Cerebral malaria: Pinpointing a potential therapeutic target

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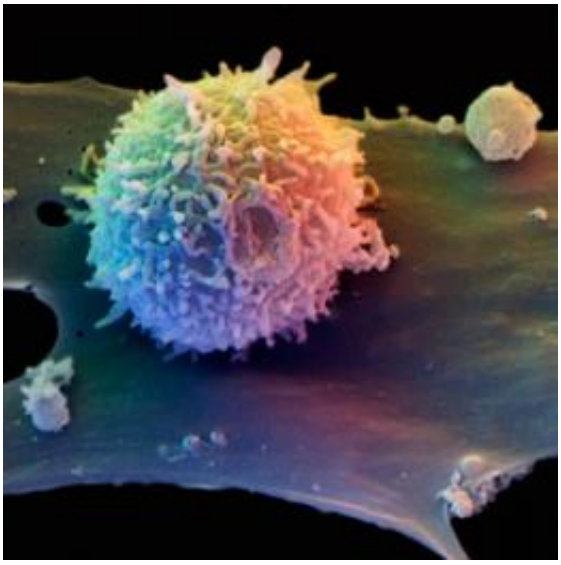

Dendritic cells from human blood are integral parts of the immune system. Credit: David Scharf/Science Faction/Corbis

An excessive response of the immune system to malarial infection can lead to serious complications, such as cerebral malaria. While the mechanism causing the onset of cerebral malaria is unclear, immunologists think that contributing factors include cells of the immune system and the inflammation that they cause. Laurent Renia and co-workers at the A*STAR Singapore Immunology Network and collaborators from Nanyang Technological University, Singapore, have now singled out one subtype of immune cells that is key to the onset of

this often fatal disease.

The researchers used an established mouse model of the disease, called experimental cerebral malaria (ECM). Accumulation of $CD8^+$ T cells, immune cells that destroy infected or damaged cells, is one known contributing factor in this model. Dendritic cells (see image), another type of immune cell, are important in activating certain types of T cells and are also known to be involved in experimental cerebral malaria.

"Dendritic cells are essential for the development of the immune response in particular T cells," explains Renia. "These cells express different markers and are present in many tissues like the spleen. It was previously shown that splenic dendritic cells are important for ECM to develop."

In the earlier work, dendritic cells were modified so that they could be selectively destroyed. A marker that all dendritic cells express, called CD11c, was targeted with a diphtheria toxin receptor, allowing them to be killed using this toxin. The targeted destruction of dendritic cells prevented experimental cerebral malaria. However, this method did not discriminate between the several subtypes of dendritic cells that express CD11c, so the exact dendritic cell type responsible remained elusive.

Renia and his co-workers used a similar approach in this study, but targeted a marker called Clec9A with the diphtheria toxin receptor. Clec9A is expressed by one subtype of dendritic cells only. The subtype, called $CD11c^{high}CD8^+$, is a candidate in experimental cerebral malaria because its cells are involved in activating $CD8^+$ T cells.

Destroying the $CD11c^{high}CD8^+$ cells provided mice with complete protection from experimental cerebral malaria. Renia and co-workers also showed that without these cells, fewer $CD8^+$ T cells were activated in the spleen and fewer were found in the brain. "Our findings show that

these dendritic cells are essential to $CD8^+$ T cell development and thus to experimental cerebral malaria," says Renia.

Although this work was done in an artificial model of the disease in mice, Renia notes that it provides a starting point in overcoming the disease in people.

More information: Piva, L., et al. Clec9A+ dendritic cells mediate the development of experimental cerebral malaria. *The Journal of Immunology* 189, 1128–1132 (2012). www.jimmunol.org/cgi/doi/10.4049/jimmunol.1201171

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