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Endothelial integrins and their role in maintaining the integrity of the vessel wall

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Integrin receptors

The subendothelial matrix is, in general, a thrombogenic surface that promotes platelet adhesion and the activation of the coagulation system. In normal conditions the presence of the endothelium represents a good protection against thrombotic phenomena and plasma protein infiltration in the vascular media. The capacity of endothelial cells to remain attached to the vascular surface and to migrate and proliferate to cover exposed subendothelial structures is an important defense mechanism against the development of vascular injury.

Endothelial cell interaction with matrix proteins is also of importance in neovascularization. The components of the extracellular matrix can promote cell proliferation and motility and provide an anatomical guide for the formation of new vessels [1].

The extracellular matrix therefore exerts a more complex role than just providing a substrate for cell attachment. Matrix proteins bind to specific receptors on the cell surface and this interaction can transfer intracellular signals.

Many of endothelial receptors for matrix proteins, characterized so far, belong to the family of integrins.

The integrin family consists of a series of heterodimers involved in a variety of cell adhesion functions [2–9]. Almost all cell types express these structures and integrins extend through most of the phylogenetic tree. These receptors have several structural and functional homologies so that it is believed that they differentiated from a common ancestral gene. All integrins are formed by two non-covalently linked subunits: the larger termed α chain and the smaller β chain.

A subclassification of the integrin family has been attempted based on the observation that some members have the same β chain but different α chains [2]. This resulted in the original definition of three subfamilies: the β_1 or VLA (very late antigens) [6], the β_2 or leu-cam (leukocyte adhesion molecules) [10], and the β_3 or cytoadhesins [11].

However, three additional β chains have been recently sequenced: β_4 [12–15], β_5 [16] also called β_x [17, 18] or β_s [19], and β_6 [20]. At least three additional β chains have been described: β_p in lymphocytes [21], the β chain of the melanoma laminin receptor [22], and β_{3b} in macrophages [23].

In addition, it was found that some α subunits have the capability to link to more than one β subunit. For instance, α^v can bind to β_3, β_1 [24–26], β_6, β_5 [17], and β_{3b} [23]; α^4 can bind to β_1 [6] and β_p [21], and α^6 to β_1 [27] and β_4 [12–15], thus making the original subfamily definition insufficient.

Some integrins, but not all of them, recognize a sequence of only three amino acids (arginine, glycine and aspartic acid, RGD) in the ligand [3]. Many proteins containing this sequence, but not all of them, are recognized by an integrin receptor. The list includes a large number of extracellular matrix and plasma proteins such as fibrinogen, vitronectin, fibronectin, thrombospondin, von Willebrand factor, bone sialoprotein [28] but also non-adhesive proteins such as thrombin [29]. Despite the similarities in the cell binding sequence in ligand proteins, the cell can recognize them individually through specific and separate receptors.

Integrin receptors expressed by endothelial cells

Table 1 lists the members of the integrin family identified in endothelial cells. These cells possess five members of the β_1 subfamily.

The $\alpha^1\beta_1$ complex has only been found in the endothelium cultured from the microvasculature but not from large vessels. In contrast, in situ, it was found to be present in endothelial cells from most type of vessels [7].

The $\alpha^2\beta_1$ integrin is apparently identical to the platelet Ia-IIa complex [30]. In endothelial cells it behaves as a receptor for laminin, binding less efficiently fibronectin and collagen [31].

The $\alpha^3\beta_1$ receptor is in general a multifunctional integrin; it binds to fibronectin, collagen and laminin [32].

$\alpha^5\beta_1$ in endothelial cells (as well as in other cell types) [33] preferentially binds fibronectin [34].

The $\alpha^6\beta_1$ integrin is poorly expressed in cultured endothelial cells. This molecule is the laminin receptor in platelets [35] and probably plays an identical role in endothelial cells.

The $\alpha^v\beta_3$ integrin in endothelial cells in addition to vitronectin also recognizes fibrinogen [36–39], von Willebrand factor [37, 40], fibronectin [18, 41], thrombospondin [42], laminin [43] and thrombin [29].

Endothelial cells also express $\alpha^v\beta_5$ [19]. This receptor, in its purified form, recognizes vitronectin and with much lower affinity fibronectin and fibrinogen [17, 18]. It can be heavily phosphorylated when the cells are treated with phorbol esters [19].

