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Review

Endothelial adherens and tight junctions in vascular homeostasis, inflammation and angiogenesis

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Abstract

Endothelial cells lining the vessel wall are connected by adherens, tight and gap junctions. These junctional complexes are related to those found at epithelial junctions but with notable changes in terms of specific molecules and organization. Endothelial junctional proteins play important roles in tissue integrity but also in vascular permeability, leukocyte extravasation and angiogenesis. In this review, we will focus on specific mechanisms of endothelial tight and adherens junctions.

Keywords: Adherens junction; Tight junction; VE–cadherin; Claudin; Endothelium

Contents

1. Introduction

The endothelium is located at the inner side of all vessel types and is constituted by a monolayer of endothelial cells.

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Interendothelial junctions contain complex junctional structures, namely adherens junctions (AJ), tight junctions (TJ) and gap junctions (GJ), playing pivotal roles in tissue integrity, barrier function and cell–cell communication, respectively. The endothelium constitutes the vascular barrier with regulated permeability properties between the blood and the underlying tissues. Quiescent endothelium may be subjected to stimuli inducing leukocyte extravasation at inflammatory sites and sprouting angiogenesis. Both processes have a strong impact on endothelial cell–cell junctions. In this review, we will focus on endothelial AJ and TJ as well as interendothelial-specific molecules or mechanisms in resting and activated vessels.

1.1. Histology of endothelial junctions

The junctional structures located at the endothelial intercellular cleft are related to those found in epithelia; however, their organization is more variable and in most vascular beds their topology is less restricted than in epithelial cells. AJ, TJ and GJ are often intermingled and form a complex zonular system with variations in depth and thickness of the submembrane plaque associated with the junctional structure [1,2]. As opposed to epithelial cells, GJs are often observed close to the luminal surface. Therefore, the term "apical junction" used to collectively designate epithelial TJ and AJ may not be applied to the endothelium.

Another distinction comes from the difference in cell thickness. With some exceptions, cell body thickness of microvascular endothelium is less than 0.3 μm [2]. Overlapping strands of adjacent endothelial cells form contact domains of 0.5–0.9 μm. However, endothelial cell–cell contacts of some other vessels, including arteries and high endothelial venules, may reach 3–10 μm (Fig. 1) (deduced from [1,2]). Outside of the electron-dense junctional structures, the intercellular cleft is lined by parallel plasma membranes of neighbor cells separated by 10–20 nm.

Finally, endothelial intercellular domains differ from those of epithelial cells by the absence of desmosomes [2]. The intermediate filaments, constituted in the endothelium by vimentin molecules, are poorly linked to cell–cell contacts. However, as opposed to the situation in epithelia, the vimentin filaments may be linked to endothelial AJ in junctional structures similar to desmosomes, called complexus adherens [3–8]. These structures originally described in lymphatic endothelium may have a broader distribution in the vascular tree.

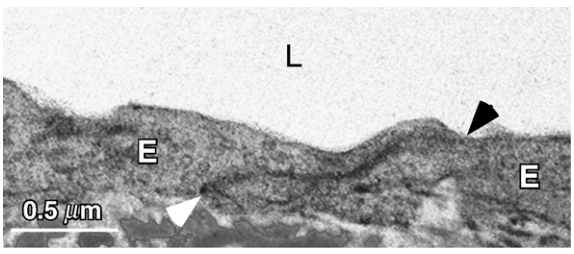

Fig. 1. Electron micrograph showing an endothelial junction in mouse aorta. The intercellular cleft (between arrowheads) is lined by two endothelial (E) strands and extands from basal lamina to lumen (L).

It must be stressed that interendothelial junctions are dynamic structures, subjected to multiple regulations. Furthermore, leukocytes extravasate at inflammatory sites (mostly in post-capillary venules) either through transcellular or paracellular routes. Extravasation through the intercellular junction is a rapid and regulated process, during which the leukocyte is squeezed in the cleft (diapedesis), followed by rapid junction reformation.

1.2. Adhesive proteins located at endothelial cell–cell contacts

A number of proteins exhibiting homophilic adhesive activities are located at interendothelial contacts (Fig. 2). Some of them are specific to endothelial cells (e.g., VE–cadherin [9,10], claudin-5 [11]) while others are common with epithelial cells (e.g., occludin [12], junctional adhesion molecule (JAM)-A [13], nectins [14,15], claudins (see references below) and connexins [16]), blood cells (e.g., PECAM/CD31 [17], endothelial cell-selective adhesion molecule (ESAM) [18,19], JAM-A, -C, CD99 (reviewed in [20])), smooth muscle cells (S-endo-1/CD146 [21]) or mesangial/trophoblast cells (protocadherin (Pcdh)12/VE–cadherin-2 [22]). These proteins may be part of organized junctional structures, such as VE–cadherin in AJ, claudins and occludin in TJ, or connexins in GJ, while others are independent, such as PECAM, CD99, S-endo-1 or Pcdh12. The JAMs are associated with TJ through intracellular components without being directly involved in TJ strand formation.

Interendothelial adhesive proteins are implicated at different levels in endothelial cell–cell interaction and tissue integrity. Some of them have a dual function as they also participate in leukocyte extravasation via homophilic (PECAM, CD99, JAM-A, -C) or heterophilic (JAM-A, -B, -C) interactions (reviewed in [20]).

2. The endothelial adherens junction

2.1. The VE–cadherin-based complex and its physiological role

VE–cadherin is the transmembrane component of endothelial AJ [23]. It is a type II cadherin harboring high adhesive activity [24]. Several biochemical evidences showed that VE–cadherin extracellular domains form hexamers in solution [25,26]. Electron microscopy data support this view and allowed to propose a model in which VE–cadherin dimers interact in trans through their extracellular domain 1 and VE–cadherin trimers interact in cis via their extracellular domain 4 (Fig. 3) [27].

VE–cadherin intracellular domain is similar to other classical cadherins. It contains a proximal binding site for p120 and p0071, and a distal binding site for β-catenin and plakoglobin (Fig. 4, left). Both β-catenin and plakoglobin are linked to α-catenin, which may further interact with α-actinin and vinculin (see [28] and references therein). The identity of the molecular link for the actin filament anchorage to the cadherin–catenin complex is still a question of debate [29]. As previously indicated, the VE–cadherin complex may associate with the vimentin cytoskeleton in some vascular locations [3–8]. This association is mediated by either plakoglobin or p0071, both interacting with desmoplakin, which in turn associates with