CRITICAL CARE

LETTER

Unraveling the mechanisms involved in endothelial barrier protective effects of angiopoietin-1 variant MAT.Ang-1

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With great interest we read the recent article by Alfieri and colleagues [1], demonstrating that angiopoietin (Ang)-1 variant MAT.Ang-1 improved endotoxemia-induced microvascular dysfunction and microvascular hyperpermeability. The authors suggested that MAT.Ang-1-induced recovery of microcirculatory tissue perfusion during sepsis is due to preservation of endothelial barrier integrity. To further elucidate the mechanism, they investigated the possibility of involvement of VE-cadherin, a major adherens junctions protein responsible for microvascular leakage in inflammation. They found, however, while there was no change in overall expression of VE-cadherin, MAT.Ang-1 increased VE-cadherin phosphorylation in the treated mice, which appears unable to explain the observed endothelial barrier protective effects of MAT.Ang-1.

The work by Dejana and co-workers [2] highlights the critical role of VE-cadherin for maintenance of endothelial barrier function. It is generally accepted that the tyrosine phosphorylation of VE-cadherin and other components of adherens junctions induced by permeability-increasing agents is associated with weak junctions and impaired barrier function via regulating VE-cadherin member localization [2]. Recently, among the nine tyrosines in the cytoplasmic tail of VE-cadherin, Potter and colleagues [3] revealed that tyrosine phosphorylation of VE-cadherin at two critical tyrosines, Tyr-658 and Tyr-731, was sufficient to disrupt VE-cadherin-mediated cell-cell junctions, leading to inhibition of cell barrier function.

Previous studies have shown that Ang-1 restores the endothelial barrier function via phosphorylation-dependent redistribution of VE-cadherin [4,5]. While in the present study the total amount of VE-cadherin was not changed, intriguingly MAT.Ang-1 increases VE-cadherin phosphorylation (at Y658) in sepsis. This is unexpected because the endothelial barrier protective effects of MAT.Ang-1 do not seem to be consistent with its effect on an important cellular junction molecule involved in endothelial cell integrity, namely VE-cadherin; however, other mechanisms of action cannot be ruled out. Nevertheless, further studies are needed to investigate the mechanisms by which this novel Ang-1 variant rescues the endothelial barrier function.

Authors' response

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We appreciate the interest and insightful comments made by Zhang and colleagues concerning our recent research article. The functional *in vivo* studies presented in our manuscript demonstrated that MAT.Ang-1 reduced macromolecular leak and improved tissue perfusion without significantly changing the diameter of microvessels, thus suggesting that the protective effects induced by MAT.Ang-1 depend on preserving the endothelial barrier integrity. In addition to the well-recognized role in controlling vascular permeability, VE-cadherin and associated junctional proteins form part of complex signaling cascades regulating important cellular functions [6]. In particular, as discussed in our manuscript, disassembly of the VE-cadherin complex triggers an intracellular negative signal reducing transendothelial leukocyte migration in mice 6 hours after challenge with lipopolysaccharide [7]. Therefore, an increase in VE-cadherin phosphorylation paralleled by reduced interleukin-1β protein

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expression may be a mechanism by which MAT.Ang-1 induces protection against microvascular stasis in sepsis. Furthermore, lipopolysaccharide-induced endotoxemia increases the expression of several inflammatory cytokines (for example, tumor necrosis factor-α), which in turn cause macromolecular leak [8]. Therefore, *in vivo* a complex mechanistic scenario develops in sepsis with regards to the endothelial barrier function, which is difficult to unravel. The elegant studies referenced by Zhang and colleagues concerning Ang-1 and VE-cadherin phosphorylation report *in vitro* findings, whereas all our results are from septic mice *in vivo* with or without MAT.Ang-1 post-treatment. Nevertheless, we agree that further investigations are required before making firm conclusions on the effects of MAT.Ang-1 on the endothelium in sepsis - for instance, studies aimed at providing a complete *in vivo* time-course of the expression, localization and phosphorylation of endothelial junctional proteins would be extremely informative.

Abbreviations
Ang, angiopoietin.

Competing interests
The authors declare that they have no competing interests.

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