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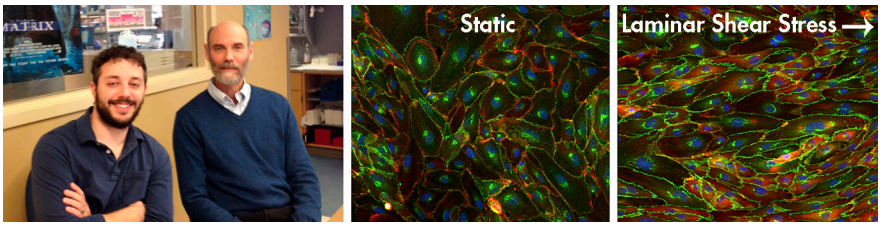
How VE-cadherin goes with the flow

Study describes how the adhesion molecule's transmembrane domain helps endothelial cells respond to fluid shear stress.

Focal Point



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Brian Coon (left), Martin Schwartz (right), and colleagues (not pictured) reveal that the transmembrane domain of VE-cadherin allows endothelial cells to respond to fluid shear stress by binding to the transmembrane domains of the growth factor receptors VEGFR2 and VEGFR3, recruiting them into a mechanosensory complex at endothelial cell junctions. Fluid shear stress signaling can activate proinflammatory pathways and/or vascular remodeling. In vitro, human umbilical vein endothelial cells align in the direction of fluid flow, as shown in the images above. Cells are stained for VE-cadherin (green), F-actin (red), and DNA (blue).

Vascular endothelial cells respond to changes in blood flow (1). Increased flow, for example, causes vasodilation and blood vessel remodeling. Collectively, these responses are critical for both vascular development and the maintenance of adult blood vessels. Moreover, disturbed blood flow patterns—at artery branch points, for instance—can activate inflammatory pathways that may initiate the formation of atherosclerotic plaques. Coon et al. reveal that the transmembrane domain of the cell adhesion molecule VE-cadherin mediates flow signaling by binding to the growth factor receptors VEGFR2 and VEGFR3 (2).

A decade ago, Martin Schwartz and colleagues discovered that VE-cadherin, VEGFR2, and the adhesion molecule PECAM-1 form a mechanosensory complex at endothelial cell–cell junctions (3). PECAM-1 appears to transduce the mechanical forces generated by blood flow (4), leading to the ligand-independent activation of VEGFR2 and the initiation of downstream signaling pathways. "But the function of VE-cadherin was a bit mysterious," explains Schwartz, who now works at Yale University in New Haven, Connecticut. "We wanted to understand its role in fluid shear stress signaling."

Whatever VE-cadherin does, it's a function that isn't shared by other members of the cadherin family. Endothelial cells lacking VE-cadherin maintain their intercellular adhesions by up-regulating its close homologue N-cadherin, but these cells are unable to respond to fluid shear stress. Schwartz and colleagues, led by postdoc Brian Coon, therefore generated a series of chimeric proteins containing different parts of VE- and N-cadherin and determined which of them were able to restore flow signaling to VE-cadherin–deficient mouse cells (2). "To our absolute astonishment, the crucial region was VE-cadherin's transmembrane domain," Schwartz says. Chimeric proteins containing this region enabled endothelial cells to respond to fluid shear stress, whereas chimeras containing VE-cadherin's extracellular and cytoplasmic domains, but N-cadherin's transmembrane domain, were unable to support flow signaling.

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Coon et al. therefore looked for proteins that specifically bound to VE-cadherin's transmembrane domain and identified VEGFR3. "That was also a surprise," Schwartz explains, "because we'd previously found that VEGFR2 was the key component of this junctional mechanosensory complex." In fact, the researchers discovered, the transmembrane domains of VEGFR2 and VEGFR3 bind equally well to the transmembrane domain of VE-cadherin, and both receptors are activated in response to fluid shear stress. "It seems that they can substitute for each other, at least for the outputs that we looked at," says Schwartz, referring, for example, to the activation of proinflammatory signaling pathways in endothelial cells subjected to oscillatory shear stress in vitro.

To investigate whether VEGFR3 contributed to endothelial flow signaling in vivo, Coon et al. first examined the receptor's expression pattern in mice. VEGFR3 expression is relatively low in adult arteries, but the researchers found that it was somewhat up-regulated at the aortic arch, a site of disturbed blood flow where chronic inflammation can lead to atherosclerosis. Knocking out *Vegfr3* reduced the activation of proinflammatory pathways at this site.

Thus, VEGFR3, along with VEGFR2, activates flow signaling pathways downstream of PECAM-1 and VE-cadherin. In another recent paper, Schwartz and colleagues found that different parts of the vascular system are set to respond to different levels of fluid shear stress and that the levels of VEGFR3 expression determine what this set point is (5). The researchers think that VE-cadherin acts as an adapter molecule that links the mechanosensory complex's components together, allowing the mechanical forces transduced by PECAM-1 to transactivate the VEGFRs, perhaps via the Src family kinase Fyn. Having established that VE-cadherin's transmembrane domain binds to VEGFR2 and VEGFR3, Schwartz now wants to examine the adhesion molecule's interaction with PECAM-1.

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3. Tzima, E., et al. 2005. *Nature*. 437:426–431.
4. Conway, D.E., et al. 2013. *Curr. Biol.* 23:1024–1030.
5. Baeyens, N., et al. 2015. *eLife*. 4:e04645.