Malaria's weakest link

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A group of researchers from EPFL's Global Health Institute (GHI) and Inserm (Institut National de la Santé et de la Recherche Médicale, the French government agency for biomedical research) has discovered that a class of chemotherapy drugs originally designed to inhibit key signaling pathways in cancer cells also kills the parasite that causes malaria. The discovery could quickly open up a whole new strategy for combating this deadly disease.

The research, published online in the journal *Cellular Microbiology*, shows that the malaria parasite depends upon a signaling pathway present in the host – initially in liver cells, and then in red blood cells – in order to proliferate. The enzymes active in the signaling pathway are not encoded by the parasite, but rather hijacked by the parasite to serve its own purposes. These same pathways are targeted by a new class of molecules developed for cancer chemotherapy known as kinase inhibitors. When the GHI/Inserm team treated red blood cells infected with malaria with the chemotherapy drug, the parasite was stopped in its tracks.

Professor Christian Doerig and his colleagues tested red blood cells infected with Plasmodium falciparum parasites and showed that the specific PAK-MEK signaling pathway was more highly activated in infected cells than in uninfected cells. When they disabled the pathway pharmacologically, the parasite was unable to proliferate and died. Applied in vitro, the chemotherapy drug also killed a rodent version of malaria (P. berghei), in both liver cells and red blood cells. This indicates that hijacking the host cell's signaling pathway is a generalized strategy

used by malaria, and thus disabling that pathway would likely be an effective strategy in combating the many strains of the parasite known to infect humans.

Malaria infects 250 million and kills 1-3 million people every year worldwide. Efforts to find a treatment have been marred by the propensity of the parasite to quickly develop drug resistance through selection of mutations. Once in the body, it hides from the immune system inside liver and blood cells, where it proliferates. The discovery that the parasite hijacks a signaling pathway in the host cell opens up a whole new strategy for fighting the disease. Instead of targeting the parasite itself, we could make the host cell environment useless to it, thus putting an end to the deadly cycle. Because this strategy uniquely targets host cell enzymes, the parasite will be deprived of a major modus operandi for development of drug resistance - selection of mutations in the drug target.

Several kinase-inhibiting chemotherapy drugs are already used clinically, and many more have passed stage 1 and stage 2 clinical trials. Even though these drugs have toxic effects, they are still being used or considered for use over extended periods for cancer treatment. Using them to combat malaria would involve a much shorter treatment period, making the problem of toxicity less acute. The authors of the study suggest evaluating these drugs for antimalarial properties, thus drastically reducing the time and cost required to put this new malaria-fighting strategy into practice.

Provided by Ecole Polytechnique Federale de Lausanne

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