Table 1. Integrin receptors in human endothelial cells

Subunit	Ligand/function
$\alpha^1\beta_1$	lm, coll
$\alpha^2\beta_1$	lm, coll, fn, cell-cell
$\alpha^3\beta_1$	fn, lm, coll
$\alpha^5\beta_1$	fn, cell-cell
$\alpha^6\beta_1$	lm
$\alpha^v\beta_3$	vn, fg, vW, tsp, fn, lm, thr
$\alpha^v\beta_5$	vn

Abbreviations are: vn, vitronectin; vWf, von Willebrand factor; fg, fibrinogen; lm, laminin; tsp, thrombospondin; thr, thrombin; coll, collagen; cell-cell, endothelial cell contacts, see the text and Lampugnani et al [76]. For more information see the text and Albeda and Buck [7].

No evidence is as yet available documenting differences in the structure or in the synthetic pathways of endothelial integrins compared with other cells [44]. However, some integrins present cell-specific functional differences. As mentioned above, in endothelial cells $\alpha^2\beta_1$ behaves as a laminin receptor while in other cells it acts as a collagen receptor [30, 31]; $\alpha^v\beta_3$ in endothelial cells binds at least seven different substrata while in osteosarcoma it only attaches to vitronectin [45].

When a comparison has been attempted among cultured endothelial cells from different parts of the vasculature [46] the integrin composition appeared to be essentially similar, with the exception of $\alpha^1\beta_1$ that is expressed by cultured endothelial cells from small but not from large vessels [7, 43].

There are, however, discrepancies comparing the pattern of integrins expressed in cultured cells in respect to in vivo distribution [7]. For instance $\alpha^v\beta_3$ is found abundantly in all types of cultured endothelium [37, 47] but is present in scarce amount in vivo [48, 49, and L. Ruco, personal communication]. Similarly $\alpha^1\beta_1$ is found in large vessel endothelial cells in situ but not in cultured cells [7].

Regulation of integrin function

The same integrin might behave differently in different types of cells. This suggests that the diversity of the integrin system can be further augmented by a cell-specific type of regulation.

Possible mechanisms of such regulation could include mRNA splicing, post-translational modification of the receptor or association of the receptor with modifying components (gangliosides, glycosaminoglycans). Alternative splicing for integrin subunits have been described, but these processes were present equally in all the cell types studied [50]. Ionic concentration and the phospholipid composition of the membrane can dramatically modify integrin receptor affinity and specificity for different substrata [51, 41].

Modulation of integrin synthesis in endothelial cells is still a relatively unexplored area of research. Tarone et al [52] reported that the combination of tumor necrosis factor and γ-interferon induces a 50 to 70% decrease in $\alpha^v\beta_3$ number while no change was found in the β_1 subgroup of integrin molecules. Other stimuli, such as chemical transformation [53] and transforming growth factor β [54], have been reported to change integrin synthesis in other cell types.

During the first hours of endothelial cell attachment to substrata, the basal surface of the cells forms several types of contacts (called focal contacts or adhesion plaques, [36, 55] which are the areas of closest interaction between the substratum, the cell membrane and the membrane insertion sites of actin microfilament bundles [56]. During cell adhesion integrins have been found to be clustered in focal contacts [56, 57].

Integrins do not directly interact with actin microfilaments but do so indirectly through a chain of different proteins [56, 57]. It has been proposed that the protein directly recognizing the integrin β_1 cytoplasmic domain is talin [58]; however, recent evidence suggests that β_1 is linked to actin microfilaments via α-actinin [59]. Among the other cytoskeletal proteins found at focal contacts, vinculin does not directly interact with integrins but binds to talin in quaternary assemblies [57, 60, 61], and this probably acts as an amplification mechanism for further recruitment and organization of the cytoskeletal components.

Not all the integrins expressed in endothelial cells organize into focal contacts. We have been unable to demonstrate any localization of $\alpha^1\beta_1$, $\alpha^2\beta_1$, $\alpha^3\beta_1$, $\alpha^6\beta_1$ or $\alpha^v\beta_5$ in these structures after seeding the cells on a variety of substrata [39, M.G. Lampugnani, unpublished results]. In other cell types [62, 63], however, clustering of these integrins might occur, thus indicating that this phenomenon might be regulated more by cell-specific factors than by integrin structural properties.

