Key substance for treatment of visceral leishmaniasis identified

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A study shows that stimulating the production of interleukin-17A (IL-17A), one of the cytokines released by cells of the immune system, can be an effective strategy for the treatment of visceral leishmaniasis, considered one of the six most important parasitic diseases affecting humans.

The principal investigator in this research is João Santana da Silva, Full Professor at the University of São Paulo's Ribeirão Preto Medical School (FMRP-USP).According to the article, increased levels of IL-17A in an infected organism not only help to reduce parasite load but also protect organs against the lesions caused by an exacerbated inflammatory response, which is common in such cases.

"These findings pave the way to new therapeutic strategies," Santana da Silva explained. "Drugs can be developed to stimulate production of IL-17A directly and also to neutralize the action of interleukin-27 [IL-27], another cytokine that is released by defense cells that inhibits synthesis of IL-17A."

In the study, the group used parasites of the species Leishmania infantum, which are transmitted to humans by insect bites, and especially those of the sandfly *Lutzomyia longipalpis*.

"As soon as the parasite enters the organism, the host responds with a surge of cytokines," Santana da Silva said. "Successful control of the infection depends on which substances are produced by the immune system. Some individuals are more resilient, others more susceptible. Even the former may develop lesions in their organs as a result of their inflammatory response."

In susceptible individuals, the protozoan spreads to the liver, spleen, bone marrow and lymph nodes, causing these organs to swell and become inflamed and also leading to anemia, fever and immunosuppression. Without treatment, the disease is fatal in more than 90% of cases.

The new findings of the research group at FMRP-USP show that if IL-17A is produced in appropriate amounts in addition to IFN?, the parasite can be eliminated without causing damage to the organism's tissues. This is because IL-17A attracts neutrophils to the site of the infection. Neutrophils are defense cells capable of phagocytizing pathogens and diseased cells. When the parasite load decreases, so does the production of cytokines, such as IFN?, that can damage tissue.

Objectives

"In this study, we set out to understand what modulates the release of IL-17A," Santana da Silva said. "We suspected one of the regulatory factors was IL-27, and this hypothesis proved correct. In experiments with mice, we investigated which receptors recognize the parasite and then produce IL-27, which ends up inducing a cascade of reactions that leads to the inhibition of IL-17A."

In one of the experiments, a group of mice was genetically modified to silence the gene that codes for Ebi3, a key protein for the functioning of IL-27 as well as another cytokine, called interleukin-35 (IL-35). Hence, IL-27 and IL-35 were inactive in these genetically modified (GM) mice.

The researchers then compared the response of these animals without Ebi3 to infection by *L. infantum* with the response of wild-type (not genetically modified) mice. The former produced more IL-17A and less IFN?. In other words, the group of GM mice controlled infection better and did not develop lesions in their organs. Flow cytometry analysis showed twice as many neutrophils in the spleen and liver of the mice without Ebi3.

"Next, we repeated the same experiment, except

that this time, we administered an antibody to neutralize IL-17A in the group without Ebi3," Santana da Silva said. "We found that the two groups had a very similar immune response when this cytokine was neutralized. Parasite load and organ inflammation were equivalent in both groups, and the number of neutrophils in the organs of the group without Ebi3 didn't double. This result confirmed the importance of IL-17A."

According to Santana da Silva, strategies based on stimulating production of this cytokine should also be studied for treatment of cutaneous leishmaniasis, caused by *L. amazonensis*, *L. guyanensis* and *L. braziliensis*. The vector in this case is also the sandfly *L. longipalpis*, but the lesions resulting from the host organism's inflammatory response affect the skin and can cause deformations.

To further investigate the genetic factors that determine the progression of visceral leishmaniasis, the researchers have sequenced the genomes of resistant and susceptible patients and are currently performing comparative analyses in a search for differently expressed genes.

They are also investigating the bacteria present in acute lesions to see whether these bacteria influence the immune system's response in any way.

Besides *L. infantum*, visceral leishmaniasis can also be caused by *L. donovani*. The World Health Organization (WHO) estimates that 300,000 new cases and about 20,000 deaths occur per year worldwide.

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