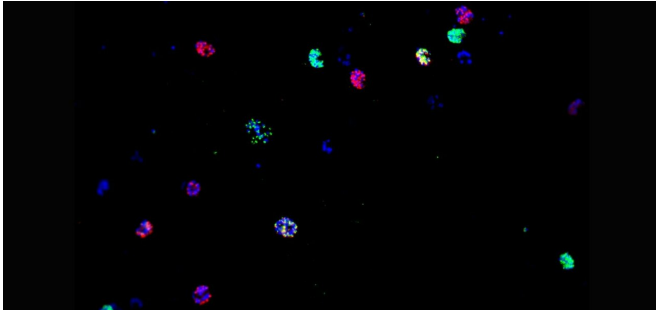


A quick path to antimalarial resistance

5 March 2019



Immunofluorescence detection of the CLAG3 proteins, which play a role in resistance to some antimalarial compounds. Credit: Mira et al, 2019

Resistance to antimalarial drugs is thought to result mainly from changes in the parasite's genome. However, *P. falciparum* can also develop resistance to some antimalarial compounds by epigenetic changes, according to a new study led by ISGlobal, an institution supported by "la Caixa", and the Institute of Tropical Medicine (ITM), Antwerp. This is of concern because resistance acquired at the epigenetic level can arise quickly, even during the course of a single infection.

P. falciparum, the most deadly malaria parasite, has developed resistance to all antimalarial drugs, including artemisinin combination therapies (ACTs), which are the current frontline treatment. Most of the known mechanisms by which *P. falciparum* parasites develop resistance to antimalarial drugs are due to changes in the genome. However, a team led by Alfred Cortés (ISGlobal) and Anna Rosanas-Urgell (ITM) explored the role of epigenetics (i.e. changes in [gene expression](#) that do not involve alterations in DNA sequence) in antimalarial drug resistance.

Particularly, they looked at two parasite genes—*clag3.1* and *clag3.2*—whose expression is regulated by [epigenetic mechanisms](#) and that determine the activity of a channel called

Plasmodial Surface Anion Channel (PSAC), which regulates the entry of nutrients and other molecules into [red blood cells](#) infected by the parasite. Previously, Cortés and his team had found that switches in the expression of *clag3* led to changes in PSAC permeability and resistance to compounds toxic for the parasite.

In this study, the researchers investigated whether other [antimalarial drugs](#) require *clag3* to reach their intracellular target and could consequently be prone to parasite resistance by epigenetic mechanisms. They found that certain compounds such as bis-thiazolium salts T3 and T16 require the product of *clag3* genes to enter infected erythrocytes. Furthermore, *P. falciparum* populations could develop resistance to these compounds through the selection of parasites with reduced expression of both genes. In contrast, other compounds predicted to use transport pathways to enter infected erythrocytes, such as doxycycline, azithromycin or lumefantrine, did not require expression of *clag3* genes for their anti-malarial activity.

"These results show that *P. falciparum* can develop resistance to certain antimalarial compounds by [epigenetic changes](#) in the expression of *clag3* genes," explains Sofia Mira, co-first author of the study together with Anastasia Pickford and Nuria Rovira. "These results are of relevance to drug development efforts, since [resistance](#) by epigenetic mechanisms can arise quickly, even during the course of a single infection," adds Cortés. "It is also easily reversible, providing the parasite with an extraordinary level of plasticity."

More information: Sofia Mira-Martínez et al, Identification of antimalarial compounds that require CLAG3 for their uptake by *P. falciparum*-infected erythrocytes, *Antimicrobial Agents and Chemotherapy* (2019). [DOI: 10.1128/AAC.00052-19](#)

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