Perspective

Changes of junctions of endothelial cells in coronary sclerosis: A review

Li-Zi Zhang*, Sun Lei

Dalian Municipal Women and Children Medical Center, Pathological Department, Dalian Medical University, Dalian, Liaoning 116000, China

Abstract

Atherosclerosis, the major cause of cardiovascular diseases, has been a leading contributor to morbidity and mortality in the United States and it has been on the rise globally. Endothelial cell—cell junctions are critical for vascular integrity and maintenance of vascular function. Endothelial cell junctions dysfunction is the onset step of future coronary events and coronary artery disease.

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Atherosclerosis, the major cause of cardiovascular diseases, has been a leading contributor to morbidity and mortality in the United States[1] and it has been on the rise globally. Endothelial cell—cell junctions are critical for vascular integrity and maintenance of vascular function. Endothelial cell junction dysfunction is the onset step of future coronary events and coronary artery disease. After a brief review of the pathophysiology of coronary atherosclerosis, we will discuss the changes of junctions between endothelial cells during coronary sclerosis.

Junctions of coronary artery endothelial cell (ECs)

Vascular endothelial cells are a continuous flat monolayer cells which constitute a dynamic and highly effective cellular barrier between the vessel wall and bloodstream. It regulates fluid and solute balance in addition to movement of molecular/cellular components between the bloodstream and tissues[2] and presents a nonthrombogenic surface for blood flow. As such, the regulation of the endothelial barrier integrity (or permeability) is a central pathophysiologic mechanism of many vascular processes, including wound healing, angiogenesis, and vascular diseases.[3] The endothelial barrier function is predominantly maintained by the interendothelial junction structures

including tight junctions, adherence junctions, and gap junctions[4] which is regulated by a complex signaling network.

The formation of coronary sclerosis

Atherosclerosis, the major cause of cardiovascular diseases, has been a leading contributor to morbidity and mortality in the United States and it has been on the rise globally.

Endothelial dysfunction is a predictor of future coronary artery disease (CAD).[5] The changes of endothelium in atherosclerosis include ECs proliferation, atrophy and degeneration. The damaged structure of degenerative EC junctions leads to bareness of subendothelial proliferative fibrous tissue. The barrier functions of vascular endothelium are reduced or lost, leading to extracellular edema and lipid in the blood easily penetrating into the vascular wall. When the functions of vascular enthothelium are damaged and subendothelial collagen tissue is exposed, platelets adhere and aggregate and inflammatory cells and monocytes infiltrate, and then a thrombus is formed.

Changes of tight junction

The tight junction (TJ) is localized at cell−cell contact sites between ECs. It serves as a paracellular barrier to restrict the movement of ions and proteins across tissue boundaries.[6] Dysfunction of the TJ occurs in response to a variety of inflammatory stimuli and also during ischemia, leading to tissue edema and damage. The proteins that form tight junctions include occludin, claudin family members, junctional adhesion molecules 1 to 3, cingulin 7H6, spectrin, and linker proteins, such as the zonula occludens family members (ZO-1/2/3).[7]

Occludin

Occludin, which has four transmembrane domains, forms a rate-limiting transport structure within the intercellular cleft.[8] Occludin contains two extracellular loops forming a junctional seal. The carboxy tail of occludin is linked to the actin cytoskeleton via ZO-1, ZO-2 and ZO-3. ZO-1 plays a central role in the organization and assembly of the transmembrane proteins. ZO-1 protein levels, in contrast to occludin levels, are most likely not regulated by oxidized lipids, vascular endothelial growth fact (VEGF), or shear stress; however, they may be affected by oxidants.[9] The most prominent changes induced by oxidative

stress were decreased tyrosine phosphorylation of occludin and increased serine/threonine phosphorylation of ZO-1.

