Malaria's severity reset by mosquito

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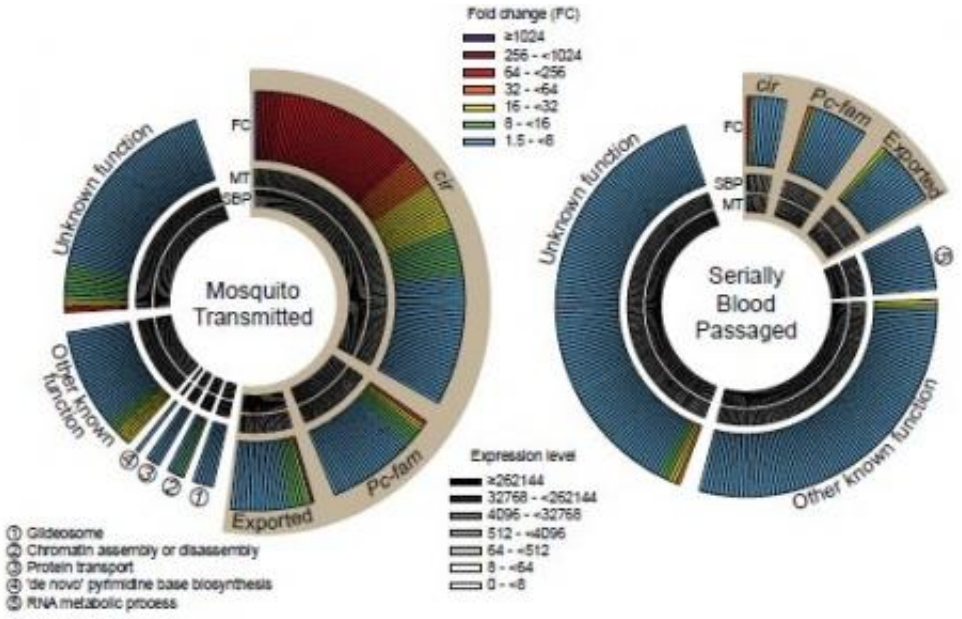

Mosquito transmission of P.c. chabaudi modifies parasite gene expression in the blood stage of the cycle.

(Medical Xpress)—For the first time, researchers have proven that the way in which malaria is transmitted to the host affects how severe the resulting infection will be.

The route of infection modifies the malaria parasite's gene activity levels and regulates the parasite's spread in the blood by controlling the mouse's

immune response. This study begins to understand how protective immunity to malaria occurs, an important step for the development of effective vaccines.

Researchers have known that the severity of symptoms of malaria increases when the malaria parasite is transferred repeatedly through blood samples in mice rather than by a mosquito, but up until now they have not known why.

"Understanding how malaria becomes more or less virulent is central to understanding how to manage and treat the disease," says Dr Matt Berriman, a senior author from the Wellcome Trust Sanger Institute. "We studied a rodent malaria species, that exhibits many of the same responses as seen in a human malaria infection. Our understanding of how the parasite interacts with the immune system is fundamentally changed by this study."

To explore the effect that the route of transmission had, the team examined the levels of gene activity in the malaria parasite during its life cycle in mice.

They found that P.c. chabaudi 'resets' its genetic activity when it is transmitted between the mosquito and mouse, making it less virulent. However, transferring the parasite through multiple blood transfers between mice in the laboratory loses this resetting. Because there is no reset the malaria parasite multiples much more quickly in mice after blood transfers, and causes an increase in disease severity.

The team uncovered a direct association between a specific gene family in the malaria parasite, known as cir genes, and the control of severity of the disease symptoms in mice. It appears that malaria parasite genes control the immune response of mice to the disease.

"Our research is helping to better understand vaccine targets," says Dr Adam Reid, author from the Wellcome Trust Sanger Institute. "RNA sequencing allowed us to identify a set of Plasmodium genes that control the immune response and the degree of severity of the disease in mice. We anticipate that we will be able to transfer the findings from our study in mice to human malaria studies, the next phase of our research."

The team expect that the cir gene family plays a role in activating the immune system and controls the level of parasite in the blood to keep malaria from harming the host. This is the largest gene family in malaria parasites, including the deadly human parasite, P. falciparum.

The study was led by Dr Jean Langhorne based at the Medical Research Council National Institute for Medical Research: "These results place the mosquito at the centre of our efforts to pick apart the processes behind protective immunity to malaria. Malaria is both preventable and curable but still has a huge burden on those who are vulnerable to severe forms of the infection, mostly young children. Understanding protective immunity in the body would be an important first step towards developing an effective vaccine."

More information: Spence, P. et al. Vector transmission regulates immune control of Plasmodium virulence, *Nature* 2013. DOI: 10.1038/nature12231

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