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CELLULAR MICROBIOLOGY

HO1 tips the balance

In a recent issue of *Cell Host and Microbe*, two groups report that haem oxygenase 1 (HO1), an enzyme that has previously been scrutinized by scientists for its cytoprotective properties, has a role in modulating the progression of tuberculosis (TB) and the hepatic stage of malaria.

Previously, Maria Mota and colleagues had shown that in the blood stage of *Plasmodium* spp. infection, HO1 can prevent the development of experimental cerebral malaria. In this work, they focused on the hepatic stage of malaria infection, in which sporozoites infect the liver and develop into merozoites that then invade the bloodstream in large numbers. Using a mouse model, Mota and colleagues showed that infection of the liver with *Plasmodium* spp. sporozoites induced expression of host HO1 in macrophages and hepatocytes, and that HO1 expression was essential to establish efficient malaria infection. *Plasmodium*-infected *Hmox*$^{-/-}$ mice (which lack the gene that encodes HO1) had significantly reduced numbers of malaria parasites in their livers and, importantly, did not go on to develop blood-stage infection. The authors showed that the livers of HO1-deficient mice were replete with neutrophils and macrophages, pro-inflammatory cytokines and chemokines. By contrast, in an infected liver in which HO1 was overexpressed, there was no evidence of a host inflammatory response. This indicates that HO1 protects the malaria parasite from destruction by dampening down the host inflammatory response, presumably through the anti-inflammatory effects of CO and/or biliverdin (two of the major products of HO1 enzymatic activity).

The study by Jeffery Cox and colleagues, in accordance with another new study by Adrie Steyn and co-workers, reveals that the enzymatic activity of host HO1 also affects *Mycobacterium tuberculosis*. However, rather than promoting productive infection as in malaria, the CO that is produced by HO1 is sensed by *M. tuberculosis* and activates the dormancy regulon to promote latency. The dormancy regulon is controlled by the DosS/T–DosR two-component system, which comprises two sensor kinases, DosS and DosT, and a cognate response regulator, DosR. The authors showed that infection of mouse macrophages with *M. tuberculosis* promoted expression of HO1 and that CO induced expression of dormancy regulon genes. They were also able to show that the DosS/T–DosR two-component system transmitted the CO signal, with the different sensor kinases having distinct effects on dormancy regulon expression.

These intriguing results strongly implicate HO1 and the CO that is produced by HO1 in the pathogenesis of murine malaria and TB. The divergent effects observed reveal the complexities of HO1–pathogen interactions. Whether HO1 is similarly exploited in human infection remains an important unanswered question.

Shannon Amoils

ORIGINAL RESEARCH PAPERS Epiphanio, S. *et al.* Heme oxygenase-1 is an anti-inflammatory host factor that promotes murine *Plasmodium* liver infection. *Cell Host Microbe* **3**, 331–338 (2008) | Shiloh, M. *et al.* *Mycobacterium tuberculosis* senses host-derived carbon monoxide during macrophage infection. *Cell Host Microbe* **3**, 323–330 (2008)

FURTHER READING Kumar, A. *et al.* Heme oxygenase-1 derived carbon monoxide induces the *Mycobacterium tuberculosis* dormancy regulon. *J. Biol. Chem.* 9 Apr 2008 (doi:10.1074/jbc.M802274200)