Discovery provides new drug targets for malaria cure

January 11 2010

Researchers are a step closer to developing new antimalarial drugs after discovering the normal function of a set of proteins related to the malaria parasite protein, which causes resistance to the front-line drug chloroquine. The findings also provide a novel tool for studying the malarial chloroquine-resistance factor.

The study examined transporter proteins which are known to move compounds around the cell. The genes for these proteins are present in plants as well as the malaria parasite Plasmodium falciparum (known as clt and PfCRT respectively), so researchers used the model plant Arabidopsis to reveal that these proteins normally transport glutathione, an antioxidant which protects the cell from stresses.

In the malaria parasite (a single cell organism), this type of transporter protein has mutated so that it no longer functions normally, enabling it to remove the drug chloroquine from its cell and survive.

Plasmodium falciparum is the most dangerous of the malaria infections being transmitted by the female Anopheles mosquito. It has the highest rates of complications and mortality and is responsible for up to one million deaths per year, mostly children in Africa under the age of five. The evolution of drug-resistant Plasmodium strains, especially those resistant to chloroquine, has had major impacts on global public health. The economic toll is also huge with malaria infection destroying more than 1% of African GPD.

The work was led by Dr Spencer Maughan who began researching these genes in Prof. Chris Cobbett's lab in the Department of Genetics at the University of Melbourne and involved an international team from the Universities of Melbourne, Cambridge (UK), Heidelberg (Germany), Liverpool (UK) and Rothamsted Research (UK). It will be published in the prestigious international journal *PNAS* this week.

"Our findings set in motion the chance of reclaiming the efficacy of chloroquine which could turn the tide on the war against malaria and ultimately may help save millions of lives," said Dr Maughan.

"The transporter is normally essential to the survival of the malaria parasite and when mutated, provides the extra advantage of removing the drug chloroquine from its cell.

"We hope that understanding the normal role of the transporter in plants will be a key step in malaria research. Unlike in the plant, if the gene for the transporter is inactivated in malaria, the parasite dies, preventing more study into its role. The plant could therefore provide a useful tool in malaria research."

"These results describe the first missing link in understanding this class of proteins and could provide a two-pronged treatment approach- preventing malaria removing chloroquine from its cell and enabling the design of new drugs based on the shape of glutathione."

Provided by University of Melbourne