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Commentary

Mosquito-transmitted *Plasmodium falciparum* infection can cause human cerebral malaria (HCM) with high mortality rates. The abundance of infected red blood cells that accumulate in the cerebral vasculature of patients has led to the belief that these brain-sequestered cells solely cause pathogenesis. However, animal models suggest that CD8$^+$ T cells migrate to and accumulate in the brain, directly contributing to experimental cerebral malaria (ECM) mortality. In this issue of the *JCI*, Riggle et al. explored the brain vasculature from 34 children who died from HCM or other causes and frequently found CD3$^+$ CD8$^+$ T cells in contact with endothelial cells. Further, the authors show that coinfection with HIV enhanced such CD3$^+$ CD8$^+$ T cell luminal distribution. These findings suggest that the mouse model for cerebral malaria may accurately reflect human disease pathology. This study sheds new light on the mechanisms behind blood-brain barrier breakdown in this complicated neurological disease and opens up alternative approaches for treatment.

CD8+ T cells and human cerebral malaria: a shifting episteme

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Sequestration, sequestration, sequestration

Human cerebral malaria (HCM), the most severe pathology induced by *Plasmodium falciparum* infection, encompasses a wide range of neurological complications, including seizures and impaired consciousness (1). Due to obvious ethical and logistical constraints, studies to understand HCM pathogenesis have largely relied on a limited number of postmortem series.

The intravascular accumulation of *P. falciparum*–infected red blood cells has been repeatedly reported over the years, leading to the dogma that parasite sequestration in the brain is the leading cause of HCM (2). Although necessary, sequestration does not explain the progression to pathology on its own. Several parallel contributing mechanisms have been proposed, including exaggerated immune response to *P. falciparum* infection and dysregulated coagulation, both impacting the integrity of the blood-brain barrier (3). Surprisingly, only a few histopathological studies reported leukocytes accumulated in the cerebrovasculature (4, 5), and thus their role in HCM pathogenesis was mostly dismissed or ignored. This starkly contrasted with experimental evidence obtained by researchers using an animal model called experimental cerebral malaria (ECM), where susceptible mouse strains such as C57BL/6 or CBA/J infected with *P. berghei* ANKA develop brain pathology and die with overt neurological signs between 6 and 14 days after infection (6). This model allows the investigation of parasite dynamics and distribution in vivo in the brain of infected animals, as well as parasitized erythrocyte interactions with brain-residing and immune host cells (7).

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Conflict of interest: LR possesses shares in Immunoscape Private Limited.

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An enduring rift within the malaria research community

In 2002, a landmark study showed that CD8+ αβ T cells migrate to and sequester in the brains of mice when neurological symptoms appear, and are directly responsible for ECM mortality (8). While these observations initially suggested a potentially unifying mechanism between murine and human pathology, the use of the ECM model was deemed questionable in 2009 (9), causing an enduring rift within the malaria research community (10–12).

In this issue of the *JCI*, Riggle et al. bring closure to the long-standing debate of the role of CD8+ T cells in HCM (13). Using multiplexed histology with new and validated anti-CD8 antibodies, the authors elegantly and unequivocally demonstrate the frequent presence of CD3+ CD8+ T cells in the brain of a postmortem series of 31 fatal pediatric HCM cases from Malawi. A higher number of CD8+ T cells were detected in patients coinfected with HIV. A more detailed analysis showed that a substantial number of these cells were in contact with vessel walls, both in close association with the endothelium in the lumen of the venous vasculature as well as in the perivascular spaces on the abluminal side of vessels, a feature previously described in ECM (14). The observation that the apoptosis-mediating molecule, granzyme B, was distributed inside and sometimes outside the CD8+ T cells in contact with endothelial cells, suggested, for the first time, target cell recognition in HCM (13). Granzyme B is released when CD8+ T cells engage with MHC molecules that are loaded with their cognate antigens. Further, there is compelling in vivo and in vitro evidence that the endothelium is capable of acquiring and cross-presenting *P. falciparum* and *P. berghei* antigens during infection, an essential step for antigen-specific T cell receptor (TCR) ligation and cytolysis of brain microvascular endothelial cells