Claudin

Claudins play an essential role in the control of paracellular ions flux and in the maintenance of cell polarity.[10] Claudin has four transmembrane domains but no sequence similarity to occludin. It has not yet been defined as to how these novel proteins interact with occludin or other TJ components. The claudin-5 protein was initially considered to be a TJ component of the claudin protein family.[11]

Junctional adhesion molecules

Junctional adhesion molecules (JAMs), currently are composed of JAM-A, -B, -C,[12] JAM-4, ESAM (EC-selective adhesion molecule), and CAR (coxsackie virus and adenovirus receptor) that localize at cell−cell contacts and are specifically enriched at tight junctions with some being directly implicated in leukocyte transendothelial cell migration.[13]

JAM-A

JAM-1, also known as JAM-A, is a transmembrane protein which is found on endothelial and epithelial cells at cell−cell contacts in particular within tight junctions. JAM-A binds in a homotypic manner to regulate tight junction integrity and permeability.[14] JAM-A may regulate the basic fibroblast growth factor (bFGF) and extracellular signal−regulated kinases (ERK) signaling pathways involved in EC migration, leading to wound repair. JAM-1 has a PDZ domain−binding motif, through which it binds other PDZ domain−containing tight junction proteins, such as zona occludens protein 1 (ZO-1), partitioning defective-3 homologue (PAR-3), and Afadin 6 (AF-6).[15]

JAM-B

In contrast, JAM-B, also referred to as vascular endothelial-junctional adhesion molecule (VE-JAM) is prominently expressed at intercellular boundaries of the endothelium, particularly in venules. JAM-B is also involved in adhesive processes of lymphocytes.[16]

JAM-C

JAM-C provides a novel molecular target for antagonizing interactions between vascular cells that promote inflammatory vascular pathologies such as in

atherothrombosis. In contrast to healthy vessels, atherosclerotic arteries display increasing expression of JAM-C in EC layers and intimal smooth muscle cells (SMCs), and Oxidized LDL (oxLDL) induces the redistribution of JAM-C from inter endothelial contacts supporting leukocyte recruitment.

Endothelial Cell−selective adhesion molecule (ESAM)

ESAM localizes to EC tight junctions and is involved in leukocyte adhesion and transmigration across the endothelium into areas of atherosclerotic plaque formation and progression. Increased levels of soluble ESAM (sESAM) are independently associated with measures of both coronary calcium and atherosclerosis, based on the putative role of sESAM in mediating endothelial damage attributable to chronic inflammation.

Adherence junction

Adherens junctions (AJs) are important subcellular structures responsible for endothelial cell−cell attachment, and they represent multiprotein complexes that consist of cadherin, γ-catenin, and p120 catenin (p120ctn). Cadherins have two major forms, vascular endothelial cadherin (VE−cadherin) or cadherin-5, and N-cadherin. VE-cadherin, a major regulator of endothelial adherens junctions, regulates the integrity of EC monolayers, EC growth, vascular development and angiogenesis. Elevated levels of soluble VE-cadherin are associated with coronary atherosclerosis. Under inflammatory conditions, VE-cadherin junctions disassemble, which facilitates paracellular passage. A previous report showed that reduced expression of the adherens junction marker VE-cadherin in plaque microvessels coincided with open junctions.[17]

Tobacco smoke (TS)

TS augments cytokine effects on endothelial permeability and VE-cadherin/β-catenin complexes.[18] The TS potentiation of cytokines operates through suppression of phosphatase and tensin homolog (PTEN) activity, leading to Phospho-Tyrosine Mouse mAb (p-Tyr) and dissociation of VE-cadherin/β-catenin complexes in endothelium.

Laminar shear stress

Under laminar shear stress conditions, VE−cadherin expression was significantly increased and associated with enhanced human coronary artery endothelial motility and wound closure with a physiologic arterial level of flow compared with static conditions. This enhancement in motility may in part result from stimulation of VE−cadherin signaling pathways involving catenin intermediaries such as γ-catenin and p120ctn.

