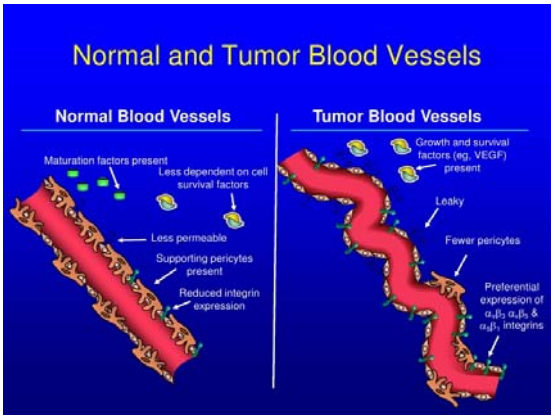


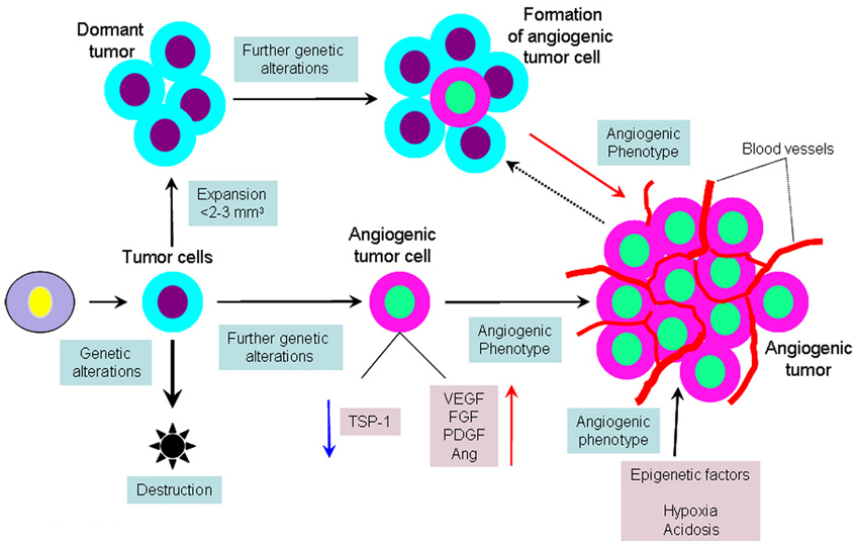
Seminari

Struttura capillari normali e tumorali

Ruolo della VE-caderina

http://image.slidesharecdn.com/treatinglatestagecolorectalcancer-dr-saltz-120718165505-phpapp02/95/treating-late-stage-colorectal-cancer-dr-saltz-22-728.jpg?cb=1342630678

Vedi didascalia



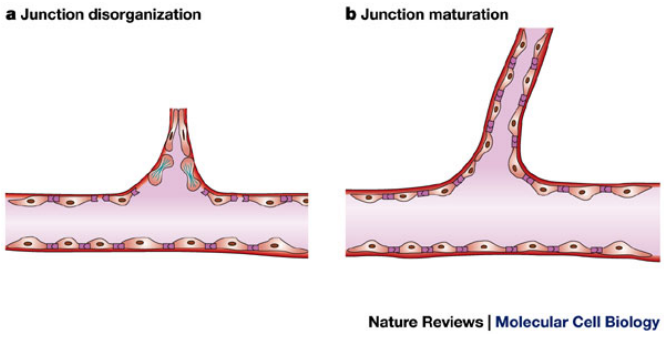
Cao Y.: **Tumor angiogenesis and molecular targets for therapy**. Frontiers in Bioscience 14, 3962-3973, January 1, 2009
http://www.bioscience.org/2009/v14/af/3504/figures.htm

Didascalia Figura Cao

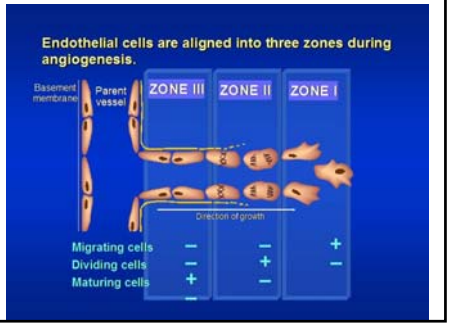
Meccanismi per la promozione di un fenotipo tumorale angiogenico

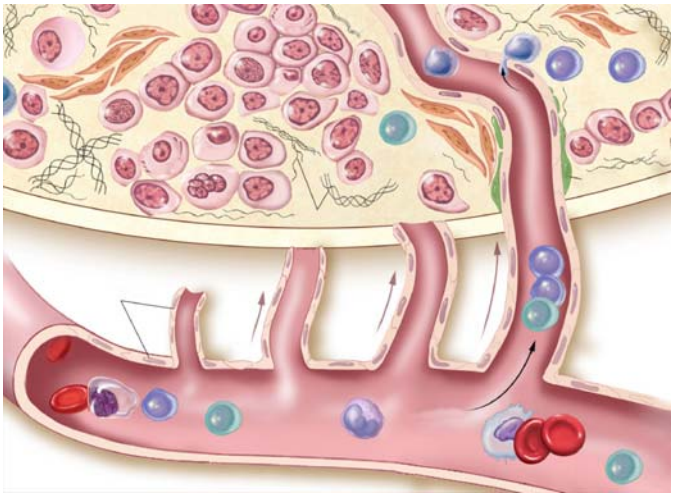
- Mutazioni in oncogeni e geni soppressori dei tumori portano alla trasformazione di una **cellula normale** in **cellula maligna**, che in molti casi è distrutta dai meccanismi di immunosorveglianza e da altri meccanismi (cellule scure).
- Alcune cellule maligne possono scappare al sistema immunitario ed espandersi fino a formare una massa microscopica con alcune centinaia di cellule (cellule verdi). Queste popolazioni non possono crescere ulteriormente oltre le dimensioni di 2-3 mm^3 senza il reclutamento di nuovi vasi sanguigni e rimangono nel corpo per mesi o anni.
- Tuttavia, le cellule tumorali possono ancora dividersi nel tumore microscopico inattivo finchè non diventano cellule tumorali angiogeniche (cellule rosse).
- Solo in rari casi una cellula maligna acquisisce un fenotipo angiogenico dall'inzio. Una volta che il fenotipo angiogentico viene innescato, la crescita e la progressione tumorale sono esponenziali.

Cao Y.: **Tumor angiogenesis and molecular targets for therapy**. Frontiers in Bioscience 14, 3962-3973, January 1, 2009
http://www.bioscience.org/2009/v14/af/3504/figures.htm



