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Leishmaniasis: A review of the disease and the debate over the origin and dispersal of the causaitive parasite *Leishmania*

Molly MacMorris-Adix

ABSTRACT

The vector borne disease Leishmaniasis, caused by the *Leishmania* parasite, is estimated to affect the lives of 12 million people. Manifesting itself into three different clinical forms that center on disfiguring sores and enlargement of several organs, Leishmaniasis is a devastating disease impairing economic productivity and impeding socioeconomic development. The complex life cycle of this parasite, involving a host, vector, and reservoir, has played a major role in defining the dispersal and prevalence of this disease on a global level. The prevalence of Leishmaniasis is highly concentrated due to the close relationship of this parasite and its single vector (the female Phlebotomine sand fly), and the socioeconomic and environmental factors that are beneficial to the sand fly habitat. Yet, there is a wide and varied distribution of *Leishmania* species. Some species belonging to the subgenera of *Leishmania* are found in both Old and New Worlds, while others belonging to the subgenera *Viannia* are found only in the New World. Interest in the origin and dispersal of *Leishmania* has risen from this disjointed distribution and a need for a complete comprehensive understanding of this parasite in order to determine the best approach in the eradication of this disease. The two main hypotheses from the literature that have become established in this debate are a Palaearctic origin and a Neotropical origin. These hypotheses are presented along with a third hypothesis of an African and Neotropical origin. The conflicts between molecular, entomological, biogeographical, and ecological data, along with insufficient research that have rendered this debate unresolved are also discussed. Complexity of this diseases' epidemiological cycle demands a comprehensive understanding of the parasite, including its origin and dispersal, to maintain the most effective prevention, treatment, and hopefully eradication.

LEISHMANIASIS

Leishmaniasis and its global impact

Leishmaniasis is a vector borne disease caused by a parasite of genus *Leishmania*. The parasite was first described as early as 1756, by Alexander Russell (Hide *et al.,* 2007). In early 1903, L.H. Donovan and W.B. Leishman independently demonstrated the causative parasite in splenic tissue in autopsies from infected patients in India (Bern & Chowdhury, 2006). The disease on the other hand has been thought to have evolved with the human species and plagued ancient civilizations (Tuan *et al.,* 2008). Leishmaniasis is a devastating disease that impairs economic productivity and impedes socioeconomic development; epidemics can be significantly detrimental to the progress of an entire country (World Health Organization, 2006). It is currently found in 88 countries in inter-tropical and temperate regions of the world where an estimated 350 million people live; among these countries 72 are developing countries, 13 of which are among the poorest and least developed (Campino *et al.,* 1997). More than 90% of reported cases are located in 11 countries, India, Bangladesh, Nepal, Sudan, Brazil, Bolivia, Peru, Afghanistan, Iran, Saudi Arabia, and Syria (Hide *et al.,* 2007). The social stigma associated with Leishmaniasis prevents many cases from being reported but it is estimated that the overall prevalence is 12 million people and the daily burden (absence from work, increased health costs, and loss of family member) is 860,000 for men and 1.2 million for women (Campino *et al.,* 1997).

The female Phlebotomine sand fly is the only vector of Leishmaniasis, thus it is the main mode of transmission. Other modes of transmission include vertical transmission, blood transmissions, and the use of contaminated needles, which has led to an alarming rise in HIV/Visceral Leishmaniasis co-infection that will be discussed later. The life cycle of the parasite begins when an uninfected female sand fly bites an infected host for the mammalian blood needed to develop eggs. With the blood, the sand fly ingests macrophages containing *Leishmania* parasites in an amastigote stage that develop into promastigotes in the mid gut and then move to the salivary glands (Division of Parasitic Diseases, 2006). When the infected vector bites another host the promastigotes travel from vector to host where they are ingested by macrophages within which they return to amastigotes. At this point the amastigotes multiply until the macrophage bursts and they can spread throughout the body to other cells and macrophages where they will continue to multiply and destroy the cell. Leishmaniasis is found to be both anthroponotic, where human are the sole reservoirs and sole sources of infection for the vector, and zoonotic, where animal hosts are involved in the transmission cycle and act as reservoirs (Hide *et al*., 2007). The most common animal reservoirs include dogs, wild

carnivores, rodents, hyrax, sloths, and opossums. It is important to note that a wide range of mammals can act as reservoirs for this disease as well (Hide *et al*., 2007).