Rap1

Rap1, a member of the Ras family small G proteins, plays a key role in EC functions, including migration and the formation of intercellular junctions. Activation of the Rap1 GTPase in ECs accelerated *de novo* assembly of endothelial cell−cell junctions and increased the barrier function of endothelial monolayers. In contrast, depressing Rap1 activity by expressing Rap1 GAP led to disassembly of these junctions and increased their permeability.[19]

ADMA10

ADAM10-mediated VE-cadherin cleavage contributes to the dissolution of adherens junctions during EC activation and apoptosis. Endothelial activation by lipopolysaccharide, tumor necrosis factors α (TNF-α), or anti-graft antibodies induces an upregulation of ADAM10 at the EC surface.[20] ADAM10 overexpression is functionally associated with an increase in endothelial permeability. ADAM10 activity also contributes to the thrombin-induced decrease of endothelial cell−cell adhesion.[21]

Gap junction

Gap junction (GJ) channels, composed of six connexins to form a hemichannel in the cell membrane, allow the direct intercellular communication between intracellular and extracellular spaces.[22] The proteins connexin (Cx)37, Cx40, and Cx43 are expressed in the endothelium coexisting within a given plaque. *In vivo* abundant Cx43 expression has been associated with disturbed flow conditions at atherosclerotic lesions of vessel constrictions and bifurcations, where no Cx37, and, in some cases, no Cx40 are found. Recent studies have suggested that Cx43 was upregulated in the early stage of atherosclerosis or neointimal formation after vascular injury.[23]

Aging

Aging seems to induce a general decrease in connexin expression, with Cx40, being relatively undisturbed for a long time.[24]

Hypertension

Hypertension is a cause of ECs dysfunction and a major risk factor of atherosclerosis. In mice, Cx40 and Cx37 are strongly expressed in the EC, and ablation of Cx40 produces marked hypertension. Deletion of Cx37 does not alter blood pressure. The polymorphism of Cx37 in humans has been associated with myocardial infarction, coronary artery disease, and atherosclerosis.[25]

Diabetes mellitus

The correlation between coronary heart disease and both type 1 and type 2 diabetes mellitus has been recognized by analysis of epidemiological data. Coronary ECs of diabetic mice show lowered protein levels of Cx37 and Cx40, but not Cx43, and a reduction of GJ communication.[26]

Tissue hypoxia

Tissue hypoxia and the subsequent reoxygenation by coronary intervention induced by reperfusion increases the production of superoxides that have different biological effects. Hypoxia/reoxygenation of ECs inhibits GJ communication. Moreover, abrupt reoxygenation of Ecs reduces protein kinase A activity and reduces electrical coupling.

TNF-α

TNF induces a progressive disruption of endothelial cell junctions and an increase in endothelial permeability and elongation. ECs are very sensitive to TNF-α, which activates ECs by promoting expression of adhesion molecules. Treatment of ECs with TNF-α decreases the expression of Cx37 and Cx40 but does not change Cx43 expression.[27]

The current morbidity and mortality and increasing age of the population with coronary heart disease require the development of new diagnostic and therapeutic strategies to treat early subclinical disease stages. In this review, we have summarized an emerging role of endothelial cells junctions in coronary atherosclerosis. A brief analysis of endothelial cells junction regulation could lead to an understanding of normal physiology as well as pathology and to the identification of novel therapeutic targets. Future challenges now include the development of specific endothelium-targeting drugs for therapeutic applications.

