Atherosclerosis 248 (2016) 97–109

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review article

Vascular endothelium – Gatekeeper of vessel health

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ARTICLE INFO

Article history:
Received 21 August 2015
Received in revised form
3 March 2016
Accepted 4 March 2016
Available online 9 March 2016

Keywords:
Endothelium
Endothelial dysfunction
Atherosclerosis
Cardiovascular disease
Vessel remodeling
Clinical therapies
Review

ABSTRACT

The vascular endothelium is an interface between the blood stream and the vessel wall. Changes in this single cell layer of the artery wall are believed of primary importance in the pathogenesis of vascular disease/atherosclerosis. The endothelium responds to humoral, neural and especially hemodynamic stimuli and regulates platelet function, inflammatory responses, vascular smooth muscle cell growth and migration, in addition to modulating vascular tone by synthesizing and releasing vasoactive substances. Compromised endothelial function contributes to the pathogenesis of cardiovascular disease; endothelial 'dysfunction' is associated with risk factors, correlates with disease progression, and predicts cardiovascular events. Therapies for atherosclerosis have been developed, therefore, that are directed towards improving endothelial function.

1. Atherosclerosis

Atherosclerosis is a chronic inflammatory disease in which the artery wall thickens as a result of the accumulation of cholesterol, macrophages and smooth muscle cells (SMC), ultimately restricting blood flow through the artery. It is the main pathologic condition underlying coronary artery and cerebrovascular disease leading to heart attack and stroke, respectively. In the pathogenesis of atherosclerosis (reviewed in Ref. [1–4]), increases in plasma low density lipoprotein (LDL) leads to a proportional increase in the entry of cholesterol laden LDL particles into the arterial wall across a 'compromised/dysfunctional' endothelial monolayer, where it accumulates. Once there, it can become oxidized, by free radical production from adjacent endothelium, smooth muscle cells or isolated macrophages [5–8]. Oxidized LDL has numerous effects on a variety of cells, many of which are believed to cumulatively exacerbate atherothrombosis ([9] for review). These include promotion of monocyte adhesion and infiltration to the intima by causing production of monocyte chemotactic protein-1 (MCP-1) by endothelium and expression by endothelium of monocyte-binding proteins including intercellular adhesion molecule-1 (ICAM-1), foam cell formation following uptake of oxidized LDL via scavenger receptors (SR-A type I and II and CD36), and stimulation of the migration of medial SMC into the intima where they proliferate in response to growth factors such as platelet derived growth factor (PDGF) [13]. In the intima, SMC produce extracellular matrix molecules including collagen and elastin. The most common clinical complication of atherosclerosis occurs upon plaque rupture that allows blood components to come into contact with plaque lipids and tissue factor, resulting in thrombus formation. While several cell types are clearly involved in the pathogenesis of atherosclerotic plaques, endothelial compromise/dysfunction is deemed of particular importance as it is a necessary and initiating occurrence for atherogenesis to proceed. The endothelial lining can be viewed as the first line of defense between risk factors and vascular disease.

2. Arterial endothelium: structure, function

The vascular endothelium lines the entire circulatory system. In coronary arteries, this single layer, together with some extracellular matrix, comprises the tunica intima. Originally thought of simply as a passive barrier, it is now viewed as an organ whose normal functioning is crucial to maintaining vascular health, and whose dysfunction is key in the initiation, progression and clinical complications of vascular disease. Vascular endothelium acts as a selectively permeable barrier between extravascular and

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http://dx.doi.org/10.1016/j.atherosclerosis.2016.03.007
0021-9150/

intravascular compartments and provides a nonthrombogenic lining for the cardiovascular system. It is poised in an anatomic location that allows interaction not only with circulating blood components and cells, but also with cells in the vessel wall. Endothelial cells are long, flat cells orientated in the long axis of the vessel. An average endothelial cell is 20–40 μM long, 10–15 μM wide and only 0.1–0.5 μM thick. Electron microscopy of arterial endothelium reveals it to be of the continuous type characterized by tight junctions at the lateral borders of each cell that restrict the movement of macromolecules, and a complex micro-vesicular system implicated in macromolecular transport. Despite its apparent morphological simplicity and relative homogeneity, there is evidence of regional and species variation manifested by differences in permeability, responsiveness and biosynthesis.

3. Barrier function

The role of the endothelium as a semipermeable barrier is one of its most basic functions. It regulates transport of macromolecules between the vascular lumen and vascular smooth muscle. There are several different mechanisms by which macromolecules cross the endothelial barrier; through the endothelial cells themselves, by diffusing laterally within the endothelial cell membrane and thus around the cell, through endothelial cell-to cell junctions, through endothelial gaps, or via vesicular transport. As most biologic molecules are large, hydrophilic, anionic molecules, which are unable to diffuse into and through bilayer membranes, most are thought to move through intercellular junctions between cells or by vesicular transport, or the formation of transient channels resulting from vesicle fusion [10]. Reorganization of the inter-cellular junctions, involving actin and myosin or direct dissolution of junctional contacts, is believed to be the primary mechanism by which endothelial permeability to water, small and large solutes is increased [11].

