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Endothelial cell-cell adhesion and signaling

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ABSTRACT

Endothelial cells line blood vessels and provide a dynamic interface between the blood and tissues. They remodel to allow leukocytes, fluid and small molecules to enter tissues during inflammation and infections. Here we compare the signaling networks that contribute to endothelial permeability and leukocyte transendothelial migration, focusing particularly on signals mediated by small GTPases that regulate cell adhesion and the actin cytoskeleton. Rho and Rap GTPase signaling is important for both processes, but they differ in that signals are activated locally under leukocytes, whereas endothelial permeability is a wider event that affects the whole cell. Some molecules play a unique role in one of the two processes, and could therefore be targeted to selectively alter either endothelial permeability or leukocyte transendothelial migration.

1. Introduction

Endothelial cells (ECs) form a semi-permeable barrier to separate the blood stream from the underlying organs and tissues and control the transport of fluids, solutes and cells across blood vessel walls. The barrier is mediated by endothelial cell-cell adhesions including tight junctions (TJ), adherens junctions (AJ) and a variety of other adhesion molecules including PECAM-1 and nectins, which are connected to the actin cytoskeleton via different adaptor molecules (Fig. 1). The architecture and the composition of cell-cell junctions varies between vascular beds depending on the organ-specific requirements [1,2]. In addition to maintaining adhesion between ECs, cell-cell junctions control vascular permeability and leukocyte migration via a complex balance between multiple signaling molecules (Figs. 1 and 2) [3,4].

TJs regulate the diffusion of ions and polar solutes and block penetration of large macromolecules across ECs. TJs are formed by the homophilic cell-cell adhesion molecules occludin, claudins and junctional adhesion molecules (JAMs) (Fig. 1) [5,6]. Claudins are the principal barrier-forming proteins, in particular claudin-5 is critical for endothelial permeability in vivo and in vitro [7]. Occludin and claudins are linked to zonula occludens (ZO)-1, ZO-2, ZO-3, cingulin and other protein complexes, which mediate the interaction between the adhesion molecules and actin filaments [5]. The JAM family is composed of three closely related proteins JAM-A, -B and -C, and by the coxsackie and adenovirus receptor (CAR). The JAMs mediate endothelial cell-cell interaction and regulate leukocyte transendothelial migration (TEM) [8]. Both JAMs and CAR regulate permeability by supporting TJ function and assembly [9].

VE-cadherin is the key transmembrane component of endothelial AJs and is expressed only in ECs [10]. VE-cadherin together with PECAM-1 initiates and maintains endothelial cell-cell contact, holding the ECs together to give mechanical support to the endothelium and provide endothelial junction stability [11,12]. AJs can regulate expression of TJ components and TJ organization follows AJ formation [11,13]. In addition, AJs and TJs are interconnected [14], for example ZO proteins crosstalk with AJs [15]. VE-cadherin is linked indirectly via its cytoplasmic tail to actin filaments by a complex of proteins including α- and β-catenins, plakoglobin (γ-catenin), p120-catenin, vinculin and α-actinin (Fig. 1) [16], which are vital for junctional stability and also for the dynamic opening and closing of junctions [17].

Here we discuss the roles of endothelial cell-cell junctions in signaling leading to changes to endothelial permeability and during leukocyte transendothelial migration (TEM), with a particular focus on small GTPases.

2. Regulation of small GTPases

Several members of the Ras superfamily of small GTPases contribute to endothelial cell-cell adhesion and hence regulate endothelial permeability and/or leukocyte TEM. These include Rap1, Rap2 and several Rho family GTPases (Figs. 2 and 3). Most small GTPases cycle between an inactive GDP-bound conformation and an active GTP-bound conformation. This cycling is regulated by guanine nucleotide exchange factors (GEFs), which catalyse the exchange of GDP for GTP, thereby activating the proteins, and by GTPase-activating proteins (GAPs), which stimulate GTP hydrolysis and inactivate the proteins. The interaction between small GTPases and their downstream effectors often requires their localisation to membranes, which is mediated by

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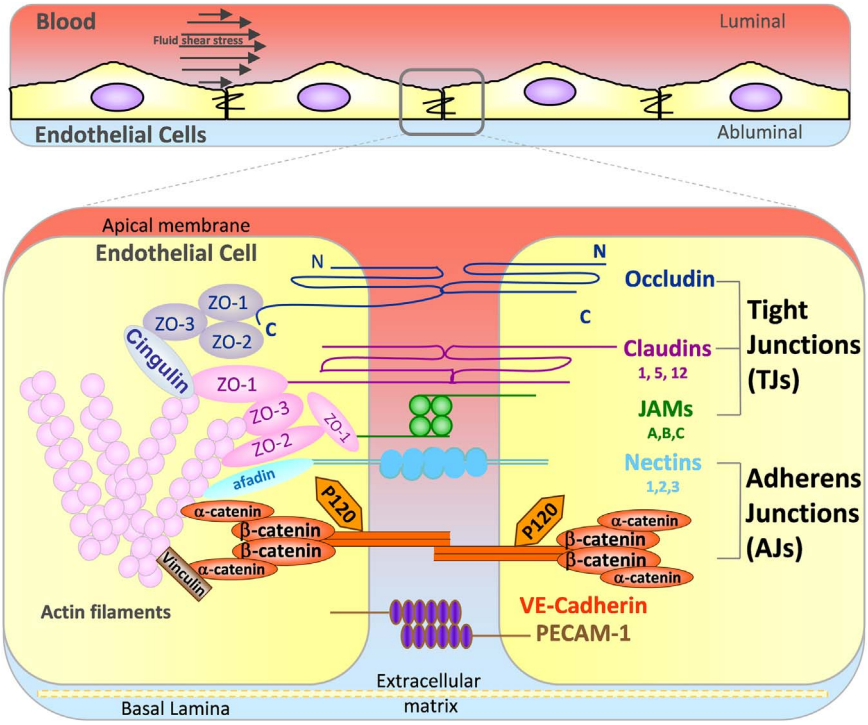

