

Dhafer Laouini Interview



Dhafer Laouini

Dhafer Laouini is a researcher at the Institut Pasteur de Tunis in Tunisia. After completing his PhD, he held postdoctoral positions at the Institut Pasteur in France and the Harvard Medical School in the USA. His main research focus is on leishmania host-pathogen interactions.

We recently spoke to Dhafer about leishmaniasis and how his research has aided in understanding the immune response towards leishmania and possible vaccine strategies against it.

Name: Dhafer Laouini

Position: Senior Scientist

Research Interest: Immunobiology of leishmaniasis, Host-pathogen interactions

What is leishmaniasis? The leishmaniases are a group of

vector-borne diseases caused by obligate parasites from the genus *Leishmania* and transmitted to humans and other mammals by phlebotomine sandflies. Parasites are able to survive and replicate within the harsh and potentially hostile phagolysosomal environment of mammalian mononuclear phagocytes.

Leishmaniasis are endemic in large areas of the tropics, subtropics and Mediterranean basin and responsible for increasing health problems in large parts of the world. Indeed, they are considered by the World Health Organization (WHO) as one of the leading neglected tropical diseases (NTD) in terms of mortality and morbidity. They caused about 50,000 deaths caused in 2010 and more than 3.3 million disability adjusted life years (DALY).

Up to 20 *Leishmania* species worldwide distributed can cause these diseases. *Leishmania* infections may take different and diverse clinical forms, depending on the causing species and the location of the parasite, i.e. cutaneous (CL), visceral (VL), muco-cutaneous (MCL), diffuse cutaneous, disseminated cutaneous, mucosal (ML), and post-kala-azar dermal leishmaniasis (PKDL). The two main forms are the CL and VL. Over 90% of cases of the former are distributed across Afghanistan, Iran, Saudi Arabia, Syria; Algeria, Tunisia, Brazil and Peru, whereas about 90% of cases of the later occur in Bangladesh, India and Nepal, Ethiopia, Kenya, Sudan, and Brazil. Infected people often develop skin lesions around the bite site and may recover on their own

VL is the most severe form; it engages the vital prognosis in the absence of adapted treatment. It is caused by two species: *L. donovani*, an anthroponotic parasite that is highly endemic in East Africa and the Indian subcontinent, and *L. infantum*, a zoonotic with a canine reservoir, which affects all age groups, whereas *L. infantum* affects mainly children and immune-compromised individuals, especially those infected with HIV. The symptoms are dominated by irregular and prolonged

fever, splenomegaly and anemia, and their intensity reflects a significant increase of parasites in hematopoietic organs. Later on, nearly half of the VL patients develop maculopapular and nodular lesions, affecting the face and often the limbs. This cutaneous involvement, or PKDL, is difficult to treat and could play an important role in the transmission of the parasite. CL presents as inflammatory lesions, often ulcerated and superinfected, which heal spontaneously after a few months to a few years, but give way to scars. Their prejudice is both functional and aesthetic. MCL is characterized by secondary mucosal involvement occurring one to five years after an initial CL.

In terms of immunity, the demonstration of the functionally distinct (Th1 and Th2) T CD4 + cell subpopulations and the cytokines they produce was demonstrated in the experimental leishmaniasis model. In response to the experimental inoculation of *L. major*, C57BL/6 mice develop a Th1-like response, which leads to the control of parasitic growth and resistance to infection, particularly through the production of factors Activation of macrophages such as interferon (IFN)- γ and tumor necrosis factor (TNF)- α . In contrast, BALB/c mice develop a Th2-type response, with the production of IL-4, IL-5, IL-6, and IL-10, which correlates with the development of progressive disease. In addition, these animal models demonstrated the role of regulatory T cells in the fine-tuning of the immuno-pathogenic responses, the role of the cytokine network in macrophage activation and in the induction of a memory response against re-infection. Studies of the cellular immune responses during human leishmaniasis are often descriptive. Data obtained in humans seem to confirm the dichotomy of the CD4+ T cell response (Th1/Th2) observed in mice. Indeed, in patients with localized cutaneous forms, the cellular immune response is characterized by the proliferation of blood lymphocytes and the production of IFN- γ and IL-2 in response to parasitic antigens. This is also the case for individuals having been in contact with the parasite.