Manifestations of Leishmaniasis

Due to a complex pathology, the clinical outcome of the infection depends on a multifaceted association of factors among the three main players involved: hosts, parasites, and vectors. The disease has three different manifestations that differ in symptoms and consequences. The most common and most widespread of the three is Cutaneous Leishmaniasis (CL), characterized by painful skin sores located at the site or within close proximity of a sand fly bite (Hide *et al*., 2007). These lesions are generally self-healing with no need for specific treatment; however the remaining scars often cause debilitating social stigma (Center for Disease Control, 2006). Mucocutaneous Leishmaniasis (MCL) is a severe form of CL that is mainly characterized by lesions that often lead to extensive and disfiguring destruction of mucous tissues of the nose, mouth and face, as well as the arms and legs, causing serious disability (Hide *et al*., 2007). MCL is often classified simply as a severe form of CL and thus most discussions of the disease include MCL in CL. This review will follow this trend except for occasionally discussing specific vector parasite relationships and phylogeny. Visceral Leishmaniasis (VL), also commonly known as kala-azar, is arguably the most severe with a mortality rate of essentially 100% if untreated. It is characterized by irregular bouts of fever, substantial weight loss, swelling of spleen and liver, and anemia, and it is known to especially affect children (Hide *et al*., 2007). Post Kala-azar Dermal Leishmaniasis (PKDL) is a resurgence of VL months to years after treatment and is characterized by macular, maculopapular, and nodular rashes in patients who have recovered from VL and are otherwise well (Hide *et al*., 2007).

Treatment for these diseases is available; however, like most infectious diseases, cost, toxicity, and resistance are constant obstacles of mass treatment. Species-based approaches to treatment are often advocated, thus treatment has been centered on pentavalent antimonials, an injection, as it is used to treat CL, VL, and PKDL in both Old and New World (Hide *et al.,* 2007). However there has been in increase in antimony resistance, especially in North Bihar, India, thus amphotericin B has become a drug of choice. Unfortunately, at the price of a cure rate of approximately 100%, this treatment requires close monitoring includes the risk of serious, even fatal, side effects (Hide *et al.,* 2007), which renders it impractical for many undeveloped countries or impoverished communities. Several lipid- associated amphoterins, such as AmBisome, have been introduced as one of the safest treatments for MCL (Hide *et al.,*

2007). Miltefosine is a well-tolerated and effective oral treatment of VL with only minor side effects. Unfortunately, this particular treatment is unsafe for childbearing age women due to the risk of teratogenicity, or the capability of producing fetal malformation (Hide *et al.,* 2007). A vaccine has yet to be produced for Leishmaniasis due to the complexity of the disease interaction with the immune system. However, that fact that many patients who recover from VL are usually immune to re-infection, suggests that a vaccine against VL is possible (Hide *et al.,* 2007). The same can be said of CL where many people who suffer from the self healing lesions are usually immune to re-infection; however the wide variety of species causing CL make this system more complicated.

Distribution of the disease

Migration, and urbanization and deforestation that often result from socio-economic, cultural, religious, political, and environmental factors are the main forces causing the highly concentrated distribution of Leishmaniasis. Significant increases in rural to urban migration and unplanned development often leads to shantytowns and poor suburbs in many developing countries (Mott *et al.,* 1990). These communities are characterized by inadequate urban development, most notable in poor sanitation, high population density, high rates of malnutrition, and human residence co-insiding with domesticated livestock, such as chickens, cows, and dogs. The breeding sites of the sand fly are hot and humid places where organic matter exists, such as old trees, rodent burrows, animal shelters, cracks in walls and trash (Mott *et al.*, 1990). In these shantytowns, all of these habitats can exist in very close proximity, creating a favorable environment for the vector species (Weekly Epidemiological Record, 2002). When combined with the migration of populations from rural to urban, there is a high risk for increased transmission. This is particularly true because Leishmaniasis is generally a rural disease and the migration from rural to urban results in uninfected urban populations, lacking any tolerance to the disease, mixing with infected rural populations that have some level of tolerance.

Due to civil and international war, increased migration, and the disruption of health centers, Afghanistan, Iraq, Iran, and Syria have seen an increase in marginalized communities as well as the incidence of anthroponotic CL (Weekly Epidemiological Record, 2002). In Saudi Arabia, city suburbs have quickly expanded into rural areas and expanded into formerly uninhabited areas, where the disease cycle used to be contained as zoonotic but has since transitioned to include human hosts as well (Weekly Epidemiological Record, 2002). Brazil has a similar story due to a prolonged drought causing starvation, ruined crops, and miserable conditions that led to rapid migration from rural areas into urban. Deforestation for the growth of

cities located in close proximity to primary forest (a natural shelter for several species of reservoirs and vectors of this disease) also creates an increased risk for Brazilian populations. Because these populations consist of the country's marginalized and poorest populations, a lack of resources and health education means little chance for prevention and interruption in this epidemiological cycle (Desjeux, 2001; Bhattacharya, 2006). As illustrated, this disease affects the poorest of the poor and aggravates poverty (Bhattacharya, 2006).

