New studies show how malaria parasite grows and escapes from red blood cells

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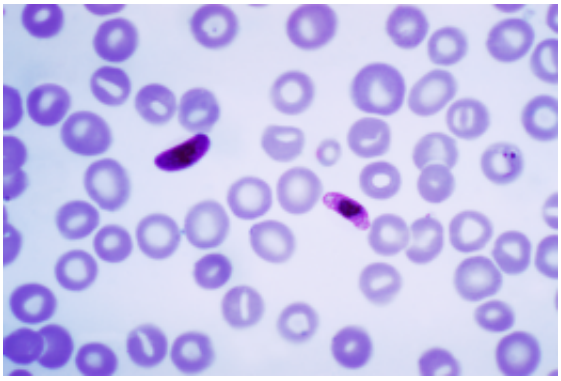

This photomicrograph of a blood smear contains a macro- and microgametocyte of the Plasmodium falciparum parasite. Credit: Wikipedia.

Two new studies from the Francis Crick Institute shed light on how the malaria parasite grows inside a host's red blood cells and breaks out when it's ready to spread to new host cells.

Our red blood cells transport oxygen and carbon dioxide to and from the organs of our body. The malaria parasite is one of only a few pathogenic microorganisms that can infect red blood cells. After invading them, it multiplies inside an internal compartment called a parasitophorous vacuole.

Eventually, both the vacuole and the red blood cell membranes break, destroying the red cells and allowing the release (known as egress) of a

new generation of parasites. These immediately invade new red blood cells. The clinical symptoms of malaria are caused by repeated rounds of parasite growth and egress.

To grow within its host red blood cell, the malaria parasite needs to drastically change the cell surface to promote the production of channels to import the nutrients and other molecules it needs to grow.

Mike Blackman's team at the Crick wanted to understand how it does this. Previous research has shown that one of the parasite proteins involved (called RhopH1) comes from 'rhoptries' - these are structures that the parasite discharges as it invades red blood cells. It's known that RhopH1 binds tightly to two other proteins called RhopH2 and RhopH3, but what these proteins do is unclear.

To understand the role of RhopH3 in the parasite's life cycle, the researchers genetically modified RhopH3 in the human malaria parasite Plasmodium falciparum so it could no longer interact with its partner proteins. The results showed that RhopH3 is essential for the function of the newly-induced nutrient import channels in the red cell. In addition, the researchers found that RhopH3 is needed for efficient invasion of red blood cells, showing that the protein has an indispensable, dual role that links invasion to formation of the channels essential for parasite survival inside red blood cells.

"It's remarkable that the malaria parasite has evolved a means of using the same protein family for both gaining entrance to host cells and then modifying them to help it grow," says Emma Sherling, first author of the work.

Christiaan van Ooij, another lead author, adds: "Most antimalarial drugs work by preventing parasite growth in red blood cells, but there is increasing resistance across the world to all these drugs. The new

knowledge generated here may help the development of entirely new classes of drugs that stop the parasite from invading and establishing growth within red blood cells."

In a second independent study, Professor Blackman's team worked with Roland Fleck's team from King's College London and Helen Saibil's group at Birkbeck College London to learn how the malaria parasite escapes from host red blood cells. The group used sophisticated imaging methods to visualise the changes that take place in infected red blood cells as the malaria parasites approach the point of egress. This revealed that the parasitophorous vacuole membrane first becomes leaky, before breaking into fragments several minutes later. Over the next few minutes, the red blood cell's cytoskeleton - a mesh-like protein network that provides mechanical support to the cell - undergoes a dramatic collapse.

Professor Blackman says: "Our collaborative effort with the Fleck and Saibil groups was crucial to the success of this project, as it brought together malaria biologists with highly specialist expertise in electron microscopy and tomography. Our finding that the parasite induces an early step of vacuole membrane leakage before its breakdown, followed by the breakdown of the red blood cell cytoskeleton over the course of only a few minutes right before egress changes the way we think about how egress is controlled. Increasing our understanding of egress might help us find ways to prevent it, trapping the parasite inside red blood cells and stopping the progression of the disease."

The first paper, Plasmodium falciparum rhoptry protein RhopH3 plays essential roles in host cell invasion and nutrient uptake, is published in *eLife*.

The second, Parasitophorous vacuole poration precedes its rupture and rapid host erythrocyte cytoskeleton collapse in Plasmodium falciparum

egress, is published in the *Proceedings of the National Academy of Sciences*.

More information: Emma S Sherling et al. Therhoptry protein RhopH3 plays essential roles in host cell invasion and nutrient uptake, *eLife* (2017). DOI: 10.7554/eLife.23239

Parasitophorous vacuole poration precedes its rupture and rapid host erythrocyte cytoskeleton collapse in Plasmodium falciparum egress, *Proceedings of the National Academy of Sciences*. www.pnas.org/cgi/doi/10.1073/pnas.1619441114

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