PARASITOLOGY

Transmission key to *Leishmania* vaccine

Many experimental vaccines against leishmaniasis have shown promising results in the laboratory but have failed to translate into success in the clinic. In a detailed evaluation that was recently published in *PLoS Pathogens*, David Sacks and colleagues now shed light on this conundrum.

The obligate intracellular protozoan parasite *Leishmania* is transmitted to humans by a bite from an infected phlebotomine sand fly vector. The WHO estimates that 350 million people worldwide are at risk of leishmaniasis, with 2 million new cases occurring annually. In cutaneous leishmaniasis, which is caused by *Leishmania major*, individuals can only be infected once and the persistence of low numbers of parasites within healed cutaneous lesions is thought to be responsible for this life-long protection. Many different experimental vaccines that have been developed over the past decade have proven to be efficacious in generating protection against experimental needle

challenge in mouse models. One such vaccine, which used autoclaved *L. major* (ALM) antigen with or without *Mycobacterium bovis* bacille Calmette–Guérin (BCG) as adjuvant, has been tested extensively in human trials but failed to protect against natural exposure.

Sacks and colleagues were interested in solving this problem. They began by going back to basics and characterizing the immune response that occurs following natural *L. major* transmission. Mice with healed primary lesions were infected with *L. major* from the bite of infected sand flies. By 3 days post-challenge, the authors found that there was a dramatic infiltration of interferon- γ (IFN γ)-producing, *L. major*-specific CD4⁺ effector T cells and that this response correlated with a significant reduction in parasite load.

Previous studies had shown that vaccination with ALM plus CpG oligodeoxynucleotides protected mice against experimental needle challenge. The authors tested whether this vaccine could also protect against natural transmission, and found that vaccinated mice, although protected against needle inoculation, were not protected against natural exposure to *L. major*. What accounts for this difference in protection? There was no inherent difference in the dose of parasite delivered by the two inoculation methods and no difference in the virulence of the inoculated parasites, which indicates that it is the act of vector transmission that is the

key factor. More detailed analysis revealed that the CD4⁺ T cell response to natural exposure in the vaccinated mice was slower and weaker than that observed in mice bearing healed lesions. Finally, the authors had previously shown that the localized inflammatory response that is induced by a bite from an infected sand fly includes the extensive recruitment of neutrophils. Here, they further characterized this response and found that in both vaccinated and healed mice, although there was neutrophil infiltration to both needle and sand fly inoculation sites, this infiltration was only transient at needle inoculation sites but persisted for more than 4 weeks at sand fly inoculation sites. Furthermore, they showed that neutrophil depletion promoted the efficacy of the killed vaccine.

These results indicate that the ALM plus CpG vaccine fails to protect against natural transmission of *L. major* because although an effector T cell response is induced, this response is not sufficient or rapid enough to counteract the neutrophil-dominated local inflammatory response that is induced by a sand fly bite. These data emphasize the importance of using natural challenge models in future vaccine development studies.

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ORIGINAL RESEARCH PAPER Peters, N. C. et al. Vector transmission of *Leishmania* abrogates vaccine-induced protective immunity. *PLoS Pathog.* 5, e1000484 (2009)