Another rising concern in the modern distribution of Leishmaniasis is the occurrence of HIV and VL co-infection that has been attributed to the urbanization of VL and the ruralization of AIDS (Weekly Epidemiological Record, 2002). This co-infection is a fatal synergy characterized by both infections mutually reinforcing their impact on the immune system. In HIV-positive cases, VL accelerates the onset of AIDS by cumulative immunosuppression and stimulates reproduction of the virus while the co-infection rapidly activates VL disease in the parasite carrier as well (WHO, 2006). The rise in prevalence of HIV/VL co-infection is most notable in southern Europe among the population of intravenous drug users (Weekly Epidemiological Record, 2002).

Vector: Phlebotomine sand fly

Simply as the single vector of the *Leishmania* parasite, the sand fly has a significant role in the dispersal and distribution of this disease; yet the diversity of the sand fly has also been influential. The sand fly is very diverse with some 500 described species, however only 30 have been positively described as vectors of pathagetic species of *Leishmania* and an additional 43 as probable vectors (Hide *et al*., 2007). In the order Diptera, family Psychodidae, there are two genera, *Phlebotomus* in the Old World and *Lutzomyia* in the New World (Hide *et al*., 2007). Some species, such as *Phlebotomus Phlebotomus papatasi* and *P. Paraphlebotomus sergenti,* can only be infected by one species of the parasite, whereas *Lutzomyia longpalpis* can transmit several parasite species (Hide *et al*., 2007).

Parasite: Leishmania

Leishmaniasis is caused by approximately 21 species of morphologically similar kinetoplastid protozoa belonging to the genus *Leishmania* (Croan *et al.,* 1997), which is divided into two subgenera; *Leishmania* of the Old World and *Viannia* in the New World (Hide *et al*., 2007), though only *Viannia* is restricted to the Neotropical region and *Leishmania* is found in both Old and New Worlds (Kerr, 2000). As mentioned before these parasites are morphologically similar, but biologically diverse (World Health Organization, 1989), thus a

combination of biological, immunological, biochemical and molecular data has been used to classify the *Leishmaniasis* species (Croan *et al.,* 1997). Though SSU rRNA gene sequences have been used successfully to infer phylogenetic relationships within other genera of Kintoplastida, the small inter-specific variability among the sequences of *Leishmania* prevents such success at a finer taxonomic scale (Croan *et al.,* 1997). Molecular phylogenetic trees of Leishmania have thus relied upon other sequence comparisons, but no single method has proven to be useful in studying relationships among all *Leishmania* species complexes (Croan *et al.,* 1997). While this has resulted in the lack of a comprehensive phylogeny of this genus, five assemblages of *Leishmaniasis* or species complexes have been distinguished within the division of the genera (Croan *et al.,* 1997).

The placement, and inclusion, of reptile *Sauroleishmania* in the phylogeny of *Leishmania* is highly debated. Croan *et al.* (1997), Momen & Cupolillo (2000), and Noyes (2000) suggest its placement at the crown of the phylogeny while Kerr (2000, 2006), Kerr *et al.* (2000) suggests its placement at the root. There has also been an over arching separation of the genus *Leishmania* into two divisions, Euleishmania (comprised of subgenera *Leishmania* and *Viannia*) and Paraleishmania (consisting several species including *L. hertigi, L. herreri, L. deanei, L. colombiensis, L. equatorensis*, as well as strains of *Endotrypanum*). The distribution of these species however is complex and scattered because it is dependent on the distribution of its nosogeographical forms, which are determined by the composition of the parasitic system (parasite-vector-host) and environmental conditions (Lysenko, 1971). In general VL in the Old World is caused by the *L. donovani* complex *L. L. chagasi* (also known as *L.L. infantum*) in the New World. The *L. L. tropica* complex in the Old World and the *L.L. mexicana* and *L.V. braziliensis* complexes in the New World cause CL. MCL is caused by *L.V. braziliensis* in the New World.

