

Endothelial permeability and VE-cadherin

A wacky comradeship

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The endothelium forms a selective semi-permeable barrier controlling bidirectional transfer between blood vessel and irrigated tissues. This crucial function relies on the dynamic architecture of endothelial cell–cell junctions, and in particular, VE-cadherin-mediated contacts. VE-cadherin indeed chiefly organizes the opening and closing of the endothelial barrier, and is central in permeability changes. In this review, the way VE-cadherin-based contacts are formed and maintained is first presented, including molecular traits of its expression, partners, and signaling. In a second part, the mechanisms by which VE-cadherin adhesion can be disrupted, leading to cell–cell junction weakening and endothelial permeability increase, are described. Overall, the molecular basis for VE-cadherin control of the endothelial barrier function is of high interest for biomedical research, as vascular leakage is observed in many pathological conditions and human diseases.

Cell–cell interactions are dynamic structures allowing cohesion and plasticity of organs. In vascular endothelial cells, endothelial junctions have to maintain homeostasis of blood vessels, while they retain their ability to rearrange during angiogenesis. Both adherens (AJs) and tight junctions (TJs) join neighboring cells together, and can adapt quickly to changes in the perivascular microenvironment, such as angiogenic/antiangiogenic cues, blood flow, shear stress, inflammatory conditions, etc. The AJ protein, VE-cadherin (vascular endothelial cadherin, also known as cadherin 5 and CD144) is specifically responsible for endothelial AJ assembly and barrier architecture. In this review, VE-cadherin properties will be presented, along with the mechanisms involved in endothelial cell–cell junction remodeling.

Building VE-Cadherin Junctions and the Endothelial Barrier

The vascular wall compartmentalizes blood circulation from surrounding tissues, while allowing finely tuned exchanges of metabolites, fluids, and cells. Blood vessels are constructed with endothelial cells, pericytes, and smooth muscle cells, embedded

within a specific basal membrane. From a molecular standpoint, the endothelial barrier is sealed by cell–cell adhesion molecules, among which VE-cadherin serves as a cornerstone.

VE-cadherin expression

VE-cadherin belongs to the super-family of classical cadherins, and as such, mediates homotypic calcium-dependent cell–cell interactions.¹ VE-cadherin expression is tissue-specific and exclusive to endothelial cells, in a way that its promoter is repressed in other cell types and can be used to target the endothelial compartment in transgenic mice.^{2,3} Importantly, VE-cadherin gene knockout is lethal in mouse embryos that exhibit severe angiogenic defects, attributed to endothelial apoptosis and abnormal VEGF (vascular endothelial growth factor) signaling.^{4,5} Moreover, interfering with VE-cadherin in embryos and adult mice affects vascular integrity.^{6,7} Besides, silencing VE-cadherin expression and blocking its adhesive function in vitro provided evidence that this adhesion molecule is essential for AJ formation and endothelial barrier maintenance.^{8–11} Accordingly, VE-cadherin emerges as the mastermind of endothelial cell–cell junctions, as it dictates the level of expression and/or the localization of other junctional molecules, including claudin-5 and N-cadherin.^{9,12,13}

VE-cadherin and its partners

Similarly to classical cadherins such as E- or N-cadherins, VE-cadherin recruits catenins through its cytosolic tail. These accessory molecules, mainly β - and p120-catenins, bridge cadherin multimers to the actin cytoskeleton via actin binding proteins, among which are α -catenin, vinculin, and eplin.^{14–18} Interestingly, it has been recently observed that β -catenin dephosphorylation, together with VE-cadherin mobility, contribute to endothelial cell–cell junction stabilization.¹⁹ However, the role of β -catenin in the endothelial barrier remains complex, as this multifaceted protein is also an essential mediator of the Wnt signaling cascade, operating as a transcription factor in the nucleus. Thus, β -catenin may exert broader effects on gene expression and vascular plasticity, including barrier function.^{20–22} Additionally, γ -catenin (also known as plakoglobin) can directly interact with VE-cadherin. Although β - and γ -catenins appear somehow interchangeable, only γ -catenin conveys VE-PTP adhesive function.²³

On the other hand, p120-catenin, which interacts with VE-cadherin on its juxtamembrane domain, is a key regulator of VE-cadherin expression, trafficking, and stability at the plasma membrane.^{24–27} Nonetheless, VE-cadherin rescue is not sufficient to maintain the endothelial barrier integrity in

