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Importance of microvesiculation in the immunopathology of cerebral malaria

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We analyzed the involvement of microparticles (MP) in a model of blood-brain barrier, to study cerebral malaria (CM) pathogenic mechanisms. This model is based on co-cultures of human brain microvascular endothelial cells (HBEC) with *Plasmodium falciparum*-infected red blood cells (RBC), leucocytes and platelets. CM pathogenesis includes a sequestration of the later cell types within brain microvessels, an excessive release of pro-inflammatory cytokines and a blood-brain barrier disruption.

Another aspect of inflammatory and infectious diseases is to often lead to activation of vascular and blood cells. Such activation results in an enhanced vesiculation, i.e., the release of circulating MP, which we found in dramatically high numbers in CM patients' plasma. MP are submicron membranous elements carrying on their surface proteins from their cell of origin, which bestow on them specific biological properties. Because platelet-derived MP (PMP) represent the majority of circulating MP and because platelets have been shown to modulate parasitised RBC (PRBC) cytoadherence, we analyzed the role of PMP in this phenomenon. Confocal laser microscopy of the co-cultures showed that PMP adhere to and penetrate in HBEC. By flow cytometry, we found that PMP can upregulate ICAM-1 and VCAM-1 expression on HBEC. Furthermore, PMP adhere to parasitized, but also to non-infected and normal RBC, as revealed by quantitation of the platelet specific antigen CD41 expression on RBC surfaces. PMP binding to PRBC binding was significantly reduced when PRBC were treated with proteolytic enzymes or incubated with PMP in the presence of blocking antibodies against platelet-specific antigens. Lastly, PMP, while interacting with the two other cell types, dramatically increased the binding of parasitised but also of normal RBC to HBEC and altered endothelial functions, particularly the trans-endothelial electrical resistance.

Using the same *in vitro* model of CM, we showed that parasite antigens were transferred to HBEC surface from PRBC, a mechanism dependent on their binding to and on their engulfment in HBEC, suggesting trogocytosis of parasite antigens onto HBEC. These results might be related to previous studies that showed deposition of IgE, IgG, malaria antigens and fibrin on brain vessels from patients who died of CM. This capture of malaria antigens can transform microvascular endothelium in a target for the immune response of the patient.

MP thus appear to be an important element in sequestration and in endothelial pathology, suggesting novel mechanisms in CM pathogenesis.