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Further Support for a Palaearctic Origin of *Leishmania*

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The fossil record and systematics of murid rodents, reservoirs of zoonotic cutaneous leishmaniasis in the Palaearctic, Oriental, African, Nearctic and Neotropical, strongly support a Palaearctic origin of Leishmania. *The fossil record and systematics of phlebotomine sand flies reinforce this idea. Interpretations of molecular data that place the origin of* Leishmania *in the Neotropical are inconsistent with the natural histories of reservoirs and vectors. The evolutionary pattern of New World rats (Sigmodontinae) indicates that they may be the most important reservoirs of zoonotic cutaneous leishmaniasis throughout their range.*

Key words*: Leishmania mexicana* - Sigmodontinae - Muridae - *Lutzomyia* - coevolution - biogeography

While there is consensus on the taxonomic groupings (summarized in Kerr 2000) and antiquity (Noyes 1998, Kerr 2000) of the *Leishmania*/*Endotrypanum* clade, the geographic locality of origin and root are disputed. Noyes (1998) hypothesized a Neotropical origin with the root between the *Endotrypanum*/*L. hertigi* clade and the *L.* (*Viannia*)/*L.* (*Leishmania*) clade; Kerr (2000) hypothesized a Palaearctic origin with the root between the Old World and New World *L. Leishmania*. The strength of the Palaearctic hypothesis lies in the congruence of the systematics and fossil record of reservoirs and vectors of *Leishmania* with the molecular data (Kerr 2000). Congruence between molecular and morphological patterns is strong evidence that the historical pattern has been discovered (Hillis 1987).

The cosmopolitan role of murid rodents as reservoirs for cutaneous leishmaniasis in the Palaearctic, Oriental, African, Nearctic, and Neotropical zoological regions (Ashford 1996) is the strongest evidence that *Leishmania* originated in the Palaearctic. According to Ashford (1996), reservoirs include Gerbillinae (*Rhombomys* in Central Asia, *Psammomys* in West Asia and North Africa, *Meriones* in Pakistan and India), Murinae (*Arvicanthis* and *Mastomys* in sub-Saharan Africa), and Sigmodontinae (*Neotoma* in the USA and *Ototylomys* in Belize). Lainson and Strangways-Dixon (1964) reported an infection in *Nyctomys*, indicating that it may also be a reservoir. It seems reasonable to conclude that the pattern of origination, dispersal and diversification of *Leishmania* would be congruent with that of its reservoirs (Kerr 2000). For example, the evolution of Sigmodontinae progressed from the neotomines of North America (including *Neotoma*), to tylomyines (including *Ototylomys*) and nyctomines (including *Nyctomys*) of Central America. Nyctomines form a phenetic link between North American neotomines and South American groupings such as the thomasomyines and the oryzomyines (Eisenberg 1989), suggesting that these groups deserve closer investigation as possible reservoirs of *L. mexicana* in South America. Sigmodontinae are identifiable as early as the Miocene in North America; although most investigators date entry into South America at the Pliocene, there is some support for initial entry in the Miocene before the uplift of the Isthmus (Eisenberg 1989). Noyes et al. (1997) suggested that the presence of *L. mexicana* in the Dominican Republic indicated that *Leishmania* parasites can be carried across open water in hosts or vectors. If this was the case, then *Leishmania* may have also been introduced into South America during the Miocene, allowing a much longer time span for its diversification and dispelling one of the greatest difficulties with the hypothesis of a Palaearctic origin.

Noyes (1998) cited reclassification of the *Lutzomyia vexator* series into the new subtribe Sergentomyiina with Old World *Sergentomyia* (Galati 1995), which includes the vectors of *Sauroleishmania*, as support of a Neotropical origin of *Leishmania*. He incorrectly stated that a member of the *vexator* series was implicated as a vector of *L. mexicana* in Texas; the only known vector of

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Leishmania in the USA is *Lu. anthophora* (McHugh et al. 1993), which Galati places in the subtribe Lutzomyiina. Dujardin et al. (1999) state that the close relationship they found between *Lutzomyia* and *Phlebotomus* was predicted by Noyes (1998) hypothesis of a Neotropical origin of *Leishmania*. In fact, classifications by either Galati (1995) or Dujardin et al. (1999) support either a Neotropical or Palaearctic origin of *Leishmania* equally.