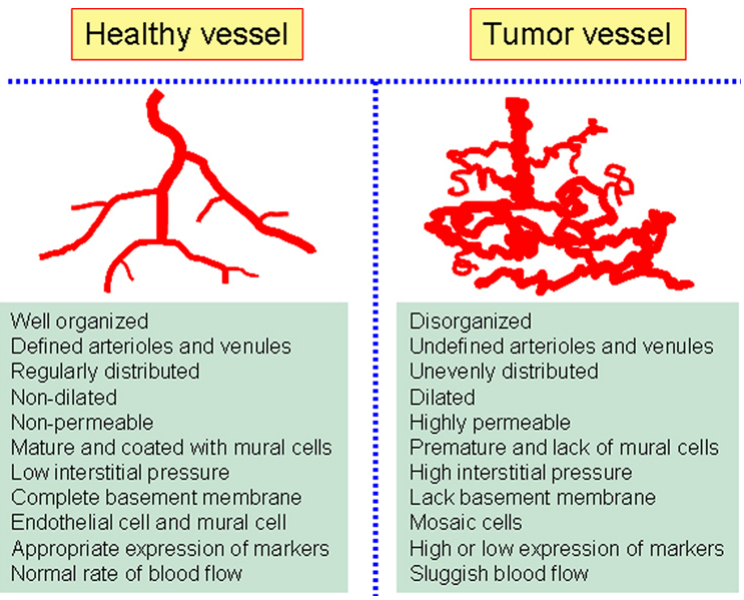
ANGIOGENESI





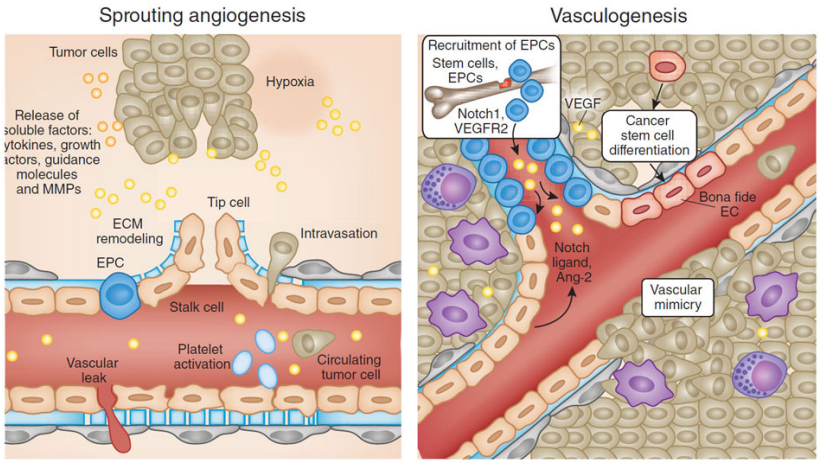
Schema del microambiente tumorale, includendo cellule tumorali, cellule endoteliali, CD^+ e CD^- e componenti della matrice extracellulare.

Burton ER, Libutti SK. **Targeting TNF-alpha for cancer therapy**. J Biol. 2009 Oct 23;8(9):85.
http://jbiol.com/content/figures/jbiol189-1-l.jpg



Cao Y.: **Tumor angiogenesis and molecular targets for therapy**. Frontiers in Bioscience 14, 3962-3973, January 1, 2009
http://www.bioscience.org/2009/v14/af/3504/figures.htm

Multiple origins of tumor-induced neovascularization



Vedi didascalia

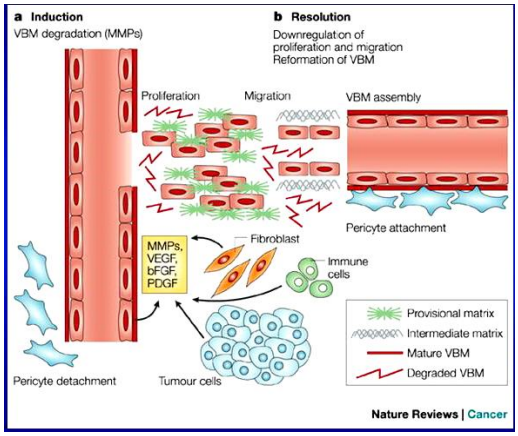
Weis SM, Cheresh DA. **Tumor angiogenesis: molecular pathways and therapeutic targets**. Nat Med. 2011 Nov 7;17(11):1359-70.

Didascalia Figura Weis & Cheresh

The combination of **stimulatory signals within the tumor microenvironment prompts changes in multiple cell types**. Perivascular cells detach from the mature blood vessels, compromising their integrity, permitting their remodeling and promoting an activated phenotype. Once the vascular barrier is disrupted, multiple cell types are exposed to **angiogenic and inflammatory stimuli** to escalate the response. **Platelets** are recruited to sites of exposed basement membrane, where they become activated and release their stores of **stimulatory factors into the tumor microenvironment**. **Endothelial progenitor cells** (EPCs) and **myeloid cells from the bone marrow move to the perceived wound**, where they release even more soluble factors locally. **Cancer stem cells** can **differentiate** to become bona fide **endothelial cells**, or tumor cells can physically participate in the formation of new vessels through **vascular mimicry**. However, the escalation of this response does not lead to the production of mature and proper blood vessels that improve the initial hypoxic situation because **the tumor microenvironment is characterized by pockets of hypoxia amid the leaky and tortuous blood vessels**. This environment also makes the **tumor cells more invasive**, allowing them to intravasate into the vasculature or lymphatics for metastasis to distant tissues. Effective strategies for cancer therapy must consider targets on multiple cell types and address issues of poor drug delivery in the leaky and poorly perfused tumor microenvironment.

Weis SM, Cheresh DA. **Tumor angiogenesis: molecular pathways and therapeutic targets**. Nat Med. 2011 Nov 7;17(11):1359-70.

Transizioni della matrice durante l'angiogenesi



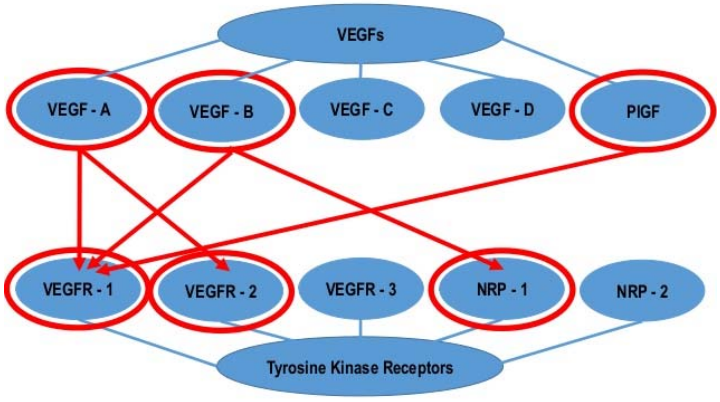
Angiogenesis is associated with degradation and reformation of the vascular basement membrane (VBM)

a | In response to growth factors and matrix metalloproteinases (MMPs), the VBM undergoes degradative and structural changes. This transition from mature VBM to provisional matrix promotes the proliferation and migration of vascular endothelial cells. Growth factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and platelet-derived growth factor (PDGF), are released from the BM, and are also produced by tumour cells, fibroblasts and immune cells.

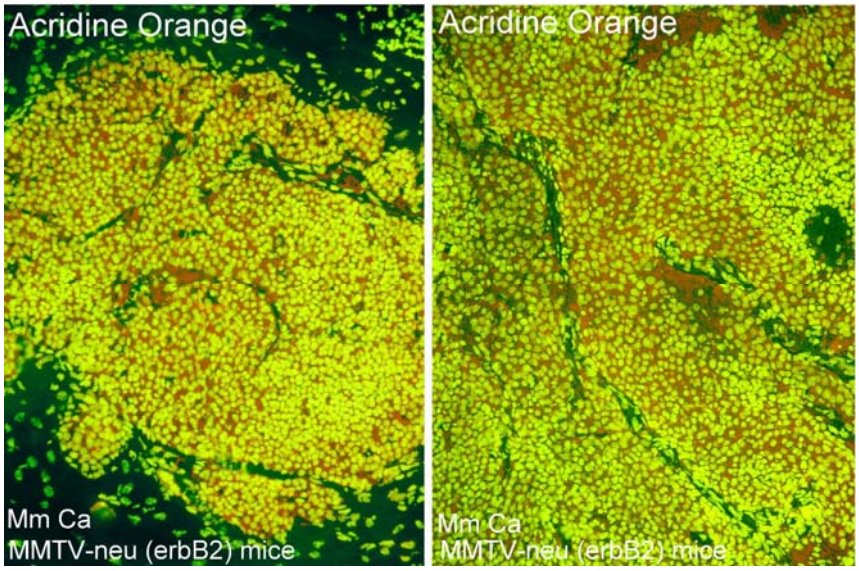
b | This induces formation of an intermediate, and then a new (mature) VBM. Together with the vascular endothelial cells and pericytes, the VBM mediates formation of a new blood vessel. The degraded VBM during this process has a crucial role in regulating angiogenesis.

Kalluri R. **Basement membranes: structure, assembly and role in tumour angiogenesis**. Nat Rev Cancer. 2003 Jun;3(6):422-33.

