Semiconducting malaria drugs

The semiconductor gallium could find a place in the battle against *Plasmodium falciparum*, the parasite that causes malaria, according to David Piwnica-Worms [*Chem. Commun.* (1997) 2223–2224]. A complex of gallium selectively attacks certains strains of *P. falciparum* that have developed resistance to the standard chloroquine drug therapy, which, paradoxically, seems to work in a very similar way.

Piwnica-Worms a molecular radiopharmacologist from the Mallinckrodt Institute at Washington University Medical School (St Louis, MO, USA), has found a group of metal complexes with selective activity against *P. falciparum*, one of which contains the semiconductor gallium. He and his team have used X-ray crystallography, among other analytical techniques, to determine the exact atomic structure of the gallium complex. The results offer several clues to the origin of the efficacy of the drug against resistant malaria.

P. falciparum extracts haemoglobin from the host organism and catabolizes it to release amino acids for production of its own proteins. During this process, the toxic, central haem units are released and quickly metabolized into a polymeric form called haemozoin, which is stored in a digestive vacuole (a cellular organelle).

Conventional chloroquine drugs work by interfering with the polymerization process of the host's haem molecules, but it is well known that *P. falciparum* has evolved methods to circumvent this attack.

Therapeutic approaches

Several groups have been working on iron-chelating compounds that interfere with iron and haem metabolism in the parasite and thus reduce the symptoms of malaria. However, these chelating agents have several undesirable side effects, such as visual and auditory disturbances and abdominal discomfort. Haemozoin formation is unique to the malaria parasite, and new lead compounds that work like chloroquine, but without resistance are keenly sought.

Piwnica-Worms and his team, including chemist Vijay Sharma, have found that a gallium complex – {[1,12-bis(2-hydroxy-3-methoxybenzyl)-1,5,8,12-tetraazadodecane]gallium(III)}, more simply referred to as $[Ga(madd)]^+$ or MR045 – interferes with haem polymerization but, paradoxically, only works against chloroquine-resistant malaria in whole cell assays. The parasite cannot extract the free haem, and toxic levels kill it.

The crystal structure reveals the anticipated central N_4O_2 core found in other related metal complexes prepared by Piwnica-Worms and his coworkers. This core locks in a gallium ion until enters the digestive vacuole of the parasite, where haemoglobin metabolism takes place. It is believed that the gallium complex replaces iron in the formation of haemozoin, resulting in a build-up of the toxic haem. 'Interestingly,' says Piwnica-Worms, 'free gallium ions, which are similar in size and have the same charge as iron, cannot disrupt haem polymerization, thus the drug action at the target and the ability to bypass chloroquine resistance would appear specific to the complex itself.' He adds that an iron analogue of this gallium complex behaves identically.

According to Piwnica-Worms, selectivity and bioavailability of the drug are being considered with a view to further development.

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