

# Tolerance to malaria by means of iron control

November 14 2012

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Iron sculpture "Awaking" (2004) from the Portuguese artist Rui Chafes. Credit: CHAFES, Rui, *Contramundo esculturas 2002-2011*, Fundación Luis Seonane, A Coruña, 2011.

Malaria is a life-threatening condition that exposes approximately half of the world's population to the risk of developing a severe and often lethal form of disease. In a study published in the latest issue of the journal

*Cell Host & Microbe*\*, Miguel Soares and his team at Instituto Gulbenkian de Ciência (IGC), Portugal, discovered that the development of severe forms of malaria can be prevented by a simple mechanism that controls the accumulation of iron in tissues of the infected host. They found that expression of a gene that neutralizes iron inside cells, named H Ferritin, reduces oxidative stress preventing tissue damage and death of the infected host. This protective mechanism provides a new therapeutic strategy against malaria.

Malaria is the disease caused by infection with the parasite *Plasmodium* through the bites of infected mosquitoes. Infected individuals activate a series of defence mechanisms that aim at eliminating the parasite. However, this is not totally efficient in terms of avoiding severe forms of the disease and eventually death. There is another defence strategy that provides disease tolerance to malaria, reducing disease severity without targeting the parasite, as recently highlighted by Miguel Soares and collaborators in the journal *Science*\*\* . The study now published in the journal *Cell Host & Microbe*\* shows that this defence strategy acts via the regulation of [iron](#) metabolism in the infected host.

It was known that restricting iron availability to pathogens can reduce their virulence, that is, their capacity to cause disease. However, this defence strategy has a price, namely the accumulation of toxic iron in tissues and organs of the infected host. This can lead to tissue damage, enhancing rather than preventing disease severity. In the experimental work now conducted Raffaella Gozzelino, a senior researcher in Miguel Soares' laboratory, demonstrates that the infected host overcomes this problem by inducing the expression of H-Ferritin, which detoxifies iron. The protective effect of H-Ferritin prevents the development of severe and often lethal forms of malaria in mice.

The researchers also investigated if there is a correlation between the severity of malaria and the expression of ferritin in humans. Together

with Bruno Bezerril Andrade (currently at the National Institute of Allergy and Infectious Diseases, NIH, USA), Nivea Luz and Manoel Barral-Netto (at Fundação Oswaldo Cruz and Faculdade de Medicina, Universidade Federal da Bahia, Brazil) they analyzed samples from individuals infected with *Plasmodium* in Rondônia, a state in the north-western part of Brazil. Their results showed that, among the infected individuals, those with higher levels of ferritin presented reduced [tissue damage](#). Together with the experimental data obtained in mice, these observations reveal that ferritin confers protection against malaria, without interfering directly with the parasite causing the disease, that is, that ferritin confers disease tolerance to malaria.

Miguel Soares says: 'Our work suggests that individuals that express lower levels of Ferritin and hence are not so efficient at sequestering toxic iron in their tissues might be at a higher risk of developing severe forms of malaria. Furthermore, our study also supports a theory that explains how protection against malaria, as well as other infectious diseases, can operate without targeting directly the causative agent of disease, namely *Plasmodium*. Instead, this defence strategy works by protecting cells, tissue and organs in the infected host from dysfunction, thus limiting the severity of disease.'

This study opens the way to new therapeutics that could confer tolerance to [malaria](#).

**More information:** \*Raffaella Gozzelino, Bruno Bezerril Andrade, Rasmus Larsen, Nivea F. Luz, Liviu Vanoaica, Elsa Seixas, António Coutinho, Sílvia Cardoso, Sofia Rebelo, Maura Poli, Manoel Barral-Neto, Deepak Darshan, Lukas C. Kühn and Miguel P. Soares. (2012) Metabolic Adaptation to Tissue Iron Overload Confers Tolerance to Malaria. *Cell Host & Microbe* 12: 693-704.

\*\* Ruslan Medzhitov, David S. Schneider and Miguel P. Soares. (2012)

Disease Tolerance as a Defense Strategy. *Science* 335: 936-941.

Provided by Instituto Gulbenkian de Ciencia

Citation: Tolerance to malaria by means of iron control (2012, November 14) retrieved 11 May 2024 from <https://medicalxpress.com/news/2012-11-tolerance-malaria-iron.html>

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