Study suggests metabolism influences parasite's resistance to drugs

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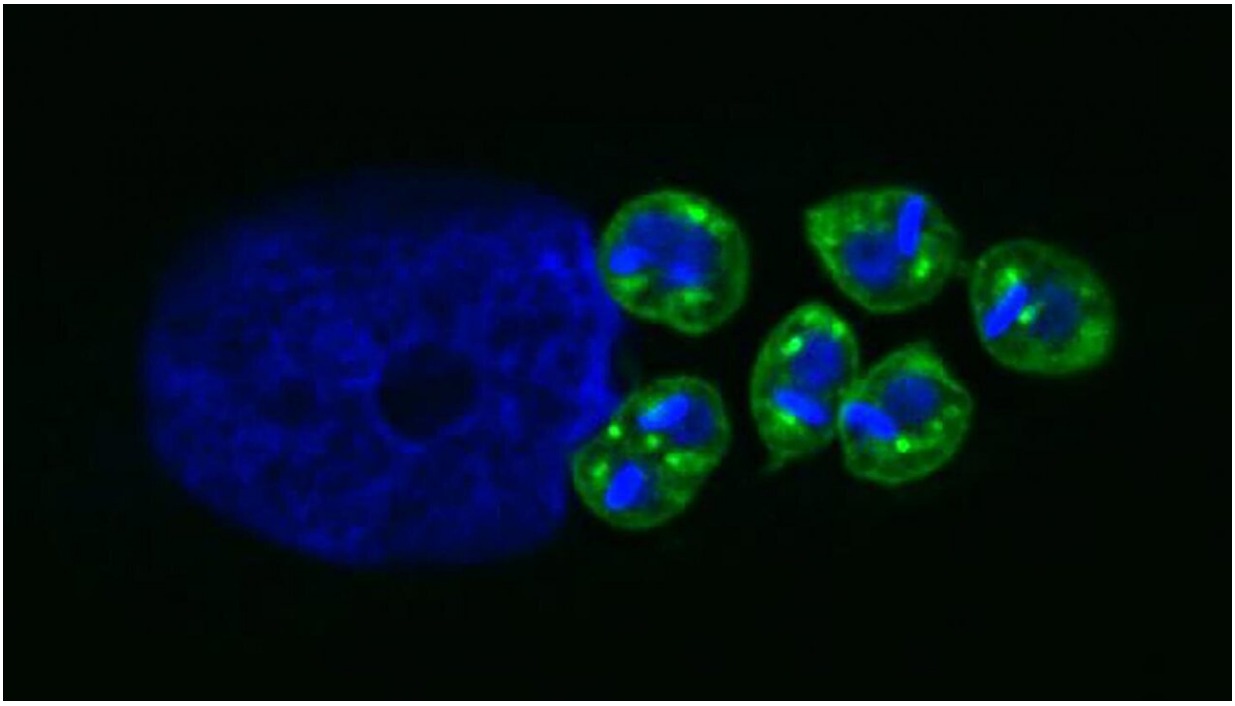

Intracellular amastigotes inside a mammalian host cell. Credit: Dumoulin et al. (CC BY 4.0)

New insight on how a parasite can resist current therapies has been published today in the open-access *eLife* journal.

The study in cultures of human cells infected with *Trypanosoma cruzi (T. cruzi*), the parasite that causes Chagas disease, suggests that its

metabolic state influences the effectiveness of azole drugs that inhibit its growth. These findings could be useful for the development of more effective antimicrobial treatments.

Chagas disease, also known as American trypanosomiasis, can cause a sudden, brief (acute) illness, or it may be a long-lasting (chronic) condition. Around six to seven million people worldwide are estimated to be infected with the *T. cruzi* pathogen that causes the disease, according to the World Health Organization. Symptoms can range from mild to severe, but do not often appear until the chronic stage of disease.

"The goal for the treatment of Chagas and other infectious diseases is to eliminate the pathogen from the infected host," explains first author Peter Dumoulin, Postdoctoral Fellow at senior author Barbara Burleigh's lab, Harvard T. H. Chan School of Public Health, Boston, US. "There are a few ways in which pathogens can survive antimicrobial treatment. One of the less explored options is the impact of their metabolic and environmental diversity (or heterogeneity) on the effectiveness of a given treatment, and we wanted to find out if these factors play a role in *T. cruzi*'s drug resistance."

There is an intracellular stage in the *T. cruzi* life-cycle where they become amastigotes—replicative forms of the parasite that persist in the infected host. The team's work revealed that the sensitivity of amastigotes to azole drugs increases significantly in the presence of certain concentrations of the amino acid glutamine, independent of the parasite's growth rate.

Further metabolic labeling and inhibitor studies showed that *T. cruzi*'s glutamine metabolism leads to the enhanced production of steroid alcohols (sterols), along with an accompanying accumulation of non-standard sterols and toxicity to the parasite in the presence of azoles. These findings suggest that metabolic heterogeneity in the parasite-host

interaction may contribute to the failure of some drugs to achieve sterile cure, demonstrating a novel link between metabolism and drug efficacy.

"Our work provides further evidence that the metabolic state of a microorganism is important for determining its susceptibility to antimicrobials, and lays the groundwork for further studies," concludes Burleigh, Professor of Immunology and Infectious Diseases at Harvard Chan School. "Gaining a better understanding of metabolism in *T. cruzi* and other parasites, and why current drug candidates can fail to treat infection, could lead to more effective therapies for Chagas disease and other infections."

More information: Peter C Dumoulin et al, Glutamine metabolism modulates azole susceptibility in Trypanosoma cruzi amastigotes, *eLife* (2020). DOI: 10.7554/eLife.60226

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