As a genus, *Leishmania* is characterized by great phenotypic diversity, which is expressed in the high number of species described in the literature (Hide *et al.,* 2007). A majority of *Leishmania* species have been characterized and defined on the basis of epidemiological, clinical, geographical, and biological data as morphological data is insufficient for species identification. This and multiple hybridization events, make it hard to define these organisms on the basis of the biological concept of species (Hide *et al.,* 2007). These obstacles in understanding and resolving the phylogeny of the *Leishmania* parasite and its disjointed geographical distribution have (encouraged continued investigation of its origin and dispersal (Kerr, 2000).

ORIGIN AND DISPERSAL OF *LEISHMANIA*

Origin and dispersal dispute and hypotheses

A complicated distribution and problematic taxonomy and phylogeny of the genus *Leishmania* has led to a divided dispute of the origin and dispersal of this parasite. It is generally agreed upon that the genus *Leishmania* is monophyletic (Thomaz-Soccol *et al.,* 1993; Croan *et al.,* 1997) yet beyond this, little is agreed upon. In this debate there are two main hypotheses in the literature; first a Palaeartic origin (Lysenko, 1971; Kerr, 2000, 2006; Kerr *et al.,* 2000) and second a Neotropical origin (Croan *et al.,* 1997; Noyes, 1998; Noyes *et al.,* 2000). A third hypothesis of a Neotropic origin of *Leishmania Viannia* and *Paraleishmania* and an African origin of *L. L. leishmania* (Momen and Cupolillo, 2000) will also be discussed. These hypotheses use a variety of methods and rationalities as support, yet the origin of *Leishmania* remains an open question as the arguments against these hypotheses generally consists of inconsistency in the data, the debate on the importance of molecular data over other sources of data such as the fossil record, and overall lack of information. However, understanding the origin and dispersal in the context of maintaining a comprehensive understanding of the parasite is fundamental in determining the best approach to use against it, such as the development of an efficient vaccine.

Palaearctic origin

The hypothesis of a Palaeartic origin of the genus *Leishmania* was first made by Lysenko in 1971. In 2000, Kerr published a paper supporting this hypothesis with biochemical, molecular, biogeographical, entomological, mammalogical, and ecological studies. She also argues this evidence supports general dispersal from the Palaearctic across the Bering Land bridge to the Nearctic during the Oligocene, across the Panamanian Land bridge during the Pliocene, and then very rapid radiation after arrival in the Neotropical. Lastly she argues the importance of murid rodents (species of the genus *Muridea*) and their ancestors as reservoirs since the origin of the genus *Leishmania* (Kerr, 2000).

From biochemical and molecular evidence she argues that the phylogenetic trees indicating that *L. Viannia* and *Endotrypanum* are ancestral to *L. Leishmania* can be reversed because they are un-rooted. This reversion would put *Sauroleishmania* and *L. Leishmania* at the base and *L. Viannia* and *Endotrypanum* at the crown, without changing taxonomic groupings, distance between species groups, or parsimony. Kerr argues that the post-revision phylogenetic trees were based on assumptions of constant rates of evolution that may have underestimated the antiquity of *Sauroleishmania* and *L. Leishmania* (Kerr, 2000). A study by

MacMahon-Pratt *et al.* (1992) concluded that the most parsimonious explanation for the contrasting absence and presence of the GP46/M-2 gene in respectively *L. Viannia*, and *L. Leishmania* and *Sauroleishmania*, is that a loss of the GP46A gene family occurred following separation of the *L. braziliensis* complex but prior to speciation with the complex (MacMahon-Pratt *et al.,* 1992). Kerr argues that this molecular support is consistent with the placement of *L. Viannia* at the crown of the phylogenetic tree.

During a global period of net cooling and drying about 2.5-1.5 million years ago (mya), grassland biomes shifted toward the equator and murid rodents, a common host of *Leishmania,* moved with this habitat. These rodents moved across the Panamanian land bridge into South America where they would undergo accelerated speciation after distribution due to vicariance, which was a product of climate change and the extreme topographic diversity of Central and South America (Kerr, 2000). Due to the close relationship of parasite, vector, and host, it is reasonable to believe that both *Leishmania* and *Lutzomyia* were closely associated with these rodents and underwent similar radiation, causing the high species diversity found today in the Neotropics. This view is supported by the entomological evidence presented by Killick-Kendrick (1985) that the close evolutionary fit between species of *Leishmania* and their sand fly vectors is presumably due to co-evolution. This study along with the fossil record indicates that the genus *Phlebotomus* evolved in the Palaearctic in the late Eocene and *Lutzomyia* diverged during the Oligocene after the break in the Bering land bridge (Kerr, 2000, 2006; Kerr *et al.,* 2000)

Kerr argues that the role of mammalian reservoirs have played a crucial role in the persistence of infection in an area and the dispersal of *Leishmania* into new localities because they may live for several years, while infected vectors will only live for a few weeks. Presently, murid rodents, which are the most significant reservoir of cutaneous leishmaniasis in both the Old World and New World, originated in the Palaearctic in the Oligocene and dispersed across the Bering land bridge to the Nearctic. New World mice and rats evolved in the Nearctic before crossing the Panamanian land bridge to the Neotropical during the Pliocene and undergoing rapid radiation (Kerr, 2000). Further evidence for the close relationship of reservoir and parasite is demonstrated by the studies of Wirth & McMahon-Pratt (1982), which demonstrate a similar rapid evolutionary rate in New World *Leishmania*.

