Stressed-out parasites: Overcoming drug-resistant malaria

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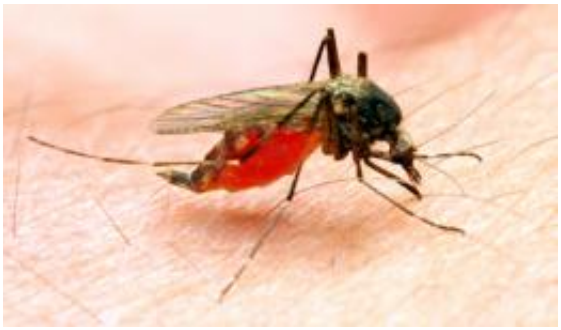

Drug resistance to the critical antimalarial therapeutics of the artemisinin family has emerged in Southeast Asia, highlighting the need to understand how these drugs work and how they can be used more effectively. Research now shows that artemisinins may function by chemically damaging the malaria parasite's proteins, causing them to activate a cellular stress response. Parasites resistant to artemisinins have developed a more vigorous stress response, making them impervious to the normal drug treatments. However, it appears that with prolonged artemisinin treatment, even this improved stress response can be overwhelmed, leading to parasite clearance. This work suggests that extending artemisinin treatment or co-administering drugs that target the stress response can overcome drug resistance.

Research publishing April 22 in the open access journal *PLOS Biology* from the research group of Leann Tilley at the University of Melbourne, working with colleagues from Thailand, Singapore and the USA, demonstrates that resistant strains of *Plasmodium falciparum* sourced from the Pailin region of Cambodia can be made susceptible to artemisinin treatment either through extended drug treatment or through a combination therapy of artemisinins and clinically-used proteasome inhibitors. This work supports a previous clinical study that showed a 97.7% efficacy of a six-day treatment course in a region where artemisinin resistance is endemic.

To investigate the response to artemisinin treatment, the authors developed a method for predicting parasite clearance in humans from a test-tube assessment of artemisinin sensitivity. "Our detailed kinetic observations are used to develop a mathematical model that allows, for the first time, a simulation of parasite responses to artemisinin chemotherapy in patients," says Professor Tilley, lead author of the study. Importantly, this model can be used in a clinical setting to assess whether parasite strains have developed artemisinin resistance to a level that will cause clinical failures, thus improving detection and treatment options.

The authors' studies of the responses of resistant and sensitive parasites to artemisinin treatment revealed that drug treatment slows growth and targets proteins for degradation by the cellular garbage bin, the proteasome. Resistant parasites had fewer proteins primed for degradation than sensitive parasites after equivalent drug treatments. These findings suggest that artemisinin-resistant parasites are better able to combat and respond to the damage inflicted by the drugs. Despite this improved response, the researchers were able to overcome and kill the parasites by extending the artemisinin treatment or by using a combination therapy with proteasome inhibitors, which cause the accumulation of damaged proteins and increased cellular stress.

According to Professor Tilley, "This calls for urgent testing of extended treatments in areas with artemisinin resistance and artemisinin combination therapy failure."

The WHO, in their Global Plan for Artemisinin Resistance Containment, states that "There is a finite window of opportunity to contain artemisinin resistance. If the current foci of artemisinin-resistant parasites are not contained or eliminated, the costs, both human and financial, could be great". The research of Professor Tilley and colleagues makes an important step towards preventing the spread of drug resistance by identifying treatments that can kill resistant parasites.

More information: *PLOS Biology*: www.plosbiology.org/article/in … journal.pbio.1002132

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