Angiogenic Factors:



http://image.slidesharecdn.com/sanofimeeting2evolvingroleofanti-angiogenesisinmetastaticcrc-150220060238-conversion-gate01/95/evolving-role-of-anti-angiogenesis-in-metastatic-crc-10-638.jpg?cb=1424433864



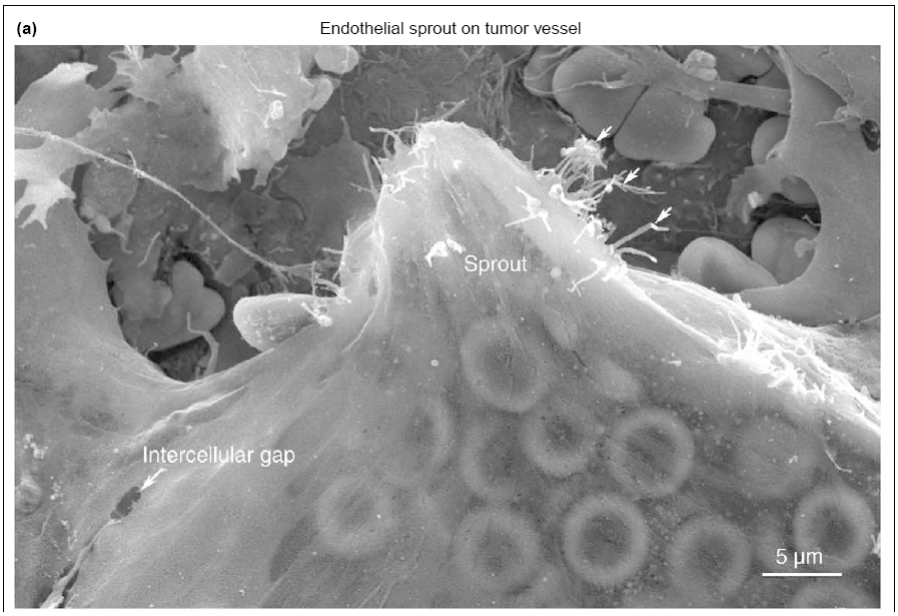
Freitas et al.

Cellular abnormalities of blood vessels as targets in cancer

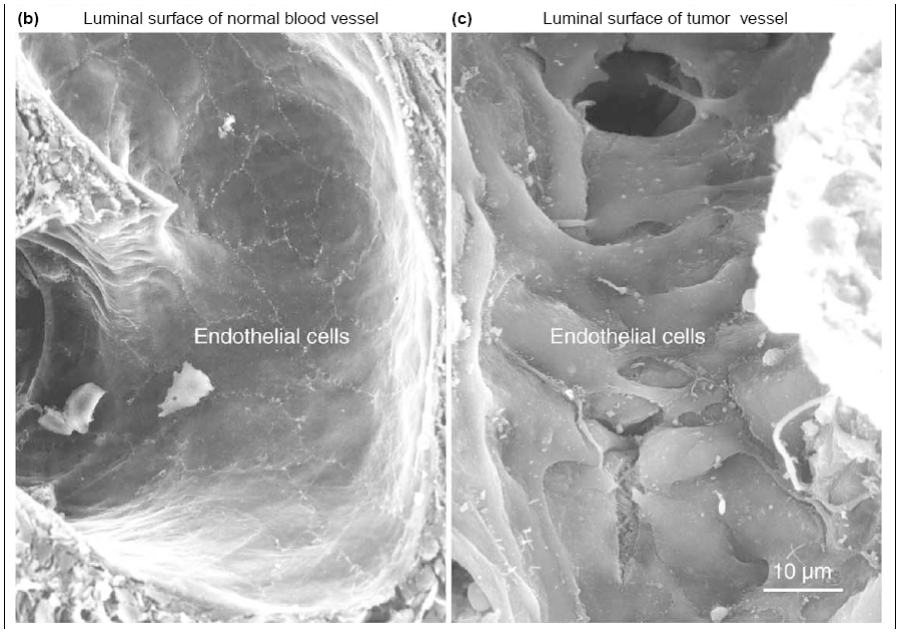
Peter Baluk, Hiroya Hashizume and Donald M McDonald

Current Opinion in Genetics & Development 2005, **15**:102–111

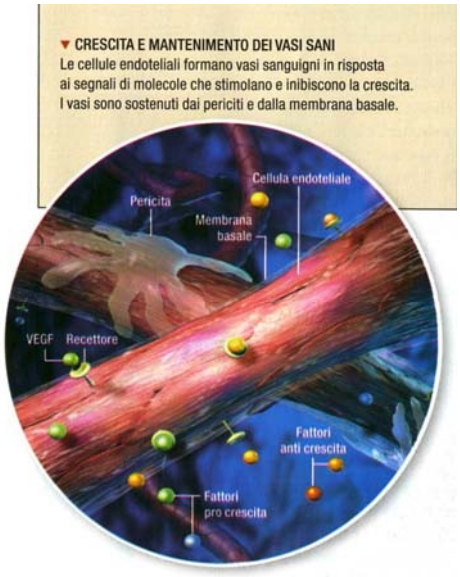
Tumor blood vessels have multiple structural and functional abnormalities. They are unusually dynamic, and naturally undergo sprouting, proliferation, remodeling or regression. The vessels are irregularly shaped, tortuous, and lack the normal hierarchical arrangement of arterioles, capillaries and venules. Endothelial cells in tumors have abnormalities in gene expression, require growth factors for survival and have defective barrier function to plasma proteins. Pericytes on tumor vessels are also abnormal. Aberrant endothelial cells and pericytes generate defective basement membrane. Angiogenesis inhibitors can stop the growth of tumor vessels, prune existing vessels and normalize surviving vessels. Loss of endothelial cells is not necessarily accompanied by simultaneous loss of pericytes and surrounding basement membrane, which together can then provide a scaffold for regrowth of tumor vessels. Rapid vascular regrowth reflects the ongoing drive for angiogenesis and bizarre microenvironment in tumors that promote vascular abnormalities and thereby create therapeutic targets.



Baluk P, Hashizume H, McDonald DM. **Cellular abnormalities of blood vessels as targets in cancer**. Curr Opin Genet Dev. 2005 Feb;15(1):102-11.



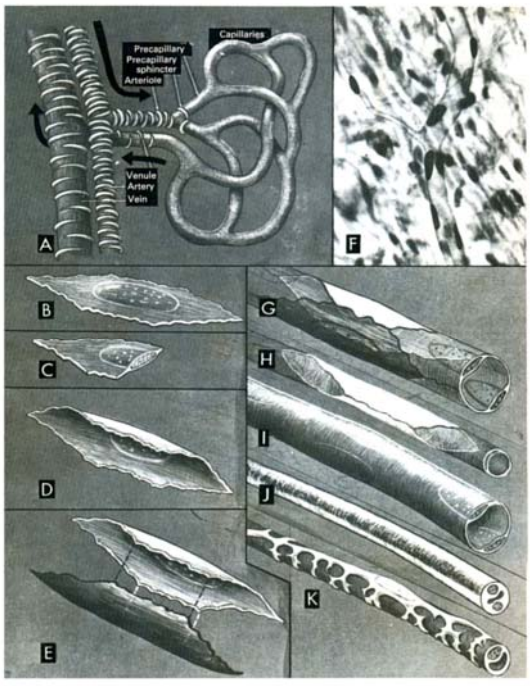
Baluk P, Hashizume H, McDonald DM. **Cellular abnormalities of blood vessels as targets in cancer**. Curr Opin Genet Dev. 2005 Feb;15(1):102-11.

