JCB Journal of Cell Biology

SPOTLIGHT

Pulling the strings: Contractile VE-cadherin junctions to stabilize angiogenic sprouts

Stephan Huveneers[1]

Dynamic yet stable endothelial interactions during angiogenesis remain poorly understood despite their importance in development and regeneration. Mayo et al. (https://doi.org/10.1083/jcb.202503146) identify Scribble and myosin-1c as key regulators of stable cell–cell junctions during angiogenic sprouting, coordinating junctional stability with vascular dynamics.

Angiogenesis, the formation of new blood vessels, is important for embryonic development, tissue regeneration, and involved in disease progression. Angiogenic sprouting is controlled by the formation of endothelial tip cells that lead migration from preexisting parental blood vessels. During this process, the tip cells remain connected to following stalk cells that in turn will contribute to sprout elongation. The contacts between endothelial cells are formed through VE-cadherin–based adherens junctions, crucial cell–cell adhesion structures that maintain vascular integrity. To branch off an angiogenic sprout, transient remodeling of endothelial junctions is needed to enable tip cell migration, whereas in later phases, junction stabilization is important to maintain connections to stalk cells and to establish a functional new microvessel within the vasculature (1). What can control such precise junctional angiogenic switches?

VE-cadherin, like other classical cadherins, requires binding to a core group of cytoplasmic proteins that include p120-catenin, β-catenin, and α-catenin, to form stable adherens junctions that are connected to the actin cytoskeleton (Fig. 1 a). Once formed, endothelial junctions adopt different cytoskeletal-dependent organizations that are dynamically interchangeable in time, allowing the endothelial barrier to remain resilient during physiological changes. In endothelial monolayers, stable junctions are supported by parallel actin bundles and actin protrusions, whereas their remodeling is driven by pulling forces generated by the actomyosin cytoskeleton. However, it remains unclear through which mechanisms VE-cadherin–based junctions adapt to facilitate angiogenic sprout formation.

To find regulators of endothelial adherens junctions, Mayo et al. (2) performed proximity ligation mass spectrometry using BirA-tagged VE-cadherin in cultured microvascular endothelial cells. This unbiased VE-cadherin-BioID approach identified the cell polarity scaffolding protein Scribble (*SCRIB*) and its effector, the unconventional myosin-1c (*MYO1C*), as novel junction-associated proteins (Fig. 1 b). Immunofluorescence imaging showed that Scribble is recruited during the formation of cortical, near-junctional actin clusters. Using CRISPR-Cas9 with sgRNA targeting the *SCRIB* gene, the authors generated knockout endothelial cells. Strikingly, loss of Scribble abolished the cortical actomyosin bundles that normally support stable junctions, demonstrating its essential role in their formation. As a consequence the junctional interface between endothelial cells adopted undulated shapes, less linear, which is a sign of junction instability.

The authors further demonstrate that the formation of Scribble-induced cortical actin clusters occurs independently of the well-studied α-catenin–mediated linkage between VE-cadherin and the actin cytoskeleton. Live cell imaging revealed that the near-junctional actin clusters arise from the coalescence of a retrograde actin flow originating at the cell–cell junction interface in normal endothelials cells. This mode of actin dynamics is perturbed in the absence of Scribble.

How does Scribble mediate this process? In epithelial cells, Scribble interacts with GEFs and GAPs for Rho GTPases to regulate polarity and actomyosin contractility at apical junctions (3, 4). However, junctions between microvascular endothelial cells are less polarized along the apical-basal axis than in epithelia, and Mayo et al. show that Scribble-mediated actin clusters still form upon knockout of the polarity proteins Erbin or DLG5. To further dissect Scribble function in endothelial cells, the authors performed gel-based proteomics following immunoprecipitation of Scribble, identifying *MYO1C* as a prominent interactor, a protein that was also detected in the earlier VE-cadherin-BioID dataset. The molecular motor *MYO1C* is known to support coupling between actin and E-cadherin–based adhesions upon force (5) and may function in an analogous manner at the Scribble-based clusters formed from VE-cadherin junction-derived actin flows. Consistent with this, endothelial junction dynamics were altered and junctions became undulated upon *MYO1C* depletion. Interestingly, the authors show that the interaction between Scribble and *MYO1C* does not require VE-cadherin, and conversely, the binding of *MYO1C* to VE-cadherin occurs independently of Scribble. These findings suggest that *MYO1C* acts as a dynamic tether linking Scribble-based actin clusters to nearby VE-cadherin junctions.

[1]Department of Medical Biochemistry, Amsterdam Cardiovascular Sciences Institute, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands.

Correspondence to Stephan Huveneers: s.huveneers@amsterdamumc.nl.

