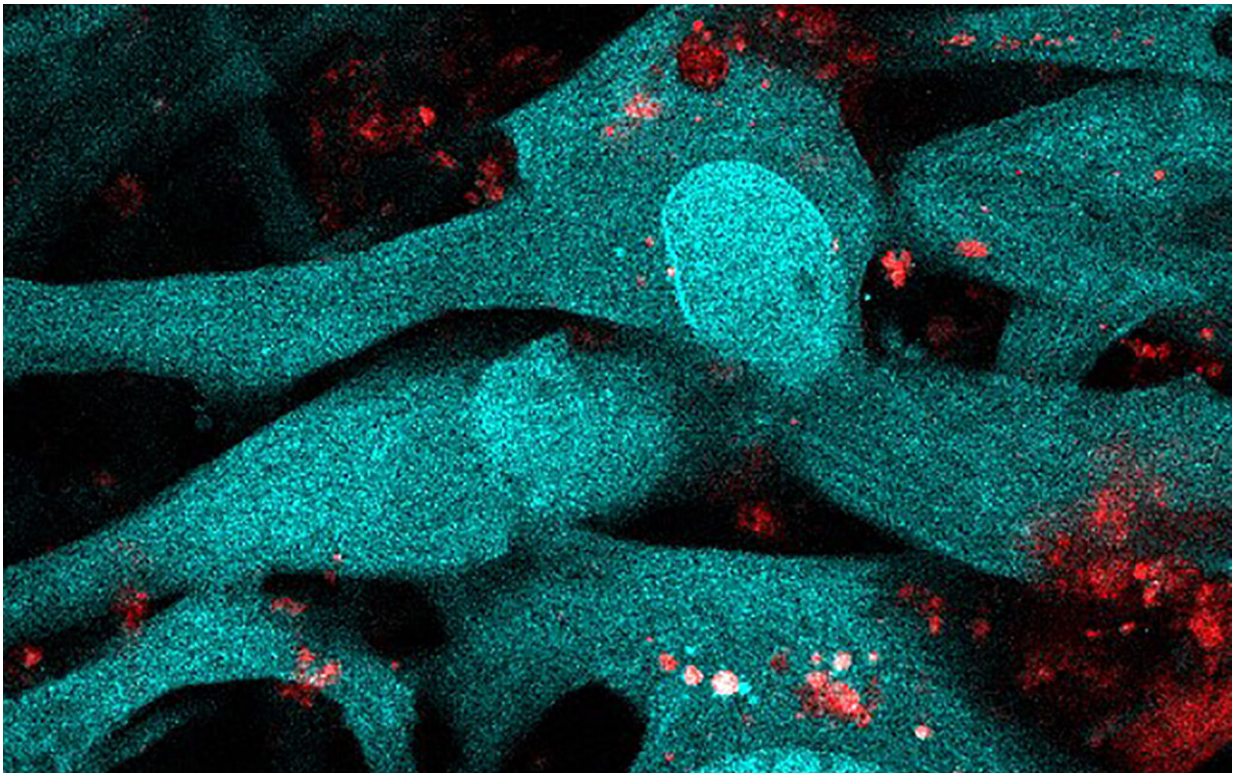
The brain can detect infection with malaria

September 5 2022



Brain vascular endothelial cells (blue) internalize particles released by erythrocytes infected with the malaria parasite (pink and red). Credit: Teresa Pais, 2022

A team of researchers from the Instituto Gulbenkian de Ciência (IGC) revealed that cells of the brain can detect the presence of malaria parasites in the blood, triggering the inflammation underlying cerebral malaria. This discovery brought to light new targets for adjuvant

therapies that could restrain brain damage in initial phases of the disease and avoid neurological sequelae.

Cerebral malaria is a severe complication of infection with Plasmodium falciparum, the most lethal of the parasites causing malaria. This form of the disease manifests through impaired consciousness and coma and affects mainly children under 5, being one of the main causes of death in this age group in countries of Sub-Saharan Africa. Those who survive are frequently affected by debilitating neurological sequelae, such as motor deficits, paralysis, and speech, hearing, and visual impairment.

To prevent certain molecules and cells from reaching the brain, which would disturb its normal functioning, specialized cells from the inner lining of blood vessels, the endothelial cells, are tightly kept together, forming a barrier between the blood and this organ. Cerebral malaria results from an unrestrained inflammatory response to infection which leads to significant alterations in this barrier and, consequently, neurological complications.

Over the last years, specialists in this field have turned their attention to a molecule, named interferon-β, which seems to be associated with this pathological process. So called for interfering with viral replication, this highly inflammatory molecule has two sides: it can either be protecting or cause tissue destruction. It is known, for example, that despite its antiviral role in COVID-19, at a given concentration and phase of infection, it can cause lung damage. A similar dynamic is thought to occur in cerebral malaria. However, we still don't know what leads to the secretion of interferon-β, nor the main cells involved.

A recent study led by the IGC and published in *Proceedings of the National Academy of Sciences*, revealed that endothelial cells in the brain play a crucial role, being able to sense the infection by the malaria parasite at an early phase. These detect the infection through an internal

sensor which triggers a cascade of events, starting with the production of interferon-β. Next, they release a signaling molecule that attracts cells of the immune system to the brain, initiating the inflammatory process.

To reach these conclusions, researchers used mice that mimic several symptoms described in human malaria and a genetic manipulation system that allowed them to delete this sensor in several types of cells. When they deleted this sensor in brain endothelial cells, they concluded that the animal's symptoms were not as severe and that they died less from the infection. That was when they realized these brain cells contributed greatly to the pathology of cerebral malaria.

"We thought brain endothelial cells acted in a later phase, but we ended up realizing that they are participants from the very beginning," explains Teresa Pais, a post-doctoral researcher at the IGC and first author of the study. "Normally we associate this initial phase of the response to infection with cells of the immune system. These are already known to respond, but cells of the brain, and maybe other organs, also have this ability to sense the infection because they have the same sensors," she adds.

But what really surprised the researchers was the factor activating the sensor and triggering this cell response. This factor is nothing more nothing less than a byproduct of the activity of the parasite. Once in the blood, the parasite invades the host's red blood cells, where it multiplies. Here, it digests hemoglobin, a protein that transports oxygen, to get nutrients.

During this process, a molecule named heme is formed and it can be transported in tiny particles in the blood that are internalized by endothelial cells. When this happens, heme acts as an alarm for the immune system. "We weren't expecting that heme could enter cells this way and activate this response involving interferon-βin endothelial

cells," the researcher confesses.

This work of about 6 years allowed the researchers to identify a molecular mechanism that is critical for the destruction of brain tissue during infection with the malaria parasite and, with that, new therapeutic targets. "The next step will be to try to inhibit the activity of this sensor inside the endothelial cells and understand if we can act on the host's response and stop brain pathology in an initial phase," explains Carlos Penha Gonçalves, principal investigator of the group who led the study.

"If we could use inhibitors of the sensor in parallel with antiparasitic drugs maybe we could stop the loss of neuronal function and avoid sequelae which are a major problem for children surviving cerebral malaria," he concludes.

More information: Teresa F. Pais et al, Brain endothelial STING1 activation by Plasmodium -sequestered heme promotes cerebral malaria via type I IFN response, *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2206327119

Provided by Instituto Gulbenkian de Ciência (IGC)