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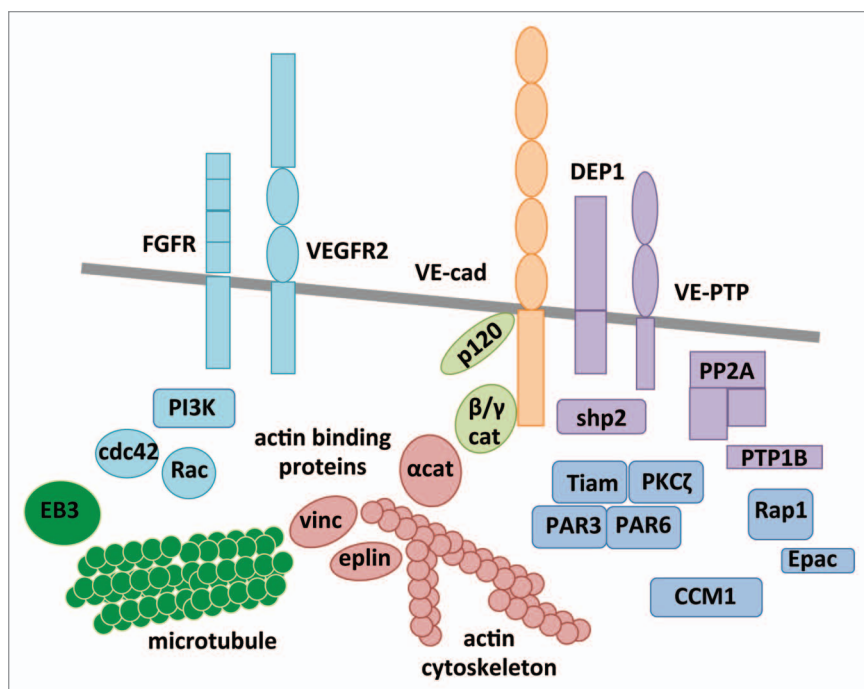


Figure 1. Assembly of VE-cadherin-mediated cell–cell contacts. Different classes of molecules interact with VE-cadherin (orange) and modulate its adhesive function: catenins (light green), actin binding proteins (red), phosphatases (purple), polarity complex (dark blue), signaling molecules and growth factor receptors (light blue), and microtubule (dark green). cat, catenin; cdc42, cell division control protein 42 homolog; CCM1, cerebral cavernous malformation protein 1; DEP1, density enhanced protein tyrosine phosphatase 1; EB3, end binding protein 3; FGFR, fibroblast growth factor receptor; PP2A, protein phosphatase 2A; PAR3/6, partition defect protein 3/6; PI3K, phosphoinositide 3 kinase; PKC, protein kinase C; PTP1B, protein tyrosine phosphatase 1B; Shp2, Src homology protein tyrosine phosphatase; Tiam, T-cell lymphoma invasion and metastasis; VE-cad, VE-cadherin; VEGFR2, vascular endothelial growth factor receptor 2; VE-PTP, vascular endothelial protein tyrosine phosphatase; vinc, vinculin.

p120-depleted cells.²⁷ This suggests a more complex role of p120-catenin in regulating cell–cell junction assembly in endothelial cells. In addition to catenins, a myriad of molecules are found in the vicinity of VE-cadherin, and could impact on the assembly and/or stability of VE-cadherin-mediated cellular interactions (Fig. 1). For instance, polarity complex proteins, including PAR3 and PAR6, accumulate at cell–cell junctions and interact with VE-cadherin.²⁸ They were shown to modulate the overall architecture of endothelial cell–cell contacts, including AJs and TJs. Although their mode of action in endothelial AJs is not fully elucidated and probably differs from what is known in the context of epithelial cells, the polarity complex might engage additional signaling components required for the assembly of VE-cadherin junctions. This includes CCM1 (cerebral cavernous malformation protein 1), the GTPase Rap1, the atypical PKC ζ (protein kinase C), and the G-protein exchange factor (GEF) Tiam (T-cell lymphoma invasion and metastasis).²⁹ It is noteworthy that Rap1, together with its GEF, namely Epac, have extensively been demonstrated to favor the formation of VE-cadherin-based junctions.^{17,30–34}

Finally, serine/threonine and tyrosine phosphatases are part of the VE-cadherin interactome. Indeed, VE-PTP (vascular endothelial protein tyrosine phosphatase), shp2 (src homology

protein tyrosine phosphatase2), PP2A (protein phosphatase 2A), DEP-1/CD148 (density enhanced protein tyrosine phosphatase 1), and PTP1B (protein tyrosine phosphatase 1B) were all found to directly stabilize VE-cadherin-based adhesion.^{19,23,35–39} These enzymes are suspected to maintain VE-cadherin and associated catenins in a non-phosphorylated status, which in turn strengthens cell–cell adhesion.

