Research team announces new class of compounds that appear to be effective against malaria

November 27 2014, by Bob Yirka

Credit: CDC

(Phys.org) —A large team of researchers with members from around the globe has announced that a class of compounds they've been studying (pyrazoleamides) appears to be successful in fighting malaria. In their paper published in the journal *Nature Communications*, the team describes how the compounds impact plasmodium parasites which are

responsible for the disease and why they believe it will be a successful treatment.

Malaria, as most are aware, causes misery in millions of people every year, and kills approximately 600,000 of them. It also, unfortunately, tends to impact people who are least equipped to deal with it in places such as Africa, India, parts of Asia and South America. Scientists around the world have been working tirelessly to come up with new treatments for the disease as those that have been used in the past are becoming less effective as the parasites becomes more resistant to them.

The plasmodium parasite is transmitted via mosquitoes—blood from an infected person is injected into one that is not, causing them to be infected. The parasites takes up residence inside red blood cells and causes changes to occur in the cell membranes which in turn causes sodium to build up in the cells. The parasite has a protein that it uses to prevent itself from being contaminated by the excess sodium. In this new effort, the researchers have found a new class of compounds that overcomes that protein protection, which means the parasites exposed to them take in too much sodium, resulting in too much fluid being drawn in, causing them to burst. They noted that it appears likely that in some instances the parasite could leave the red blood cell to escape the salty environment, but that wouldn't save them, as they cannot survive without their host. As an added bonus, they found that some of the same compounds also caused disruption to the sexual development of the parasite.

Several types of the compound have been tested in mice thus far, with very promising results. The team reports also that speeding up the process that normally leads to resistance showed that the parasite had a low frequency of adjustment, which suggests that should one or more of the compounds pass clinical trials, it might take a long time for the parasite to develop resistance, giving researchers more time to work on

the next generation of treatments for the disease.

More information: Pyrazoleamide compounds are potent antimalarials that target Na+ homeostasis in intraerythrocytic *Plasmodium falciparum*, *Nature Communications* 5, Article number: 5521 DOI: 10.1038/ncomms6521

Abstract

The quest for new antimalarial drugs, especially those with novel modes of action, is essential in the face of emerging drug-resistant parasites. Here we describe a new chemical class of molecules, pyrazoleamides, with potent activity against human malaria parasites and showing remarkably rapid parasite clearance in an in vivo model. Investigations involving pyrazoleamide-resistant parasites, whole-genome sequencing and gene transfers reveal that mutations in two proteins, a calcium-dependent protein kinase (PfCDPK5) and a P-type cation-ATPase (PfATP4), are necessary to impart full resistance to these compounds. A pyrazoleamide compound causes a rapid disruption of Na+ regulation in blood-stage Plasmodium falciparum parasites. Similar effect on Na+ homeostasis was recently reported for spiroindolones, which are antimalarials of a chemical class quite distinct from pyrazoleamides. Our results reveal that disruption of Na+ homeostasis in malaria parasites is a promising mode of antimalarial action mediated by at least two distinct chemical classes.

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