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Can brain endothelial activation lead to neuronal damage? Lessons from cerebral malaria

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Cerebral malaria (CM) is a serious complication of *Plasmodium falciparum* infection, especially in young children, but also in non-immune travelers and military personnel visiting or sent out to malaria endemic regions. Clinically, CM features symptoms such as seizures and reversible coma. Without proper supportive care often leads to death, despite anti-malarial chemotherapy. Upon clearance of the infection, patients are often left with neurologic sequelae, such as seizures, learning and behavioral disorders such as ADHD in African children. Post malaria syndromes can also include psychotic or acute confusional episodes and tremors. Sequestration of Plasmodium infected erythrocytes (PRBC) in high endothelial venules is a hallmark of CM. It is unclear as to how these intracellular parasites, while confined to the lumen of the brains vasculature induce neurological dysfunction. In CM, the blood brain barrier (BBB) lies at the interface of the events occurring in blood and brain. The BBB is part of the neurovascular unit (NVU), a concept that emphasizes homeostatic interactions between its components to ensure optimal functioning of the central nervous system. It is hypothesized that activation of the BBB endothelium disturbs the homeostasis between the astroglial and neuronal components of the NVU leading to neurological dysfunction. Using in vitro models for the human BBB, PRBC increase ICAM-1 expression and decrease the barrier function of monolayers in a dose dependent manner. Microarray and gene ontology (GO) analysis indicated a predominance of the NFB mediated pro-inflammatory responses among the host signaling pathways. RT-PCR and protein analysis confirmed the increase in transcripts and directional release of both cytokines and chemokines in various *in vitro* models. Basal directed BBB secretions caused dose-dependent abnormal astroneuronal morphology and cell death. Determination of the underlying pathogenesis of observed BBB activation and astroneuronal effects may lead to development of adjunctive neurotherapeutics to ameliorate neurologic sequelae.

Recent Publications

1. Marion Avril, Abhai K Tripathi, Andrew J Brazier, Cheryl Andisi, Joel H Janes, Viju Soma, David J Sullivan J, Peter C Bull, Monique F Stins, and Joseph D Smith (2012) A restricted subset of var genes mediates adherence of Plasmodium falciparum infected erythrocytes to brain endothelial cells. PNAS 26:1782.

2. Dennis J Grab, Srabasti J Chakravorty, Henri van der Heyde and Monique F Stins (2011) How can microbial interactions with the blood brain barrier modulate astroglial and neuronal function? Cell Microbiol.

3. Wu Y, Szestak T, Stins M, Craig A G (2011) Amplification of P falciparum cyto-adherence through induction of a pro-adhesive state in host endothelium. PLoS One 6(10):e24784.

4. Langhorne J, Buffet P, Galinski M, Good M, Harty J, Leroy D, Mota M M, Pasini E, Renia L, Riley E, Stins M, Duffy P (2011) The relevance of non-human primate and rodent malaria models for humans. Malar J. 2:23.

5. Tripathi A K, Sha W, Shulaev V, Stins M F, Sullivan D J (2009) Plasmodium falciparum infected erythrocytes induce NFB regulated inflammatory pathways in human cerebral endothelium. Blood 5(114):4243-52.

Biography

Monique F Stins has her expertise in Blood Brain Barrier research and is seeking to dissect underlying molecular relations between Blood brain barrier activation and neurological damage. This may lead to identification of pharmacologic targets for therapeutic intervention to improve neurological outcomes of infections with neurotropic microbes. She is using various models of the blood brain barrier in microbial disease to target these pathogenic mechanisms. She has experience teaching students at levels ranging from middle and high school to undergraduate college and upper level college courses.

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