VE-cadherin signaling

In addition to being associated with molecules that control its adhesive behavior, VE-cadherin coalesces signaling platforms at cell–cell contacts, involved in the endothelial biology, and in particular, barrier integrity.⁴⁰ First, it has been early described that VE-cadherin function combines with VEGF-R2 (vegf receptor 2, also known as Flk1). They biochemically and functionally interact in quiescent endothelial cells, where VE-cadherin regulates VEGF-R2 antiapoptotic action.^{4,37,41} Interestingly, signaling pathways, which affect the endothelial plasticity in the course of angiogenesis, such as cell sprouting, migration, and permeability, frequently converge on the modulation of VE-cadherin/VEGF-R2 interaction.^{42–47} In addition, VE-cadherin contributes to convey the proper activity of other receptors in endothelial cells, such as angiopoietin 1 receptor Tie2, TGF β -R2 (transforming growth factor receptor), and FGF (fibroblast growth factor) signaling.^{46,48–52} Besides membrane receptors, VE-cadherin triggers the activation of

intracellular molecules, such as small GTPases from the Ras superfamily, which can loop on cell–cell adhesion. Notably, VE-cadherin induces Rac activation through Tiam.^{53–55} In addition, VE-cadherin is able to increase PI3K (phosphoinositide 3 kinase) catalytic activity, which can signal through the nucleus via FoxO1 and β -catenin transcription factors, to maintain endothelial features.^{4,9} Finally, it has been elegantly demonstrated that VE-cadherin could stabilize cell–cell contacts and organize the endothelial barrier through an original outside-in signaling mechanism, involving calcium signaling and microtubule dynamics.⁵⁶

There are a growing number of molecules detected at endothelial AJs that can adjust VE-cadherin expression, cell surface availability, phosphorylation status, turnover, and signaling. Targeting each of these properties could be employed to tune endothelial permeability and vascular leakage.

Breaking Down VE-Cadherin Junctions and the Endothelial Barrier

VE-cadherin is instrumental for vascular integrity, and therefore, is the target of a plethora of signaling events, which can

provoke endothelial barrier disruption and vascular permeability increase (Fig. 2).

VE-cadherin phosphorylation

The cytosolic tail of VE-cadherin harbors nine putative phospho-tyrosine sites, among which Y645, Y658, Y685, Y731, and Y733 that could be implicated in barrier integrity.⁵⁷⁻⁶⁰ In addition, VE-cadherin serine phosphorylation on the S665 residue has been shown to modulate AJ assembly.^{8,38} Indeed, many vascular-promoting agents, such as VEGF and histamine, were extensively documented to increase the phosphorylation of VE-cadherin and of associated catenins; resulting in the loosening of VE-cadherin/catenin binding.¹ Conversely, the artificial stabilization of VE-cadherin/catenin complexes hampers vascular permeability and leukocyte extravasation.⁶¹ Several kinases were proposed to catalyze VE-cadherin phosphorylation, while the exact molecular mechanisms linking phosphorylation to vascular leakage remains to be elucidated. To this regard, the non-receptor tyrosine kinase Src was demonstrated to contribute to the phosphorylation of VE-cadherin and catenins, and to AJ disassembly.^{8,38,47,62-64} However, Src-directed VE-cadherin phosphorylation appears insufficient to drive endothelial barrier opening, even when its activity was upregulated through the expression of a Src dominant active mutant or a Csk (C-terminal Src kinase) dominant negative form.⁶⁵ Besides Src, FAK (focal adhesion kinase) emerges as a prominent mediator of VE-cadherin-mediated AJ disorganization and permeability elevation.^{66,67} PAK (p21-activated kinase) could also phosphorylate VE-cadherin on serine, causing its internalization and cell-cell junction weakening.⁸ An alternate mechanism for VE-cadherin/catenin dissociation and enhanced permeability relies on caveolin phosphorylation, which could, in its phosphorylated form, trap catenins away from VE-cadherin.⁶⁸

VE-cadherin and mechanical forces

It is now widely accepted that mechanical tension exerted on endothelial cells, such as shear stress, can be sensed and integrated through VE-cadherin and VEGF-R2 complexes, although an additional adhesion molecule, namely PECAM (also referred to as CD31), is essential to transduce tensile forces.⁶⁹⁻⁷¹ Multiple signaling pathways have been further demonstrated to convey and adapt the endothelial cellular responses to environmental forces.⁷⁰ The most studied one corresponds to the modulation of the acto-myosin contractility apparatus via the activation of small GTPases, including RhoA, Rac, and cdc42, and myosin light chain (MLC) phosphorylation.⁷² However, the individual contribution of RhoA, Rac, and cdc42 to the endothelial barrier function might depend on cellular context and extracellular cues.⁷² For instance, thrombin primarily operates through RhoA that induces stress fiber formation and endothelial barrier

