ABSTRACT

Sand flies serve as the vectors of leishmaniasis and their saliva was shown to affect the outcome of *Leishmania* infection by immunomodulation of the host. On the other hand, sand fly saliva contains a large scale of farmacologically active proteins that are strongly immunogenous for bitten hosts and specific anti-saliva immunity initiated by repeated sand fly feeding provides protection against *Leishmania* infection. Specific cell-mediated immunity was shown to be the core of the protectivity; however, our data suggests that the protective immunity has certain limitations. In mice bitten by sand flies for prolonged periods, we observed the desenzitization in term of abrogation of the protective immunity. Thus, we can speculate that the protective effect of immunity is linked solely with the short-term exposure. Nevertheless, our experiments showed that this aspect is also conditioned by the immediate infection after the protective short-term immunization. Taken together, it seems that these limitations may explain the circulation of leishmaniasis in endemic areas, even though humans and animals are frequently immunized by bites of uninfected sand flies.

Repeated sand fly feeding on various hosts also promotes production of anti-saliva antibodies that reflect the intensity of exposure. We demonstrated these findings in dogs and rodents, the natural reservoir hosts of visceral and cutaneous leishmaniasis, respectively. Therefore, in endemic areas, specific humoral response might be used as the effective epidemiological tool. Moreover, our study showed remarkable relationship between the canine anti-saliva antibody response and the status of visceral leishmaniasis. As the specific IgG2 response negatively correlated with the risk of *Leishmania infantum* infection, in endemic areas these antibodies might be employed as the risk marker of *Leishmania* transmission for dogs.

For a broader use of sand fly salivary antigens in epidemiological studies it would be beneficial to replace the whole saliva with the individual salivary proteins possessing required antigenic properties. Therefore, we broaden the repertoir of salivary proteins of *P. orientalis*, *P. perniciosus*, and *P. papatasi* and we proved the feasibility of using the recombinant proteins instead of whole sand fly saliva. Furthermore, we showed that the non-endemicity of visceral leishmaniasis in certain areas in Ethiopia, albeit the presence of the vector, is not caused by the difference in composition of salivary proteins in *P. orientalis* populations.