The ecology of particular species of *Leishmania* provides further evidence for this hypothesis. Two species of *Leishmania* are ecologically similar in that they are both of reservoirs of burrowing rodents inhabiting grasslands, but they are located in the USA and central Asia. The USA species are less ecologically like conspecifics in Central and South America where the sand flies have adapted to occupy forest canopies and new reservoirs

because of humid conditions and warm weather throughout the year in the Neotropics (Kerr, 2000).

In summary, Kerr proposes the following; in the Palaearctic region, *Sauroleishmania* originated in Cretaceous reptiles that declined during the Cenozoic due to a cooling of the earth as mammals radiated. Around this time, phlebotomine species ancestral to both *Phlebotomus* and *Lutzomyia* adapted to feed on rodents instead of reptiles. Parasite, phlebotomine vector, and rodent reservoir could have evolved and dispersed out of the Palaearctic to the Nearctic at the end of the Eocene, when the Bering land bridge was intact and climate was warm enough for sand fly dispersal. Radiation of murid rodents increased in both the Palaearctic and the Nearctic following the Oligocene with the break of the Bering land bridge. With the warm and humid climate and formation of the Panamanian land bridge, rodents underwent rapid radiation, sand flies were able to disperse more widely, a variety of arboreal mammals became hosts, and *Leishmania* also underwent rapid radiation (Kerr, 2000, 2006).

Neotropical origin

Noyes proposes a Neotropical origin of the genus *Leishmania* during the first half of the Cenozoic, which was followed by descendents of this *Leishmania/Endotrypanum* clade migrating through the Nearctic to the Palaearctic by the mid-Miocene at the latest. According to this hypothesis, Noyes argues that *L. Sauroleishmania* subsequently evolved from mammalian parasites in the Palaearctic (Noyes *et al.,* 2000). Most of the support for this evidence comes in the form of a number of rooted phylogenetic trees placing Neotropical species at the root of the tree and Palaearctic at the crown. Medina-Acosta *et al.* (1993) used nucleotide sequences of the surface proteinase (gp 63) to construct a phylogenetic tree of this genus is consistent with that mentioned above. Thomaz-Soccol *et al.* (1993) also constructed a similar tree with Neotropical species based on isoenzyme analysis of 13 different enzymes. Brewster and Barker (1999) places the root of the *Leishmania* clade in a rooted phylogenetic tree between *L. Viannia* clade and the *L. Leishmania/L (Sauroleishmania)* clade based on the ATPase gene.

In addition to these studies, Noyes extends the work of Croan *et al.* (1997) and presents a phylogenetic analysis of 2,171 nucleotides from protein–coding regions of 16 *Leishmania* and associated species. By combining the RNA and DNA polymerase gene sequences into a single dataset for analysis, it effectively doubled the amount of sequence data analyzed compared to previous phylogenies (Noyes *et al.,* 2000). Noyes contends that this is the most robust phylogeny of the *Leishmania* genus available to date because adding data in this way has been shown to be more effective than adding taxa for resolving inconsistencies caused by unequal

rates of evolution (Noyes *et al.,* 2000). The phylogenetic tree presented by Noyes is compatible with that of Croan *et al.* (1997), and Noyes argues that this optimal tree cannot be rooted to make Old World *Leishmania* monophyletic (which contradicts Kerr's phylogenetic hypothesis). Noyes discussed the effect that changes in the rate of evolution in different branches of a tree can have on the phylogeny as a whole. The focus of this distortion is with *L. Sauroleishmania*, which is the only species that appears to not have evolved in a clock like manner due to its long branch and low bootstrap value, Noyes argues that this is a result of *L. Sauroleishmania* evolving at a faster rate than other clades. Distortion caused by change of evolutionary rate can usually be detected by a variety of tests that lead to a reduction of bootstrap value (Noyes *et al.,* 2000). By demonstrating that all other clades within the phylogeny were behaving in a clock like manner and all the bootstrap values are at or close to 100%, Croan's phylogeny is robust and unlikely to have been distorted by rate changes (Noyes *et al.,* 2000). This supports the validity of the comparable phylogenies built by Noyes.

