Drug resistance mutations also enhance growth in malaria parasite

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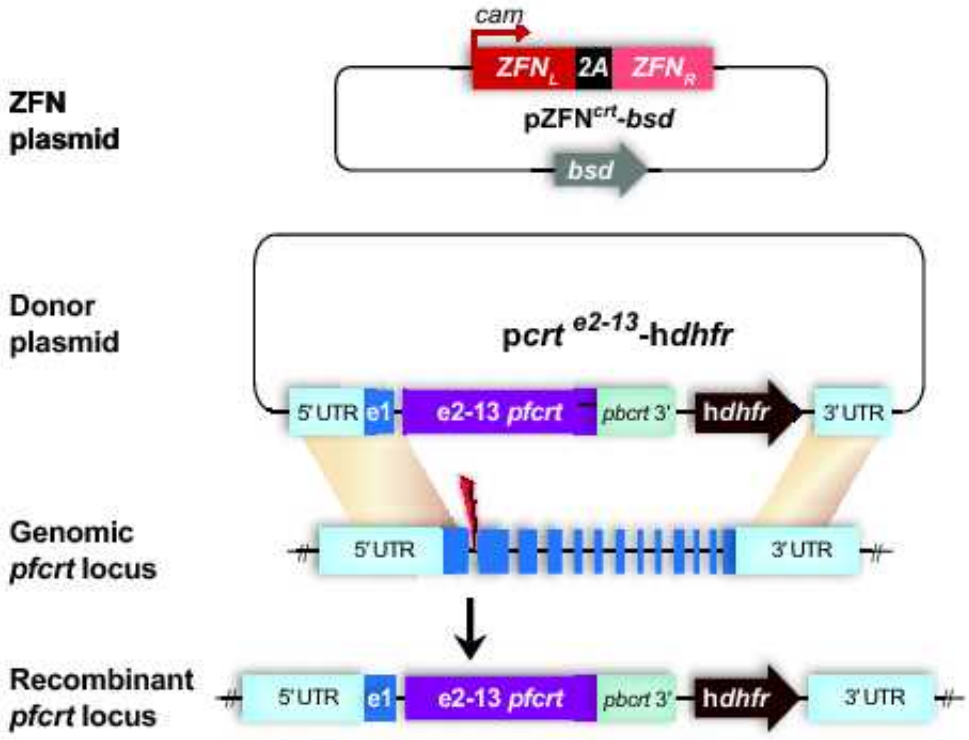

Gabryszewski used a gene editing technique based on "zinc-finger nucleases" to investigate the gene pfcrt that when mutated makes the malaria parasite Plasmodium falciparum resistant to chloroquine. These authors introduced multiple mutations into parasites cultured in human red blood cells in the laboratory, and characterized a novel set of mutations that make parasites drug resistant and grow even faster than drug-sensitive parasites. The caption shows how the genomic pfcrt sequence was changed into a recombinant form using this gene editing method involving two DNA plasmids that are introduced into the parasite. Credit: Stanislaw Gabryszewski and David Fidock

Some mutations that enable drug resistance in the malaria-causing parasite *Plasmodium falciparum* may also help it grow, according to a new study published in *PLOS Pathogens*.

P. falciparum is a single-celled parasite that infects the human bloodstream and causes the most severe form of malaria. Some strains of P. falciparum have evolved resistance to antimalarial drugs, including the commonly used drug chloroquine. Often, chloroquine resistance mutations hinder P. falciparum's ability to infect the bloodstream and grow. However, in a previous study, Stanislaw Gabryszewski of Columbia University Medical Center, New York, and colleagues discovered that a uniquely mutated version of the P. falciparum gene known as pfcrt provides drug resistance while avoiding the detrimental impact of growth seen with more widely distributed mutated pfcrt variants.

In the new study, Gabryszewski's team investigated this version, or allele, of the pfcrt gene, which is called Cam734 and has been found in certain regions in Southeast Asia. Using DNA-modifying proteins called zinc-finger nucleases, they characterized the individual mutations unique to Cam734 in terms of their effects on drug resistance, metabolism, and growth rates in living parasites.

The researchers found that a mutation called A144F is required for the chloroquine resistance enabled by Cam734 and that this mutation also contributes to resistance to first-line drugs amodiaquine and quinine. Additional mutations were identified that contributed to resistance to chloroquine and impacted the potency of other antimalarials. When the scientists reversed these mutations in living parasites that had the Cam734 allele, growth slowed, indicating that these mutations also enhance infection.

Additional experiments identified specific effects of Cam734 mutations

on several metabolic pathways in P. falciparum, including the digestion of human hemoglobin that parasites use to obtain amino acids for protein synthesis.

They also found evidence that Cam734 helps to maintain an electrochemical gradient that allows the protein encoded by the pfcrt gene to thwart the cellular effects of chloroquine.

These new findings significantly broaden scientists' understanding of Cam734, the second most common variant of the pfcrt gene in Southeast Asia. The findings identify multiple intracellular processes and multidrug resistance phenotypes impacted by changes in PfCRT and can help inform future malaria treatment efforts.

More information: *PLOS Pathogens*: dx.plos.org/10.1371/journal.ppat.1005976

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