Examination of widely used antimicrobial compound reveals new strategies to fight malaria

10 December 2008

Scientists working on a common antimicrobial compound with antimalarial activity have discovered a range of new therapeutic strategies to combat malaria. The research, published by Cell Press in the December 11th issue of the journal *Cell Host and Microbe*, provides valuable insight into how the human malaria parasite's requirement for fatty acids can be exploited as it progresses through the distinct stages of its complex life cycle.

Infection with the human malaria parasite, *Plasmodium falciparum*, begins when an infected mosquito bites a human. Injected parasites migrate to the liver where they copy themselves inside liver cells and prepare to enter the bloodstream, invading red blood cells and initiating the blood stages that cause the clinical manifestations of the disease.

P. falciparum changes and proliferates rapidly during these life stages and requires an abundant source of fatty acid molecules to build new cell membranes. Blood stage parasites synthesize fatty acids using a type II fatty acid biosynthesis (FAS-II) pathway that is also employed by bacteria. FAS-II had been viewed as an excellent therapeutic target in parasites and bacteria as it is distinct from the type I (FAS-I) pathway used by mammals.

The FAS-II inhibitor triclosan has been widely used in antimicrobial creams, lotions and soaps and is often present as an additive in plastics, textiles and implantable medical devices. Earlier studies identified FabI, an enzyme in the FAS-II pathway, as the predicted target of triclosan in malaria parasites, propelling extensive research efforts to develop novel antimalarials based on this compound.

However, a new research study led by Dr. David A. Fidock from Columbia University showed that disruption of the FabI gene in *P. falciparum* or the rodent parasite *P. berghei* did not impede blood stage growth and that FabI was not the antimalarial target of triclosan. Fidock and colleagues also showed that triclosan was not as effective against the blood stage of the malaria parasite as was previously thought. "Although this enzyme has been extensively studied as a candidate drug target for blood stage malaria parasites, our data argue against the therapeutic potential of FabI, and indeed the entire FAS-II pathway, during infection of red blood cells," explains Dr. Fidock.

Nevertheless, Dr. Fidock and his colleagues went on to make an additional discovery. They demonstrated that an absence of FabI results in *P. berghei* parasites that, coming from the mosquito, are less infective and fail to complete the liver stage of development. These parasites are then typically unable to initiate the symptomatic blood stage infection. In contrast, during the blood stage, the parasites do not rely on FabI and appear to obtain fatty acids primarily by acquiring them from the host.

"We propose that therapeutic strategies to interfere with fatty acid processes in blood stage parasites should focus on scavenging these molecules taken from the host. This contrasts with liver stage parasites that depend on synthesizing their own fatty acids to meet their metabolic needs. Interference with FAS-II in liver stages now offers novel perspectives for prophylactic intervention," explains Dr. Fidock. "Our work also highlights the need for additional studies to elucidate how triclosan acts on blood stage parasites."

Source: Cell Press