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Drug resistance may make malaria parasites vulnerable to other substances

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Malaria parasites that develop resistance to the most effective class of anti-malarial drugs may become susceptible to other treatments as a result. The discovery could reveal potential new drug options, which would be essential in the event of resistance to the best anti-malarials.

In a new study, researchers have shown how the anti-malarials artemisinins attack the malaria parasite by inhibiting the action of a crucial protein, and that genetic mutations in this protein can reduce the effect of the drugs. While demonstrating this, however, they also discovered that a mutation that gives the parasite resistance to artemisinins makes it more sensitive to attack by another substance, cyclopiazonic acid (CPA). CPA is thought to be too toxic to be a suitable anti-malarial treatment, but the findings suggest it could be worth pursuing derivatives of the acid as treatment options.

The study was led by researchers at St George's, University of London and has been published in The *Journal of Infectious Diseases*.

The artemisinin group of drugs are the most effective and widely used treatments for malaria – used most powerfully with other drugs as artemisinin-based combination therapies – but little is known about their mechanism of action on the malaria parasite. There are signs that the malaria parasite is developing resistance to artemisinin-based combination therapies, meaning further understanding of the drugs could be crucial to prevent them becoming obsolete.

The St George's researchers have now demonstrated that artemisinins work by acting on a protein within the parasite called a calcium pump. Calcium is essential for all living organisms as it is needed for vital cellular processes. The calcium pump regulates calcium levels in cells, and if it is not functioning properly the parasite dies.

In previous studies, the team had witnessed the same effect on the calcium pump in genetically engineered malaria parasites. However, in these studies the parasites' sensitivity to artemisinins fluctuated, so they did not give a clear indication of the drugs' mechanism of action and the findings could not be confirmed.

To provide more consistent results, the latest study used yeast cells instead of parasite cells. Yeast can be a convenient way to display and test the function of proteins from other organisms.

After confirming that artemisinins inhibited the calcium pump in the yeast model, the researchers mutated the pump to mimic three mutations previously observed to give parasites resistance to the drugs. When they did this, they saw similar resistance.

Following this, they tested whether these mutations had any effect on the action of another five substances known to have an anti-malarial effect. They found that one particular mutation that gave the pump resistance to artemisinins made it more susceptible to CPA.

Their findings also showed that the yeast model could be used to identify other drugs that harm the parasite.

Lead author Professor Sanjeev Krishna said: "CPA is a compound used in science and not in clinical practice in any way. However, it points to a proof of concept that we can look for weaknesses in the more resistant strains of the parasite. The yeast model provides a convenient and

reliable method to study anti-malarials and this particular mechanism of resistance to them."

He added: "This new research supports our earlier work suggesting that the calcium pump is crucial for artemisinins' action. Understanding how this lifesaving drug works on this calcium pump and how the pump can develop drug resistance will not only allow us to better understand how to use artemisinins more effectively, but it will help us contribute to the development of new drugs to counter the potentially serious effects of artemisinin resistance."

More information: J Infect Dis. (2013) doi: 10.1093/infdis/jit171 jid.oxfordjournals.org/content … fdis.jit171.abstract

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