The biological role of cytoskeleton organization is still uncertain, but apparently this is not required for endothelial cell adhesion. Agents that increase intracellular cAMP inhibit integrin clustering, focal contact and actin microfilament formation [64]. This is not accompanied by a decrease in the ability of the cells to adhere to substrata. Similarly, deletion of the cytoplasmic domain of β_1 integrin subunit [65, 66], which blocks cell spreading and cytoskeletal organization, does not essentially modify cell adhesion.

Matrix organization is also regulated by integrins and by their interaction with cytoskeletal proteins. There is coallignment of fibronectin fibers, integrin receptors and actin microfilaments. In addition, the fibronectin receptor $\alpha^5\beta_1$, is required to form an appropriate fibronectin matrix [67–70].

Integrins and endothelial cell function

Endothelial cell interactions with matrix proteins via integrin receptors are of importance for a series of endothelial cell functions. This implies that integrin molecules can transfer intracellular signals. This can be achieved by biochemical signalling pathways and/or via cytoskeletal organization.

Little is known about the intracellular biochemical messages induced by integrins. The platelet integrin IIb-IIIa regulates Ca^{2+} and Na^+/H^+ exchanges [71, 72] and tyrosine-specific protein phosphorylation [73]. However, we still do not have any evidence that these pathways are activated after integrin receptor occupancy in endothelial cells or other cell types.

Cell adhesion has been associated with induction of activation genes in monocytes [74]. Different matrix proteins induce the expression of a distinct pattern of genes, suggesting that this phenomenon is regulated by specific receptors.

Binding of $\alpha^5\beta_1$ integrin by specific antibodies induces the expression of genes for lytic enzymes such as collagenase or stromolysin in other cell types [75]. These enzymes can facilitate cell migration by digesting the matrix network.

Besides their role in promoting cell attachment to matrix protein, integrins have been found to be located at cell-cell contacts in endothelial cells [76]. The two integrin receptors,

$\alpha^2\beta_1$ and $\alpha^5\beta_1$, in the confluent endothelium line the boundaries between the cells. Interestingly, α^v but not β_3 follows the same pattern of distribution, suggesting that another β chain is involved. All the other integrins considered $\alpha^6\beta_1$, $\alpha^3\beta_1$ and $\alpha^v\beta_5$ remain diffuse on the cell membrane.

In epithelial cells, two β_1 integrins are located at cell-cell contacts ($\alpha^2\beta_1$ and $\alpha^3\beta_1$) [63, 77–79], while no such distribution was found in smooth muscle cells or skin fibroblasts [76]. This suggests that integrin distribution at cell-cell contacts is a specific feature of polarized cells.

In endothelial cells other molecules have been described to be localized at intercellular contacts: PECAM (or endoCAM or CD 31), a recently sequenced integral protein belonging to the immunoglobulin family [80–82], endoglin [83], the Ca^{2+}-dependent cell adhesion molecule, endocadherin [84], and cadherin-5 [85].

The interrelationship between these molecules and integrins at cell-cell contacts is still unclear.

The observation that addition of antibodies to integrin receptors causes discontinuities in the endothelial cell monolayer at times of incubation too short to cause cell detachment suggests that these molecules play a role in maintaining the integrity of endothelial cell junctions. This is further documented by the fact the integrin antibodies alter endothelial cell permeability properties and induce a significant change in their capacity to restrain macromolecules at the luminal compartment [76].

Conclusions

Integrin receptors exert an important role in promoting endothelial cell attachment to matrix proteins, but also in modulating endothelial cell migration, proliferation and in the maintenance of vascular wall permeability properties.

The list of integrins characterized so far is extremely complex and rapidly expanding. Endothelial cells express only some of them.

An important issue is the differential distribution of integrins in the vascular tree and in cultured cells in comparison to the endothelium in situ. This suggests that integrin expression might be regulated by local, tissue specific factors and by culture conditions.

Finally, it is worthwhile to consider that integrins might regulate a series of specialized endothelial cell functions.

An interesting development in the field is the observation that these receptors are not only involved in the formation of cell-matrix but also in cell-cell bonds. It is not yet clear whether this additional role of integrins implies a new molecular recognition mechanism analogous to the homotypic interaction displayed by cadherins or may simply due to integrin binding to matrix molecules organized in between cells.

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