from mild cutaneous lesions to fatal visceral involvement [3, 4]. It is one of the world's most neglected disease, affecting mostly very poor people in developing countries. The parasite is transmitted through the bite of sandfly to the mammalian hosts. The leishmaniases are diseases of the tropical and subtropical regions, prevalent in theOld World (parts of the Mediterranean, Africa and Asia with the Middle East andIndia) and the New World (parts of Central and South America) [5].*Leishmania* species differ in the degree to which they are associated with different host species and reservoirs, among which rodents are considered to be of most important [30].

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The transmission of *Leishmania* parasites is zoonotic (animal to vector to human), where dogs and rodents act as reservoir, it is anthroponotic (human to vector to human) in the Indian subcontinent and Asia, while in Europe, Africa and the Americas [6, 7, 31]. Leishmaniases are widespread in 88 countries with an estimated 350 million people at risk. It has been predicted that more than 12 million people infected by this group of disease with around 1.5 to 2 million new cases occurring annually; and this number is still rising [8].

Life cycle

Leishmaniasis is transmitted by the bite of an infected female sand fly, which tend to feed during dusk [9]. Old World disease is primarily transmitted by the *Phlebotomus*species of sand fly, while New World disease is transmitted through the *Lutzomyia*species [10]. *Leishmania*parasites have two distinct morphologies, the infective form is the elongated, flagellated promastigote that is approximately 10 to 20 µm in length and 2 µmin width, responsible for human disease (VL, CL and MCL), which is injected into the mammalian host as a sand fly takes a blood meal [11]. After the fly has taken up *Leishmania*with a bloodmeal, the short and ovoid *Leishmania*promastigotes live in the fly gut, where they adhere to the midgut walls and start to replicate. They develop into long, slender nectomonadpromastigotes which then migrate to the anterior of the insect gut and become short and broad leptomonadpromastigotes [63]. These secrete a gel that consists mainly of filamentous proteophosphoglycan

(fPPG) and forms a plug in the gut. This allows the promastigotes to proliferate and develop further into the infective metacyclicpromastigotes[59], which are then transmitted to a mammalian host during the blood meal of the infected sandfly.Promastigotes enter host cells, specifically macrophages dendritic cells and neutrophils [55], via receptor-mediated phagocytosis. Following phagocytosis, promastigotes are contained within membrane-bound compartments that mature from early phagosomes to late phagosomes. Ultimately these late phagosomes will fuse with lysosomes to become phagolysosomes. These parasite-containing organelles are referred to as parasitophorousvacuoles (PV) [56]. Once inside host cells, promastigotes begin differentiating into the intracellular form of the parasite, the amastigote. This process takes place over a period of 24-72 hours. Amastigotes are smaller (2-6μm), have a vestigial flagellum [60,61] and are covered by a densely packed glycocalyx primarily composed of glycoinositolphospholipids and glycosphingolipids [57]. Amastigotes are able to survive and multiply within the harsh, highly acidic (pH 4.0), environment of the phagolysosomeby binary fission, but maintain a neutral internal pH [58]. The amastigote are then release by the rupture of macrophages and eventually leads to local spread of parasites [12]. The life cycle is completed when the sand fly takes a blood meal from an infected host, ingesting host cells containing amastigotes. Amastigotes travel to the midgut of the insect where they become promastigotes& multiply and can then again be transmitted to another human (anthroponotic transmission) or to animals that act as reservoirs (zoonotic transmission) (Figure 1) [6,7].

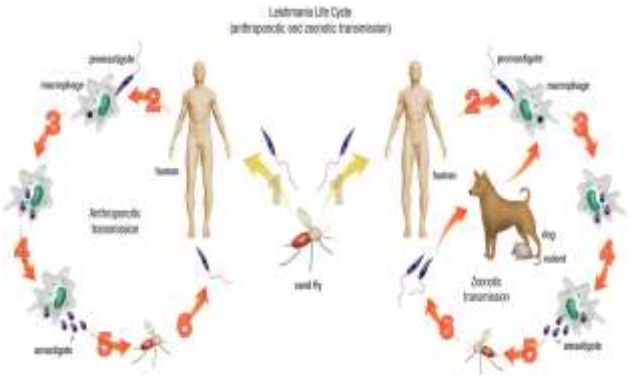

Figure 1Life cycle and transmission of *leishmania* parasites. (**1**)Promastigotes transmitted into mammalian host by sand fly bite. (**2**) Phagocytosis of promastigote into host cellby macrophage (**3**) Promastigote develops into intracellularamastigote. (**4**) Amastigotes proliferate within parasitophorous vacuole by binary fission.(**5**) Amastigotes are released from host cell and can infect others. (**6**) And can then the amastigotes taken up by the female sand fly during another blood meal, where amastigote form again converts in the promastigote form in the midgut of the sandfly and can then again be transmitted to another human or animals. [5]

