THE FASEB JOURNAL
The Journal of the Federation of American Societies for Experimental Biology

Evidence of Degradation of Endothelial Glycocalyx in African Children with Falciparum Malaria

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First published: 19 April 2020
https://doi.org/10.1096/fasebj.2020.34.s1.09367

Abstract

The microvasculature and endothelium play a pivotal role in pathophysiology of malaria. The endothelial glycocalyx (eGC) is a layer on the luminal side of vascular endothelial cells with involvement in homeostatic functions including regulation of vascular permeability, cellular adhesion and blood flow-mediated nitric oxide formation. Breakdown products of eGC degradation include glycosaminoglycans (GAG) and syndecan-1, a core protein. The objective of this study was to evaluate a possible role of eGC breakdown in the pathogenesis of malaria. We prospectively evaluated measures of endothelial glycocalyx integrity in children with severe and moderately severe malaria and healthy controls, and determined the relationship between glycocalyx integrity and markers of malaria severity, microvascular reactivity, and endothelial activation. At the Hubert Kairuki Medical Center in Dar es Salaam, Tanzania we studied 146 subjects, aged 2–11 years, including 60 healthy controls (HC), 49 patients with moderately severe malaria (MSM) and 37 patients meeting WHO criteria for severe malaria (SM). Ethics committee

approvals were obtained prior to study initiation. We assessed eGC integrity biochemically by measuring plasma syndecan-1 (ELISA) and total urinary glycosaminoglycan (GAG) breakdown products (dimethylmethylene blue assay). Angiopoietin-2 has been reported to cause breakdown of eGC and was measured by ELISA. Quantitative measures of eGC were assessed using non-invasive, side-stream dark field (SDF) microscopy of the pinna and axilla. Levels of urinary GAG were increased in malaria patients compared with HC (mean±SEM 4.3±0.4 g/mol creatinine); MSM (12.4±1.0); SM (13.4±1.0); $p<0.0001$. Plasma levels of angiopoietin-2 and syndecan-1 were also elevated in MSM and SM compared with HC ($p<0.0001$), and significantly correlated with each other. For HC compared with MSM, imaging results showed eGC degradation [an increase in the perfused boundary region (mean±SEM 1.55±0.04 microns vs.1.68±0.05; $p<0.05$)], increased microvascular density (549± 34 μm/mm2 vs. 649 ±38; $p<0.05$)], and a decrease in the extent of RBC filling (79.1± 0.98% vs. 74.9±1.02%; $p<0.01$). In conclusion, these results provide evidence for degradation of the eGC that could contribute to pathogenesis of vascular dysfunction in malaria. Decreased nitric oxide formation, endothelial activation and increased adhesion of infected RBC are potential consequences of the eGC degradation and vascular dysfunction. Administration of an agent that prevents or repairs eGC degradation may be helpful as adjunctive therapy for malaria.