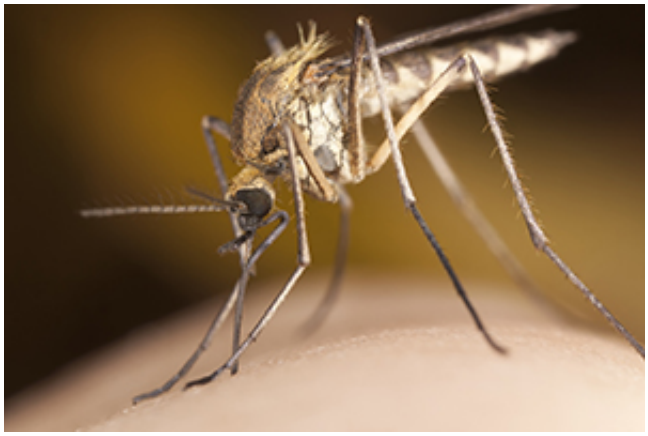
Brain-damaging complications of malaria arise from immune response to parasite antigens absorbed by blood vessels

11 September 2013



Without prompt medical attention, cerebral malaria can manifest as early as 10 days after being bitten by a mosquito infected with Plasmodium falciparum. Credit: iStockphoto/Thinkstock

Most deaths caused by the malarial parasite Plasmodium falciparum result from the onset of cerebral malaria. This severe neurological condition arises when parasites accumulate within the brain vasculature. Numerous studies over the years, using a mouse model of experimental cerebral malaria (ECM), have also revealed that host immune cells play a critical part.

Previous research from Laurent Rénia at the A*STAR Singapore Immunology Network had highlighted the prominent contribution of cells known as cytotoxic T lymphocytes (CTLs). His team has now uncovered the mechanism by which these cells promote ECM. CTLs are normally responsible for destroying cancerous or infected cells, but the researchers suspected that ECM may result from parasite-targeting CTLs that also attack and damage blood vessels in the brain.

Rénia and co-workers developed tools for detecting these CTLs and their target cells. They then determined that mice infected with Plasmodium berghei ANKA (PbA), an ECM-causing parasite subtype, specifically elicit CTLs targeted against a particular polypeptide chunk from a parasite-derived protein. Mice infected with PbA began producing CTLs that recognize this polypeptide within five days, and these cells migrated to the brain shortly afterward. The researchers also examined three Plasmodium parasite strains that do not trigger ECM and were surprised to find that these elicited a similar CTL response.

A closer examination of blood vessels from the brains of infected mice revealed the missing piece of the puzzle. Red blood cells infected by ECM-causing parasites exhibit a tendency to accumulate within these vessels, while those from non-ECM-causing parasites do not. Rénia and co-workers determined that when this accumulation occurs, the endothelial cells that line these blood vessels absorb and then display CTL-targeted parasite proteins via a mechanism termed 'cross-presentation'.

These cross-presenting cells subsequently become targets for CTL-mediated destruction, creating leaks that give malarial parasites access to the brain. Importantly, prompt treatment with antimalarial drugs can rapidly clear these parasites from the blood vessels, thereby preventing the onset of ECM.

Rénia hypothesizes that ECM specifically arises from parasite species possessing some innate characteristic that makes infected cells 'stickier'. "We were surprised that this subtle difference in parasite biology of sequestration versus non-sequestration leads to such huge differences in pathology," he says. Despite there being other

known examples of endothelial cross-presentation, the mechanism remains poorly understood. Rénia is keen to uncover how Plasmodium deflects the immune response. "This is an interesting biological question, because endothelial cells are not infected by these parasites," he says.

More information: Howland, S. W., Poh, C. M., Gun, S. Y., Claser, C., Malleret, B. et al. Brain microvessel cross-presentation is a hallmark of experimental cerebral malaria, *EMBO Molecular Medicine* 5, 984–999 (2013). onlinelibrary.wiley.com/doi/10 … m.201202273/abstract

Provided by Agency for Science, Technology and Research (A*STAR), Singapore