Lastly Noyes looked to the fossil record for evidence of his Neotropical hypothesis. The earliest fossil sand flies were found in Lebanon which was south of the Tethys sea during the Cretaceous, and thus was in Gondwana 120 mya. Before this, the Phlebotomine sand fly probably had lived for a long time in Pangaea from where separate lineages could have developed in Neotropics as well as the Old World (Noyes *et al.,* 2000). In summary Noyes uses a combination of phylogenies produced from different sources to support a hypothesis of a Neotropical origin the genus *Leishmania* that dispersed via migration north through the Nearctic to the Palaearctic by mid-Miocene at the latest.

Neotropical/African origin

Momen & Cupolillo propose an alternative hypothesis to the Palaearctic and Neotropical origins of the genus *Leishmania*. In this hypothesis *L. Leishmania (*and possibly *Sauroleishmania*) originated in Africa, while *L. Viannia and Paraleishmania* originated in the Neotropics. These researchers also explain the current distribution and diversity of Leishmaniasis parasites in the Neotropics as a result of multiple introductions into the New World (Momen & Cupolillo, 2000). This hypothesis is based on an alternative proposal for the phylogeny of *Leishmania* based on major divisions within the genus.

Based on a variety of molecular techniques Cupolillo *et al.* (2000) proposed the separation of the genus *Leishmania* into two divisions into sections; *Euleishmania* (comprised of the subgenera *Leishmania and Viannia*) and *Paraleishmania (*consisting of *L. hertigi, L. deanei, L. colombiensis, L. equatorensis,* and *L. herreri)*. (Momen & Cupolillo, 2000) An examination of

the major groupings presently recognized indicates that the most parsimonies explanation to be an Old World origin of *Sauroleishmania* and a New World origin for *Paraleishmania* and *L. Viannia* (Momen & Cupolillo, 2000) (Table 1). To support the origin of *L. Leishmania* out of Africa, Momen & Cupolillo (2000) uses the restricted geographical range of *L. Aesthiopica* that only occurs in the Ethiopian and Kenyan highlands and has the specific reservoir, the rock hyrax, and vector, *P. larroussius.* The parasite-ecology system of the rodent *Arvicanthis* and rodent *Phlebotomus* has been assumed to be the most primitive system because *Arvicanthis* is restricted to sub-Saharan Africa, thus supporting an African origin.

Old World species *L. donovani* and *L. infantum* have been thought to have a common origin in East Africa due to the results of a cladistic analysis of isoenzymes by Moreno *et al.* (1999). Momen & Cupolillo additionally argue that it is reasonable to consider that Old World parasites such as *L. tropica* and *L. Donovani,* which have evolved with man, originated in Africa along with the proposed origin of man in Africa. In line with the significance of man in the origin and dispersal of *Leishmania*, Momen & Cupolillo (2000) cite several authors that have suggested *L. chagasi* of the New World to have originated in *L. infantum* of the Old World and dispersed from Old to New World with the dispersal of humans in historical times. While a more distant dispersal, Momen & Cupolillo also speculate that the separation of Gondwana in the Mesozoic resulted in Euleishmania evolving into *L. Leishmania* in Africa and *L. Viannia* in South America with a similar separation of Paraleishmania through the dispersal of hystricomorph rodents, commonly known as porcupines, because this reservoir hosts no other *Leishmania* species.

Momen & Cupolillo (2000) also question the inclusion of *Sauroleishmania* at the crown of the phylogeny because it conflicts with the opinion of most field parasitologists who think it should be its own separate genus due to extrinsic and intrinsic characteristics. They cite Telford, 1985 as an example of what they deem a common misidentification of reptile *Leishmania*. Nevertheless, they conclude by proposing an African origin for *Leishmania* as well as the associated *Sauroleishmania*, with four additional and separate events or introductions of the genus *Leishmania* into the Neotropics. These include the separation of Gondwana in the Mesozoic resulting in *L. (Viannia)* located in its present location of the Neotropics, Paraleishmania with the introduction of porcupines in the early Cenozoic, *L. mexicana* migrating over the Panamanian land bridge in the Pliocene, and *L. chagasi* with the historic dispersal of human (Momen & Cupolillo, 2000).