A difficulty with the idea that *Endotrypanum* is at the base of the *Leishmania*/*Endotrypanum* clade is the fact that published trees of this clade are inadequately rooted. For example, Croan et al. (1997) used *Endotrypanum* as an outgroup for a tree of the *Leishmania*/*Sauroleishmania* lineage and Noyes et al. (1997) used an unnamed trypanosomatid intermediate between *Crithidia*/*Leptomonas* and *Endotrypanum*/*Leishmania* as an outgroup for the *Leishmania*/*Endotrypanum* lineage. In neither case was the outgroup clearly demonstrated to have evolved first, nor were plesiomorphic, synapomorphic or apomorphic character states made explicit. A well-rooted tree of the *Leishmania*/*Endotrypanum* clade that supports the Palaearctic origin of *Leishmania* can be constructed based on the presence or absence of the GP46/M-2 gene family, using *Crithidia* as an outgroup (Fig. 1). The gene family is present in *L. mexicana, L. major, L. donovani, S. tarentolae* and *C. fasciculata* and absent in *L.* (*Viannia*) (McMahon-Pratt et al. 1992), *L. enrietti* (Hanekamp & Langer 1991) and Paraleishmania (Cupolillo et al. 2000). Another simplistic but congruent tree can be constructed based on reservoir hosts (Fig. 2), with *Leishmania* coevolving with the murid lineage, then expanding first to endemic hystricomorph rodents (including porcupines and echimyid rodents), and then sloths in South America.

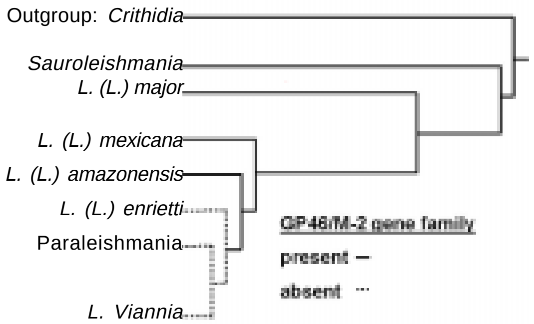

Fig. 1: phylogenetic tree of *Leishmania* based on the assumption that presence of the GP46/M-2 gene family is a primitive character.

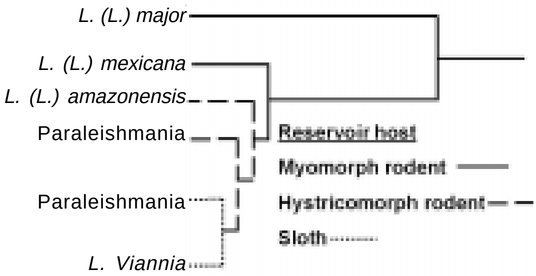

Fig. 2: phylogenetic tree of *Leishmania* based on reservoir hosts.

The concept that the locality where a taxa encompasses the greatest genetic diversity is the locality where a lineage originated permeates the molecular literature (Kerr 2000), but ignores the influence of isolation (on islands or mountain peaks) and climatic change on diversification (Vrba 1992, Cox & Moore 2000). The observation by Noyes et al. (1997) of a distinctive strain of *L. mexicana* in the Dominican Republic is a classic example of diversification resulting from isolation which illustrates one mechanism that caused rapid diversification of *Leishmania* in South America and supports a Palaearctic origin of the genus. Empirical evidence that adaptive differentiation occurs when populations are subdivided on islands may be found in studies of *Anolis* lizards by Losos et al. (1997).

The evolutionary origin of *Leishmania* can be investigated further with molecular analyses of intraspecific DNA diversity. The great intraspecific diversity of *L. mexicana* reported by Cupolillo et al. (1998) may be the result of isolation of populations on islands and mountain peaks, or within various reservoir hosts. This hypothesis could be tested with isolates of *L. mexicana*, which is very widely dispersed geographically, from Arizona in the USA (Kerr et al. 1999), to the Andes in Ecuador (Hashiguchi et al. 1991). Ecological investigations of enzootic foci of *Leishmania*, in the style of Lainson and Strangways-Dixon (1964), but with the collaboration of molecular biologists, are of critical importance to clarify the evolution of the genus.

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