New iron transporter essential for Leishmania parasite virulence is potential drug target

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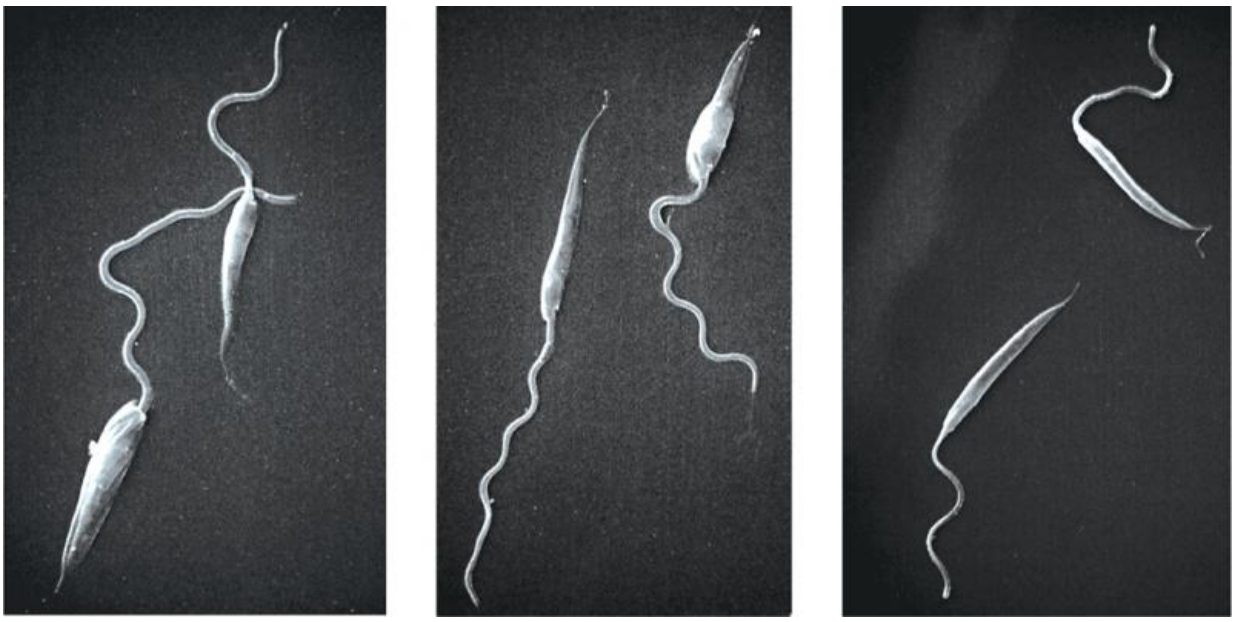

Credit: Mittra et al. (2015), CC BY

Leishmaniasis is a serious parasitic disease that affects 12 million people worldwide. Like for many neglected tropical diseases that disproportionately affect poor populations, existing drugs have serious side-effects and face increasing parasite resistance. A study published on January 7th in *PLOS Pathogens* identifies a new drug target, and supports the conclusion that iron-dependent signals generated in the mitochondria

are essential for the development of parasite stages that cause disease in humans.

Following introduction into mammalian hosts (including humans) by the bite of a sand fly, *Leishmania* parasites undergo extensive changes to adapt to survival and multiplication inside the new host cells and tissues. The resulting disease-causing (virulent) parasite forms, called amastigotes, infect and multiply in immune cells called macrophages at the bite site and after dissemination of the infection to secondary sites.

Norma Andrews from the University of Maryland in College Park, USA and colleagues are studying the transformation of the parasite from the stage present in the sand fly (called promastigote) to the amastigote stage that causes disease in humans. The researchers had previously demonstrated a role for reactive oxygen species (ROS) in initiating amastigote development. Because the amount of ROS present in cells is tightly regulated by iron-dependent processes in the mitochondria (the cellular compartments in which energy is generated), the researchers had proposed iron import into the mitochondria to be essential for this process. However, evidence supporting this hypothesis was lacking, because there was no known mitochondrial iron transporter in *Leishmania*.

In this study, they identify LMIT1, a *Leishmania* protein that functions as a mitochondrial iron transporter and is also present in related trypanosomatid parasites. The researchers were unable to generate *Leishmania* parasites without LMIT1, suggesting that transporter function is essential for parasite viability. They were, however, able to generate and study parasites that had reduced LMIT1 function.

Promastigotes with reduced LMIT1 activity showed growth defects and were more susceptible to ROS toxicity, consistent with a role of iron as an essential co-factor of mitochondrial enzymes called superoxide

dismutases that detoxify ROS. Moreover, the researchers found that infective metacyclic stages derived from these promastigotes, which correspond to the parasite forms transmitted by sand flies, were unable to differentiate into amastigotes and multiply in mouse macrophages or cause cutaneous lesions in mice.

Moreover, when induced to differentiate into amastigotes extracellularly, in host cell-free culture, the parasites with reduced LMIT1 function showed incomplete differentiation and severe defects in iron content and iron-dependent mitochondrial metabolism. Amastigotes with such compromised mitochondrial function were unable to multiply in mouse macrophages (i.e. mammalian *Leishmania* target cells), suggesting that inhibition of LMIT1 can abolish parasite virulence.

"Our results demonstrate", the researchers say, "the importance of mitochondrial iron uptake in trypanosomatid parasites, and highlight the role of LMIT1 in the iron-regulated process that orchestrates differentiation of *Leishmania amazoniensis* into infective amastigotes". They add, that "by identifying and characterizing LMIT1 as a mitochondrial iron importer, we established a direct connection between iron uptake, mitochondrial redox balance and the development of virulence in *Leishmania*, significantly expanding future options for controlling these serious human infections."

More information: Mittra B, Laranjeira-Silva MF, Perrone Bezerra de Menezes J, Jensen J, Michailowsky V, Andrews NW (2016) A Trypanosomatid Iron Transporter that Regulates Mitochondrial Function Is Required for Leishmania amazonensis Virulence. *PLoS Pathog* 12(1): e1005340. DOI: 10.1371/journal.ppat.1005340