Beyond tie-ing up endothelial adhesion: new insights into the action of angiopoietin-1 in regulation of microvessel permeability

Pingnian He*

Department of Physiology and Pharmacology, School of Medicine, West Virginia University, Morgantown, WV 26506-9229, USA

Online publish-ahead-of-print 8 May 2009

This editorial refers to ‘Angiopoietin-1 alters microvascular permeability coefficients in vivo via modification of endothelial glycocalyx’ by A.H.J. Salmon et al., pp. 24–33, this issue.

The growth factor angiopoietin-1 (Ang1) has been identified as the primary activating ligand for Tie2, a tyrosine kinase receptor highly expressed in vascular endothelial cells. Genetic studies using targeted mutations in mice have demonstrated that Tie2 activation by Ang1 is crucial for angiogenesis, vascular remodelling, and vascular maturation. However, the angiogenic functions of Ang1 are distinct from those of vascular endothelial growth factor (VEGF). Transgenic mice studies have revealed that blood vessels induced by VEGF overexpression are leaky, whereas blood vessels induced by Ang1 overexpression are not only non-leaky, but also resistant to vascular leakage during inflammation. Previous studies using inflammatory mediator-stimulated animals or cultured endothelial cells have identified the permeability protective effects of Ang1 to be mediated through inhibition of endothelial gap formation and strengthening of endothelial adhesion. In a new study featured in this issue of Cardiovascular Research, Salmon et al. report the effect of Ang1 on the endothelial glycocalyx and propose a novel mechanism for the permeability protective action of Ang1.

Using individually perfused mesenteric microvessels with the Landis-Michel technique, Salmon et al. quantified the direct effect of Ang1 on water and albumin permeability in intact microvessels by measuring permeability coefficients, hydraulic conductivity (Lp), and the albumin reflection coefficient (r). Permeability in whole animal or whole vascular bed studies is usually determined by measuring the extravasation of Evans blue-labelled albumin. These measurements can be affected by changes in microvessel permeability as well as by variations of flow dynamics and surface area. Permeability studies in individually perfused microvessels allow precise measurements of perfusion pressure and surface area, thus providing a more direct assessment of Ang1 effects on the permeability properties of the vascular walls. Salmon et al. also assess Ang1-induced permeability changes in glomerular capillaries using an oncopressive technique. They report that Ang1 increased the reflection coefficient in frog mesenteric microvessels and reduced baseline permeability in both mesenteric and glomerular capillaries. Taken together, these results suggest that Ang1 affects both the continuous endothelia of mesenteric vessels as well as the fenestrated endothelia of glomerular capillaries.

Most importantly, Salmon et al. report that Ang1-induced permeability protection is associated with the restoration of the endothelial glycocalyx, a mechanism independent of the previously established role of Ang1 in strengthening endothelial adhesion in inflammatory agent-stimulated vessels. An earlier study by Adamson implicated glycocalyx function as being critical in maintaining vascular permeability, as brief perfusion with pronase, a proteolytic enzyme that degrades the endothelial glycocalyx, moderately increased Lp, and was accompanied by structural changes in the glycoperoxidase with intact intercellular clefts. Salmon et al. show through electron microscopy that Ang1 perfusion for 30 min increased glycoperoxidase depth with an associated reduction of baseline Lp. More importantly, Ang1 both prevented and reversed Lp increases induced by pronase. The studies by both Adamson and Salmon et al. support the fibre matrix hypothesis that the endothelial glycocalyx contributes to the hydraulic resistance and molecular selectivity of the microvessel walls. An interesting observation from Salmon et al. is that pronase treatment induces only a moderate change in glycoperoxidase depth, whereas the main change is the separation of glycoperoxidase from plasma membrane.

Currently, glycoperoxidase function is mainly understood to be correlated with depth. However, Salmon et al. find that, although Ang1 prevented and reversed the increase in Lp due to glycoperoxidase degradation, glycoperoxidase depth was not fully preserved or restored by Ang1 perfusion. It appears that Ang1 perfusion brought the increased Lp back to baseline by reassembling the glycoperoxidase, enabling the separated...
glycocalyx to re-attach to the plasma membrane. It will be important for future studies to elucidate whether glycocalyx separation or detachment from the plasma membrane plays an equal or perhaps even more important role in affecting microvessel permeability than changes in glycocalyx depth.

The quick action of Ang1 to reduce microvessel permeability leads the authors to speculate that Ang1 modifies the rate of endothelial glycocalyx turnover rather than synthesis. The reported Ang1 effects on maintaining or restoring baseline permeability in pronase-treated vessels all occurred within 20–30 min of perfusion. The authors proposed that glycocalyx is inserted onto the cell surface by vesicle fusion regulated by Golgi-mediated translocation, a hypothesis they tested by pre-perfusing vessels with the Golgi vesicle translocation inhibitor, Brefeldin-A, before treatment with Ang1. Interestingly, Brefeldin-A abolished Ang1-induced reduction of basal Lp. However, more direct evidence is needed to establish the link between Ang1 and Golgi-mediated vesicle translocation. It should also be noted that, although most of glycosaminoglycans of mammalian cells are synthesized in the Golgi, hyaluronate synthesis has been reported to be a Golgi-independent mechanism, with synthesis being exclusive to the inner side of the plasma membrane and followed by extrusion to the cell surface. It will be interesting for the future studies to establish whether Golgi vesicles involved in the synthesis and transfer of glycocalyx constituents are modulated by Ang1 perfusion.

Finally, though Salmon et al. demonstrate Ang1-mediated reduction of permeability in vessels with continuous endothelium as well as in vessels with fenestrated endothelium such as glomerular capillaries, it remains to be established whether the Ang1 effect on glomerular capillaries is also mediated via regulation of the glycocalyx.

In summary, the study by Salmon et al. presents the first measurements of Ang1-induced changes in water and albumin permeability coefficients in intact microvessels. Most importantly, this study brings a new perspective of the action of Ang1 in the regulation of microvessel permeability: modulation of the endothelial glycocalyx. Growing evidence has implicated the glycocalyx as being crucial for normal vascular functions. The potential role of Ang1 in restoration of disrupted glycocalyx, together with its protective action on endothelial adhesion, makes it an ideal therapeutic target for the treatment of vascular inflammation such as that which occurs in sepsis and acute lung injury.15

Funding
This work was supported by National Heart, Lung, and Blood Institute grant HL56237 and HL084338.

Conflict of interest: none declared.

References