New insights into the survival and transmission strategy of malaria parasites

August 13 2014

Credit: CDC

HP1 proteins are found in most eukaryotic organisms and are important regulators of gene silencing. In short, HP1 induces heritable condensation of chromosomal regions. As a result genes located within these regions are not expressed. Importantly, since this conformation is reversible HP1-controlled genes can become activated without requiring changes in the underlying DNA sequence.

The team led by Till Voss at the Swiss Tropical and Public Health Institute in collaboration with colleagues from the Nanyang Technological University in Singapore engineered a mutant parasite in which HP1 expression can be shut down at the push of a button. The researchers observed that in HP1-depleted parasites all of the 60 so-called var genes became highly active.

Each var gene encodes a distinct variant of the virulence factor PfEMP1, which is displayed on the surface of the parasite-infected red blood cell. PfEMP1 is a major target of the immune system in infected humans. Individual parasites normally express only one of the 60 different var/PfEMP1 proteins, while keeping all other members silenced. By switching to another var/PfEMP1 variant the parasite is able to escape existing immune responses raised against previous variants. The new study shows that HP1 protects the PfEMP1 antigenic repertoire from being exposed to the immune system at once.

The new study shows that HP1 protects the PfEMP1 antigenic repertoire from being exposed to the immune system at once. "This finding is a major step forward in understanding the complex mechanisms responsible for antigenic variation," says Till Voss from the Swiss Tropical and Public Health Institute in Basel. "Furthermore, the tools generated in our study may be relevant for future research on malaria vaccines and immunity."

Lack of HP1 triggers production of malaria transmission stages

Importantly, the study also reveals that parasites lacking HP1 fail to copy their genomes and are hence unable to proliferate. "Initially, we thought all parasites in our culture dish were dead," says Till Voss.

However, it turned out that over 50% of these parasites were fully viable and differentiated into gametocytes, the sexual form of the malaria parasite. Gametocytes are the only form of the parasite capable of infecting a mosquito and therefore a prerequisite to transmit malaria between humans. "Such a high sexual conversion rate is unprecedented. Usually only around 1% of parasites undergo this switch," the researcher explains.

Further experiments show that a master transcription factor triggering sexual differentiation (termed AP2-G) is expressed at much higher levels in parasites lacking HP1. Under normal conditions, HP1 silences the expression of AP2-G and thus prevents sexual conversion in most parasites.

"The switch from parasite proliferation to gametocyte differentiation is controlled epigenetically by a HP1-dependent mechanism," says Till Voss. "This is really exciting. With this knowledge in hand, and with the identification of another epigenetic regulator involved in the same process (published in the same issue of *Cell Host & Microbe*), we are now able to specifically track the sexual conversion pathway in molecular detail." This may pave the route for the development of new drugs preventing sexual conversion and consequently malaria transmission.

Malaria infection cycle

Malaria is a devastating infectious disease caused by unicellular parasites of the genus Plasmodium. Over 1 billion people worldwide live at high risk of contracting malaria and each year the disease causes more than 200 million clinical cases and 700'000 deaths, mostly among young African children. Plasmodium falciparum, one of five species known to elicit malaria in humans, is responsible for the vast majority of severe and fatal malaria outcomes.

Plasmodium parasites invade red blood cells, undergo intracellular replication, destroy their host cell and release up to 32 daughter parasites ready to infect new red blood cells. Repeated rounds of this vicious cycle lead to a massive expansion of the parasite population in the blood, which is responsible for all malaria-related morbidity and mortality. During each replication cycle a small number of parasites cease to proliferate and differentiate into sexual precursor cells called gametocytes. Only this form is able to infect the mosquito and therefore to transmit malaria to other humans.

More information: Heterochromatin Protein 1 Secures Survival and Transmission of Malaria Parasites. Nicolas M. B. Brancucci, Nicole L. Bertschi, Lei Zhu, Igor Niederwieser, Wai Hoe Chin, Rahel Wampfler, Céline Freymond, Matthias Rottmann, Ingrid Felger, Zbynek Bozdech, and Till S. Voss. *Cell Host & Microbe* 16, 165-176. 2014.

Provided by Swiss Tropical and Public Health Institute