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Cytoadherence and virulence - the case of *Plasmodium knowlesi* malaria

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Abstract

Background: Cytoadherence of infected red blood cells to brain endothelium is causally implicated in malarial coma, one of the severe manifestations of falciparum malaria. Cytoadherence is mediated by specific binding of variant parasite antigens, expressed on the surface of infected erythrocytes, to endothelial receptors including, ICAM-1, VCAM and CD36. In fatal cases of severe falciparum malaria with coma, blood vessels in the brain are characteristically congested with infected erythrocytes. Brain sections from a fatal case of knowlesi malaria, but without coma, were similarly congested with infected erythrocytes. The objective of this study was to determine the binding phenotype of *Plasmodium knowlesi* infected human erythrocytes to recombinant human ICAM-1, VCAM and CD36.

Methods: Five patients with PCR-confirmed *P. knowlesi* malaria were recruited into the study with consent between April and August 2010. Pre-treatment venous blood was washed and cultured *ex vivo* to increase the proportion of schizont-infected erythrocytes. Cultured blood was seeded into Petri dishes with triplicate areas coated with ICAM-1, VCAM and CD36. Following incubation at 37°C for one hour the dishes were washed and the number of infected erythrocytes bound/mm^2 to PBS control areas and to recombinant human ICAM-1 VCAM and CD36 coated areas were recorded. Each assay was performed in duplicate. Assay performance was monitored with the *Plasmodium falciparum* clone HB3.

Results: Blood samples were cultured *ex vivo* for up to 14.5 h (mean 11.3 ± 1.9 h) to increase the relative proportion of mature trophozoite and schizont-infected red blood cells to at least 50% (mean 65.8 ± 17.51%). Three (60%) isolates bound significantly to ICAM-1 and VCAM, one (20%) isolate bound to VCAM and none of the five bound significantly to CD36.

Conclusions: *Plasmodium knowlesi* infected erythrocytes from human subjects bind in a specific but variable manner to the inducible endothelial receptors ICAM-1 and VCAM. Binding to the constitutively-expressed endothelial receptor CD36 was not detected. Further work will be required to define the pathological consequences of these interactions.

Keywords: *P. knowlesi*, Cytoadherence, SICAvar, ICAM-1, VCAM, CD36, Malaria, Coma

Background

Coma is one of the manifestations of *Plasmodium falciparum* malaria in children and adults [1,2] and it carries a poor prognosis. The accumulation of cytoadherent parasitized erythrocytes in post-capillary venules of the brain is strongly causally implicated in precipitating malarial coma [3-5]. Adherence to brain and other endothelial surfaces is mediated by the expression of variant parasite-derived proteins (Pf EMP1 *var* family) on the *P. falciparum* infected erythrocyte surface [6]. PfEMP1 proteins predominantly bind to CD36, but also to inducible Intercellular Adhesion Molecule 1 (ICAM-1) [7-10]. Binding to up-regulated ICAM-1 is particularly important in cytoadherence to brain endothelium because CD36 is not expressed in this endothelial compartment [8,9].

Malarial coma is rare in other infections by the human host-adapted *Plasmodium* species and coma has not been a feature of severe and fatal zoonotic *Plasmodium*

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