Endothelial Activation and Dysfunction in the Pathogenesis of Microvascular Obstruction in Severe Malaria—A Viable Target for Therapeutic Adjunctive Intervention

TO THE EDITOR—We read with interest the recent review by White et al [1]. While we agree with the authors’ assertion that microvascular obstruction plays a fundamental role in the pathogenesis of lethal falciparum malaria [1], we would like to express a contrasting opinion on the potential impact of innovative adjunctive treatment strategies for severe (and cerebral) malaria.

White et al contend that “malaria researchers have often been distracted by epiphenomena,” (p. 193) prompting misguided trials of adjunctive therapeutic strategies in individuals with severe falciparum malaria [1]. Although the authors acknowledge the critical role of inflammation-induced endothelial activation in the binding of parasitized red blood cells to vascular endothelium [1], they neglect to discuss endothelial activation and dysfunction as viable targets for development of novel adjunctive strategies to improve clinical outcomes in life-threatening malaria [2–4].

The angiopoietin-1/2 (Ang-1/2) and Tie2 receptor system plays a key mechanistic role in the regulation of endothelial quiescence and activation. Notably, Ang-1 levels are high and Ang-2 levels are low in the peripheral blood of healthy individuals with quiescent endothelium. In contrast, systemic inflammation causes depressed Ang-1 levels and elevated Ang-2 levels in serum/plasma, contributing to an activated and/or dysfunctional endothelial state [4, 5]. Over the past decade, multiple groups have reported angiopoietin-1/2 dysregulation (ie, low Ang-1/high Ang-2) in the peripheral blood of children and adults with severe and/or cerebral malaria [6–11]. Furthermore, the degree of dysregulation has been shown to correlate with falciparum malaria disease severity and prognosis in multiple populations [6–11]. These observations strongly suggest that Ang-1/2 dysregulation and associated endothelial activation/dysfunction are integral components of the complex pathogenesis of severe and cerebral malaria. Moreover, these observations are consistent with a growing body of evidence supporting a central role for endothelial dysfunction and Ang-Tie2 dysregulation in the pathobiology of other life-threatening infections, including sepsis, multiple organ dysfunction syndrome, acute respiratory distress syndrome, toxic shock syndrome, and hemorrhagic-uremic syndrome [5, 12–17].

In conclusion, we contend that endothelial activation/dysfunction represents an attractive target for the development of innovative adjunctive strategies to improve clinical outcome in life-threatening infections, including severe and cerebral malaria. Potential interventions for investigation to decrease endothelial activation/dysfunction and improve clinical outcome in severe malaria include administration of Ang-1 agonists, Ang-2 antagonists, Tie2 phosphatase inhibitors, recombinant slit2N, sphingosine-1-phosphate agonists, and nitric oxide [4, 6, 18–20].
The content of the manuscript have been disclosed.

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