Malaria parasite protein identified as potential new target for drug treatment

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Scientists have discovered how a protein within the malaria parasite is essential to its survival as it develops inside a mosquito. They believe their findings identify this protein as a potential new target for drug treatments to prevent malaria being passed to humans.

The researchers found that when this protein – a transporter responsible for controlling the level of calcium inside cells – is absent during the parasite's sexual reproduction stages inside a mosquito, the parasite dies before developing fully. They discovered that the calcium transporter protein is responsible for protecting the parasite from potentially lethal levels of calcium during these stages.

The findings suggest that new drug treatments could be developed to target the parasite's sexual reproduction stages. These, unlike most current anti-malarial drugs, would block transmission of the parasite from human to mosquito, disrupting the cycle of infection.

The study was led by Dr Henry Staines at St George's, University of London and Dr Rita Tewari of the Centre of Genetics and Genomics at the University of Nottingham. It has been published in the journal *PLoS Pathogens*.

All living organisms require calcium to survive, as it is needed for vital cellular processes. Calcium concentration within cells is regulated by specific transporter proteins. The most effective class of anti-malarial drugs – artemisinins – are understood to inhibit one of the parasite's two known calcium transporters, so these transporters are already thought of as viable targets for drug treatments. The other calcium transporter is a type called CAX, so the researchers set out to investigate its role in the parasite's development.

Using the mouse malaria parasite Plasmodium berghei as a stand-in for the most dangerous form of human malaria, Plasmodium falciparum, the scientists removed the gene from which CAX is produced. While parasites without this functioning calcium transporter grew normally inside their animal host, they did not survive after ingestion into a mosquito's gut. This is the stage when the parasite should begin sexual reproduction, allowing it to multiply. When calcium surrounding the parasite was removed at this stage, the parasite developed normally. This suggests that the calcium transporter helps the parasite cope with changing levels of calcium.

Dr Staines said: "Increasingly, research is focusing on developing new drugs and vaccines to stop transmission of malaria, and the protein we studied seems to be a good place to target. The fact that the transporter is essential to the parasite's sexual development provides a focus for new transmission-blocking strategies."

To move from humans to mosquitoes, malaria requires a small group of specialised parasites that are produced in the infected human's blood stream but lie dormant until they are taken up by a feeding mosquito. To target CAX, a new drug treatment would need to accumulate within these dormant parasites and remain active throughout their sexual reproduction inside a mosquito, when CAX is essential. This could kill the parasite before it developed fully and prevent the infection from being passed on.

Most current anti-malarials do not target these dormant parasites capable of sexual reproduction, which have little if any effect on the health of the host. So they do not prevent them from being passed to mosquitoes. Instead, they target the parasite's asexual reproduction cells, which spread infection by multiplying inside the red blood cells of the host.

Dr Staines said: "Although this study has identified CAX as an excellent drug target and provides the

necessary tools to exploit this discovery, further work is needed to identify potent inhibitors of the transporter. This work is a step in the right direction towards preventing infection transmitting between humans."

More information: Guttery, D. et al. (2013) The Plasmodium berghei Ca2+/H+ Exchanger, PbCAX, Is Essential for Tolerance to Environmental Ca2+ during Sexual Development. *PLoS Pathog* 9(2): e1003191. doi:10.1371/journal.ppat.1003191

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