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New insights into Malaria research: How molecular tethers and Asynchronous replication drive parasite proliferation

Researchers from Heidelberg University's Faculty of Medicine, Harvard Medical School, and the German Cancer Research Center (DKFZ) have uncovered key mechanisms underlying the proliferation of the malaria parasite Plasmodium. The molecular processes that govern the formation of infectious daughter parasites and new nuclei are essential for parasite survival and may therefore represent targets for future antimalarial therapies. The findings have recently been published in The EMBO Journal and Nature Communications.

Malaria parasites proliferate in an unusual way. Rather than dividing into two daughter cells like human cells, they first amplify their genetic material tenfold, hundredfold, or even thousandfold before simultaneously producing a corresponding number of daughter parasites. Until now, the mechanisms controlling these processes were only partly understood. Two recently published studies by researchers from Heidelberg University's Faculty of Medicine, Harvard Medical School, and the German Cancer Research Center (DKFZ) provide important insights into the molecular basis of this proliferation strategy and reveal how the parasite makes particularly efficient use of limited resources within infected blood cells. The findings open new perspectives for the development of future antimalarial drugs.

Growing Daughter Parasites Secure Their Nucleus with a Molecular Tether

The first project, published in *The EMBO Journal*, was conducted through a close collaboration between the research groups of Professor Friedrich Frischknecht of Heidelberg University's Faculty of Medicine and the Department of Parasitology at the Center for Infectious Diseases of Heidelberg University Hospital (UKHD), and Professor Jeffrey Dvorin of Boston Children's Hospital and Harvard Medical School, Boston, USA. Together, the teams investigated an enigmatic structure within the malaria parasite that had previously been observed in electron microscopy images, but whose function remained unknown. The researchers identified two proteins that form this structure, creating a molecular tether that links each of the parasite new nucleuses to the tip of a budding daughter parasite. In the absence of this tether, the formation of daughter parasites within blood cells was severely impaired.

Genetically modified parasites lacking one component of the tether were still able to replicate their genomes normally but could no longer produce viable progeny. The consequences were particularly dramatic in mosquitoes, where the formation of sporozoites, the infectious stage transmitted to humans during a mosquito bite, was almost completely abolished. "Without this connecting structure, the entire process of daughter parasite formation collapses," explains Professor Frischknecht. "The developing parasites are unable to pull their nucleus inside and cannot orient cellular structures correctly that are important for host-cell invasion. These *Plasmodium* parasites are not viable."

A Limiting Protein Resource Coordinates Nuclear Multiplication

In the second project, recently published in *Nature Communications*, the researchers investigated how parasite nuclei are generated. For this study, the group of Dr. Markus Ganter of Heidelberg University's Faculty of Medicine and the Department of Parasitology at UKHD collaborated with scientists from Heidelberg University's Institute for Theoretical Physics and BioQuant Center, as well as the Division of Theoretical Systems Biology at DKFZ led by Dr. Nils Becker. During the blood stage of infection, the malaria parasite multiplies its nuclei through an unusual asynchronous process, despite residing in a shared cell. While one nucleus may be replicating its genome, a neighbouring nucleus may already be undergoing division. Using high-resolution live-cell microscopy and mathematical modelling, the researchers demonstrated that the nuclei compete for a shared and limiting protein resource required for genome replication. As a result, the nuclei replicate their genomes at different times. While one nucleus gains access to this limiting protein resource and duplicates its genetic material, the remaining nuclei must wait until the resource becomes available again. That way, asynchronous nuclear multiplication can be established within the parasite.

Unexpectedly, this system does not slow parasite proliferation. On the contrary, mathematical modelling and experimental

validation showed that available resources are used with virtually no idle time, allowing the parasites to proliferate particularly efficiently and even somewhat faster than would be possible if all nuclei replicated in a fully synchronized manner. “If all nuclei were to duplicate their genomes simultaneously, they would have to share the available protein resources, which would ultimately slow down the process,” says Dr. Ganter, who carried out his earlier research together with Jeff Dvorin during their time together as postdoctoral fellows at the Harvard T.H. Chan School of Public Health.

Highly Specialized Proliferation Mechanisms May Prove to Be an Achilles’ Heel

“Malaria parasites have evolved highly specialized strategies to reproduce as rapidly and efficiently as possible. These unusual mechanisms may prove to be their Achilles’ heel,” says Professor Frischknecht. “The better we understand them, the more precisely we can identify new targets for future drug development.” Currently used antimalarial drugs interfere with parasite multiplication in blood cells, while some also target parasites in the liver. However, the pathogens adapt rapidly and frequently develop drug resistance.

Malaria parasites proliferate both in humans and in the mosquito vector. In humans, a single parasite inside a liver cell can generate a population of many tens of thousands of offspring that subsequently disperse and infect red blood cells. Within red blood cells, each parasite produces approximately 30 daughter parasites. In mosquitoes, the parasite undergoes extensive multiplication within cyst-like structures in the wall of the mosquito intestine. A single parasite can give rise to around 5,000 offspring, which migrate to the salivary glands and are transmitted to a human host during the mosquito’s next blood meal.

Publications

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Press release

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Further information

Heidelberg Faculty of Medicine at Heidelberg University
Department of Parasitology, Center for Infectious Diseases
Heidelberg University Hospital

Prof. Dr. Friedrich Frischknecht
Email: freddy.frischknecht(at)med.uni-heidelberg.de

Dr. Markus Ganter
Email: markus.ganter(at)med.uni-heidelberg.de

- Heidelberg University Hospital (German)