PhD defence Sofía Mira Martínez

A new mechanism of antimalarial drug resistance regulated at the epigenetic level

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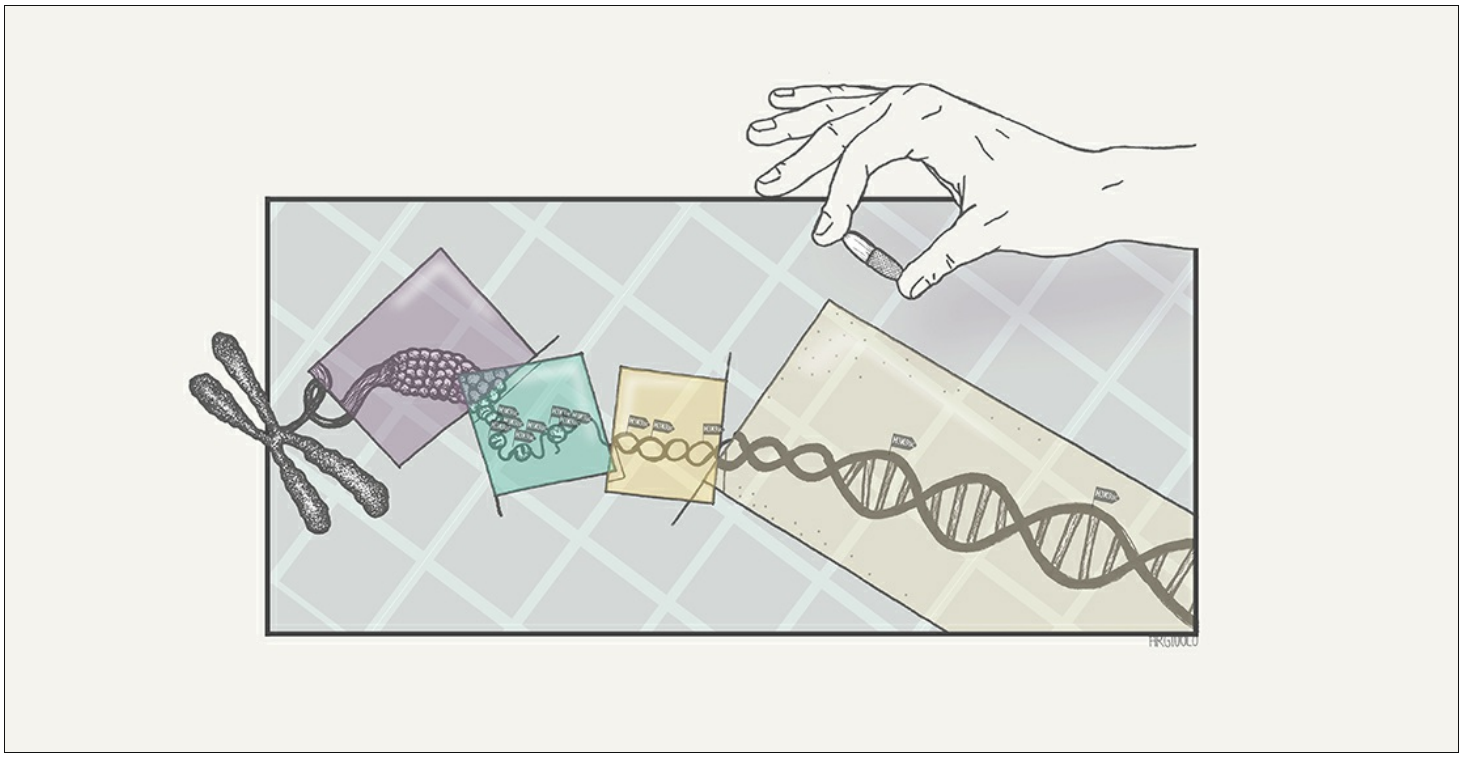
Barcelona Institute for Global Health, ISGlobal - Barcelona
Reservatie aangeraden



Dit is de omschrijving

Supervisors

- Prof. Dr. Anna Rosanas - Urgell (ITM)
- Prof. Dr. Alfred Cortés Closas (Barcelona Institute for Global Health, ISGlobal)
- Prof. Dr. Jacqueline W. Broerse (VU Amsterdam)

The defence at the University of Barcelona, ISGlobal, will take place on **Friday 23 February 2018** at 11 am, in Aula 5, Facultat de Medicina, University of Barcelona, Spain.

The defence at the VU Amsterdam will take place on **Tuesday 27 March 2018** at 11.45 am, in Aula VU, VU University Amsterdam, the Netherlands.

Summary

Malaria is responsible of almost half a million deaths every year. Currently, campaigns for the control and elimination of malaria are implemented in malaria endemic areas. However, drug resistance is one of the major impediments to achieve malaria elimination. In this thesis we have investigated how *P. falciparum* parasites develop resistance to some toxic compounds by functional variation linked to epigenetic regulation of *clag3* genes. These genes present clonally variant expression and determine the formation of the main channel for the transport of solutes at the membrane of the infected RBC: Plasmodium Surface Anion Channel (PSAC). Hence, we hypothesized that *P. falciparum* parasites can modify the permeability of the membrane to specific solutes by epigenetic regulation of *clag3* genes expression; this way, parasites could develop resistance to antimalarial drugs. To test this hypothesis, we have investigated the role of switches in *clag3* expression in the acquisition of resistance to the antibiotic BS, the dynamics of *clag3* genes expression in human infections and we have tested drugs susceptible to failure by this drug resistance mechanism.

First, we show that BS pressure at low concentrations selected for parasites expressing *clag3.1,* whereas parasites exposed to higher concentrations of BS had repressed the expression of both *clag3* genes. We did not find any mutation in the genome of these parasites that could explain the change in their phenotype. Thus, we concluded that parasites can develop resistance to toxic compounds through epigenetic regulation of *clag3* genes. Then, we found that parasites collected from patients with uncomplicated malaria predominantly express one of the two paralogues, consistent with the property of mutually exclusive expression, previously described in lab-adapted parasite lines. Adaptation to culture conditions or selection with toxic compound results in isolate-dependent changes in *clag3* expression, implying functional differences between the proteins encoded. We also observed that samples collected at day 9 post-infection in human experimental infections (when parasites had been in the peripheral blood for approximately one erythrocytic cycle) showed a mix of parasites expressing either *clag3.1* or *clag3.2*, suggesting that the epigenetic memory of *clag3* genes is reset during transmission stages. Finally, we tested whether other drugs, that are suspected to require facilitated transport to reach the cell, could be susceptible of failure by this drug resistance mechanism. We found that the antimalarial compounds T3 and T16 (bis-thiazolium salts) require the product of *clag3* genes to enter the infected erythrocyte and that *P. falciparum* populations can develop resistance to these compounds by selection of parasites with dramatically reduced expression of both genes. The rest of the drugs that we tested might use alternative routes in which *clag3* genes are not involved.

We have described for the first time an antimalarial drug resistance mechanism regulated at the epigenetic level in *P. falciparum* parasites. This phenomenon may be of

relevance for parasite adaptation to the presence of toxic compounds in human blood, selecting rapidly those parasites that present the less permeable phenotype and developing drug resistance in a single infection.