Conversely, in patients with VL there is cellular anergy to parasitic. Expression of IL-10 expression decreases after an effective treatment, suggesting a conflict between a Th1-type cellular response and an accumulation of suppressive cytokines whose cellular origin can be multiple (Th2, macrophage, others). During VL, hyper-gamma globulinaemia, including anti-leishmania antibodies (ineffective for parasite neutralization) is also noticed in patients. MCL is also characterized by cellular anergy and negativity of skin tests with leishmanin. During ML form, a mixed response of Th1 and Th2 type is often detected in circulating lymphocytes and cutaneous sites.

Is there a vaccine or a cure for this disease? An arsenal of different registered drugs is available for leishmaniasis treatment but has a limited impact due to its toxicity, cost, or resistance. Pentavalent antimonials (e.g.; sodium stibogluconate, pentostam, meglumine antimonite, and glucantime) are the main standard drugs and remain the primary line of treatment in many endemic regions. However, antimonial formulations have been rendered problematic in different Asian countries due to parasite resistance. Other recommended therapies include amphotericin B, miltefosine and paromomycin. Antibiotics have been developed as alternative treatments against leishmaniasis, essentially in areas of antimonial drug resistance.

The immune protection observed upon healing of cutaneous leishmaniasis suggests that designing an effective vaccine might be achievable. However, and till date, there is not yet an effective vaccine against this parasitic disease. First generation vaccines based on killed parasites were not successful, whereas those using new generations of vaccines are still very limited.

How does the *leishmania* parasite evade the immune response? To establish infection, the flagellated metacyclic promastigotes must enter macrophages and avoid triggering host responses.

Since macrophages play a dual function in infection, acting as a safe shelter for parasites but also as their ultimate killer, these cells are the alpha and the omega for host resistance or susceptibility to *Leishmania* infection. *Leishmania* have developed a range of sophisticated mechanisms to subvert the leishmanicidal activities of macrophages, by altering gene expression for cytokines, chemokines, transcription factors, membrane receptors and molecules involved in signal transduction in infected cells.

During early stage of infection, neutrophils may serve as host for *Leishmania* parasites and undergo apoptosis. Apoptotic bodies are phagocytized by macrophages, triggering a silent entry into macrophages and inducing anti-inflammatory signal pathways. Parasite lipophosphoglycans (LPG) can prevent the complement membrane attack complex insertion and parasite kinase phosphorylates the components of the complement, inhibiting its activation. *Leishmania*-macrophage interaction activates tyrosine phosphatase that dephosphorylates STAT-1 resulting to inhibition of transcription of the IL-12p40 gene. Several other mechanisms of escape have been described leading to parasite survival within the host.

How has your research contributed to the field of leishmaniasis? Our laboratory at Institut Pasteur de Tunis has, over the last thirty years, contributed to: i) the understanding of the natural history of *Leishmania* infection, the importance of asymptomatic infections and mechanisms of emergence; ii) the identification of human correlates for protection; iii) the identification and characterization of several candidate vaccines with the development of new original experimental models; iv) the identification and characterization, by genomic, transcriptomic and proteomic approaches, of parasitic molecules essential for the biology and virulence of the parasite, and : v) the development and validation of new diagnostic and control tools for leishmaniasis.

Contact details:

Dhafer Laouini

Laboratory Transmission, Control and Immuno-biology of
Infections

Institut Pasteur de Tunis

13, place Pasteur. BP 74

1002 Tunis-Belvedere

Tunisia

e-mail address: dhafer.laouini@pasteur.tn

Interview by Thandeka Moyo