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Researchers find new class of highly potent antimalarial compounds

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Despite renewed global efforts for eradication, malaria continues to exert devastating effects on human health. An estimated 220 million people are infected each year by malaria-causing Plasmodium parasites, which are transmitted by the bite of an infected mosquito. This enormous infection burden leads to some 660,000 lives lost to malaria each year, the majority of these young children in sub-Saharan Africa. While a vaccine to prevent malaria remains elusive, we depend on antimalarial compounds both to treat infections and prevent disease.

Plasmodium parasites progress through two different stages of life in humans and other mammals, the first of which occurs in the liver, and causes no symptoms of disease. The second stage of Plasmodium life occurs in the red blood cells, and it is here that the parasites can cause severe illness and death. Most current antimalarial compounds target only the malaria parasites growing in the blood, but a great need exists for compounds which could successfully eliminate the parasites in the liver as well, before they begin causing illness.

In work published online today in the journal *PNAS*, researchers at the Instituto de Medicina Molecular (IMM), in Lisbon, Portugal, have discovered a new class of highly potent antimalarial compounds. These compounds, referred to as Torins, were originally developed by researchers in the Boston, MA to inhibit a key human protein involved in cell growth, mTOR, and have been shown to be effective anticancer agents in rodent models. In research perdormed by Dr. Kirsten Hanson in the laboratory of Dr. Maria Mota, the IMM team and their

collaborators have discovered that Torins are extremely effective multistage antimalarials; Torins appear to have a novel activity against the Plasmodium parasites themselves, distinct from both currently used malaria therapeutics and from their ability to target human mTOR.

Torins are capable of killing the cultured blood stages of the human parasite, Plasmodium falciparum, the species which causes most malaria deaths and severe disease, and are equally potent against the liver stages of a model rodent parasite. A single dose of the compound Torin2 delivered at the beginning of the P. berghei liver stage is sufficient to eliminate infection in mice before any Plasmodium parasites reach the blood. "Given the alarming trend of resistance to our current antimalarial therapies, this is really an exciting finding," says Dr. Mota, the senior author of the study, "and we are already working to develop Torin molecules suitable for clinical trials of antimalarial activity in humans."

More information: Torins are potent antimalarials that block replenishment of Plasmodium liver stage parasitophorous vacuole membrane proteins, www.pnas.org/cgi/doi/10.1073/pnas.1306097110

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