New agents to combat malaria

Triclosan, an antibacterial agent found in mouthwashes, acne medicines and deodorants, also prevents the growth of Plasmodium falciparum. If properly developed, this type II fatty acid biosynthesis inhibitor may be a promising new antimalarial agent (pages 167–173).

Malaria remains a leading global health problem, despite substantial efforts to control the disease over several decades. Approximately 40% of the world’s population lives in malaria-endemic areas, and about 90% of cases and most deaths occur in tropical Africa. There are up to 500 million clinical cases and 2.7 million deaths annually, and the majority of severe clinical disease is due to Plasmodium falciparum, with young children and pregnant women at highest risk. One of the barriers to effective malaria control in many regions is the emergence and spread of antimalarial drug resistance, making the development of new drugs an important priority. In this issue Surolia and Surolia describe a promising new antimalarial agent, the antibacterial drug triclosan.

Parasite resistance to chloroquine, one of the cheapest and previously most useful antimalarial agents, is now widespread. Similarly, resistance to the combination of sulfadoxine-pyrimethamine is extensive in Asia and growing in Africa, and resistance to quinine, the mainstay for treatment of severe disease, is emerging as a major problem in parts of Asia. Newer drugs, such as mefloquine, halofantrine, atovaquone-proguanil and arteether-lumefantrine retain much efficacy but have limitations, not the least of which is their high cost. Novel uses for old drugs, such as chlorproguanil-dapsone, and artemisinin combination therapy offer definite possibilities for the near future, but still have regulatory, policy and implementation hurdles to jump.

One strategy for developing new drugs is to identify and target parasite-specific metabolic pathways. A curious feature of thought to have arisen by endosymbiosis (or engulfment) of a cyanobacterial-like prokaryotic cell. Plastid biosynthetic pathways are essential for parasite growth, and are attractive therapeutic targets because of their fundamental differences from mammalian cells. One such pathway is type II fatty acid biosynthesis (Fig. 1), which has been well-studied in bacteria and plant chloroplasts. Genes encoding plastid-localized enzymes of this pathway were recently identified in P. falciparum, and thiolutamycin, which blocks enzymes in the pathway in bacteria, inhibited growth of the parasite in vitro.

Triclosan is another type II fatty acid biosynthesis inhibitor. It exerts its antibacterial action by inhibiting an enzyme known as FabI (enoyl-acyl carrier protein reductase). Surolia and Surolia found that the drug effectively inhibited growth of the intra-erythrocytic stages of P. falciparum in vitro, and was similarly effective against chloroquine-sensitive and chloroquine-resistant parasites. Following infection of mice with P. berghei (a model for human malaria), triclosan given subcutaneously cleared peripheral blood parasitemia and prevented death. From P. falciparum cultures, a protein was purified that had a similar sequence to FabI enzymes of bacteria (although the sequence available for analysis was limited), and a putative fabI gene was identified in the P. falciparum genome database. The P. falciparum enzyme showed similar in vitro properties to bacterial FabI (ref. 6), being NADH-dependent and using crotonyl-CoA and crotonyl-ACP as substrates. Triclosan seems to inhibit the oxidation of NADH and promote the binding of NAD to the enzyme, and was found to inhibit fatty acid synthesis, as measured by the incorporation of radiola beled substrates into fatty acids.

Triclosan is a synthetic 2-hydroxydiphenyl ether. It has broad antibacterial activity and an apparently favorable safety profile when used topically. Depending on the type and purity of the starting materials used and reaction conditions during synthesis, triclosan may contain small amounts of unwanted by-products such as dioxins and dibenzo-furans (http://www.quantexlabs.com/page0004.htm). Many commercially available products contain triclosan; all are topical preparations such as mouthwashes, anti-acne preparations,
and deodorants. In the study by Surollia and Surollia, triclosan was administered to animals subcutaneously, though its use as a systemic anti-microbial has not been established. The pharmacokinetics of triclosan have received little attention because the compound’s use has been confined to topical formulations. After intravenous administration of the radiolabeled drug to rats, the plasma half-life was about nine hours. Although the oral bioavailability of the compound is unknown, there is some absorption from this route.

Despite its extensive use, reports of resistance to triclosan are relatively uncommon. In E. coli, resistance is conveyed by upregulation of fabI expression or missense mutations in the fabI gene. These observations prompt the concern that triclosan or related compounds would need to be used judiciously, or in combination with other antimalarials, to avoid the potential problem of widespread resistance currently seen with drugs such as chloroquine.

The development and marketing of new antimalarials, or of existing compounds such as triclosan for new indications such as malaria, is a slow and costly process. Industrial partners are typically required early in drug development, both for the budget (at least US $20 million) and for essential expertise, such as pharmaceutical development, toxicology and clinical studies, regulatory submission and marketing. Unfortunately, the costs of developing new antimalarials are often perceived as outweighing potential profits. Industry involvement is also influenced by patent rights, the need for animal pharmacokinetics and toxicology and the likelihood of beneficial publicity. Development typically takes at least four years, with no guarantee of a marketable product. Policy-makers, such as Ministers of Health, are understandably conservative about new drugs, and even if all key parties were involved from an early stage, it would probably take at least three years after the drug became available for it to be included in public health strategy. Finally, but perhaps most importantly, the relatively high cost of new drugs is a major obstacle to their use in resource-poor settings where the burden of malaria is greatest.

The identification of inhibitors of fatty acid synthesis in Plasmodium creates some interesting opportunities for developing novel antimalarials. The challenge ahead lies in exploiting these insights and ensuring that populations most affected by malaria are reached. This will require sustained multidisciplinary effort from molecular biology through to public health, and public-private partnerships over many years.


1. Department of Medicine, University of Melbourne, Royal Melbourne Hospital, Victoria, Australia
2. Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK
3. Plant Cell Biology Research Centre, School of Botany, University of Melbourne, Victoria, Australia
email: beeson@unimelb.edu.au

Stem-cell surface appearance

Experiments with human neurogenic precursor cells have revealed the ability of these cells to be carried in culture and differentiate into neurons, astrocytes and oligodendrocytes. Neuronal stem cells have also been shown to engraft, migrate and differentiate in rodents in vivo. However, little is known about the surface antigens present on human central nervous system stem-cells (CNS-SC), affecting the ability of researchers to easily isolate and follow the development of these cells. In the 19 December issue of Proceedings of the National Academy of Sciences, Uchida et al. (Proc. Natl. Acad. Sci. USA 97, 14720–14725) report the creation of novel antibodies against CNS-SC surface molecules that can be used in fluorescent-activated cell-sorting analysis to isolate these cells from human fetal brain tissue. They demonstrated that this approach could be used to isolate a specific population of self-renewing CNS-SC. These cells were shown to initiate neurosphere cultures and differentiate into neurons and glia cells in vitro. When expanded cells were transplanted into the lateral ventricles of newborn mice, they underwent self-renewal, migration and neural differentiation in different areas of the brain. The picture shows the differentiation capacity of clonally derived neurosphere cells. Progeny of single cell-derived neurospheres differentiated into neurons (green) and astrocytes (red), while cell nuclei are stained blue. Uchida et al. showed that at 7–12 months post-transplant, the human CNS-SC could still be detected, were still able to respond to host microenvironment cues and were not neoplastic. The ability to directly isolate human CNS-SC will advance the testing of these cells in animal models of neurological disease as well as in preclinical studies for transplantability and tumorigenicity.

Kristine Novak