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Singapore's SMART researchers identify malaria parasite drug resistance mechanism

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The study found that a cellular process called transfer Ribonucleic acid (tRNA) modification influences the malaria parasite's ability to develop resistance

Researchers from the Antimicrobial Resistance (AMR) Interdisciplinary Research Group (IRG) at Singapore-MIT Alliance for Research and Technology (SMART) have discovered a link between malaria parasites' ability to develop resistance to antimalarial drugs – specifically artemisinin (ART) – through a cellular process called transfer Ribonucleic acid (tRNA) modification. tRNA modification is a mechanism that allows cells to respond rapidly to stress by altering RNA molecules within a cell.

The breakthrough discovery is accomplished in collaberation with MIT's research enterprise in Singapore, in collaboration with Massachusetts Institute of Technology (MIT), Columbia University Irving Medical Center (CUIMC), and Nanyang Technological University, Singapore (NTU Singapore).

The discovery advances the understanding of how malaria parasites respond to drug-induced stress and develop resistance and paves the way for the development of new drugs to combat resistance.

The study describes how tRNA modification can alter the parasite's response to ART and help it survive ART-induced stress by changing its protein expression profile, making the parasite more resistant to the drug. ART partial resistance causes a delay in the eradication of malaria parasites following treatment with ART-based combination therapies, making these therapies less effective and susceptible to treatment failure.

By leveraging the advanced technology and techniques for epitranscriptomic analysis developed at SMART, researchers have isolated the RNA of interest, tRNA, and using mass spectrometry to identify the different modifications present. They isolated and compared the drug-sensitive and drug-resistant malaria parasites, some of which were treated with ART and others left untreated as controls. The analysis revealed changes in the tRNA modifications of drug-resistant parasites, and these modifications were linked to the increased or decreased translation of specific genes in the parasites. The altered translation process was found to be the underlying mechanism for the observed increase in drug resistance. This discovery also expands our understanding of how microbes and cancer cells exploit the normal function of RNA modifications to thwart the toxic effects of drugs and other therapeutics.