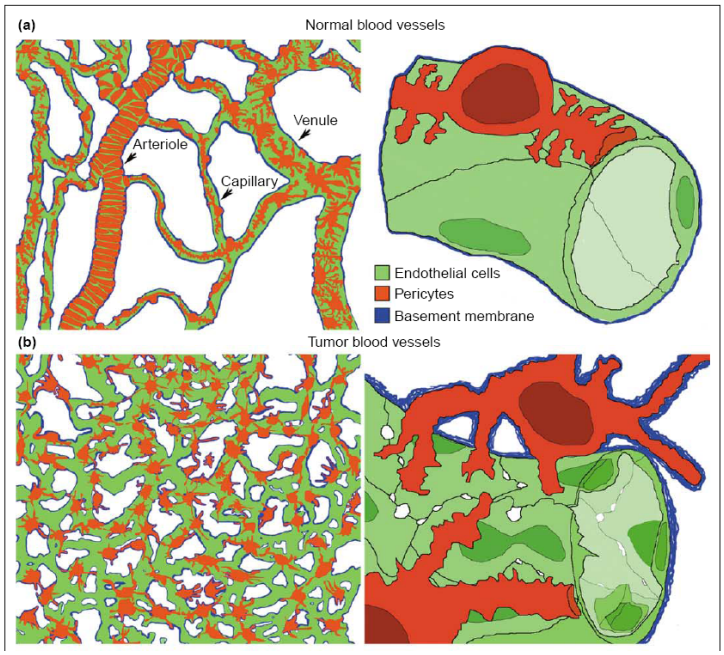


Periciti

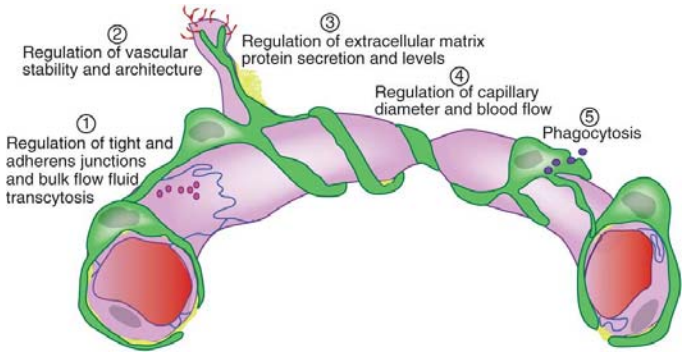
- Cellule che si trovano attorno ai capillari e sono simili alle cellule muscolari lisce.
- Circondano l'endotelio come cellule singole.
- L'associazione con i periciti riduce l'apoptosi delle cellule endoteliali e stabilizza la vascolatura.

Dejana E, Orsenigo F, Lampugnani MG. **The role of adherens junctions and VE-cadherin in the control of vascular permeability**. J Cell Sci. 2008 Jul 1;121(Pt 13):2115-22.



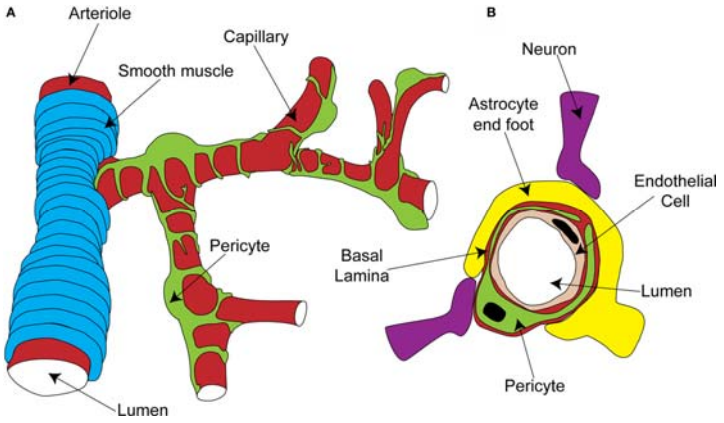


Baluk P, Hashizume H, McDonald DM. **Cellular abnormalities of blood vessels as targets in cancer**. Curr Opin Genet Dev. 2005 Feb;15(1):102-11.



Pericytes are multi-functional members of the neurovascular unit. Pericytes (1) control BBB integrity by regulating the orientation and abundance of endothelial tight and adherens junction proteins, as well as the rate of bulk flow fluid transcytosis (transendothelial transport of fluid-filled vesicles); (2) regulate the stability and architecture of newly formed cerebral microvessels; (3) contribute to secretion and regulate the levels of extracellular matrix proteins forming the basement membrane; (4) regulate capillary diameter and blood flow; and (5) provide clearance and phagocytotic functions in brain.

Winkler EA, Bell RD, Zlokovic BV. **Central nervous system pericytes in health and disease**. Nat Neurosci. 2011 Oct 26;14(11):1398-405.
http://www.nature.com/neuro/journal/v14/n11/images/nn.2946-F4.jpg



Organization of the capillary neurovascular unit. (A) Rings of smooth muscle encircle arterioles, while pericytes send processes along and around capillaries, without fully covering the vessel. (B) Pericytes are located outside the endothelial cells and are separated from them and the parenchyma by a layer of basal lamina. In the parenchyma, astrocyte end-feet and neuronal terminals are closely associated with the capillary.

Hamilton NB, Attwell D, Hall CN. **Pericyte-mediated regulation of capillary diameter: a component of neurovascular coupling in health and disease**. Front Neuroenergetics. 2010 May 21;2. pii: http://journal.frontiersin.org/Journal/10.3389/fnene.2010.00005/full

Periciti & Cervello

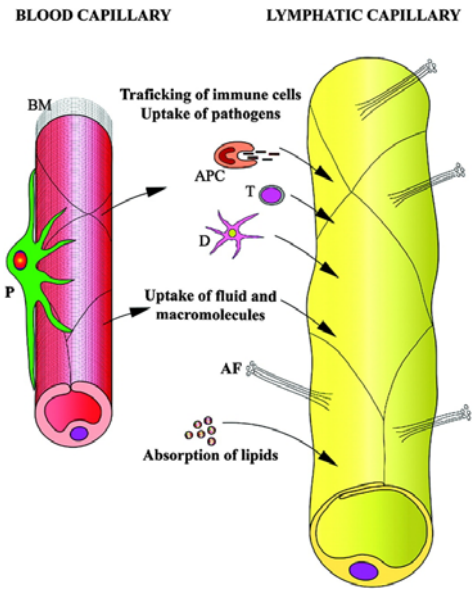
1. Controllano l'integrità della "Brain-Blood-Barrier" (BBB) regolando l'orientamento e l'abbondanza delle proteine delle giunzioni tight e aderenti delle cellule endoteliali ed anche la velocità di transcitosi di fluido (trasporto transendoteliale di vescicole piene di fluido);
2. Regolano la stabilità e l'architettura dei microvasi cerebrali neoformati;
3. Contribuiscono alla secrezione e regolano i livelli di proteine della matrice extracellulare formando la lamina basale;
4. Regolano il diametro dei capillari e il flusso sanguigno;
5. Forniscono le funzioni di "clearance" e fagocitosi del cervello.

Pericytes

Pericytes are key cells in vascular development, stabilization, maturation and remodeling [23,24]. From both structural and functional studies, pericytes are known to be intimately associated with endothelial cells. Indeed, an important criterion in the identification of pericytes is their position, along with endothelial cells, within the vascular basement membrane. Pericytes are present on capillaries, postcapillary venules and collecting venules throughout the body. Nonetheless, pericytes on different segments of the microvasculature and in different organs differ in structure and expression of marker proteins. In addition, pericytes undergo phenotypic plasticity in disease, change in response to certain treatments, and are difficult to identify under some conditions because of the lack of unambiguous markers [25]. None of the conventional immunohistochemical markers of pericytes, including α-smooth muscle actin (αSMA), platelet derived growth factor receptor-β (PDGFR-β), high molecular weight melanoma-associated antigen (NG2) and aminopeptidases A and N [19,24] is unique to pericytes or is expressed by all pericytes.

The vulnerability of newly formed blood vessels has been attributed to absence of pericytes as judged by lack of αSMA-immunoreactive cells. However, a single marker of pericytes will give misleading results when the pericytes are present but do not express the marker. Indeed, use of multiple markers has shown that pericytes are consistently present on tumor vessels [26] and other growing blood vessels at a stage when pericytes do not express αSMA [24,27,28].

Baluk P, Hashizume H, McDonald DM. **Cellular abnormalities of blood vessels as targets in cancer**. Curr Opin Genet Dev. 2005 Feb;15(1):102-11.