Discussion of hypotheses and the debate

Significant molecular, ecological, and biochemical data has strengthened the three presented hypotheses in different ways making them plausible and maintaining them in this debate. Yet, a lack of support in a particular area (usually molecular or biogeographical) and the general contradiction between these data has been a source of weakness for the three hypotheses. In the following section these strengths and weaknesses of the presented hypotheses will be discussed. A recent review of the debate that presents additional support will also be discussed. However, the inconsistencies and conflicts between the data, as well as the problematic lack of information, have prevented a conclusive and agreed upon conclusion to this question of origin and dispersal.

Molecular research and the data it produces have aided many investigations with strong support for certain hypothesis and theories. This is certainly the case with the hypothesis of Neotropical origin presented by Noyes where the strength lies in the multitude of molecular phylogenies, from a variety of sources, he uses as support. For example, in the debate over the placement of *Sauroleishmania* and other Old World subgenera and species at the root or the crown of the *Leishmania* phylogenetic tree, Noyes places it at the crown citing the work of Croan *et al.* (1997), Medina-Acosta *et al.* (1993), Thomaz-Soccol *et al.* (1993), and Brewster & Barker (1999). The work of Momen & Cupolillo (2000) that also places *Sauroleishmania* at the crown is strengthened by the support of molecular phylogenies. Alternatively, Kerr cites the molecular study by MacMahon-Pratt *et al.* (1992) to place the New World subspecies *L. Viannia* and genus *Endotrypanum* at the crown of the *Leishmania* phylogeny.

On the other hand, molecular data is often noted to be the weakness of the hypothesis of a Palaearctic origin. The main argument against this hypothesis is the lack of ability to test it with evidence that is independent of the construction of the biogeographic hypothesis (Noyes *et al.,* 2000). Kerr's hypothesis is criticized for lack of testing with quantitative evidence from the evolutionary history of the organisms and the lack of independent phylogenetic analyses (Noyes *et al.,* 2000). It is also criticized for using a biogeographic hypothesis as an independent test of that hypothesis (Noyes *et al.,* 2000). Kerr's argument that the work of Croan *et al.* (1997) could be rooted to support her hypothesis has been criticized for being a misuse of the data; therefore while it is a sufficient independent estimate of the phylogeny of *Leishmania* it cannot be used in such a manner (Noyes *et al.,* 2000).

Nevertheless, it is generally agreed upon that support found in trees resulting from molecular studies should not be used in isolation for the evaluation of ancestors (Tuan *et al.,* 2008). This is especially important in this debate due to the close relationship of the parasite with its vector and reservoir. The latter is often argued to be of the most significance due to its

key role in the persistence and dispersal of the parasite as a result of its relatively long lifespan of a couple of years, compared to a that of the sand fly vector (Kerr 2000, 2006; Kerr *et al.,* 2006; Tuan *et al.,* 2008). Thus the use of non-molecular data such as that of biogeography, epidemiology, ecology, and historical events is also significant in this debate.

It is in this point that the hypothesis of Neotropical is critiqued. Noyes does cite the fossil record (for the probable presence of the sand fly in Pangaea) as support for his hypothesis (Noyes *et al.,* 2000) however it draws criticism for being incongruous with data of the parasite, vector, and reservoir. It has been noted that there is an inconsistency between current classifications of phlebotomine sand flies and the proposed Neotropical origin (Noyes, 1998; Kerr, 2000; and Momen & Cupolillo, 2000). In his 1998 paper, Noyes noted that this is insignificant because relationships between the subgenera and species complexes of sand flies are still controversial and thus the current classification of sand flies may not reflect true relationships. Noyes' point may be accurate; however it does not completely justify the inconsistency, especially if the current classification of sand flies were found to be correct. Another key criticism of this hypothesis is the discrepancy of a Neotropical origin of the parasite and a Palaearctic origin of the murid rodents, the most important zoonotic reservoir of this disease (Kerr, 2000).

Kerr placed *Sauroleishmania* at the root of the *Leishmania* phylogeny because reptiles and phlebotomine sand flies co-existed during the Cretaceous. This support also gives way to the theory of a plausible and natural adaptation from lizard host to mammalian, which could have occurred during a cooling of the earth when reptiles declined as mammals radiated. However, this is completely incongruous with both the Neotropical hypothesis and the African/Neotropical hypothesis that place *Sauroleishmania* at the crown of the phylogeny in question. This has been cited as a contradiction in all three hypotheses (Kerr 2000, 2006; Kerr *et al.,* 2000; Noyes, 1998, 2000; Noyes *et al.,* 2000; Tuan *et al.,* 2008). In general, the support that Kerr uses for her hypothesis based on the importance of the relationship between all three players in this parasitic ecology is considered a point of strength in the literature (Tuan *et al.,* 2008). It is important to note that Momen & Cupolillo (2000) also draw upon the importance of this relationship for support of their hypothesis in citing the restricted habitat of the primitive ecology system of the *Arvicanthis* rodent and *Phlebotomus* sand fly in Africa.

