Search for the molecular basis of *Plasmodium falciparum* response to dihydroartemisinin-piperaquine in vivo

Popular Science Summary

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Malaria is an infectious disease causing hundreds of thousands of deaths every year. It is caused by the *Plasmodium* protozoan – one single cell microorganisms- of which the *Plasmodium falciparum* (*P. falciparum*) species is recognized to be one of the deadliest ones. *P. falciparum* is a parasite that infects human beings through a mosquito bite. When the mosquito carrying *P. falciparum* has a blood meal, the infective stage of the parasite invades the human organism and goes through some stages of maturation, first in the liver and then in the bloodstream, giving different symptoms.

Artemisinin (ART) is a drug whose power against malaria has been discovered in the 70s in China. It has a huge impact on the parasite but endures less than one hour in the body, therefore it has to be administered for 7 days to cure the patient.

P. falciparum is known to have developed resistance to different kinds of drugs that have been used to cure the disease, meaning that it has been able to survive the medications that once were sufficient to kill it by selection of resistant mutations. Artemisinin is being used together with other drugs which have a longer life inside of the human body, this to avoid both the long administration times of ART and also the development of resistance. The idea behind ACTs (Artemisinin combination therapies) being that the complementary drug eliminates the remaining parasites in a longer time lapse after the huge initial impact of ART. ACTs represent the first line treatment the WHO recommends to cure *P. falciparum* malaria. One of these ACTs is made by dihydroartemisinin (a metabolite of ART) together with Piperaquine (DHA-PPQ).

The aim of the study is to claim whether the parasite is developing resistance to DHA-PPQ by analyzing blood samples from *P. falciparum* malaria patients living in 3 different villages in Mali, Africa. These patients took part in a clinical trial, were followed up for a 2 years' time during which blood samples were collected at every malaria episode prior to treatment with the studied drug. Target of the analysis were genetic SNPs (single nucleotide polymorphisms) at 4 different positions on two genes which have been seen to be linked to *P. falciparum*'s resistance to drugs: *pfmdr1* (*P. falciparum* multidrug resistance 1) at allele positions 86, 184 and 1246 and *pfcrt* (*P. falciparum* chloroquine resistance transporter) at position 76.

The analysis, followed by statistical observations, showed no direct correlation between the detected genetic selections and resistance to DHA-PPQ, giving a green light to its future deployment as treatment of uncomplicated *P. falciparum* malaria in Africa.

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