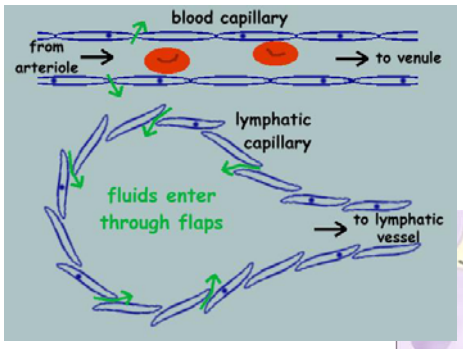


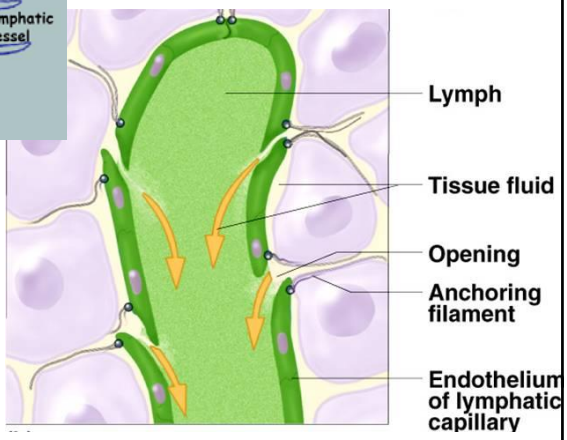
Characteristic structure and function of the lymphatic microvasculature.

The lymphatic capillary is uniquely adapted for the uptake of fluid, lipids, macromolecules, and cells from the interstitium. In contrast to the blood capillary, the lymphatic capillary has poorly developed basal lamina (BM) and is devoid of pericytes (P). Lymphatic endothelium is highly attenuated, and cells are connected directly to the interstitial collagen via anchoring filaments (AF). T, T cell; D, dendritic cell; APC, antigen presenting cell.

Pepper MS, Skobe M. **Lymphatic ndothelium: morphological, molecular and functional properties.** J Cell Biol. 2003 Oct 27;163(2):209-13.

Capillare linfatico





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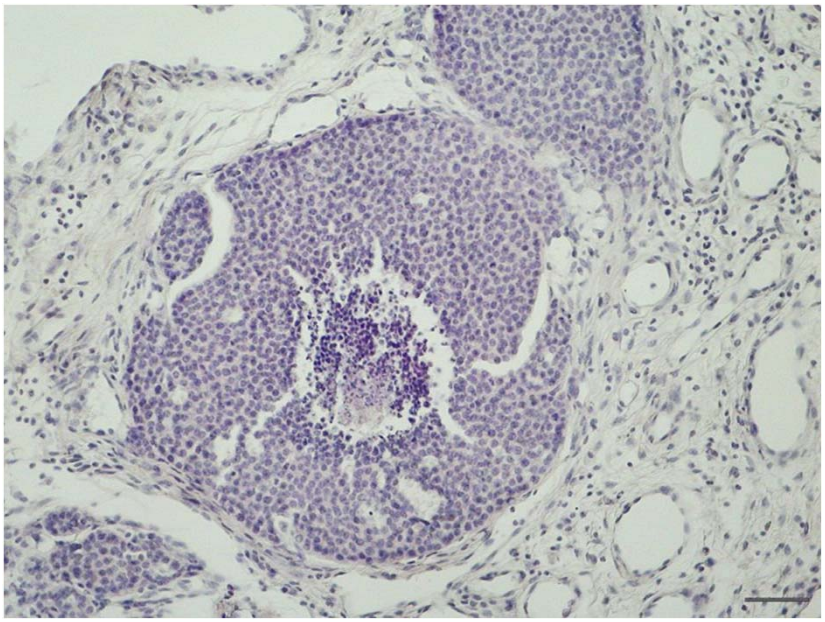
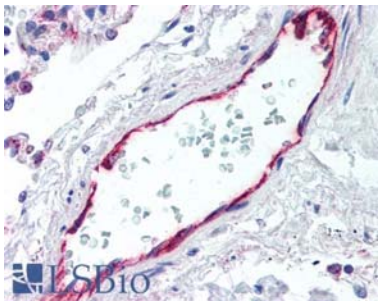
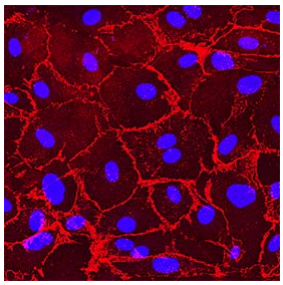
http://faculty.stcc.edu/AandP/AP/imagesAP2/immune/capillary.jpg



Mammary carcinoma, MMTV-neu transgenic mice
Freitas et al.



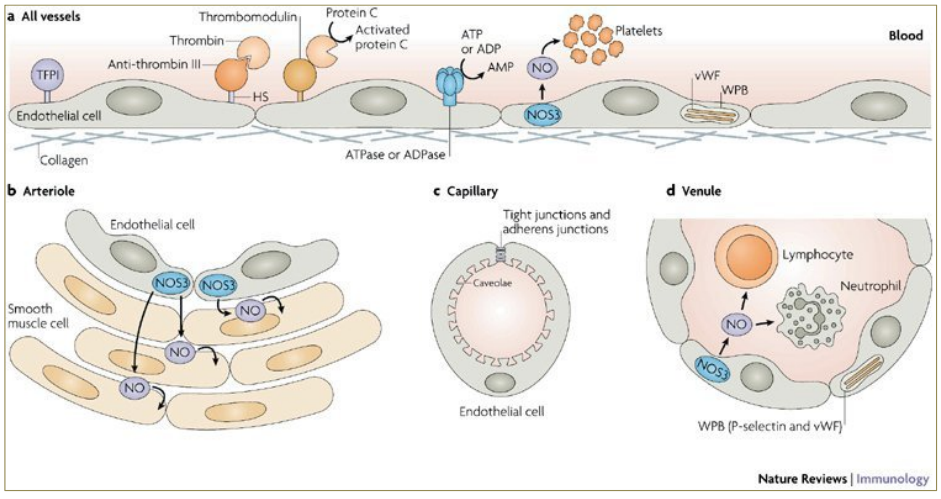


Molecole di adesione & angiogenesi

VE-CADERINA / CD144

https://www.lsbio.com/image2/anti-cd144-cdh5-ve-cadherin-antibody-aa1-258-ihc-plus-ls-b2138/14652_208924.jpg
https://resources.rndsystems.com/images/datasheets/antibody/VECadherin_MAB9381_Immunocytochemistry__Immunofluorescence_17381.jpg

Funzioni delle cellule endoteliali a riposo



Vedi didascalia

Pober JS, Sessa WC. **Evolving functions of endothelial cells in inflammation**. Nat Rev Immunol. 2007 Oct;7(10):803-15.

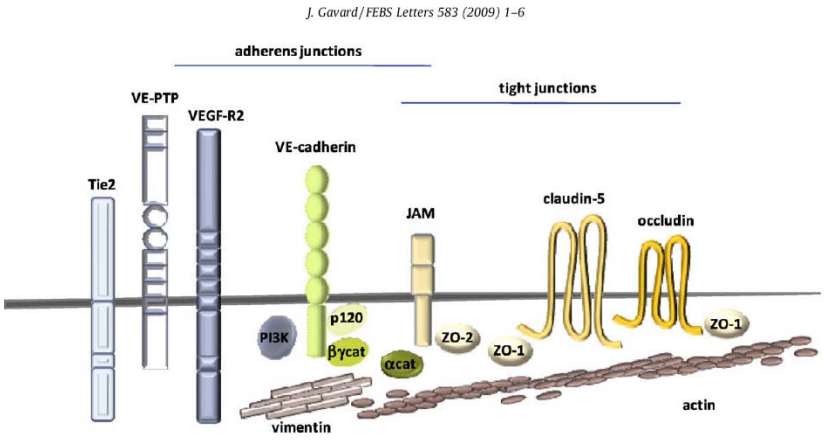
Didascalia Fig. Pober & Sessa - 1

a | **All endothelial cells inhibit coagulation of the blood**. Endothelial cells bind and display tissue factor pathway inhibitors (TFPIs) that **prevent the initiation of coagulation** by blocking the actions of the factor-VIIa–tissue-factor complex. Endothelial cells synthesize and display **heparan sulphate proteoglycans (HS)** on their cell surface, which have **anti-coagulant properties** that cause bound anti-thrombin III to be capable of inhibiting any thrombin molecules generated by the coagulation cascade. Endothelial cells also synthesize and display the **protein thrombomodulin**, which binds thrombin and converts its substrate specificity from cleavage of fibrinogen (the key step in forming a blood clot) to cleavage and activation of protein C. **Activated protein C is an enzyme that destroys certain clotting factors and inhibits coagulation**. Key processes to prevent platelet activation (and therefore coagulation) include inactivation of thrombin, conversion of ATP to inert AMP through the action of ATPases and ADPases, and blocking the physical interaction between platelets and collagen, which can activate platelets. **Endothelial cells also sequester von Willebrand factor (vWF),** a protein that strengthens the interaction of platelets with the basement membrane, by keeping it within their storage granules, known as **Weibel–Palade bodies** (WPB). **Nitric oxide** (NO), generated by nitric-oxide synthase 3 (NOS3)- mediated conversion of arginine, further inhibits platelet activation

Pober JS, Sessa WC. **Evolving functions of endothelial cells in inflammation**. Nat Rev Immunol. 2007 Oct;7(10):803-15.

