Enzyme essential to malaria replication could be a target for future treatments

December 8 2020

Credit: CDC

Researchers at the Francis Crick Institute have identified an enzyme vital to the survival of the malaria parasite. The work could lead to the development of a new class of antimalarial treatments which target this enzyme and stop the parasite replicating in the blood.

The malaria parasite has a complex life-cycle which includes invading

red blood cells in order to replicate. As the parasites multiply within a cell, they eventually cause it to burst and the new parasites are released back into the blood stream where they enter other cells and the process repeats.

In their study, published in *eLife*, the researchers identified how the malaria parasite Plasmodium falciparum needs an enzyme, called SUB2, to successfully enter and survive in red blood cells.

By creating lines of the parasite in the lab without this key enzyme, they found that when the parasites tried to enter a red blood cell, they were unsuccessful about half the time, and would instead cause the cell to rupture and disintegrate. In the other 50% of cases, the parasites were able to enter the cell but would quickly suffer from developmental defects and die.

Christine Collins, author and researcher in the Malaria Biochemistry Laboratory at the Crick, says, "The fundamental importance of this enzyme to the survival of the parasite is really striking. Without it, it is not able to enter red blood cells and replicate. Removing this enzyme really stops the parasite in its tracks."

The researchers found that, without the SUB2 enzyme, the parasite was not able to shed a surface coat of proteins as it attempted to enter a red blood cell. They suggest this process could be crucial to the parasite's survival and replication.

Fiona Hackett, author and researcher in the Malaria Biochemistry Laboratory at the Crick, says, "While we now know that this 'sheddase' enzyme and the process of shedding proteins are vital to the parasite, the exact mechanism behind this remains elusive. We suspect that the parasite isn't able to properly seal the membrane of the protective pocket it creates for itself within the red cell, but more research is needed to

confirm this."

The researchers plan to continue studying the SUB2 enzyme. They hope this could guide the development of a new class of antimalarial drugs that would target and block it.

Mike Blackman, author and group leader of the Malaria Biochemistry Laboratory at the Crick, says, "With malaria continuing to kill hundreds of thousands of people every year, mostly young children, research which aids the design of effective drugs is so important. We hope that this enzyme will become a target for new antimalarials."

More information: Christine R Collins et al. The malaria parasite sheddase SUB2 governs host red blood cell membrane sealing at invasion, *eLife* (2020). DOI: 10.7554/eLife.61121

Provided by The Francis Crick Institute