

Review Article:

ROLE OF VE-CADHERIN IN VASCULAR PERMEABILITY REGULATION

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ABSTRAK

Permeabilitas endotel sebagian diatur oleh sel-sel adheren junctions (AJs) yang membuka dan menutup dengan dinamis. Pada sel endotel, AJs sebagian besar terdiri dari kaderin endotel vaskular (VE-kaderin), anggota keluarga kaderin yaitu suatu protein adhesi yang spesifik hanya ada di sel endotel, melalui domain sitoplasmanya berikatan dengan protein-protein yang lain, termasuk p120, catenin- β -dan plakoglobin. Dengan berbagai cara jalur endogen meningkatkan permeabilitas vaskuler dengan mempengaruhi fungsi dan organisasi VE-kaderin dan protein lain di AJs. Kami akan membahas beberapa faktor yang dapat meningkatkan permeabilitas vaskuler tersebut, termasuk faktor pertumbuhan endotel vaskular (VEGF), induksi fosforilasi tirosin dari VE-kaderin, yang menyertai peningkatan permeabilitas vaskuler dan diapedesis leukosit, di samping itu, internalisasi dan perpecahan VE-kaderin dapat menyebabkan AJS menjadi dibongkar. kemungkinan penggunaan inhibitor dari SRC dan kinase lainnya, dari agen yang meningkatkan kadar cAMP, dan inhibitor enzim litik sebagai alat farmakologis untuk mengurangi permeabilitas endotel.

ABSTRACT

Endothelial permeability is regulated partly by cells adheren junctions (AJs), which opens and closes with the dynamic. In endothelial cells, AJs largely composed of vascular endothelial cadherin (VE-cadherin), cadherin family member that is a specific adhesion protein only in endothelial cells, through the cytoplasm domain binds to other proteins, including p120, catenin- β - and plakoglobin. In many ways the endogenous pathway increases vascular permeability by affecting the function and organization of VE-cadherin and other proteins at AJs. We will discuss some of the factors that can increase vascular permeability, including vascular endothelial growth factor (VEGF), induced tyrosine phosphorylation of VE-cadherin, which accompanies an increase in vascular permeability and leukocyte diapedesis, in addition, the internalization of VE-cadherin and splits can cause AJS being dismantled. Possible use of inhibitors of the SRC and other kinases, of agents that increase cAMP levels, and lytic enzyme inhibitors as pharmacological tools are to reduce endothelial permeability.

Keywords: permeability, VE-cadherin, adherens junctions, endothelial cells

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INTRODUCTION

Severe sepsis and septic shock is a major health problem in adults and children (Wolfler, Silvani et al. 2008). Subcutaneous edema and fluid retention in the body cavity in patients with sepsis showed impaired endothelial function due to increased vascular permeability. Impaired microvascular endothelial function can lead to widespread shock, microvascular thrombosis, and organ malfunction, a state that is often the cause of death in patients with severe sepsis (Lee and Slutsky 2010).

Vascular permeability partly regulated by cells Adherens Junctions (AJs) that open and close dynamically. The main components of AJs is Vascular Endothelial-cadherin (VE-cadherin), the proteins are then paired with another protein, p120, β -Catenin and plakoglobin in the cytoplasmic domain, then β -Catenin

and plakoglobin bind to β -Catenin which then interacts with several proteins, among others β -actinin, ajuba, zonula occludens-1 (ZO-1) and others, finally binds actin. Cadherin complexes formed by VE-cadherin and catenin influence the collection and is influenced by actin cytoskeleton. Retraction of endothelial cells will lead to a intercellular gap, an initial process of increased vascular permeability in some conditions, intercellular gap occurs in the absence of structural change of the endothelial cells, for example in the VE-cadherin internalization or phosphorylation of proteins AJs. Yet many theories about the mechanism of the interaction at the molecular level, therefore the chance to prove it is still open (Dejana, Orsenigo et al. 2008). According to London et al, prevent VE-cadherin internalization would improve vascular leakage and can be used as a therapeutic strategy, and decrease mortality in sepsis persists despite the spread of inflammation (London, Zhu et al.).

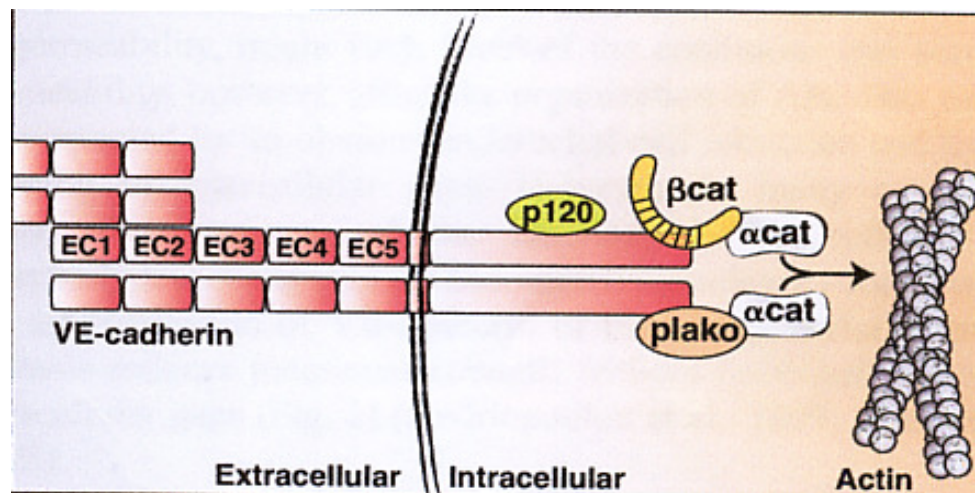


Figure 1. Molecules on endothelial AJs.

