Leishmania proteophosphoglycans regurgitated from infected sand flies accelerates dermal wound repair and exacerbates leishmaniasis via insulin-like growth factor 1-dependent signalling.

Emilie Giraud[1], Tamsyn Derrick[1], Oihane Martin[1], Rod J. Dillon[2], Tereza Leštinová[3], Petr Volf[3], Ingrid Műller[4], Paul A. Bates[2] and Matthew E. Rogers[1]

1. Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, WC1E 7HT, UK
2. Division of Biomedical and Life Sciences, Lancaster University, LA1 4YB, UK
3. Department of Parasitology, Charles University, Vinicna 7, Prague 2, 128 44 Czech Republic
4. Department of Medicine, Section of Immunology, Imperial College London, W2 1PG, UK

The promastigote secretory gel (PSG) is matrix of filamentous proteophosphoglycan secreted by *Leishmania* promastigotes inside the sand fly gut, which facilitates the transmission and infection of the mammalian host. The early host response to PSG has not been characterised.

Mice were inoculated with 1000 L*eishmania mexicana* metacyclic promastigotes into BALB/c mouse ears, with or without PSG. The Affymetrix Mouse GeneChip revealed differential expression of 7,927 transcripts (FC >1.5, 5% FDR) to PSG, i.e. 27% of the mouse genome. We found that PSG was associated with an early up-regulation of transcripts involved in inflammation, inflammatory cell recruitment, epithelial cell proliferation and fibrosis. *In vitro* and *in vivo* experiments revealed that PSG significantly accelerated wound healing. Insulin-like growth factor 1 (IGF1) is linked to macrophage alternative activation and wound repair. Dermal expression of IGF1 was enhanced following an infected sand fly bite and was acutely responsive to the PSG but not to parasites or sand fly saliva. Antibody blockade of IGF1 ablated the gel's ability to promote wound closure in mice and significantly reduced the virulence of *L. mexicana* infection delivered by sand fly bite.

These results show that PSG strongly influences multiple stages of the wound healing process in skin following *Leishmania* transmission; resulting in accelerated healing and, via IGF1-signalling, provides an environment that promotes parasite survival and growth.