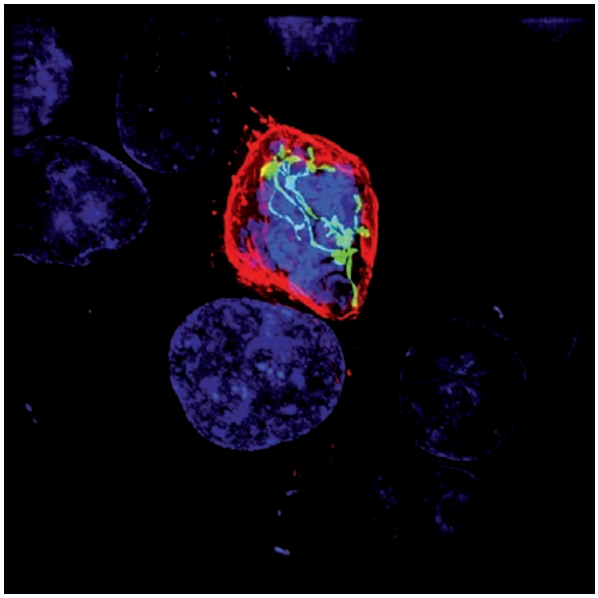
PARASITOLOGY

The fatty liver stage of malaria parasites

The discovery of a type II fatty-acid biosynthesis pathway (FAS-II) in malaria parasites has raised hopes that these enzymes could form a new target for therapeutic intervention. Two groups now report in *Cell Host & Microbe* and *Cellular Microbiology* on the requirement for the FAS-II system in the parasite's life cycle.

Parasites are introduced into the skin of a mammalian host by a mosquito bite, and subsequently infect the liver and invade hepatocytes. This leads to the production of merozoites that are competent to infect erythrocytes, which results in the symptoms of malaria. Subsequent sexual stages and transmission to the mosquito complete the life cycle.



Immunofluorescence microscopy image showing a host cell infected with *Plasmodium yoelii*. The FabI enzyme of the parasite is shown in green inside the elaborately branching apicoplast of liver stages 30 hours post-infection, the parasitophorous vacuole membrane protein UIS4 is shown in red, and parasite and host cell nuclei are shown in blue. Image courtesy of A. M. Vaughan, Seattle Biomedical Research Institute, Washington, USA.

The parasites rely on the hosts for many nutrients, but the discovery of components of the FAS-II system in *Plasmodium* species indicated that the parasite could synthesize its own fatty acids. The ability of the FAS-II inhibitor triclosan to block erythrocytic growth had suggested a requirement for the FAS-II system at this stage and established the FAS-II system as a potential drug target, but members of the Fidock and Kappe laboratories now reveal that the requirement for FAS-II is limited to the asymptomatic liver stage.

Vaughan and colleagues provide evidence that parasites only produce specific FAS-II enzymes in the late mosquito and liver stages, but not in the erythrocytic stage, which is consistent with data from Yu and colleagues. Together the groups show that deletion of FAS-II genes *fabBF*, *fabZ* or *fabI* did not affect the erythrocytic stage and only led to a measurable phenotype during growth in the liver. *In vitro* and in mice, mutant parasites invaded liver cells and grew normally but then became arrested. They did not produce the late-stage marker MSP1 (merozoite surface protein 1) and were unable to divide into daughter cells. In addition, Yu and colleagues observed that the *fabI* mutant was unable to induce the dissociation of infected hepatocytes from the surface of the culture dish. In murine models, infection with the *fabBF* and *fabZ* mutants failed to produce blood-stage parasites, whereas the *fabI* mutant produced blood-stage parasites at severely reduced levels compared with the wild type. However, the difference between the mutants could simply reflect differences in the mouse models used.

Why then does triclosan affect the erythrocytic stage? Yu and colleagues showed that certain derivatives of triclosan inhibited parasite growth better than triclosan itself, but no longer inhibited FabI activity *in vitro*. Furthermore, parasites that produced a triclosan-insensitive version of FabI were as sensitive to the drug as wild-type parasites. This elegant approach proved that triclosan must affect a different parasitic process.

It remains unclear why the FAS-II system is only required for part of the parasite's life cycle. Possibly, the prolific division of parasites inside hepatocytes that produces up to 5,000–30,000 merozoites (compared with 8–20 per infected erythrocyte) raises the fatty-acid requirement of the parasites above the levels that can be produced by the host cell, requiring the malaria parasite to synthesize its own.

Christiaan van Ooij

ORIGINAL RESEARCH PAPERS Yu, M. *et al.* The fatty acid biosynthesis enzyme FabI plays a key role in the development of liver stage malaria parasites. *Cell Host Microbe* **4**, 567–578 (2008) | Vaughan, A. M. *et al.* Type II fatty acid synthesis is essential only for malaria parasite late liver stage development. *Cell. Microbiol.* 3 Dec 2008 (doi:10.1111/j.1462-5822.2008.01270.x)