GULBENKIAN SCIENCE

PRESS RELEASE

Low sugar: A trade-off to starve malaria parasites

Oeiras, 15th July 2022 – A new study led by Miguel Soares' group at the Instituto Gulbenkian de Ciência (IGC) and published in the prestigious journal Cell Metabolism, revealed an important and unexpected defense strategy against malaria, one of the deadliest infectious diseases in the world. This response limits the extent of inflammation and organ damage, while decreasing the virulence of the malaria parasite. But everything comes at a cost.

Malaria is a disease transmitted through the bite of mosquitoes infected with parasites belonging to the genus *Plasmodium*. Once inside the bloodstream, the parasite firstly invades the liver and then the red blood cells, where it multiplies. As it causes red blood cells to rupture, the parasite is released into circulation and begins new rounds of invasion, increasing its number exponentially.

Low blood sugar levels are a common complication of severe malaria. Scientists believe this stems from a combination of events: firstly, hosts eat less during disease (a sickness-associated behavior known as anorexia of infection); secondly, the production of sugar in the liver is deregulated; and thirdly, the parasite and the cells of the immune system consume extra sugar. When sugar levels drop too low (hypoglycemia), the host cannot maintain essential functions, including the control of body temperature. This is a major cause of death in children infected with malaria.

The liver plays a crucial role in maintaining steady levels of sugar in the organism (glycemia), but until now, the mechanisms acting during malaria were not established. A previous study led by Miguel Soares reveled that when red blood cells burst, a molecule named heme is released, leading to the repression of sugar production in the liver. Convinced that this could not be a mere coincidence, researchers decided to explore if heme was responsible for the hypoglycemia seen in malaria.

To study this, the team administered heme to mice or infected them with *Plasmodium*. In both scenarios, mice presented typical features of malaria, including anorexia, low blood sugar levels, and a drop in body temperature. With the support from IGC's Genomics and Bioinformatics Units, they analyzed these animal's livers and realized that there was a profound alteration in the expression of genes related to the metabolism of sugar. This evidenced that this organ is responsible for the control of blood sugar levels associated with *Plasmodium* infection, an alteration initiated by heme.

To evaluate the impact of these changes, the researchers recurred, with the support from IGC's Animal House, to mice that were genetically modified not to produce sugar in the liver, mimicking, to a great extent, the development of hypoglycemia in human disease. When infected with *Plasmodium*, the immune system of these mice was less activated, and their liver suffered less damage. Despite suppressing the immune system, the researchers showed that repressing the production of sugar in the liver was still harmful to the malaria parasite. "It seems that this mechanism initiated by heme is not merely pathological, but is instead a defense strategy, whereby the host and the pathogen compete to access vital nutrients", explains Susana Ramos, a senior post-doctoral researcher at the IGC and co-first author of the paper with Temitope Ademolue, PhD student at the institute.

Just like immune cells, this parasite depends on sugar to thrive. Using an innovative single-cell approach, the researchers analyzed the genetic profile of each *Plasmodium* parasite contained in these mice's red blood cells. Surprisingly, they found that, in the lack of sugar, the parasite altered the expression of genes that control its growth and the severity of malaria. As a result,

it became less virulent and arrested its development, eventually dying inside these cells. "We had not anticipated the impact the reprogramming of sugar production in the host would have on the parasite", explains Temitope Ademolue. Per contra, the parasite differentiated into a transmissible form that is taken up by mosquitoes when they bite an infected person, which could favor its transmission. "It was interesting to explore how the pathogen adapted to it, promoting its transmission rather than virulence", adds the researcher. Thanks to a collaboration with Dr. Fátima Nogueira from the Instituto de Higiene e Medicina Tropical, Universidade NOVA de Lisboa, these effects were also confirmed in human cells infected with *Plasmodium falciparum*, the deadliest of the parasites causing malaria in humans.

This defense strategy against malaria seems to be guarded by a liver protein (G6pc1) that starves malaria parasites while preventing sugar levels and body temperature from decreasing below a threshold compatible with host survival. Although protective against immune-mediated liver damage and anemia caused by the destruction of red blood cells, when sustained over time this defense strategy carries two major tradeoffs: the development of hypoglycemia, a risk factor for death in severe malaria, and a possible increase in transmission of this disease.

According to Miguel Soares, these findings are particularly relevant because "they demonstrate the existence of a defense strategy against infection that does not rely on the immune system. Instead, by reducing the production of sugar in the liver, the host kills the parasite". This revealed something especially important when it comes to treating malaria: "while severe hypoglycemia needs to be prevented and treated, increasing blood sugar levels could impair the response to infection", the researcher concludes.

This study was developed by the Instituto Gulbenkian de Ciência in collaboration with the Global Health and Tropical Medicine, Instituto de Higiene e Medicina Tropical, Universidade NOVA de Lisboa, Portugal; the Center for Sepsis Control and Care, Jena University, Germany; and the Université Claude Bernard Lyon, INSERM, France. Funding was granted by Fundação para a Ciência e Tecnologia; Gulbenkian Foundation; Deutsche Forschungsgemeinschaft; Center for Sepsis Control and Care (CSCC), Jena University Hospital "La Caixa" foundation; Oeiras-ERC Frontier Research Incentive Awards; DFG Cluster of Excellence 'Balance of the Microverse' and Congento.

Original paper: Susana Ramos, Temitope W. Ademolue *et al* (2022). **A Hypometabolic Defense Strategy Against Malaria**. Cell Metabolism.

DOI: https://doi.org/10.1016/j.cmet.2022.06.011

More information:
Ana Morais
Head of Institutional Communication
@: anamorais@igc.gulbenkian.pt
Contact: +351 965 249 488