Malaria

This drug discovery research project led to the identification of the crystal structure of β-haematin. There is considerable interest in malaria pigment (haemozoin) and haem aggregates in general, due to the observation that the quinoline-based antimalarials inhibit haem detoxification mechanisms and thus the formation of haemozoin. The new detailed structural information will help to elucidate the mechanisms of action of known antimalarials such as chloroquine and, most importantly, will aid in the design and early evaluation of new antimalarial drugs.

The spread of resistance to chloroquine and the absence of a suitable replacement created an urgent need to understand the biochemistry behind the drug's action. One hypothesis is that chloroquine inhibits haem aggregation in ring or early-stage malaria trophozoites. One to two weeks after infection with plasmodia, merozoites are released from the liver and rapidly infect erythrocytes. During this trophozoite stage, haemoglobin is catabolised to deliver amino acids for de novo protein synthesis and β-haematin is formed to avoid build up and release of free haem. Synthetic phase β-haematin is identical to the malaria pigment (haemozoin), the haem-aggregated by-product of malarial trophozoites. In this study, the research team solved the crystal structure of β-haematin. The structure revealed that the molecules are linked into dimers through reciprocal iron-carboxylate bonds to one of the propionic side chains of each porphyrin, and the dimers form chains linked by hydrogen bonds in the crystal. This structural knowledge has implications for understanding the action of current antimalarial drugs and for designing new therapeutic agents. One hypothesis based on the findings is that pigment formation may occur pair-wise, with either self-assembling pairs, or protein-mediated pairs, being aggregated. Thus, it is possible that chloroquine interferes with the dimerization process, so preventing the formation of highly aggregated haemozoin in the form of completely insoluble β-haematin. The corollary is that the haem aggregate formed in the presence of chloroquine may have greater solubility and/or higher toxicity to the parasite.

With the structure known, it is possible to get answers to a variety of questions, such as at what stage and how is the ferrous haem oxidised to the ferric state and what is the biochemical basis for the reported immunosuppressive activity of haemozoin? The answers to these and other questions will lead to a deeper understanding of how quinoline-based antimalarials work and, most importantly, to suggest how more effective antimalarial drugs might be designed. ■

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Nitrosylating prodrugs as haem deaggregating antimalarials

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