A recent of mini-review of the origin and evolution of *Leishmania* since the Precambrian has presented additional data to the debate that should be considered in the context of the three hypotheses presented in this paper (Tuan *et al.,* 2008). Other than the support already cited by the previously discussed hypothesis, this review discusses data from historical events,

paleoparasitological studies, and anthropological aspects. Pre-Columbian ceramic pieces from the Andean region have revealed deformities in the face that are suggestive of injuries from Mucocutaneous Leishmaniasis (Tuan *et al.,* 2008). This may suggest the Andes as a cradle of New World Leishmaniasis (Tuan *et al.,* 2008). The review also comments on the possibility of the disease being introduced into the Brazilian northeast by Phoenicians and Syrians, but dismisses it because early oceanic travels have not been proven (Tuan *et al.,* 2008). Recent improvements in paleoparasitological studies have been applied to this debate by taking samples from Egyptian mummies from 3500-2800 BC and 2050-1650 BC and analyzing them for mtDNA of *Leishmania* (Tuan *et al.,* 2008). These studies have found parasite DNA compatible with *L. donovani* suggesting a visceral form of leishmaniasis (Tuan *et al.,* 2008). Several other similar studies that were conducted in northern Sudan, Peru, and Chile; all supporting that leishmaniasis existed before the arrival of Europeans in America were also cited in the review (Tuan *et al.,* 2008). This is interesting data in light of the similar support presented for the hypothesis of Momen & Cupolillo (2000). However, because the support for the African/Neotropical hypothesis does not specify the humans dispersing into the Neotropics as Europeans, Phoencians, nor Syrians (Momen & Cupolillo, 2000), it cannot be aided by these additional data. At best it can be critiqued for vagueness.

Lastly this review examines the relationship of the evolution and dispersal of *Leishmania* with that of the modern human. By examining the population dynamics of human history the review concludes with a proposed origin and evolution of human *Leishmania* being initially linked to the origin of man in Africa and then following these organisms throughout the Paleoarctic (Tuan *et al.,* 2008). The formation of the Bering straits allowed for further dispersal of man and *Leishmania* into the New World (Tuan *et al.,* 2008). In accordance with the Palaearctic hypothesis, Tuan *et al.* (2008) suggest the radiation of *Leishmania* in the Neotropics. Yet the possibility for the dispersal of *Leishmania* from Africa to the Neotropics before the separation of Pangea is also discussed which is compatible with the Neotropical origin and African/Neotropical origin hypotheses.

Ultimately in their review, Tuan *et al.* (2008) not only stressed the importance of evidence that supports the significance of the relationship between parasite, vector, and reservoir, but also that of molecular and biochemical data, which may currently be incongruous. Tuan *et al,* (2008) continue to discuss the point of conflict between these two sources of data and support for conclusive hypothesis of the origin of *Leishmania.*

Conclusion

Significant advances and progress has been made in understanding the classification, origin, and dispersal of *Leishmania,* unfortunately the current data is often incompatible. This has resulted in a debate over a Palaearctic, Neotropical, or African/Neotropical origin of *Leishmania* that has remained unsolved due to conflicting support amongst these hypotheses. The debate outlined in this paper is more than a pedagogical dispute amongst the scientific community. A conclusive hypothesis and comprehensive understanding of this parasite, its origin and dispersal is fundamental in the attempt to eradicate this disease through the development of vaccines. As outlined in this paper, the diversity, distribution, and phylogeny of the *Leishmania* parasites still remains in question and undetermined. This lack of understanding renders the question of one all encompassing vaccine versus several for different species complexes unanswerable. Therefore, continued research and investigation is needed in this topic, especially with the rise of new technologies and theories that may shed light on the debate. Until a conclusion can be made, the development of a vaccine will mostly likely have to wait and methods of prevention and treatment will continue to be used. While prevention through the use of bed nets and insecticide will continue to be helpful, it will also be important to target the socio-economic and cultural factors that put large populations at risk in favorable environments for the sand fly, such as refugee camps. Environmental factors, like global warming, will also become an increasing concern as the range of the sand fly increases. While not one of the infamous infectious diseases that plague the earth, Leishmaniasis is a devastating disease that is likely to become just that unless research and awareness is not only continued, but also increased.

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