Commentary

VEGF: inflammatory paradoxes

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Invited commentary on 'VEGF and LPS synergistically silence inflammatory response to Plasmodium berghei infection and protect against cerebral malaria' and 'Vascular Endothelial Growth factor (VEGF) and Lovastatin suppress the inflammatory response to Plasmodium berghei infection and protect against Experimental Cerebral Malaria' by Canavese et al.

In this issue, Canavese *et al.*¹ report an intriguing and exciting effect of VEGF: this molecule, particularly in conjunction with other compounds, protects against cerebral malaria in a well-established experimental model.

This finding is surprising for at least three reasons. First, the rapidity of its action. Cerebral malaria (CM) is an extremely acute syndrome and VEGF takes days or weeks to act as an angiogenic factor. VEGF was given on day 1 p.i. for 5 days, i.e. covering the 'induction phase of CM', consisting of cytokine overproduction, endothelial cell adhesion molecule CAM upregulation and cell sequestration in brain microvessels.

Second, it is surprising because CM is linked with neuroinflammation and increased permeability and VEGF initially was shown to cause inflammation and to increase permeability in rat's brain²: it used to be called vascular permeability factor and even a blood-brain barrier breakdown and inflammation agent.³

Third, CM is characterized by VEGF overproduction. Plasma VEGF levels are high in CM, as reviewed in Hempel *et al.*⁴ and, clearly, VEGF is involved in malarial pathogenesis, for its cerebral⁵ and its pulmonary aspects.⁶ On the basis of elevated plasma levels, agents that would antagonize Ang 2 have been proposed to treat CM.⁷

However, with the results presented here, elevated plasma levels suggest that VEGF is part of a protective response rather than an element of

pathogenesis. Along that line, Jain *et al.* had suggested the use of VEGF as adjunct therapy in CM.⁸

The associated compound found to be efficient is no less than lipopolysaccharide (LPS). LPS also is a particularly potent inducer of inflammation, but it has been recognized for decades that tolerance to LPS can be induced by small doses of LPS itself, resulting in an ablation of inflammation. Numerous studies have analyzed the mechanisms of LPS-induced desensitization, and its relationship with tumour necrosis factor (TNF).⁹ An LPS-induced desensitization of TNF expression¹⁰ offers a possible explanation for the beneficial effect in CM seen here by Canavese *et al.*¹

In a second paper, Canavese *et al.*¹¹ show that the substitution of LPS with statin also confers protection against CM and inhibition of inflammation. The conceptual link appears to be a massive upregulation of a transcription factor involved in cellular anti-oxidative defense, Nrf-2, that can be achieved by either LPS or statins.

These two papers highlight the essential need to assess *in vivo*, and more particularly in disease models, the findings generated initially *in vitro*. They also prompt more reflection on the mechanisms of action of VEGF in pathological conditions. One can speculate that a possible way VEGF exerts its beneficial effect in CM is via nitric oxide (NO) upregulation, which is able to downregulate cell adhesion molecule expression and reduce platelet aggregation, two important elements in CM pathogenesis. The issue remains, however, as to whether this response would be rapid enough.

It is remarkable that blocking VEGF exacerbates CM, a fully lethal syndrome, in CM-susceptible mice; only a few interventions can do this, e.g. blocking CTLA-4.¹² Conversely, there is no induction of CM by a VEGF inhibitor in CM-resistant mice, something that is achieved with anti-IL-10 mAb treatment,¹³ which suggests that VEGF may not be as potent as IL-10 as an endogenous anti-inflammatory mediator during malaria. A possibly captivating link between VEGF and its protective effect in CM is the induction of endothelial anergy, as described by Griffioen *et al.*¹⁴

Together, the data presented by Canavese *et al.*¹ emphasize the essential need for *in vivo* assessment of any therapeutic intervention and argue for studies to unravel new mechanisms of action of VEGF.

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