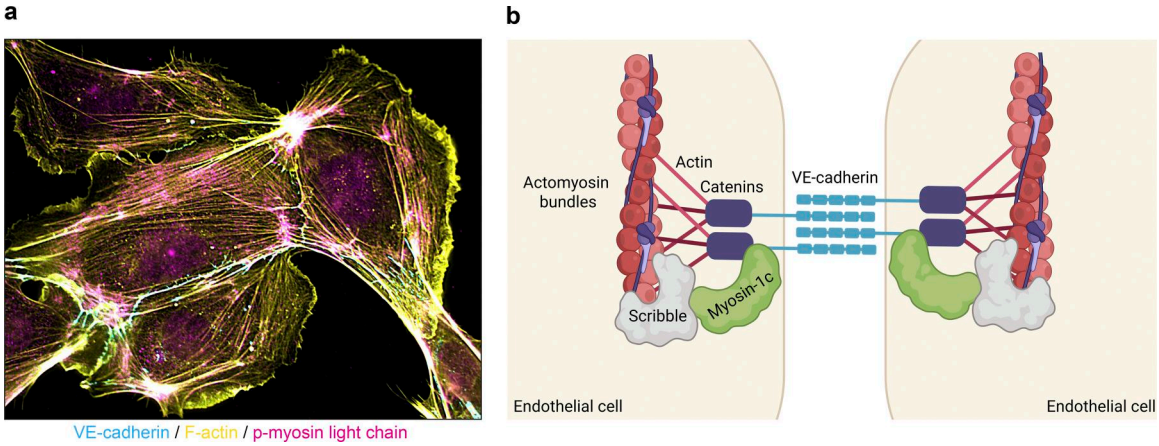

Figure 1. **Interplay between endothelial cell–cell junctions and the actomyosin cytoskeleton. (a)** Human umbilical cord endothelial cells immunostained for VE-cadherin (cyan), F-actin (yellow), and phosphorylated myosin light chain 2 (magenta) (unpublished image). **(b)** Proposed model based on the current work by Mayo et al. in which near-cortical actomyosin bundles are organized by Scribble and tethered by *MYO1C* to VE-cadherin–based junctions. Drawing was created using Biorender.com.

Together, these findings reveal a novel mechanism regulating endothelial junction stability. What is the functional relevance of this mechanism for the endothelium? Spatiotemporal activation of junctional actomyosin is essential for the initiation and stabilization of angiogenic sprouts (6, 7). To examine this, the authors used a microfluidic system to generate microvessels and visualize endothelial cell–cell interactions at high resolution during sphingosine-1-phosphate (S1P)-induced angiogenic sprouting. Comparing control with *SCRIB*- or *MYO1C*-deficient microvessels, they discovered that Scribble and *MYO1C* are specifically needed to maintain stable attachment between sprouting tip cells and the follower cells in the parental vessels.

The traditional view of VE-cadherin–based junctions as static adhesion structures composed primarily of a catenin-actin linkage is gradually evolving as additional molecular components continue to be identified. Unbiased proteomic approaches to uncover novel regulators of VE-cadherin, such as those employed by Mayo et al. hold promise for advancing our understanding of the molecular mechanisms that control VE-cadherin function in maintaining vascular integrity and enabling its dynamic remodeling during angiogenesis. The VE-cadherin interactome generated by Mayo et al. revealed close interactions with Scribble and *MYO1C* of VE-cadherin under basal culture conditions. Proximity ligation mass spectrometry for VE-cadherin has previously been used to investigate molecular changes in endothelial junctions in response to mechanical stretch (8) or angiogenic growth factors (9). In addition, numerous direct interactions with VE-cadherin have recently been identified in pull-down based proteomics (10). Integrating these datasets reveals a core set of VE-cadherin–binding proteins, while also showing context-specific interactions that likely reflect differences in endothelial cell types, stimuli, or biotin ligases used. Overlaying those VE-cadherin interactomes will help generate a complete picture of the diverse molecular interactions at endothelial junctions. Based on the observations by Mayo et al. that angiogenic growth factors promote Scribble-*MYO1C*–dependent junction remodeling, it will be informative to apply defined agonsists such as VEGF or S1P in future proteomic studies.

Finally, Scribble is needed for endothelial barrier function and it protects against the development of atherosclerosis in mouse models (11). The findings by Mayo et al. therefore open new avenues for research in both angiogenesis and cardiovascular disease. Given that *MYO1C* function is force-sensitive and that Scribble-actomyosin cluster formation is closely linked to cortical endothelial mechanics, an exciting future direction will be to investigate how this system is regulated in blood vessels under physiological and pathological levels of flow and pressure.

Acknowledgments

This work was funded by the Netherlands Organization of Scientific Research (ZonMW Vici grant 09150182310041) and the Dutch Heart Foundation (Established Investigator 03-002-2021-T087 Dekker grant).

Author contributions: Stephan Huveneers: conceptualization, visualization, and writing—original draft.

Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and none were reported.

References

1. Bentley, K., et al. 2014. *Nat. Cell Biol.* https://doi.org/10.1038/ncb2926
2. Mayo, L.N., et al. 2026. *Nat. Cell Biol.* https://doi.org/10.1083/jcb.202503146
3. Awadia, S., et al. 2019. *J. Cell Biol.* https://doi.org/10.1083/jcb.201811114
4. Hendrick, J., et al. 2016. *J. Cell Sci.* https://doi.org/10.1242/jcs.190074
5. Kannan, N., and V.W. Tang. 2018. *J. Cell Sci.* https://doi.org/10.1242/jcs.211334
6. Abraham, S., et al. 2009. *Curr. Biol.* https://doi.org/10.1016/j.cub.2009.02.057
7. Yoon, C., et al. 2019. *Mol. Biol. Cell.* https://doi.org/10.1091/mbc.E19-02-0076
8. Miroshnikova, Y.A., et al. 2021. *Mol. Biol. Cell.* https://doi.org/10.1091/mbc.E21-03-0106
9. Serafin, D.S., et al. 2024. *Nat. Commun.* https://doi.org/10.1038/s41467-024-51918-1
10. Schoon, R.M., et al. 2026. *iScience.* https://doi.org/10.1016/j.isci.2026.115450
11. Schürmann, C., et al. 2019. *Cardiovasc. Res.* https://doi.org/10.1093/cvr/cvz093