Researchers identify mechanism malaria parasite uses to spread among red blood cells

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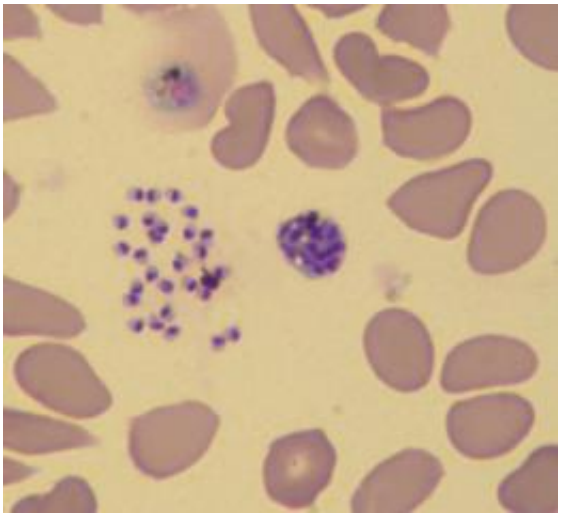

Infected human red blood cells (top; and right of center) by the human malaria parasite, *Plasmodium falciparum* (the parasite is shown in purple). The newly-formed parasites (left of center) are ready to invade new red blood cells. Credit: Le Roch lab, UC Riverside.

Malaria remains one of the most deadly infectious diseases. Yet, how *Plasmodium*, the malaria parasite, regulates its infectious cycle has remained an enigma despite decades of rigorous research.

But now a research team led by a cell biologist at the University of California, Riverside has identified a mechanism by which *Plasmodium* intensively replicates itself in human blood to spread the disease.

"If this mechanism can be stopped," said Karine Le Roch, an assistant professor of cell biology and neuroscience, who led the research, "*Plasmodium* replication would cease or be severely inhibited, thus controlling the spread of malaria."

In the cells of eukaryotes, such as the unicellular *Plasmodium* and humans, DNA, which can be as long as two meters, is closely packed to fit into the cell's tiny nucleus. Huge complex proteins called nucleosomes facilitate this DNA compaction so that eventually the DNA is coiled in an ordered manner to form chromosomes.

Made up of histone, a kind of protein, the nucleosomes are repeating units around which the double helix of DNA gets wrapped and vast amounts of genetic information get organized.

In trying to understand how the malaria parasite multiplies in red blood cells, Le Roch's team found that in *Plasmodium* a kind of "histone crash" takes place - a massive breakdown of histone that explains how the parasite can replicate extensively its DNA and coding gene in human red blood cells.

For cell multiplication to occur, the genes in a DNA strand need to first be transcribed and translated (converted) into protein. For this transcription to take place, however, the nucleosomes must first get evicted (removed), a process that opens up the DNA strand to give special "transcription factors" full access to the genes. The transcription factors then convert these genes into protein.

While in humans such eviction of nucleosomes is specific to only some sections of the DNA strand and performed only when needed, in *Plasmodium* the situation is vastly different.

Le Roch's experiments in the lab show that 18 hours after *Plasmodium*

enters a red blood cell, a huge eviction of nucleosomes occurs in the *Plasmodium* DNA. Gene transcription throughout the genome follows; after multiplication into up to 32 daughter cells, the newly-formed parasites are ready to exit the red blood cell and invade new ones about 18 hours later.

"We found in our experiments that histones are massively evicted everywhere in the *Plasmodium* genome, resulting in most of the *Plasmodium* genes to be transcribed at once," Le Roch said. "If we can find a candidate enzyme that can regulate this massive histone eviction, we could halt or greatly limit *Plasmodium* replication."

Study results appear this month in the journal *Genome Research*.

"Dr. Le Roch's findings document a global mechanism mediating significant changes in gene expression as the parasites transition through developmental stages in the human hosts," said Anthony A. James, a distinguished professor of microbiology & molecular genetics and molecular biology & biochemistry at UC Irvine, who was not involved in the research. "As well as being a major basic discovery, this provides a basis for probing the mechanisms for novel drug development."

Provided by University of California - Riverside