MECHANOTRANSDUCTION

VE-cadherin lets it flow

In response to fluid shear stress, endothelial cells activate various gene expression and signalling pathways to regulate vascular function and integrity. A protein complex comprising platelet endothelial cell adhesion molecule (PECAM1), vascular–endothelial cell cadherin (VE-cadherin) and vascular endothelial growth factor receptor 2 (VEGFR2) was previously shown to function as a flow sensor at endothelial cell–cell junctions. Force exerted on PECAM1 triggers the activation of VEGFR2 in the absence of its ligand, which in turn induces integrin-mediated signalling and ultimately leads to the activation or suppression of inflammatory pathways.

In this study, Schwartz and colleagues set out to determine the specific role of the cell–cell junction protein VE-cadherin in flow signalling. They expressed chimaeras of different protein domains of VE-cadherin and of neuronal cadherin (N-cadherin), which does not function in flow signalling, in VE-cadherin-deficient mouse cells. These experiments showed that the VE-cadherin transmembrane domain (TMD) was the critical VE-cadherin-specific region required for flow signalling. Moreover, the VE-cadherin TMD mediates the direct interaction between VE-cadherin and VEGFR2 and, surprisingly, VEGFR3. This finding suggests that VEGFR3 is another component of the junction mechanosensory complex.

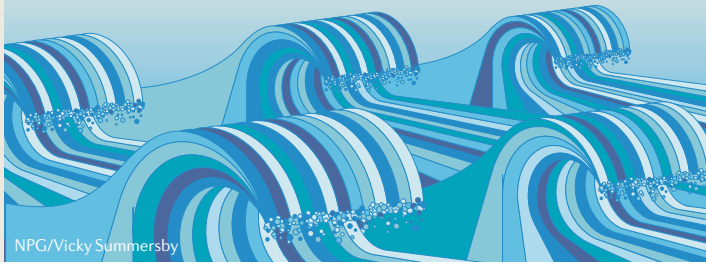
In agreement with this, the authors went on to show that both VEGFR2 and VEGFR3 are phosphorylated in response to laminar shear stress in the absence of ligand, and that they mediate PI3K–AKT signalling and shear-induced integrin activation. Moreover, knockdown and rescue experiments showed that VEGFR2 and VEGFR3 are functionally redundant. Finally, although the expression of VEGFR3 is low in stable arteries, the authors detected enriched *Vegfr3* mRNA expression in the normal mouse aorta at the inner curvature of the aortic arch, which is exposed to disturbed shear stress, and deletion of VEGFR3 reduced inflammatory signalling at this site.

> “the VE-cadherin TMD functions as an adaptor that binds not only VEGFR2 but also VEGFR3”

In summary, this study shows that the VE-cadherin TMD functions as an adaptor that binds not only VEGFR2 but also VEGFR3 to promote the ligand-independent activation of these receptors and downstream signalling. Future studies are now required to determine the interaction between VE-cadherin and the other complex component, PECAM1.

Andrea Du Toit

ORIGINAL RESEARCH PAPER Coon, B. G. *et al.* Intramembrane binding of VE-cadherin to VEGFR2 and VEGFR3 assembles the endothelial mechanosensory complex. *J. Cell Biol.* **208**, 975–986 (2015)



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