Plasmodium falciparum-infected red blood cells and serum taken from patients with malaria cause pathological alterations in the blood brain barrier

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During cerebral malaria (CM), sequestration of *Plasmodium falciparum*-infected red blood cells (PRBC) to the blood brain of barrier (BBB) is associated with BBB disruption and long term neurological sequelae in survivors of CM. To investigate the prolonged effect of sequestration on endothelial cells, PRBC were co-cultured with human brain endothelial cells (HBEC) and the co-culture supernatants were harvested.

Endothelial cell-derived proteases MMP2, MMP9 and ADAMTS-4 were identified in the PRBC-HBEC co-culture supernatants. Treatment of fresh HBEC monolayers with these co-culture supernatants caused a significant increase in endothelial permeability. Interestingly, addition of the protease inhibitor GM6001 reduced the loss of endothelial integrity mediated by the co-culture supernatants. These results suggest that proteases released by endothelial cells in response to sequestration of PRBC to the BBB may cause the observed reduction in BBB integrity.

Preliminary studies showed that, treatment of HBEC with serum from patients with uncomplicated, severe and cerebral malaria caused an increase in BBB permeability compared to serum from control patients. However, interestingly, serum from CM patients caused a more pronounced increase in endothelial permeability compared to all the other patient groups. This suggests that soluble factors in the serum of malaria patients has the ability to disrupt endothelial integrity.

In order to evaluate the impact of loss of endothelial cell integrity on astrocytes underlying the endothelial cells in the BBB, an advanced BBB model composed of HBEC (luminal side) and astrocytes (basolateral side) grown in tandem in a transwell, was treated with the PRBC-HBEC co-culture supernatants. Following treatment, a significant increase in soluble ICAM-1 was observed in the bottom chamber (basolateral side), in the HBEC-astrocyte BBB model. This suggests that soluble factors released from HBEC in response to PRBC, can cause activation of astrocytes resulting in the increased expression and release of ICAM-1 from astrocytes.

The data suggest that during CM, sequestration results in release of soluble factors such as proteases that cause BBB disruption; which in turn causes activation of astrocytes. This could be a mechanism that contributes to the neurological sequelae observed in survivors of CM.