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Investigation of the disruption of the blood brain barrier in cerebral malaria: using an *in vitro* HBEC-astrocyte tandem model

In cerebral malaria (CM) sequestration of *Plasmodium falciparum* infected red blood cells (PRBC) in the brain microvasculature, results in disruption of the blood brain barrier (BBB). Astrocyte activation, observed in patient post-mortem tissue and in the experimental CM model has been linked to neurological sequelae. Treatment of astrocytes with PRBC-HBEC (human brain endothelial cells) co-culture supernatant was shown to activate astrocytes (BSP 2015).

We have developed an advanced BBB model composed of HBEC and astrocytes grown in tandem on a transwell insert. To investigate the effect of HBEC-derived soluble factors and HBEC-associated factors on the BBB, HBEC and PRBC were co-cultured for 20 hours, the supernatant and lysate were harvested and added to the advanced BBB model.

Transendothelial electrical resistance (TEER) of HBEC alone and HBEC-astrocyte tandem, increased over time with significantly greater TEER in the HBEC-astrocyte tandem.
PRBC-HBEC supernatant markedly increased permeability of the HBEC monolayer, but had no effect on the HBEC-astrocyte tandem. A markedly amplified effect was observed when cultures of HBEC alone and HBEC-astrocyte tandem were treated with the HBEC lysates.

These studies suggest that the HBEC-astrocyte tandem culture is considerably more resistant to HBEC derived factors expressed when PRBC sequester to the BBB. Together with previous data (BSP 2015), this implies that alterations in the HBEC can potentially have a detrimental effect on the astrocytes (located in close proximity to HBEC); even in the absence of any significant permeability changes.