The malaria pathogen's cellular skeleton under a super-microscope

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The *Anopheles* mosquito transmits the *Plasmodium* parasite, which causes malaria. Credit: CDC/James Gathany

The tropical disease malaria is caused by the *Plasmodium* parasite. For its survival and propagation, *Plasmodium* requires a protein called actin. Scientists of the Helmholtz Centre for Infection Research (HZI) in Germany used high-resolution structural biology methods to investigate the different versions of this protein in the parasite in high detail. Their results, published in the scientific journal *PLOS Pathogens*, may in the

future contribute to the development of tailor-made drugs against malaria–a disease that causes more than half a million deaths per year.

Malaria is a life-threatening disease. According to World Health Organization estimates, around 207 million cases of malaria occurred in 2012. Children in Africa are at an especially high risk, and there is no approved vaccination to date. The disease is caused by *Plasmodium* parasites–single-celled parasites, which are transmitted by mosquitos. The pathogen enters the human body through a bite and induces typical symptoms like periodic fevers, nausea, and headaches.

To enter human cells and leave them again, the parasites need to be motile. To this end, they use a structural protein called actin. Actin is found in nearly all living organisms where it is one of the most abundant proteins. Inside cells, it assumes numerous tasks: It confers stability, allows cell division, and makes movement of single cells possible. The dynamical behaviour needed for these processes is enabled by individual globular actin molecules assembling together to form thread-like structures called filaments. The malaria parasite possesses two versions of actin, actin I and actin II, which differ substantially from each other. Even though these structural proteins are crucial for the pathogen's infectivity, researchers have so far not been able to demonstrate filament formation in the parasite.

Scientists of the HZI, the German Electron Synchrotron (DESY) and the European Molecular Biology Laboratory (EMBL), together with international partners, now succeeded in detecting filament assembly of the parasite actin II proteins. For this, they used electron microscopy, which overcomes the resolution limit of classical light microscopy. Male malaria parasites from which the scientists had deleted actin II were not able to form mature germ cells and consequently could not reproduce and propagate. To have only one actin variant is apparently not sufficient for this process. How filaments contribute to germ cell maturation is still

unclear. But why do the two proteins show such different behaviour?

To answer this question, the research team deciphered the structure of the globular actin proteins using X-radiation. "We were able to determine the structures of actin I and actin II at very high resolutions–down to 1.3 and 2.2 Ångström, respectively. With this, we are in the range of single atoms," says the project leader Prof Inari Kursula. "The structures show us that the two variants differ more from each other than actins in any other known living organism do." The high resolution enabled the researchers to identify areas within the proteins that cause the different behaviour. "We now understand that *Plasmodium* actin filaments are very different from other actin filaments, like for example from those found in humans, and that they are assembled in a very different manner. Now that we know the structural basis for this, we can look for ways to specifically interfere with the parasite cytoskeleton," says Kursula. This knowledge might in the future contribute to designing tailor-made anti-malarial medication.

More information: Juha Vahokoski, Saligram Prabhakar Bhargav, Ambroise Desfosses, Maria Andreadaki, Esa-Pekka Kumpula, Silvia Muñico Martinez, Alexander Ignatev, Simone Lepper, Friedrich Frischknecht, Inga Sidén-Kiamos, Carsten Sachse, and Inari Kursula Structural Differences Explain Diverse Functions of Plasmodium Actins *PLOS Pathogens*, 2014, dx.plos.org/10.1371/journal.ppat.1004091

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