4. Changes in permeability

Various physiologic and pathophysiologic stimuli can induce, acutely and chronically, dramatic changes in endothelial permeability. For example thrombin, histamine and other acute inflammatory mediators can act on endothelium to stimulate opening of their intercellular junctions at the level of adherens and tight junctional complexes [12]. The signaling involved in mediating these responses include protein kinase C (PKC)–induced phosphorylation of linking proteins at the cell-cell and cell-matrix junctions, leading to actin reorganization, cell rounding and increased paracellular transport. Myosin light chain kinase (MLCK) may also be activated by inflammatory mediators leading to actin-myosin based retraction of endothelial cells [12]. Vascular endothelial growth factors (VEGFs) are key regulators of vascular permeability via nitric oxide synthase (NOS) regulation [13,14], facilitated by multiple mechanisms including gap formation and vesiculo-vacuolar organelle formation [15] (reviewed in Ref. [16]). The bacterial endotoxin lipopolysaccharide (LPS) causes endothelial hyperpermeability by stimulating the small GTPase, RhoA, and its effector Rho Kinase (ROCK) [17]. Endothelial permeability is also influenced by fluid shear stress, the tangential frictional force exerted by flowing blood [10,18]. Investigation of the relationship between albumin permeability and shear stress magnitude *in vivo* revealed that endothelium exposed to low wall shear stresses was more likely to have elevated macromolecule permeability [19]. Of importance with respect to vascular disease, low density lipoprotein (LDL) accumulation is greater at these more permeable areas exposed to low wall shear stress [20,21]. It is now recognized that atherosclerotic lesions preferentially develop at vessel segments exposed to low, disturbed or oscillating flow, while laminar flow and high shear stress are seemingly atheroprotective [22]. In addition to inhibition of thrombosis and inhibition of endothelial apoptosis, limitation of permeability is now a well-characterized atheroprotective mechanism of laminar flow and high shear stress [22]. Conversely, at regions of pathological low shear stress, increased endothelial permeability results in enhanced infiltration of LDL and its local accumulation, which is a critical initial event in the development of atherosclerosis [23,24]. Rozenberg et al., recently reported that Histamine, acting via its H1 receptor drives the formation of atherosclerotic lesions through an increased vascular permeability for LDL [25]. Mullick et al., showed that exposure to cigarette smoke injures the endothelium, resulting in increased arterial permeability and increased LDL accumulation [26]. A recent study provided evidence of a role for lipoxygenase and its metabolite hydroxyeicosatetraenoic acid (HETE) in 'high fat diet'-induced endothelial tight junction disruption [27], thus providing a possible mechanistic link between lifestyle and atherosclerosis. Therefore, a wide variety of injurious stimuli (e.g., certain hemodynamic forces, inflammatory mediators, bacterial endotoxin LPS, environmental toxins, high fat diet) can contribute to endothelial dysfunction by increasing endothelial permeability and subsequently arterial lipid accumulation in the subendothelial space, thereby initiating atherosclerotic plaque development. On the other hand, factors shown to maintain endothelial barrier function include high density lipoprotein (HDL), and physical exercise (reviewed in [28]). With respect to the latter, there is considerable evidence of a direct relationship between exercise and vascular health. The effect of exercise on maintaining endothelial barrier function is likely a consequence of exercise increasing blood flow and shear stress, which in turn releases 'vasoprotective' molecules such as nitric oxide (NO) and prostacyclin (PGI_2). It is also appreciated that Sphingosine-1-phosphate (S1P), a bioactive sphingolipid associated with HDL and found mainly in the blood and lymph, robustly promotes endothelial barrier function [29,30]. In particular, growing evidence indicates that HDL-associated S1P mediates the beneficial effects on endothelial integrity [31,32]. Other endogenous factors known to increase endothelial barrier function and decrease permeability are angiopoietin-1 [33], and the second messenger cyclic adenosine monophosphate (cAMP) and agonists such as Serotonin and β-adrenergic agonists that increase it [34,35] (Table 1).

5. Endothelial glycocalyx

Consisting of a negatively charged, organized mesh of membranous glycoproteins, proteoglycans and associated plasma proteins, the endothelial glycocalyx (100–750 nm thick) is recognized as contributing, together with the endothelium, to the protection of the vascular wall against disease (for review [36,37]). Improved fixing and imaging techniques have allowed *in vivo* visualization of the endothelial glycocalyx and provided evidence that there are significant reductions in its extent during acute and chronic inflammatory challenge in man. Indeed, destruction of the glycocalyx has been directly and indirectly evidenced in several studies, e.g. after ischemic challenge [38–40], during redox stress [39], and after inflammation [40,41]. Deterioration or destruction of the glycocalyx is associated with pathophysiological sequelae including increased endothelial permeability, platelet aggregation and loss of vascular responsiveness [42]. There are interesting data supporting an important role for the glycocalyx in the initiation and progression of atherosclerosis. Van den Berg et al., reported thinning of the glycocalyx in mice fed a cholesterol rich diet, and demonstrated less glycocalyx in regions of the vessel at high atherogenic risk (i.e., at branch points, areas of curvature) [43]. Moreover, the authors