A Quick Path to Antimalarial Resistance

‘P. falciparum’ parasites can develop drug resistance by epigenetic changes in clag3 gene expression

Barcelona, March 4, 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.”

Reference

About ISGlobal

The Barcelona Institute for Global Health, ISGlobal, is the fruit of an innovative alliance between "la Caixa" and academic and government institutions to contribute to the efforts undertaken by the international community to address the challenges in global health. ISGlobal is a consolidated hub of excellence in research that has grown out of work first started in the world of health care by the Hospital Clinic and the Parc de Salut MAR and in the academic sphere by the University of Barcelona and Pompeu Fabra University. The pivotal mechanism of its work model is the transfer of knowledge generated by scientific research to practice, a task undertaken by the institute's Education and Policy and Global Development departments. ISGlobal a member of the CERCA programme of the Generalitat de Catalunya.

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