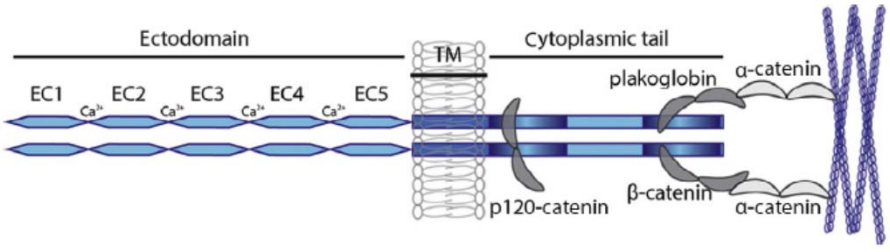
Didascalia Fig. Pober & Sessa - 2

b | **Arterial endothelial cells** have a major role in **regulating blood flow** by controlling the tone of smooth muscle cells in the medial layer of the vessel wall. Although a variety of mediators are involved, the principal regulator is the vasodilator NO produced by NOS3 in endothelial cells. **c** | **Capillary endothelial cells** are the principal **regulators of transendothelial extravasation of plasma proteins**. Although the extent of this barrier varies among different tissues, **most continuous capillary endothelial cells prevent proteins from escaping from the blood by forming intercellular junctions containing elements of both tight junctions and adherens junctions, closing off the paracellular pathway between cells**. Caveolae may initiate and control the passage of plasma proteins across the capillary layer via vesicular transport. **d** | **Venular endothelial cells** form the **principal site of leukocyte trafficking from the blood into the tissues**. Efficient recruitment of leukocytes requires that the endothelial cells are **activated**; resting endothelial cells actively inhibit this process by failing to express adhesion molecules that mediate leukocyte attachment. **P-selectin, which is expressed basally in human endothelial cells, is sequestered into WPBs along with vWF**; E-selectin, vascular cell-adhesion molecule 1 and intercellular adhesion molecule 1 are minimally synthesized; and NO may contribute to suppressing the synthesis of these molecules, but also has direct effects on leukocytes, preventing their activation to motile forms capable of entering the tissues.



Endothelial cell–cell junctions. Adherens and tight junctions sealed the endothelial cells through specific cell–cell adhesion molecules: VE-cadherin, junctional adhesion molecules (JAM), claudin-5, occludin. These adhesion complexes are linked to the actin filament cytoskeleton and the vimentin intermediate filament network through intracellular mediators: p120, a, b and c catenins (cat) and zona occludens (ZO) proteins. Endothelial cell–cell junctions can also concentrate signaling components such as phospho-inositide 3 kinase (PI3K), vascular endothelial growth factor receptor type 2 (VEGF-R2), vascular endothelial cell-specific phospho-tyrosine phosphatase (VEPTP) and the angiopoietin-1 receptor, Tie2.

Rappresentazione strutturale di un omodimero di VE-caderine nelle giunzioni aderenti



La proteina **VE-caderina** consiste in un dominio extracellulare (ectodominio) con cinque ripetizioni di tipo caderina (EC1-EC5) e siti di legame per il Ca^{2+}, un dominio transmembrana (TM) e una coda citoplasmatica. Tutti i principali partners di legame della VE-caderina, quali la catenina p120, la β-catenina, e la placoglobina asi legano alla coda citoplasmatica della VE-caderina. La β-catenina e la placoglobina si legano inoltre alla α-catenina, che si collega al macchinario actina-miosina della cellula.

Lagendijk AK, Hogan BM. **VE-cadherin in vascular development: a coordinator of cell signaling and tissue morphogenesis**. Curr Top Dev Biol. 2015;112:325-52.

Curr Opin Hematol 2015, 22:267–272

New insights in the control of vascular permeability: vascular endothelial-cadherin and other players

Marianna Trani[a] and Elisabetta Dejana[a]

Purpose of review

The control of the endothelial barrier function is essential for vascular homeostasis and is mainly mediated by cell-to-cell junctions that tightly regulate permeability to plasma solutes and circulating cells such as leukocytes and tumor cells. While in some circumstances the transient dismantling of endothelial cell junctions might be beneficial, in pathological conditions, such as cancer, severe alterations of endothelial junction composition and function are detrimental, causing massive edema and increased interstitial pressure. Here, we aim to discuss the newly and most recently identified molecular mechanisms that cooperate in the control of vascular permeability.

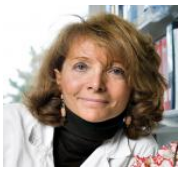
Recent findings

Although the involvement of vascular endothelial-cadherin in the regulation of vascular leakage is well known, recent findings shed light on additional molecules involved in the control of vascular endothelial-cadherin phosphorylation in physiological and pathological conditions, and identified new unknown regulators of the endothelial barrier function.

Endothelial cells and their cell-to-cell junctions play a crucial role in maintaining and controlling vascular integrity by tightly modulating vascular permeability to plasma and cells. Endothelial permeability is mediated by transcellular and paracellular pathways. Whereas the transcellular pathway requires the formation of fenestrations [1] in the endothelial membrane or the organization of vesiculo-vacuolar organelles [2], the paracellular permeability relies on the opening and closing of endothelial cell-to-cell junctions [3]. Two types of junctions are present in the endothelium – tight junctions and adherens junctions. In both types of junctions, transmembrane proteins generate a zipper-like structure along the cell border and mediate adhesion. In adherens junctions, the most important component is vascular endothelial-cadherin that is specifically expressed in the endothelial cells. Vascular endothelial-cadherin contains an extracellular region composed of five immunoglobulin-like domain repeats, a single transmembrane domain, and a short cytoplasmic region. Each molecular region accounts for a different function. While the extracellular region is responsible for homophilic interactions in *trans*, the transmembrane domain is involved in *cis* interactions and lateral clustering. In contrast, the cytoplasmic tail of the protein forms complexes with catenins, such as β-catenin, p120, and plakoglobin, and many other signaling and cytoskeletal partners

Apart from acting as adhesive structures, the cell-to-cell junctions are also signaling units that tightly regulate endothelial responses and control vascular homeostasis through different mechanisms. Vascular endothelial-cadherin interacts with several growth factor receptors such as vascular endothelial growth factor receptor 2 (VEGFR2) [10], transforming growth factor-β receptor [11], and fibroblast growth factor (FGF) receptor [12], and modulates their signaling. Besides regulating endothelial proliferation and survival [3], the association of VEGFR2 and vascular endothelial-cadherin provides regulation of cell-to-cell junctional integrity and represents a mechanism for localized disruption by vascular endothelial growth factor (VEGF). Several studies have shown the role of vascular endothelial-cadherin tyrosine phosphorylation in the response to inflammatory mediators and growth factors [13–16]. VEGF as well as other factors are able to induce tyrosine phosphorylation of vascular endothelial-cadherin, β-catenin, and p120, and this is associated with increased permeability of endothelial layers *in vitro*

Trani M, Dejana E. **New insights in the control of vascular permeability: vascular endothelial-cadherin and other players**. Curr Opin Hematol. 2015 May;22(3):267-72.



