SEPSIS

Unpicking the pathogenesis of sepsis

Severe sepsis, which results from the body's response to infection, remains a leading cause of death and disability, despite decades of intensive research and billions of dollars of investment in the development of potential therapies. Aird and colleagues, reporting in the *Journal of Experimental Medicine*, now show that vascular endothelial growth factor (VEGF) seems to have a key role in the pathogenesis of sepsis, and could represent a promising new target for therapeutic intervention.

A major challenge in drug development for sepsis is that the complex interplay between mediators of the inflammatory and coagulation pathways that are involved in the disorder is poorly understood. Recently, however, studies have indicated an association between severe sepsis and elevated levels of VEGF, a key promoter of endothelial permeability and proliferation that also seems to have pro-inflammatory and procoagulant effects. Aird and colleagues therefore set out to test the idea that VEGF has a pathogenic role in sepsis.

First, the authors assayed plasma levels of VEGF and the related placental growth factor (PlGF) in mouse and human models of infection, and found that sepsis is associated with increased expression and circulating levels of VEGF and PlGF. Peak levels occurred later than those of early-response cytokines such as tumour-necrosis factor-α (TNFα), interleukin-1 (IL-1) and IL-6.

VEGF mediates its effects through binding to two transmembrane receptor tyrosine kinases, VEGFR1 (also known as Flt-1) and VEGFR2 (also known as Flk-1), whereas PlGF binds to VEGFR1. A naturally occurring soluble form of VEGFR1 is also known to bind to VEGF and PlGF, and thereby block their interaction with cell-surface receptors. So to investigate the potential for therapeutic intervention, and the roles of these various proteins, Aird *et al.* assessed the effects of several anti-VEGF strategies on sepsis pathogenesis.

In the first strategy, adenovirus-mediated overexpression of a soluble form of VEGFR1 in mouse models of sepsis attenuated the rise in free VEGF and PlGF levels, and blocked the adverse effects of endotoxaemia on cardiac function, vascular permeability and mortality. A second strategy, involving pre-treatment with anti-VEGFR1 or anti-VEGFR2 antibodies, revealed that anti-VEGFR2 antibodies, but not anti-VEGFR1 antibodies, reduced mortality, which suggests that it is VEGF, and not PlGF, that is a crucial mediator of the sepsis phenotype. In addition, assessing the expression levels of several inflammatory and coagulation mediators indicated that VEGF sensitizes endothelial cells to TNF.

Finally, to investigate whether VEGF inhibition might be used therapeutically, mice were treated with soluble VEGFR1 after the onset of sepsis, which resulted in a marked improvement in cardiac physiology and survival. It therefore seems that further studies to determine both the diagnostic/prognostic value of VEGF and the therapeutic potential of anti-VEGF strategies in sepsis are warranted. Such studies might be initiated relatively rapidly, as several anti-VEGF agents have been approved for cancer treatment: the anti-VEGF antibody bevacizumab, and the small-molecule VEGFR kinase inhibitors sunitinib and sorafenib.

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ORIGINAL RESEARCH PAPER Yano, K. *et al.* Vascular endothelial growth factor is an important determinant of sepsis morbidity and mortality. *J. Exp. Med.* **203**, 1447–1458 (2006)
FURTHER READING Buras, J. A., Holzmann, B. & Sitkovsky, M. Animal models of sepsis: setting the stage. *Nature Rev. Drug Discov.* **4**, 854–865 (2005)