Types & symptoms of *leishmaina* disease

The disease is mainly classified in three forms; life threatening visceral leishmaniasis (VL), commonly known as kala-azar, self-healing cutaneous leishmaniasis (CL), mucosal leishmaniasis (MCL).The visceral, most severe form of the disease (VL) commonly known as kala azar, iscaused by *L. donovani*and *L. infantum*in the Old World and *L. chagasi*in the New World [29]. VL is ranked second in mortality and fourth in morbidity among tropical diseases [52], with up to 40 000 deaths per year [53] and over 2 million disability-adjusted life years lost [54]. Symptoms can include fever, anaemia, organ swelling, intestinal ulcers, weight loss and oedema and VL is often fatal if not treated [3]. Ninety per cent of those affected by VL live in five developing countries namely, India (especially Bihar), Bangladesh, Nepal, northeastern Brazil and Sudan [8]. Kala-azar distribution and incidence in East Africa are greatly influenced by environmental, behavioural and socio-economic factors in addition to the HIV coinfection and genetic susceptibility [43-48]. In East Africa and the Indian subcontinent, VL is caused by the *L.donovani* complex, unlike Europe, North Africa and Latin America where the agent is *L. infantum*[49, 50]. Ethiopia has second largest number of annual VL cases (4000–7000) in Africa, next to Sudan [51].In 1999, approximately 57,000 deaths reported in India due to VL. The annual rate of VL in India is approximately 100 000 cases, and in which 90% cases are account only in the state of Bihar [13].Cutaneous leishmaniasis (CL) is the most common form of leishmaniasis worldwide, representing 50–75% of all new cases.This type of disease is caused by species of *L. tropica, L. aethiopica* and *L. major* in the Old world, and by *L. mexicana, L. guyanensis, L. amazonensis and L. braziliensis* in the New world and symptoms extendfrom small, localised and self-healing ulcers to large disfiguring lesions that leadto necrosis of the skin and dissemination of the parasites through the body. According to the World Health Organization (WHO), the number of CL cases is around 1–1.5 million annually, and over 90% of CL cases occur in seven countries; Afghanistan, Algeria, Brazil, Iran, Peru, Saudi Arabia and Syria [14,7]. Muco-cutaneous form of the disease (MCL) is prevalent only in the New

Worldand caused by the *L. Viannia*subgenus, mainly *L. braziliensis*. Symptoms includelesions of nasal and oral tissue and the destruction of facial cartilage and bone. Over 90% of all MCL cases occur in Bolivia, Brazil and Peru.The broad range of clinical symptoms of the leishmaniasis reflects the varyingimpact of the different *Leishmania*species on the human immune system [15].

Diagnosis

Cutaneous leishmaniasis can be diagnosed by direct observation of the parasites in skin scrapings, impression smears or skin biopsies stained with Giemsa, Leishman's, Wright's or other stains [17]. Amastigotes are easiest to find in recent or active lesions. They are usually found in macrophages or freed from ruptured cells but in dogs, amastigotes can sometimes be found in lymph node, spleen, or bone marrow aspirates, or in skin scrapings from lesions [18]. In sick animals, they may also be found in other affected tissues, including ocular granulomas. However, parasites are sometimes undetectable even in clinical cases, and they are often absent in asymptomatically infected animals. Histopathology with immunohistochemistry can increase the likelihood of detecting the organism when few parasites are present [16].

Polymerase chain reaction assays (PCR) are often used for diagnosis can be used to detect *Leishmania*spp. in blood, skin biopsies, lymph nodes, and bone marrow. *Leishmania*spp. can also be cultured. However, each species will grow only in certain media, and some species can be difficult to isolate. Novy-MacNeil-Nicole (NMN) medium, brain–heart infusion (BHI) medium, Evan's modified Tobie's medium (EMTM), Grace's medium and Schneider's *Drosophila* medium might be used initially [17]. Animal inoculation into hamsters may also be valuable, especially with contaminated material. Diagnosing leishmaniasis by *in vitro* culture requires 5 to 30 days, while animal inoculation can take weeks or months. The species, subspecies and/or strain can be identified by PCR, DNA hybridization, kinetoplast DNA restriction endonuclease analysis, isoenzyme analysis, or immunological techniques that use monoclonal antibodies. A delayed hypersensitivity test, the leishmanin skin test (Montenegro skin test), is useful in the diagnosis of cutaneous and mucocutaneousleishmaniasis, but it is usually negative in the diffuse cutaneous form but in case of dogs is not useful [18].

