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The role of vascular endothelial growth factor (VEGF) as a pro-inflammatory or a neuro-protective player in the pathogenesis of cerebral malaria and its therapeutic implications

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Cerebral malaria (CM) is a serious neurological complication that occurs in about 1% of *Plasmodium falciparum* infections. Human CM is characterized by severe vasculopathy, coagulopathy, vascular leakage, edema and microhemorrhages. Vascular Endothelial Growth Factor (VEGF) has been found over-expressed in CM brain patients to the extent to which it has been even thought of VEGF as possible biomarker, although its function was still controversial. Using a *P. berghei* ANKA (PbA) mouse model, histology, immunohistochemistry and gene expression profiling analysis we demonstrated that lipopolysaccharide S (LPS) at doses that normally induce inflammation tolerance, protects *P. berghei* infected mice against experimental cerebral malaria (ECM) and that the addition of VEGF, to preserve blood vessel integrity, results in a synergistic effect. The synergy achieved by combining LPS and VEGF reflect their respective activities on the two pathogenic mechanisms leading to cerebral malaria: An unregulated activation of the inflammation response and obstruction-hypoxia endothelial cell damage. On one hand LPS induces antioxidant genes thereby protecting endothelial cells from injury while down regulating the inflammatory response on the other hand VEGF induces endothelial cells proliferation and restores blood vessel integrity, therefore it has a protective role. Furthermore, we have interestingly showed that the substitution of LPS with statins, particularly Lovastatin, also confers protection against CM and inhibition of inflammation. The conceptual link appears to be an extensive up-regulation of a transcription factor involved in cellular anti-oxidative defense, Nrf-2 that can be achieved by either LPS or statins. Consequently, the synergistic effect of Lovastatin and VEGF was able to prolong the lifespan of treated mice *vs.* infected controls and strongly ameliorate clinical symptoms until preventing death of cerebral malaria. These findings provide the rationale for investigating the therapeutic potential of these compounds in human CM as well as in other inflammatory pathologies that respond poorly to steroid and non-steroid anti-inflammatory therapy.

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