References

1. AHA. *Heart Disease and Stroke Statistics − 2008 Update*. 2008.
2. Balda MS, Matter K. Tight junctions. *J Cell Sci*. 1998;111:541−547.
3. Van Nieuw-Armerongen GP, Van Hinsbergh VW. Targets for pharmacological intervention of endothelial hyperpermeability and barrier function. *Vasc Pharmacol*. 2002;39:257−272.
4. Bazzoni G, Dejana E. Endothelial cell-to-cell junctions: molecular organization and role in vascular homeostasis. *Physiol Rev*. 2004;84:869−901.
5. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. *Arterioscler Thromb Vasc Biol*. 2003;23:168−175.
6. Staddon JM, Rubin LL. Cell junctions and the blood-brain barrier. *Curr Opin Neurobiol*. 1996;6:622−627.
7. Hirase T, Staddon JM, Saitou M. Occludin as a possible determinant of tight junction permeability in endothelial cells. *J Cell Sci*. 1997;110:1603−1613.
8. Kevil CG, Okayama N, Trocha SD. Expression of zonula occludens and adherens junctional proteins in human venous and arterial endothelial cells: role of occludin in endothelial solute barriers. *Microcirculation*. 1998;5:197−210.
9. DeMaio Lucas, Rouhanizadeh Mahsa, Reddy Srinivasa, Sevanian Alex, Hwang Juliana, Hsiai Tzung K. Oxidized phospholipids mediate occludin expression and phosphorylation in vascular endothelial cells. *Am J Physiol Heart Circ Physiol*. 2006;290:H674−H683.
10. Krause G, Winkler L, Mueller SL. Structure and function of claudins. *Biochim Biophys Acta*. 2008;1778:631−645.
11. Morita K, Sasaki H, Furuse M. Endothelial claudin: claudin-5/TMVCF constitutes tight junction strands in endothelial cells. *J Cell Biol*. 1999;147:185−194.
12. Keiper T, Al-Fakhri N, Chavakis E. The role of junctional adhesion molecule-C (JAM-C) in oxidized LDL-mediated leukocyte recruitment. *FASEB J*. 2005;19:2078−2080.
13. Aurrand-Lions M, Duncan L, Ballestrem C, Imhof BA. JAM-2, a novel immunoglobulin superfamily molecule, expressed by endothelial and lymphatic cells. *J Biol Chem*. 2001;276:2733−2741.
14. Bazzoni G, Martinez-Estrada OM, Mueller F. Homophilic interaction of junctional adhesion molecule. *J Biol Chem*. 2000;275:30970−30976.
15. Ebnet K, Schulz CU, Meyer Zu Brickwedde MK. Junctional adhesion molecule (JAM) interacts with the PDZ domain containing proteins AF-6 and ZO-1. *J Biol Chem*. 2000;275:27979−27988.
16. Cunningham SA, Arrate MP, Rodriguez JM, et al. A novel protein with homology to the junctional adhesion molecule. *J Biol Chem*. 2000 Nov 3;275(44):34750−34756.
17. Bobryshev YV, Cherian SM, Inder SJ. Neovascular expression of VE-cadherin in human atherosclerotic arteries and its relation to intimal inflammation. *Cardiovasc Res*. 1999;43:1003−1017.
18. Mullick AE, McDonald JM, Melkonian G. Reactive carbonyls from tobacco smoke increase arterial endothelial layer injury. *Am J Physiol Heart Circ Physiol*. 2002;283:H591−H597.
19. Wittchen Erika S, Worthylake Rebecca A, Kelly Patrick. Rap1 GTPase inhibits leukocyte transmigration by promoting endothelial barrier function. *Biol Chem*. 2005;280:11675−11682.
20. Boulday G, Coupel S, Coulon F. Antigraft antibody-mediated expression of metalloproteinases on endothelial cells. Differential expression of TIMP-1 and ADAM-10 depends on antibody specificity and isotype. *Circ Res*. 2001;88:430−437.

21. Navaratna D, McGuire PG, Menicucci G, Das A. Proteolytic degradation of VE-cadherin alters the blood-retinal barrier in diabetes. *Diabetes*. 2007;56:2380−2387.

22. Burnier Laurent, Fontana Pierre, Angelillo-Scherrer Anne, Kwak Brenda R. Intercellular communication in atherosclerosis. *Physiology*. 2009;24:36−44.

23. Chadjichristos CE, Derouette JP, Kwak BR. Connexins in atherosclerosis. *Adv Cardiol*. 2006;42:255−267.

24. Yeh HI, Chang HM, Lu WW. Age-related alteration of gap junction distribution and connexin expression in rat aortic endothelium. *J Histochem Cytochem*. 2000;48:1377−1389.

25. Isakson BE, Damon DN, Day KH. Connexin 40 and connexin 43 in mouse aortic endothelium: evidence for coordinated regulation. *Am J Physiol Heart Circ Physiol*. 2006;290:H1199−H1205.

26. Makino A, Platoshyn O, Suarez J. Downregulation of connexin 40 is associated with coronary endothelial cell dysfunction in streptozotocin-induced diabetic mice. *Am J Physiol Cell Physiol*. 2008;295:C221−C230.

27. van Rijen HV, van Kempen MJ, Postma S. Tumour necrosis factor alpha alters the expression of connexin 43, connexin 40, and connexin 37 in human umbilical vein endothelial cells. *Cytokine*. 1998;10:258−264.

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