MALARIA

New chink in malaria's armour

Each year, malaria parasites infect nearly 500 million people, and cause around 2 million deaths. With resistance to current treatments such as chloroquine becoming increasingly widespread, new approaches are urgently needed. Writing in the February 15 issue of *Science*, Wengelnik *et al.* describe the effects of a new type of antimalarial compound, which potently inhibits the synthesis of membranes containing phosphatidylcholine, an activity that is vital when the parasite is developing within infected red blood cells, but which is absent from non-infected cells.

The compound that was analysed, named G25, was identified in previous studies on a series of compounds designed to disrupt phosphatidylcholine biosynthesis by mimicking choline, which showed that *in vitro* antimalarial activity correlated closely with specific inhibition of phosphatidylcholine biosynthesis. In the present study, G25 was found to potently inhibit the *in vitro* growth of the most common malaria parasite — *Plasmodium falciparum* — including strains resistant to current drugs, and was 1,000-fold less toxic to mammalian cells. Encouraged by these observations, Wengelnik *et al.* assessed the *in vivo* activity of G25 in monkeys infected with *P. falciparum*, and found that it could cure infections at doses about 30-fold lower than those that cause toxicity. The doses were also far lower than those used for current therapies, which often cause nausea. Similar curative effects were observed in a different species of monkey infected with *P. cynomolgi*, a primate parasite closely related to the other main human malaria parasite, *P. vivax*.

To clarify the mechanism of action of G25, the authors studied the interaction of a radiolabelled analogue of G25 with blood cells. The analogue specifically accumulated in infected blood cells at levels several-hundred-fold higher than in the surrounding medium. In combination with further analysis of lysed cells, this led the authors to suggest that G25 accumulates at the parasite

PARASITE INFECTION

Pyrimidines to go

Whether a computer bug or a tapeworm, parasites are organisms that evolve to exploit their surroundings in many kinds of system. Biological parasites cause many of the world's crippling diseases, such as malaria and sleeping sickness, and show a remarkable diversity of intracellular and extracellular habitats, from gut to liver to eye. *Toxoplasma gondii*, a member of the protozoan Apicomplexa group of intracellular parasites, causes toxoplasmosis in humans and animals. In the 21 February issue of *Nature*, Barbara Fox and David Bzik show that *T. gondii* parasites that lack a crucial pyrimidine biosynthetic pathway become severely weakened and cannot survive when injected into mice.

Parasites rely on their hosts for nutrients and have lost many of the anabolic pathways for generating the basic building blocks of life. *T. gondii* relies completely on its host for obtaining purines (adenine and guanine), but has retained the ability to synthesize pyrimidines (cytosine, thymidine and uracil). To generate pyrimidines, *T. gondii* relies on converting uridine monophosphate into cytodine and thymidine monophosphates for use in making nucleic acids. Uracil can be salvaged from the host and is converted into uridine monophosphate, but it can also be synthesized from scratch. By using targeted gene insertion to eliminate carbamoyl phosphate synthetase II (CPSII) — the first enzyme in the uracil synthesis pathway — Fox and Bzik found that the parasite becomes dependent on an external supply of uracil for growth. When uracil is abundant in the environment, the pyrimidine requirements of *T. gondii* are satisfied.

Surprisingly, the *in vivo* situation turned out to be different. Wild-type *T. gondii* is usually lethal when injected into mice, but the uracil-dependent mutant *T. gondii* strains were unable to kill their mouse hosts. The result was the same even if severely immunodeficient mice were used. These data indicate that the mutant parasites were hindered by pyrimidine nutrient limitation and not by immune control in the host. The short supply of pyrimidines in animal tissues gives us a clue as to why parasites have retained the ability to synthesize these molecules. Importantly, the mutant parasites acted as a vaccine in normal mice and allowed them to survive subsequent infection with the highly virulent wild-type *T. gondii*.

This study is important for several reasons. First, the development of uracil-dependent *T. gondii* strains might allow safe and reliable vaccination of livestock. Second, this could represent a broad-ranging immunization approach to treating other protozoan parasites by severely attenuating their virulence. Finally, because pyrimidine biosynthesis is now known to be an obligate *T. gondii* pathway, enzymes in that cascade are attractive therapeutic targets for drug design and chemotherapy. The CPSII enzyme has unique structural and kinetic properties that differentiate it from the mammalian enzyme, so it might be possible to design inhibitors of CPSII that selectively disrupt pyrimidine synthesis in the parasite but not the host.

Melanie Brazil

References and links

ORIGINAL RESEARCH PAPER Fox, B. A. & Bzik, D. J. *De novo* pyrimidine biosynthesis is required for virulence of *Toxoplasma gondii*. *Nature* **415**, 926–929 (2002)
FURTHER READING Sibley, L. D. No more free lunch. *Nature* **415**, 843–844 (2002)