Elisabetta Dejana
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- Le ***giunzione aderenti***, e più specificamente le ***caderine*** giocano un ruolo importante nell'*integrità* e *crescita delle cellule endoteliali* e, in genere *nella morfogenesi vascolare*.
- Oltre alla loro proprietà adesive, le caderine possono funzionare trasferendo segnali intracellulari mediante l'interazione con una rete complessa di molecole citoscheletriche e di segnalamento.
- Le caderine possono segnalare in modi diversi:
  - Attivando direttamente le vie di segnalamento, mediante interazione con recettori cellulari specifici per fattori di crescita
  - Controllando la traslocazione di beta-catenina e/o altri fattori di trascrizione fino al nucleo.

Cavallaro U, Liebner S, Dejana E. **Endothelial cadherins and tumor angiogenesis**. Exp Cell Res. 312: 659-667, 2006.

- Le cellule endoteliali presentano diversi tipi di caderine che possono trasferire segnali specifici ed esercitare ruoli funzionali diversi:
  - La VE-Caderina è specifica per l'endotelio e la principale costituente della giunzioni aderenti. Questa proteina è in grado di proteggere le cellule endoteliali dall'apoptosi e contribuisce all'inibizione di contatto per la crescita endoteliale.
  - La N-caderina è anche essa abbondantemente espressa dall'endotelio e può essere importante per modulare l'espressione della VE-caderina.
  - La T-caderina, la R-caderina e la VE-caderina 2 furono identificate in regioni specifiche dell'albero vascolare ma il loro ruolo nello sviluppo vascolare o nell'angiogenesi è ancora poco noto.

Cavallaro U, Liebner S, Dejana E. **Endothelial cadherins and tumor angiogenesis**. Exp Cell Res. 312: 659-667, 2006.

Caderine endoteliali: localizzazione e funzione.

- La ***VE-caderina*** è localizzata nelle ***giunzioni aderenti*** fra cellule adiacenti, dove media l'adesione cellula-cellula di tipo omotipico, l'inibizione di contatto e la sopravvivenza.
- Vice-versa, la N-caderina si trova nei siti di contatto fra le cellule endoteliali e le cellule della parete dei vasi ("cellule murali"), dove è coinvolta nell'adesione cellula-cellula di tipo eterotipico.
- La funzione adesiva della VE-caderina2 e della R-caderina non è ancora nota.
- La T-caderina non ha proprietà adesive e potrebbe essere coinvolta nell'indirizzamento dei vasi.

Cavallaro U, Liebner S, Dejana E. **Endothelial cadherins and tumor angiogenesis**. Exp Cell Res. 312: 659-667, 2006.

Vascular Endothelial Cadherin (VE-cadherin) (1)
(Cadherin 5, type 2 or VE-cadherin, CD144 (Cluster of Differentiation 144)

- Caderina codificata dal gene humano CDH5.
- La ***VE-caderina*** è una classica caderina della superfamiglia delle caderine il cui gene è localizzato in un cluster di sei caderine in una regione del braccio lungo del cromosoma 16 che è coinvolto nella perdita di eventi di eterozigosi nei ***tumori del seno e della prostata***.
- La proteina codificata è una glicoproteina di adesione cellula-cellula Ca^{2+}-dipendente composta da 5 ripetizioni caderiniche extracellulari, una regione transmembrana e una coda citoplasmatica altamente conservata.
- Funzionando come una **caderina classica** conferendo alle cellule la capacità di **aderire in modo omofilico**, la proteina può giocare un ruolo importante nella **biologia delle cellule endoteliali** mediante il controllo della coesione e l'organizzazione delle giunzioni intracellulari.

http://en.wikipedia.org/wiki/VE-cadherin

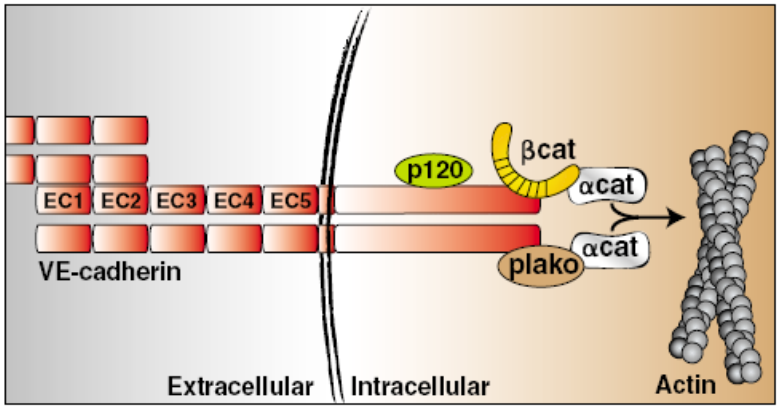
Vascular Endothelial Cadherin (VE-cadherin) (2)

- **L'integrità delle giunzioni intercellulari** è il principale determinante della **permeabilità dell'endotelio**, e si ritiene che la giunzione aderente basata sulla VE-caderina sia particolarmente importante.
- La VE-caderina è richiesta per mantenere una barriera endoteliale restrittiva:
  - Studi con anticorpi contro la VE-caderina hanno dimostrato di aumentare la permeabilità di un monostrato di cellule endoteliali e, in vivo, di aumentare l'edema interstiziale e l'emorragia.
- La VE-caderina è indispensabile per lo **sviluppo corretto dei vasi sanguigni**.

http://en.wikipedia.org/wiki/VE-cadherin

The role of adherens junctions and VE-cadherin in the control of vascular permeability

Elisabetta Dejana[1,2,*], Fabrizio Orsenigo[1] and Maria Grazia Lampugnani[1,3]



Organizzazione molecolare delle giunzione aderenti (AJs) degli endoteli - 1

- **La caderina VE è rappresentata come un dimero, la minima unità funzionale delle caderine;**
- **EC1-EC5 sono i cinque domini extracellulari omologhi della VE-caderina.**
- **L'aggregazione della VE-caderina nei punti di contatto cellula-cellula promuove la formazione di complessi multimolecolari che comprendono proteine con funzioni nel segnalamento, regolatorie e "scaffold"**.
- Le proteine ben note per l'interazione con la VE-caderina includono le proteine della famiglia della catenine **p120**, **β-catenina** (βcat) e **placcoglobina** (plako).
- La β-catenina e la placcoglobina si associano direttamente con la VE-caderina e con la **α-catenina** (α cat).

Dejana et al., 2008

Organizzazione molecolare delle giunzione aderenti (AJs) degli endoteli - 2

- Alcune proteine che interagiscono con la VE-caderina hanno **attività enzimatica** (**tirosina o serina chinasi, tirosina fosfatasi e GTPasi**).
- Altre hanno funzione di "**scaffold",** che potrebbe permettere l'organizzazione di aggregate molecolari complessi. Le proteine illustrate … si assemblano formando **complessi multimerici nelle AJs** che possono **modular la funzione della barriera endoteliale,** regolando l'attività della VE-caderina e trasducendo segnali intracellulari.
- C'è una probabile specificità nella composizione molecolare di tali complessi, che dipende dal tipo e dallo stato di attivazione dei vasi sanguigni.

NATURE REVIEWS | MOLECULAR CELL BIOLOGY VOLUME 5 | APRIL 2004 | 261

ENDOTHELIAL CELL–CELL JUNCTIONS: HAPPY TOGETHER

Elisabetta Dejana

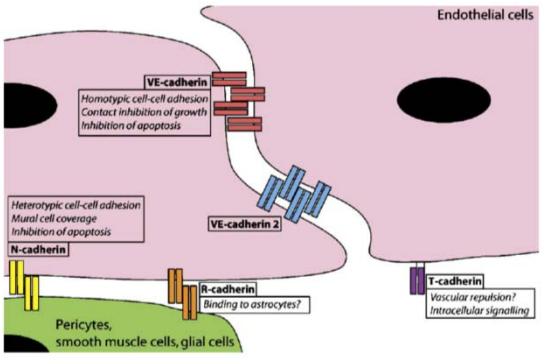
Junctional structures maintain the integrity of the endothelium. Recent studies have shown that, as well as promoting cell–cell adhesion, junctions might transfer intracellular signals that regulate contact-induced inhibition of cell growth, apoptosis, gene expression and new vessel formation. Moreover, modifications of the molecular organization and intracellular signalling of junctional proteins might have complex effects on vascular homeostasis.

