# Severe malaria: Research findings could lead to new interventions

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Researchers from Seattle Biomedical Research Institute (Seattle BioMed), the University of Copenhagen and the University of Edinburgh have uncovered new knowledge related to host-parasite interaction in severe malaria, concerning how malaria parasites are able to bind to cells in the brain and cause cerebral malaria - the most lethal form of the disease. Three related papers will be published in the May 21 online edition of *PNAS* (*Proceedings of the National Academy of Sciences*) highlighting this research.

"Identifying the molecules that allow malaria parasites to 'stick' to the brain takes us one step closer to new treatments," said Joseph Smith, Ph.D., leader of the Seattle team.

Red blood cells infected with the malaria parasite Plasmodium falciparum, the type most lethal to humans, bind to receptors on cells lining blood vessel walls, which helps the parasite avoid being detected and killed by the spleen. The binding is mediated by one of several members of a family of parasite proteins called P. falciparum erythrocyte membrane protein 1, or PfEMP1. A single PfEMP1 mediates placental malaria - the cause of malaria during pregnancy, which kills thousands of women and causes premature births and low-birth weight babies each year - but other PfEMP1 types causing life-threatening disease in young children are unknown.

To hone in on specific PfEMP1 types associated with severe malaria, Thomas Lavstsen, Ph.D., and his team from the University of Denmark used molecular techniques to compare the levels of different PfEMP1 transcripts in blood samples from children hospitalized in the pediatric ward of the Korogwe District Hospital in Tanzania. "Our research revealed that genes encoding two distinct types of PfEMP1 - named domain cassettes 8 and 13 - were tied to cases of severe malaria, suggesting that those proteins might be suitable targets in efforts aimed at curbing the disease," explained Lavstsen. Co-author Louise Turner, Ph.D. adds "Another important aspect of our study is that we show these PfEMP1 domain cassettes are recognized by natural acquired immunity in young African children, which gives us hope that we can base a vaccine on the discovered PfEMP1 types."

In a related paper in this issue, Antoine Claessens, Ph.D., who works in the lab of Alexandra Rowe, D. Phil., of the University of Edinburgh, reports that these particular PfEMP1 types - domain cassettes 8 and 13 - mediate the binding of infected red blood cells to cells that line blood vessels in the brain. "This provides us with new molecules that could be targeted to develop drugs to treat the most deadly forms of malaria," said Rowe. "In addition, because animal models for cerebral malaria are currently unavailable, we believe our findings might lead to a laboratory tool for testing drugs and vaccines that block the binding of the parasite to blood vessels in the brain."

Marion Avril, Ph.D., who works in the Smith lab at Seattle BioMed, reports in this issue that domain cassette 8 encodes binding activity for brain blood vessel cells. Additionally, the authors uncovered a potential explanation for the evolutionary persistence of parasite protein variants that mediate cerebral malaria, an often-fatal disease that tends to wipe out the parasite's host.

"Because those brain-binding variants can also bind to blood vessels in the skin, heart, and lung, the parasite might sequester in those organs," Smith explained. "Together, the findings could help researchers better address the lingering problem of childhood malaria."

"It's been a 15-year journey since this gene family was discovered, but the coming together of these three studies, which all identify the same key players in severe malaria, is an important milestone," said Rowe. "We're excited to have this knowledge and begin to apply it to developing new

solutions for malaria."

Provided by Seattle Biomedical Research Institute

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