Fig. 1. The main transmembrane proteins in endothelial cell-cell junctions. Endothelial cells line the blood stream and are constantly exposed to fluid shear stress (top panel). The bottom panel shows the main transmembrane proteins in endothelial cell-cell junctions (right). They are associated with tight junctions or adherens junctions as indicated, with the exception of PECAM-1, which is not associated with either type of junction. Three different claudin, JAM and nectin genes are reported to be expressed in endothelial cells (numbers/letters indicated under protein name). Intracellular proteins link transmembrane proteins to the actin cytoskeleton. There are additional junctional molecules, such as CD99 and ESAM, which are omitted for clarity.

post-translational modification by lipids (prenylation and/or palmitoylation) [18,19]. For example, geranylgeranylation of Rho GTPases is required for thrombin-induced permeability in ECs [20]. Some small GTPases are inhibited by binding to proteins that extract them from membranes, including guanine nucleotide dissociation inhibitors (GDIs) and 14-3-3 proteins [21,22]. Small GTPases are rapidly activated by cell-surface receptors, and a single GTPase can interact with multiple downstream targets to induce a range of cellular responses in a spatio-temporal fashion, depending on the stimulus and cell type [19].

3. Signaling to endothelial junctions in vascular permeability

Endothelial cell-cell junctions remodel dynamically in response to multiple extracellular stimuli, which transiently increase or decrease endothelial permeability and thereby regulate the entry of polar solutes and macromolecules into the tissues from the blood stream (Fig. 2) [4]. For example, pro-inflammatory stimuli such as thrombin, histamine and TNFα increase permeability, whereas anti-inflammatory mediators including sphingosine 1-phosphate (S1P) and angiopoietin-1 decrease permeability [23]. Increased vascular barrier leakage is associated with

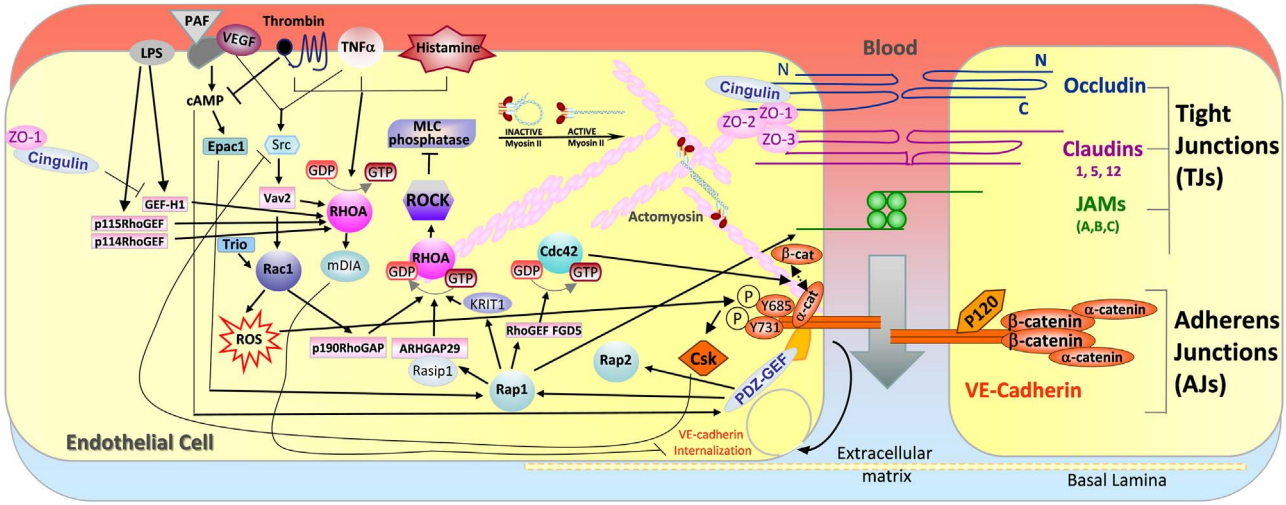

Fig. 2. Signaling molecules that regulate vascular permeability. The main junctional proteins that regulate vascular permeability are shown on the right cell. The left cell shows examples of receptors that increase vascular permeability, and the intracellular signaling molecules that contribute to this response, focusing on those regulated by Rho and Rap GTPases. ROS, reactive oxygen species.