Visceral leishmaniasis can be diagnosed using some of the same techniques, including direct observation of the parasites. Amastigotes may be found in peripheral blood, or more often, in aspirates or biopsy smears from the spleen, bone marrow or lymph nodes. PCR [42], culture or animal (hamster) inoculation may be particularly useful early, when parasite numbers are low. Serology can also be helpful in this form of leishmaniasis. Common serological tests used in humans as well as animals include the immunofluorescent antibody test (IFA), direct agglutination, enzyme-linked immunosorbent assay (ELISA), fast agglutination-screening test (FAST), and a rapid immunochromatographic assay (K39 dipstick or strip-test) [40,41]. Other assays including gel diffusion, complement fixation, indirect hemagglutination and countercurrent electrophoresis have also been used [17]. But in case of dog most, but not all, symptomatically infected dogs are seropositive. However, only a percentage of asymptomatically infected dogs have detectable antibodies, and these animals may or may not become ill. Antibodies are not always found in animals that only have localized skin lesions; in cats, titers may not be detected until the lesions are resolving. Serological studies also suggest that *Leishmania*titers may be lower in cats than dogs [16].

Many time the clinical signs and symptoms are not diagnostic of Leishmaniasis. The VL may be confused with other similar diseases such as malaria, tropical splenomegaly, schistosomiasis or cirrhosis with portal hypertension, African trypanosomiasis, milliary tuberculosis, brucellosis, typhoid fever, bacterial endocarditis, histoplasmosis, malnutrition, lymphoma, and leukaemia. Similarly, numerous primary and secondary skin conditions are frequently overdiagnosed as early lesions of cutaneous leishmaniasis in endemic countries and in non-endemic countries CL is misdiagnosed as other diseases. [19]

Current treatment and potential drug target

Several treatment options for leishmaniases are available, but effective vaccines against leishmaniases are still under development, the current treatment available for leishmaniasis relies on chemotherapy [20]. First-line drug treatments include pentavalent antimonials compounds, stibogluconate (Pentostam, Glaxo-Smith-Kline) or meglumine antimonite (Glucantime) [33,34] but their use is limited due to the emergence of resistance toward them. Pentavalent antimonials have been in use for more than 50 years and are the recommended treatment by the World Health Organization (WHO) [21, 22,3]. The other second line drugs like amphoterecin B [35], its liposomal formulations and miltefosine are being used in the treatment with more efficiencies and dramatic potential for curing Leishmaniasis [23], their use is also

limited either due to toxicity or high cost of treatment. Other drugs like paromomycin and pentamidine have shown some usefulness and could be a potential supplement in the drugs routine but their use and availability in disease widespread regions is limited [23,24].

In recent years, clinical trials of combination therapies are working [23]. Combination of two or more drugs overcome the drawback of previously available drug [62]. Combination drugs could reduce treatment period, drug doses and subsequently drug toxicity but chances of resistance development against current available drug regimen can be denied. At present, main combination drugs under consideration are LAmB (Liposomal amphotericin B) and miltefosine, LAmB and paromomycin, LAmB and antimonials and paromomycin and antimonials in India and also being evaluated in other part of the world [25]. Currently natural product antimicrobial peptides (AMPs) have been studied as a potential new source of novel antileishmanials [36, 37], in part this has been catalysed by the fact that they have displayed promising activity against other cutaneous infectious diseases [38]. The activity of AMPs against Leishmania species that give rise to CL has recently been reported [39]. New potential drug targets mainly focus on biochemical and metabolic pathways which is essential for parasite survival [25]. The target enzymes of these pathways should have functional and structural difference from its mammalian counterparts for selective inhibition of target sites. Further strategies to target more than one enzyme for a metabolic pathway simultaneously may prove more usefulness and effectiveness [26, 27]. Some important enzymes that use as drug target like cycline dependent kinases (cdks) play important role in cell division cycle, transcription, apoptosis and differentiation, Peptidases serve as potential drug targets, a total of 154 peptidases were found to be present in the *Leishmania* major genome, Mitogen-activated Protein (MAP) kinases are mediators of signal transduction and important regulators of cell differentiation and cell proliferation in eukaryotic cells. MAPKs are not only important to amastigotes but also for promastigotes. Some important pathway in *leishmania* should also take a serious consideration for drug target such as Sterol biosynthetic pathway, Glycolytic pathway,GPI biosynthetic pathway,Purine salvage pathway,thiol metabolic pathway, Folate biosynthesis and many more [28].

Conclusion

Leishmaniasis is a life threatening disease ranging from mild cutaneous to fatal visceral leishmaniasis, which is mainly caused by the protozoan parasite *leishmania*. On an estimate, there are about 350 million people at risk and the disease is continuously spreading globally. Leishmaniasis mainly affect the people of developing countries living below poverty line.Current therapy for leishmaniasis is inadequate because of emergence of resistance to the existing drugs, their toxicity and lack of cost-effectiveness.Therefore, it is of most importance to look for effective drugs and new drug targets for the treatment of leishmaniasis.

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