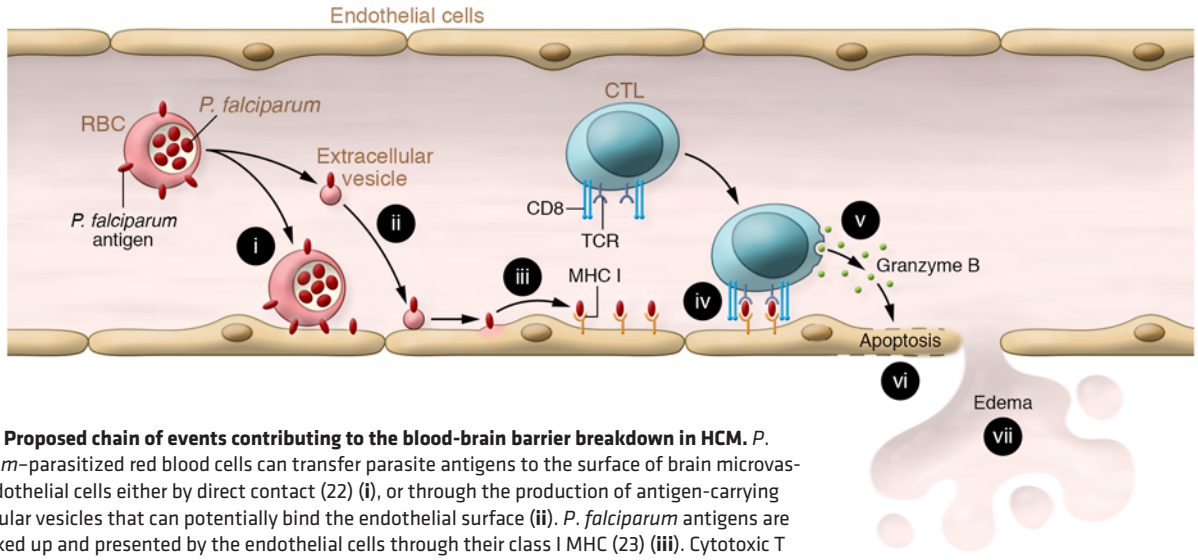

Figure 1. Proposed chain of events contributing to the blood-brain barrier breakdown in HCM. *P. falciparum*–parasitized red blood cells can transfer parasite antigens to the surface of brain microvascular endothelial cells either by direct contact (22) (**i**), or through the production of antigen-carrying extracellular vesicles that can potentially bind the endothelial surface (**ii**). *P. falciparum* antigens are then picked up and presented by the endothelial cells through their class I MHC (23) (**iii**). Cytotoxic T lymphocytes (CTL) engage with antigen-presenting endothelial cells via their TCR and CD8 receptors (**iv**), leading to the release of granzyme B by CTL (13) (**v**), the apoptosis of targeted endothelial cells (18) (**vi**), and an alteration of the blood-brain barrier, ultimately resulting in vasogenic edema (17) (**vii**).

(15). This has long been proposed as the main mechanism behind blood-brain barrier breakdown in ECM, where perforin and granzyme B are required for $CD8^+$ T cells to disrupt the blood-brain barrier and trigger the neurological syndrome (15).

A link with vasogenic edema?

The findings presented by Riggle et al. indicate that a similar mechanism may be at play in HCM, thereby contributing to blood-brain barrier disruption and the resulting vasogenic edema seen in both EMC (16) and HCM (Figure 1) (17). Coincidentally, an increase in cleaved caspase-3 was demonstrated in brain endothelial cells from a small series of fatal adult and pediatric HCM cases in Thailand, and the presence of leukocytes, albeit not phenotyped, was also reported inside the cerebrovascular lumen of patients who succumbed to the neurological syndrome (18). Previous in vitro studies showed that platelet accumulation and parasitized erythrocyte sequestration could induce human brain endothelial apoptosis (19, 20), a phenomenon that $CD8^+$ T cells may exacerbate. The extraordinary similarities in the distribution of $CD8^+$ T cells in the brains of children with HCM and in mice with ECM strongly suggest common pathophysiologic processes (5, 13). These new findings provide an additional piece of the puzzle by demonstrating that $CD8^+$ T cells may indeed participate in the pathology of HCM, and further bridge human and murine disease to support murine ECM as a useful tool, without being more than what it is: a model (21). Additional studies are now warranted to assess the potential link between $CD8^+$ T cells and microvascular brain endothelial apoptosis in HCM, evaluate its contribution to the disease, and inform new adjunct therapies targeting the induction and functions of $CD8^+$ T cells in HCM.

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