New malaria drugs kill by promoting premature parasite division

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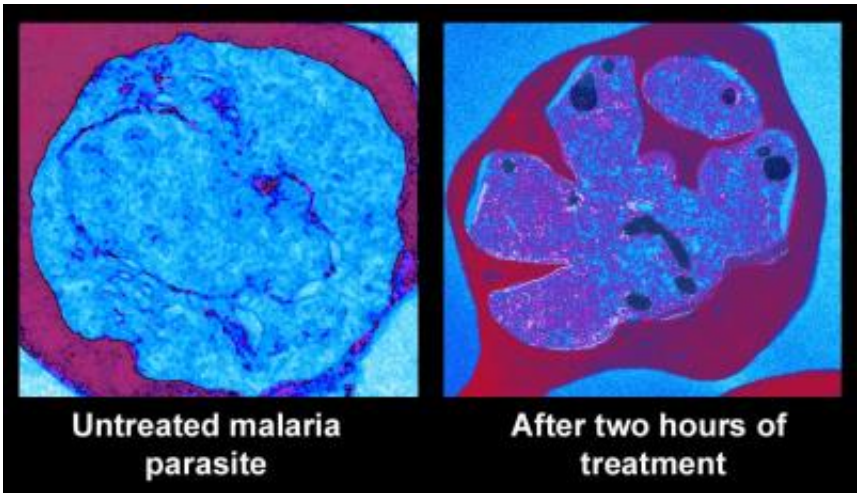

Massive morphological changes resembling premature onset of parasite division in malaria parasites after two-hour exposure to new antimalarial drugs. Credit: EM by Isabelle Coppens pseudo-colored by Avinash Vaidya

Several new malaria drugs under development share a common feature: they promote an influx of sodium ions into Plasmodium parasites that have invaded red blood cells and multiply there. A study published on May 26th in *PLOS Pathogens* suggests that this increase in sodium concentration kills the parasite by changing the composition of its outer membrane (the skin equivalent) and promoting division of the parasite before its genome has been replicated.

Amidst growing concerns about resistance against the effective

artemisinin-based therapies, several new malaria drugs are under development. Akhil Vaidya, from Drexel University College of Medicine in Philadelphia, USA, and colleagues, are studying the mechanism of action of drug candidates with the aim to learn more about vulnerabilities in the parasite that can form the basis for further rational design of therapeutic interventions.

Maintenance of appropriate intracellular ion concentrations is critical, and all cells have elaborate transport mechanisms and expend substantial amount of energy for this purpose. One consequence described for a number of anti-malarial compounds is an increase in sodium ion concentration inside the parasites when they are growing inside red blood cells (where the parasites eventually divide into daughter cells that burst open the host cell and are released in the blood where they invade more red blood cells).

In this study, the researchers focused on two small-molecule drugs, one of which is undergoing clinical trials. Despite very different molecular structures, both drugs initially increase intra-parasite sodium concentrations and subsequently kill the pathogen. Following the initial sodium influx, the researchers observed dramatic alterations in parasite membrane composition and permeability, as well as in parasite morphology.

Plasma membranes, the outer skins of cells, contain a mix of protein and lipids. The exact composition determines the membrane's permeability for different small and large molecules. The Plasmodium plasma membrane is unusual because it contains very low levels of cholesterol, a major lipid component of most other membranes, including those of human red blood cells.

Cholesterol-containing membranes are vulnerable to detergents, including one called saponin. Consequently, saponin treatment can be

used to dissolve membrane of Plasmodium-infected red blood cells, which releases intact parasites whose own membranes—because of their low cholesterol content—don't get destroyed by the detergent.

However, the researchers found that the membranes of parasites exposed to the two drugs are made permeable by saponin, and this appears to be a consequence of an increased amount of incorporated cholesterol. When drug exposure is short, the changes in membrane composition are reversible—that is, parasites regain their resistance to saponin, presumably because they got rid of the additional membrane cholesterol after the drug was washed off.

The morphological changes the researchers observed following drug treatment resemble the reproduction stage of Plasmodium in red blood cells, namely the production of multiple daughter cells that starts with fission of the parasite nucleus and includes the formation of new membranes inside the parasite cell. After just a two hours of treament with either drug, the researchers saw that many of the parasites showed fragmented nuclei and interior membranes. These changes occured without any sign of multiplying the parasite genome, a step that is necessary to create viable daughter cells and usually precedes any other division events.

Given the similarities between the drug-induced changes and the early steps of parasite cell division, the researchers propose that Na+ [i.e., sodium ion] influx is a normal step during Plasmodium division, and that this signaling event is prematurely induced by these antimalarial drugs. Their model, they say, "predicts the existence of a complex cascade of events that is unleashed by Na+ influx". "It would be of great interest", they suggest, "to identify various players that may participate in this cascade".

The study's findings were unexpected—researchers had assumed that the

drug in clinical trials killed parasites through a different mechanism—and might influence which tests participants in these trials undergo. More generally, a detailed understanding of the mechanism of action for an antimalarial drug facilitates the crucial detective work that is necessary to monitor for the emergence of resistance and to determine its origin as soon as it arises.

More information: Sudipta Das et al, Na+ Influx Induced by New Antimalarials Causes Rapid Alterations in the Cholesterol Content and Morphology of Plasmodium falciparum, *PLOS Pathogens* (2016). DOI: 10.1371/journal.ppat.1005647