Campus IFOM—IEO

Endothelial cadherins and tumor angiogenesis

Cell. Mol. Life Sci. 65 (2008) 3756 – 3788

Ugo Cavallaro[a], Stefan Liebner[d], Elisabetta Dejana[a,b,c,*]



Adherens junctions and more specifically cadherins play an important role in endothelial cell integrity and growth and, in general, in vascular morphogenesis. Besides their adhesive properties, cadherins may act by transferring intracellular signals through interaction with a complex network of cytoskeletal and signaling molecules. Cadherins may signal in different ways: through direct activation of signaling pathways, through interaction with cell-specific growth factor receptors or by controlling beta-catenin and/or other transcription factors' translocation to the nucleus. Endothelial cells present different cadherins which may transfer specific signals and exert distinct functional roles. VE-cadherin is endothelial-specific and the major constituent of adherens junctions. This protein is able to protect endothelial cells from apoptosis and contributes to contact inhibition of endothelial cell growth. N-cadherin is also abundantly expressed in the endothelium and may be important in modulating VE-cadherin expression. T cadherin, R-cadherin and VE-cadherin 2 were found in specific regions of the vascular tree but their role in vascular development or angiogenesis is still unclear.

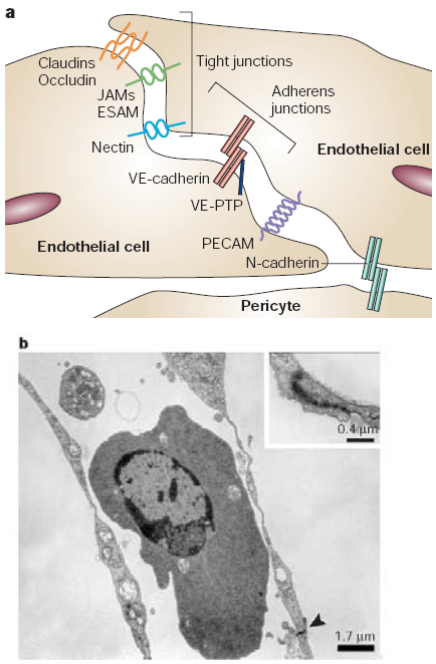
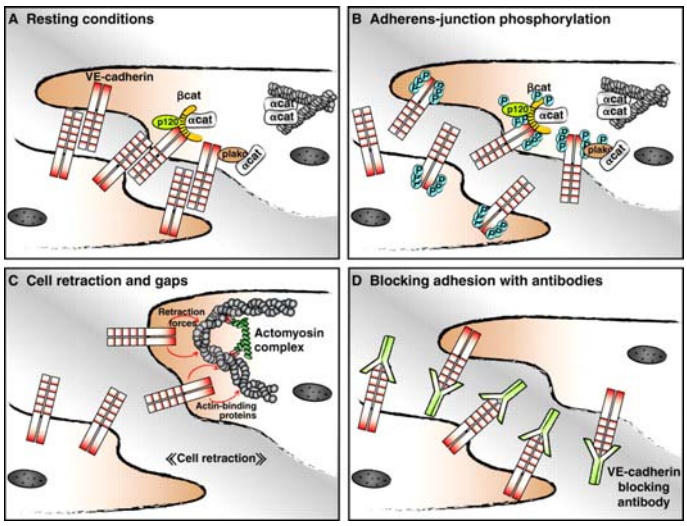


Figure 1 | **The organization of endothelial cell–cell junctions.** a | Transmembrane adhesive proteins at endothelial junctions. At tight junctions, adhesion is mediated by claudins, occludin, members of the junctional adhesion molecule (JAM) family and endothelial cell selective adhesion molecule (ESAM). At adherens junctions, adhesion is mostly promoted by vascular endothelial cadherin (VE-cadherin), which, through its extracellular domain, is associated with vascular endothelial protein tyrosine phosphatase (VE-PTP)[106]. Nectin participates in the organization of both tight junctions and adherens junctions. Outside these junctional structures, platelet endothelial cell adhesion molecule (PECAM) contributes to endothelial cell–cell adhesion. In endothelial cells, neuronal cadherin (N-cadherin) is not concentrated at adherens junctions, but instead probably induces the adhesion of endothelial cells to pericytes and smooth muscle cells. For more detail, see BOX 1. **b** | A transmission-electron-microscopy image of a blood vessel containing a monocyte. The arrow indicates an endothelial junction. The junctional zone frequently appears complex and cells partially overlap (inset). The image in part **b** was provided courtesy of S. Liebner, FIRC Institute of Molecular Oncology, Milan, Italy.

Dejana, 2004

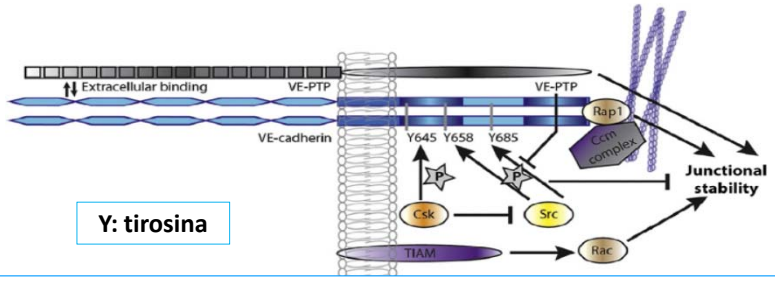
Suggested functional modifications of endothelial AJs under in vitro conditions that increase endothelial permeability.



Elisabetta Dejana et al. J Cell Sci 2008;121:2115-2122

http://d1dvw62tmnyoft.cloudfront.net/content/joces/121/13/2115/F2.large.jpg

Una selezione di interazioni funzionali fra VE-caderina con fosfatasi, chinasi e piccole GTPasi



Y: tirosina

La VE-caderine interagisce con la fosfatasi specifica dell'endotelio VE-PTP mediante l'ectodominio. Questa interazione stabiliza la VE-caderina nelle giunzioni mediante inibisione della fosforilazione della coda citoplasmatica della VE-caderina. E' stato dimostrato che la Src chinasi fosforila Y658 e Y685, il che porta a ridotta stabilità della VE-caderina nella giunzione. La Csk inibisce questa attività di Src mediante fosforilazione di Y645. Le TIAM [T-lymphoma invasion and metastasis gene product; guanine nucleotide exchange factor] associate alle giunzioni aderenti possono aumentare la stabilità della VE-caderina mediante attivazione della piccolo GTPasi Rac. Un'altra piccola GTPasi, Rap1, in associazione con il complesso proteico CCM [cerebral cavernous malformations protein], forma una connessione fra la coda citoplasmatica della VE-caderina con il citoscheletro di actina così promuovendo la stabilità giunzionale della VE-caderina.

Lagendijk AK, Hogan BM. **VE-cadherin in vascular development: a coordinator of cell signaling and tissue morphogenesis**. Curr Top Dev Biol. 2015;112:325-52.

Table 2. Outside-In Signaling, Receptor-Like Function of VE-Cadherin

Factors and Proposed Mechanisms	R
Prosurvival signals (antiapoptotic effects)	
VE-cadherin/β-catenin forms a complex with VEGFR-2 and PI3-kinase that is required for VEGF-triggered phosphorylation of protein kinase Akt and induction of Bcl2, both mediators of the antiapoptotic machinery.	
Sensing of shear forces	
PECAM-1 acts as a sensor for shear and transmits signals via VE-cadherin (acting as an adaptor) and VEGFR-2, which activate PI3-kinase.	
Antiproliferative effects, contact inhibition of cell growth	
VE-cadherin engagement reduces VEGF-triggered tyrosine phosphorylation of VEGFR-2 and expression of VE-cadherin extends the half life of VEGFR-2.	
Lack of VE-cadherin enhances VEGF-triggered VEGFR-2 phosphorylation, accelerates uptake and extends internalization times of VEGFR-2. Silencing of DEP-1 had the same effects.	
Increased cell density triggers binding of C-terminal src kinase (Csk) to phosphorylated tyrosine 685 of VE-cadherin, Csk slows down proliferation and a VE-cadherin-Y685F mutant partially abolishes contact inhibition of cell growth.	

Vestweber, 2008