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Sand flies and *Leishmania*: specific versus permissive vectors

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In her recent review in *Trends in Parasitology* [1], Kamhawi highlighted the role of sand fly midgut receptors of lipophosphoglycan (LPG) in *Leishmania* attachment. This attachment is a critical step in *Leishmania* development as it enables the parasite to avoid expulsion from the midgut when the fly defecates. Two sand fly species, *Phlebotomus papatasi* and *P. sergenti*, display remarkable specificity for the *Leishmania* species they transmit in nature. In these specific vectors the attachment is controlled by LPG receptors that bind to terminal carbohydrates of the parasite LPG. In *P. papatasi* the galactose-specific lectin PpGalec was identified as the LPG receptor [2].

It is understandable that the review deals primarily with the best studied and straightforward parasite-vector system *L. major* - *P. papatasi* but it should be also acknowledged that a more complex picture of attachment is emerging for most other species. We feel that it should be stressed that most sand fly species tested to date support development of multiple *Leishmania species* and thus fall into a second group called “permissive vectors”. A typical example is *P. arabicus*, a sand fly recently identified as a vector of *L. tropica* [3]. The broad vectorial competence of *P. arabicus* was demonstrated by its high susceptibility to both *L. major* and *L. infantum* [4], as well as by the cyclical transmission of *L. tropica* to hyraxes *Procavia capensis* [5] that serve as natural reservoir hosts for this parasite [3].

The mechanism of *Leishmania* attachment in permissive vectors is very different; unexpectedly, it was shown that another lectin-like mechanism, independent of LPG, exists in these sand flies. LPG-deficient mutants of *L. mexicana* and *L. major* grew well in permissive vectors *Lutzomyia longipalpis* and *P. arabicus* producing heavy infections, fully comparable with those caused by the wild type parasites [4, 6]. Similarly, *L. tropica* with modified LPG [7] is not able to grow in *P. sergenti* but successfully develops in a permissive vector *P. arabicus* [8]. Clear correlation was found between permissivity and the type of glycosylation of the midgut proteins; O-glycosylated proteins with N-acetylgalactosamine (GalNAc) epitopes were present in permissive flies but not in the specific vectors [4, 8]. The hypothesis about the role of O-glycosylated proteins in *Leishmania* attachment in permissive vectors is supported by two further observations: molecules with GalNAc epitopes bind to *Leshmania* surface [4] and are present on microvillar surface of the midgut, the very place of the attachment of *Leishmania* promastigotes [4, 8, 9]. It follows that GalNAc-specific lectin activity found on promastigote surface [10] serves as a receptor for this binding.

The classification of sand fly species into specific or permissive vectors is likely to be an oversimplification of the true complexity of parasite-sand fly interactions. Indeed, some sand fly species may be of an ‘intermediate’ type, since they support development of many but not all *Leishmania* species. Whether the LPG-independent paradigm seen with *L. longipalpis* or *P. arabicus* will apply generally to all permissive sand flies remains to be determined; in a single study on *P. argentipes* the LPG deficient *L. donovani* mutants failed

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to survive [11]. However, while the concept of specific versus permissive vectors may be further refined, at present it provides a useful model to work with.

The broad vectorial competence of permissive sand flies also has important epidemiological consequences as it enables successful adaptation of *Leishmania* to new vectors. This explains some unexpected findings from the field such as the circulation of LPG-impaired *L. tropica* through *P. arabicus* [3, 8] and the introduction of *L. infantum* (syn. *L. chagasi*) from the Mediterranean to Latin America [12], where it adapted to the local permissive sand fly *L. longipalpis*. Presently, changes of climate, expansion of human settlements and accelerated movements of humans and animals around the world lead all to an increased risk of the spread of vector-borne diseases including leishmaniases. The high susceptibility of permissive sand fly species thus may represent an important aspect in the establishment of new foci of leishmaniases.

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