New study on pathogenic Leishmania parasite sheds light on evolution of cell's force-producing machinery

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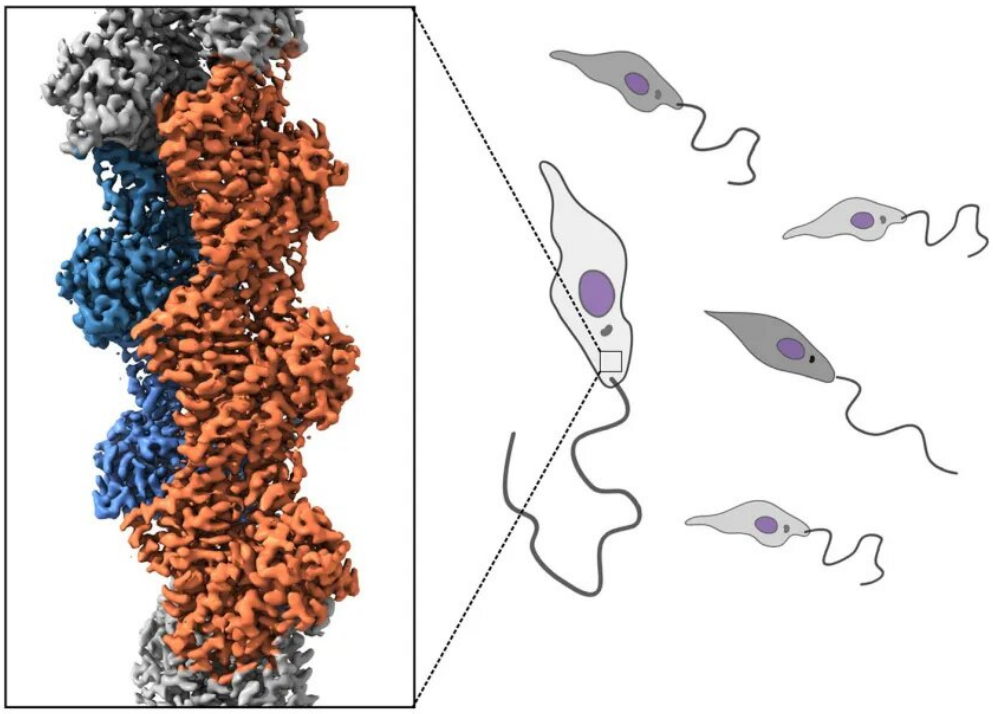

Credit: Pekka Lappalainen group

Leishmania are flagellated protozoan parasites that rely on both sandfly and mammalian hosts. Leishmania species cause severe diseases, especially in tropical countries. Due to their peculiar life cycle and their

more than one billion years of evolutionary distance from humans, the cell biology of Leishmania parasites exhibits notable differences compared to human cells.

Leishmania parasites have an actin cytoskeleton, which is a complex, dynamic network of filaments composed of a protein called actin. In humans, the actin cytoskeleton mediates many of the processes in the cells, such as migration, morphogenesis and the uptake of nutrients. In Leishmania parasites, the actin cytoskeleton appears to drive nutrient uptake only. Both the Leishmania actin itself and the proteins regulating the actin cytoskeleton of the parasite are very different from those of humans.

A new study carried out at the University of Helsinki, Finland and at Université Paris Cité, CNRS, Institut Jacques Monod, France revealed how the actin cytoskeleton is regulated in the Leishmania major parasite. According to the study, actin filaments of this evolutionarily distant parasite are much more dynamic compared to the actin filaments in human cells. Through determining the atomic structures of parasite actin filaments, the study also reveals the molecular basis of the remarkably rapid turnover of Leishmania actin filaments.

By focusing on the most divergent actin studied so far, this work sheds light on the evolutionary origins of the actin cytoskeleton.

"Our study suggests that the actin filaments of ancient eukaryotes were very dynamic. Through evolution, the actin cytoskeleton became more complex and more involved in a larger number of cellular functions. We propose that this was accompanied by the stabilization of actin filaments and the simultaneous appearance of a wide array of proteins, which accelerate and control the dynamics of actin filaments," says the lead author of the study Tommi Kotila from the University of Helsinki.

The structural differences between the Leishmania parasite and human actins can be also exploited to generate specific inhibitors against parasite actins.

"Currently available anti-leishmanial drugs have toxicity issues, and parasites have developed ways to achieve drug resistance. Thus, we need new and more specific drugs for treating leishmaniasis, and compounds against actin could be good candidates," says Academy Professor Pekka Lappalainen from the University of Helsinki.

The research is published in *Nature Communications*.

More information: Tommi Kotila et al, Structural basis of rapid actin dynamics in the evolutionarily divergent Leishmania parasite, *Nature Communications* (2022). DOI: 10.1038/s41467-022-31068-y

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