VE-cadherin internalization

Availability of VE-cadherin at the plasma membrane is instrumental in regulating cell-cell adhesion and endothelial barrier function.^{42,58,77} Indeed, it is recognized that VE-cadherin is a highly dynamic adhesion molecule, whose endosomal trafficking through clathrin-coated vesicles is tightly controlled.^{8,11,24} As cadherin internalization is associated with cell-cell junction loosening, this mechanism could contribute to endothelial behavior, such as cell migration and permeability.^{8,26,78-81} How VE-cadherin trafficking is dynamically modulated in endothelial cells has been the focus of intense investigation. In particular, it has been shown that p120-catenin could inhibit constitutive and induced VE-cadherin endocytosis.^{24,82} A cluster of three amino acids has been further identified within the core p120-binding region to the VE-cadherin cytosolic tail. This sequence is responsible for VE-cadherin uptake.²⁶ In addition, VE-cadherin phosphorylation on serine and tyrosine residues has been shown to provoke its internalization both in vitro and in vivo, leading to increase in vascular permeability.^{8,35,38,58,62,81,83-85}

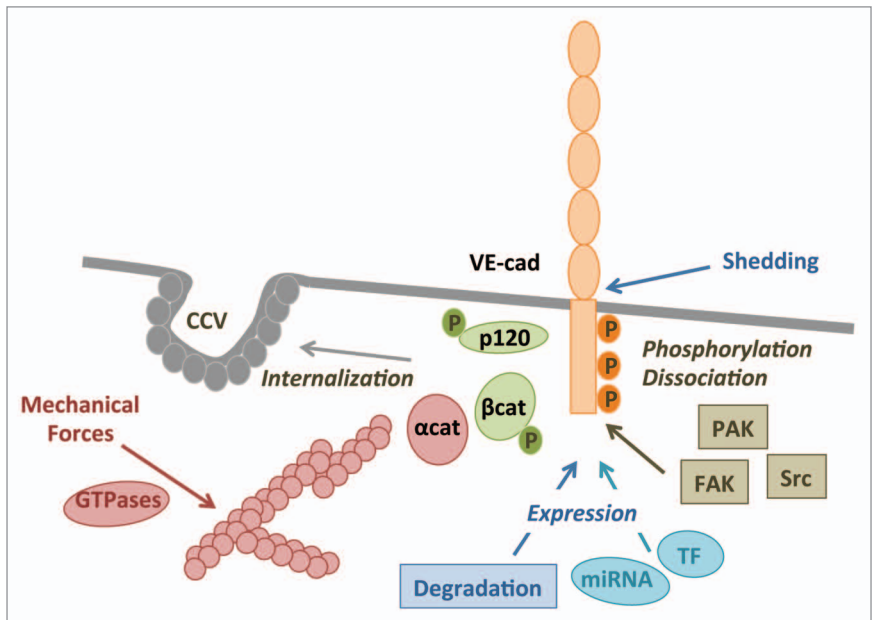


Figure 2. Disassembly of VE-cadherin-mediated cell–cell contacts. Four main routes modulate VE-cadherin disassembly and vascular permeability: (1) phosphorylation within VE-cadherin (VE-cad) C-tail and associated catenins on Y and S. At least, PAK (p21-activated kinase), Src, and FAK (focal adhesion kinase) were shown to catalyze VE-cadherin phosphorylation. This post-translational modification can ultimately lead to VE-cadherin/catenin dissociation; (2) internalization into clathrin-coated vesicles (CCV), which depends on p120-catenin (cat) and VE-cad phosphorylation; (3) mechanical forces and tension exerted on cell adhesion, notably through the actin cytoskeleton and Rho GTPases; and (4) expression regulated either at the transcriptional level through transcription factors (TF) and miRNA (miR), or at the protein level through extracellular shedding or intracellular cleavage, ubiquitin-, and lysosomal-driven degradation. P is for phosphorylation.

permeability increase, while histamine mainly uses cdc42.⁷³⁻⁷⁵ Likewise, Rac mediates VEGF-induced permeability, while it is essential for cell-cell contact formation upon VE-cadherin transactivation.^{8,75} Conversely, VE-cadherin can also impact cellular tension through direct signaling to GTPases, as mentioned earlier.^{53-55,76}