The discussion in this paper may clarify the mechanism of increased vascular permeability in several ways such as phosphorylation, cleavage and internalization of VE-cadherin. In addition, it provides an opportunity to develop a basic concept of the role of VE-cadherin to the increased vascular permeability in sepsis that can be used to inhibit vascular leakage or repair so as to prevent multi-organ failure, and reduce morbidity and mortality.

VE-cadherin

VE-cadherin identified and developed as one of the 8 new cadherin (cadherin-4 up to cadherin-11) using RT-PCR approach. The only endothelial cadherin is cadherin-5, hereinafter known as VE-cadherin. The role of cadherin as a cell adhesive molecules, is explained by the presence of extracellular cadherin domains (EC-domain) and adhesive media through interaction homofilik dependent Ca^{2+} . Most have 5 extracellular cadherin domains. Cadherin can be divided in different subfamily, 2 of them are cadherin cadherin type 1 and type 2. VE-cadherin is part of the cadherin type 2 (Vestweber 2008).

The process of leukocyte diapedesis is actively controlled by the vascular wall through adhesive cells on the path paracellular. The mechanism is largely governed by the AJs. VE-cadherin is a major component of AJs that maintain the integrity of the endothelial cell-cell adhesion and controlling vascular permeability (Vestweber, Winderlich et al. 2009). Several pathways that affect vascular permeability and VE-cadherin involved will be described below, among

others, phosphorylation, cleavage, and internalization of VE-cadherin.

Tyrosine Phosphorylation

Tyrosine phosphorylation in VE-cadherin, p120, β -Catenin and plakoglobin weakens the bond between the endothelial cells and reduced endothelial function of defense. Several studies have been conducted to support the relationship between the opening of AJs and tyrosine phosphorylation. Most of the data obtained on the relationship comes from studies using cultured cells. In vivo studies in mice showed that VE-cadherin phosphorylation can in the angiogenic and ischemic conditions (Weis, Shintani et al., 2004; Lambeng, Wallez et al. 2005). So that has not yet known whether the phosphorylation process may occur in the blood vessels in normal conditions, or only occur in pathological conditions only. Mediators trigger increased endothelial permeability such as histamine, tumor necrosis factor- α (TNF- α), Platelet-activating factor (PAF), and VEGF are reported to cause tyrosine phosphorylation in VE-cadherin, p120, β -Catenin and plakoglobin (Mehta and Malik, 2006). Leukocyte adhesion to endothelial cells through intercellular adhesion molecule 1 (ICAM 1) causes tyrosine phosphorylation of VE-cadherin on which is the earliest occurrence of leukocyte diapedesis (Allingham, van Buul et al., 2007; Turowski, Martinelli et al. 2008).

Internalization of VE-cadherin

Another mechanism that regulates vascular permeability is a process of internalization of VE-cadherin. The occurrence of this process is dependent on clathrin

(Xiao, Garner et al. 2005). Interestingly, p120 binding to VE-cadherin prevents internalization, proposed a concept that p120 acts as a signal for the plasma-membrane-retention. The new findings, VEGF interfere with the function of endothelial defense with SRC activation, with the goal of phosphorylase VAV2, a factor guanine-nucleotide-exchange (GEF) for the GTPase Rac (Gavard and Gutkind 2006). Activation (GTP-bound) Rac causes VE-cadherin phosphorylation at Ser665, not on tyrosine residues, which will be a critical requirement for vascular permeability enhancement (Figure 1)

Divisions VE-cadherin

Damage enzyme readily in VE-cadherin, suggesting there may be other pathways that lead to increased vascular permeability and leukocyte diapedesis. Exposure to metalloproteases (Luplertlop, Misse et al. 2006), elastase, cathepsin G or less trypsin concentrations causing extracellular domain of VE-cadherin in cultured cells undigested (Xiao, Allison et al. 2003). Leukocytes and tumor cells can release these enzymes in large amounts, which can lead to solving VE-cadherin and thus can increase cell extravasation and vascular leakage.

Other molecules that affect VE-cadherin adhesion

Several inflammatory mediators increase vascular permeability by affecting the stability of the adhesiveness between endothelial cells and / or other molecules that affect endothelial cell retraction. Tangle of molecules intracellular complex involved in this mechanism, such as cyclic adenosine mono-phosphate (cAMP), Ca²⁺, phosphoinositol lipids, reactive oxygen and some GTPases (Cdc42, RhoA, Rac and Rap-1) and factor-factor exchange his the guanine-nucleotide-exchange factor-H1 (GEF-H1) and exchange protein activated by cAMP (Epac) (Mehta and Malik, 2006).

cAMP proven in vivo and in vitro improve vascular endothelial function as separators and reduce edema induced Inflammation in multiple tissues. Relations and good cooperation is going on between Rap-1 and VE-cadherin. Rap-1 increase VE-cadherin adhesion. EPAC1 will reduce permeability only in endothelial cells that contain a lot of VE-cadherin, indicating that for their activities, Rap-1 requires VE-cadherin. In contrast, VE-cadherin is required for the repair that an amplifier RAP1 MAGI1 to activate PDZ-GEF1.

The combination of VE-cadherin by VEGF receptor 2 (VEGFR2) induced decrease phospholipase C γ (PLC γ) and MAP kinase activation by VEGF, so that the process of phosphorylase and VE-cadherin

internalization is inhibited. This process requires DEP1 phosphatase that causes VE-cadherin inhibits the contact of VEGF.

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