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Again, several signaling pathways have been shown to impact the entry of VE-cadherin in clathrin-coated pits. For instance, PI3K signaling is involved in VE-cadherin internalization and loss of vascular barrier, although the exact molecular mechanisms are not fully elucidated.^{81,84-86} Depending on the signal input, such as VEGF, chemokines, and inflammation, different PI3K isoforms can be engaged in VE-cadherin trafficking. For instance, class I PI3K α transduces TNF α (tumor necrosis factor α) signaling to VE-cadherin destabilization, while PI3K γ conveys chemokine's one.⁸⁴⁻⁸⁶ On the other hand, class II PI3K-C2 α deletion specifically impairs vascular sprouting and maturation in mice, most likely in response to VEGF.⁸¹ Additionally, Src kinase also triggers VE-cadherin internalization, directly through its phosphorylation or of its associated molecules, or through the activation of other kinases, such as PAK.^{8,35,58,80} Conversely, anti-permeability agents could operate through the blockade of VE-cadherin internalization.^{42,62,87}

VE-cadherin availability

During physiological and pathological blood vessel formation and in response to vascular permeability-promoting agents, the endothelial barrier function could be directly altered through the level of expression of VE-cadherin. This could be achieved by playing on either transcription of VE-cadherin mRNA or on the protein turnover. As mentioned above, VE-cadherin promoter is repressed in non-endothelial cells, and can be activated in response to angiogenic signals, such as FGF.² Interestingly, several transcription factors have been identified for their positive action on VE-cadherin expression, notably during developmental angiogenesis and inflammation. For instance, the Kruppel-like factor 4 (KLF4) binds VE-cadherin promoter and enhances its transcription, most likely downstream Wnt3a/ β -catenin signaling.⁸⁸ Interestingly, KLF4 depletion leads to VE-cadherin reduction, loss of AJ and of barrier integrity. This might ultimately aggravated lung vascular leakage in bacteria lipopolysaccharide (LPS) challenge. Likewise, Wnt3a/ β -catenin signaling controls claudin-3 expression and barrier maturation, albeit β -catenin cooperates with FoxO1 to repress claudin-5 expression.^{9,21} Thus, the respective action of Wnt signaling and β -catenin in VE-cadherin transcription remains far from being understood. Keeping with this, the catenin p120 could also play an essential role on VE-cadherin transcription, as its depletion in mice leads to VE-cadherin downregulation, microvasculature disorganization, and loss of vascular integrity.⁸⁹ Additional nuclear factors were discovered to control the endothelial barrier through their binding to the VE-cadherin promoter, including the ETS-related gene Erg, the hypoxia-inducing factor HIF2 α , the basic helix-loop-helix TAL-1/SCL, the scaffold protein β -arrestin, the Sex-determining region Y

(SRY)-related HMG box transcription factor Sox7, and the serum response element SRF.^{11,90-95}

Additionally, several miRNA, which have emerged as endogenous non-coding RNA molecules able to downregulate gene expression, have been found implicated in the regulation of VE-cadherin expression. For instance, miR27a can control VE-cadherin expression, angiogenesis, and vascular permeability. Interestingly, blocking specifically miR27a-dependent VE-cadherin repression precludes edema formation in vivo.⁹⁶ Likewise, miR101, miR125b, and miR142a can transcriptionally hamper on VE-cadherin expression, and impact on angiogenesis and permeability in vivo.⁹⁷⁻⁹⁹ Conversely, the combination of miR99b and miR181a/b enhances endothelial differentiation, and notably, the expression of VE-cadherin in human embryonic stem cells.¹⁰⁰ Finally, VE-cadherin protein expression can be regulated at the post-translational level through ubiquitination-driven processing, lysosomal degradation, and proteolytic cleavage by a desintegrin and metalloprotease ADAM10 and m-calpain.^{58,101-104} This latter can directly cleave VE-cadherin, leading to AJ disassembly and increased vascular leakage, associated with atherosclerosis lesions.¹⁰⁴ However, the molecular mechanisms that specifically control VE-cadherin turnover remain elusive. For instance, neither the ubiquitin ligases, nor the lysine residues involved in VE-cadherin ubiquitination have been identified so far.

Our knowledge on the molecular mechanisms involved in vascular permeability elevation has been improved. To this regard, any deregulation of this central function takes part in the initiation and progression of many pathological conditions and human diseases.^{77,105} It is now accepted that VE-cadherin-mediated cell-cell adhesion organizes the endothelial junctions and maintains the barrier function. Now that many partners of VE-cadherin involved in assembly/disassembly of endothelial junctions have been identified, efforts have to be done to uncover the mechanistic differences that may exist between physiological and pathological permeability increase. In addition, restoring endothelial cell-cell junctions could normalize vascular barrier function and therefore be of high interest in medicine.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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