

Endothelium: A Long Road from Mystery to Discovery

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Modern medicine boasts large volumes of information on the cardiovascular system, collected over thousands of years. In the fourth century B.C., the greatest Greek classic biologist, Aristotle, identified the cardiovascular system as the primary organ system to appear during vertebrate organogenesis. He made the important observation that the vascular architecture in the embryo functions as the 'frame' or a 'model' which gave shape to the body structure of the growing organism (*De Generatione Animalium*). Nearly a thousand years later, in 1628, William Harvey published his famous "Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus", commonly referred to as "de Motu Cordis". Shortly after, M. Malpighi, in 1661, described capillaries, which separate blood and tissues. That vessels are not merely tunnels, but canals lined by cells, was observed by Reckinghausen, in the 1800s. In 1865, the Swiss anatomist, Wilhelm His, introduced the term "endothelium" in a programmatic essay titled "Die Häute und Höhlen des Körpers (The membranes and cavities of the body)" [1].

However, the detailed study of the endothelium essentially began only in the '50s of the last century. Howard Florey [2], together with George Palade and Guido Majno, provided the essential morphological foundations for subsequent investigations on the endothelium. Recent discoveries have established the endothelium to be a very large and highly active endocrine organ. The endothelium has come a long way from being commonly perceived as an inert "cellophane" lining, to the current appreciation of it being a cellular orchestra maestro [3]! In the last decades, the recognition of the multiple functions of the endothelium has shown it to be a true blood flow regulator playing a vital role in tissue homeostasis.

The endothelium functions as a receptor-effector organ and responds to the different physical or chemical stimuli by secreting the correct substance by which it may maintain the vasomotor balance and vascular-tissue homeostasis [4]. Endothelial cells (ECs) produce vasodilators and vasoconstrictors, procoagulants and anticoagulants, inflammatory and anti-inflammatory, fibrinolytics and antifibrinolytics, oxidizing and antioxidizing, and many others [5,6]. When the ECs lose their ability to maintain this complex balance, it results in endothelial dysfunction (ED). Therefore, the ECs are seen to play a critical role in many physiological processes, including the control of vasomotor tone, transport of blood cells between the blood and underlying tissue,

and maintenance of blood fluidity, permeability, angiogenesis, and both innate and adaptive immunity. Furthermore, these ECs secrete angiocrine factors, which orchestrate several different pathways, including those of embryonic organogenesis, hematopoiesis, metastasis, and lung and liver regeneration. Thus, endothelial cell signaling is currently believed to promote fundamental cues for cell fate specification, embryo patterning, organ differentiation, and postnatal tissue remodeling [7]. The ECs and the megakaryocyte are the only cells that synthesize von Willebrand factor, strengthening the concept of a functional endothelial cell-megakaryocyte axis. The orchestration of platelet and endothelial secretion and the release of intracellular constituents significantly influence vascular bed behavior [3].

The ECs show remarkable heterogeneity in structure and function, time and space, as well as health and disease [8]. Endothelial cell heterogeneity has been described at the level of cell morphology, function, gene expression, and antigen composition [9,10]. Endothelial cell phenotypes vary between different organs, different segments of the vascular loop within the same organ, and between neighboring endothelial cells of the same organ and blood vessel type. The spatial and temporal differences in the structure and function of ECs ultimately reflect differences in the messenger RNA and protein expression. The apparently endless repertoire of structural and functional phenotypes determines the ability of the endothelium to satisfy the needs of the underlying tissues.

The importance of the endothelium was first recognized by its effect on vascular tone. Maintaining vascular tone directly affects the balance of the tissue oxygen supply and metabolic demand by regulation of vessel tone and diameter; it is also involved in the remodeling of the vascular structure and long-term organ perfusion [11]. Among the vasoregulators, the most potent, is termed the endothelium-derived relaxing factor (EDRF), discovered by Furchgott and Zawadzki [12] and identified as nitric oxide (NO) in 1987 [13,14].

NO is generated from L-arginine by the action of endothelial NO synthase (eNOS) in the presence of cofactors such as tetrahydrobiopterin [15]. In normal physiology, shear stress is a key activator of eNOS [16]. The enzyme may also be activated by the signaling molecules such as bradykinin, adenosine, vascular endothelial growth factor (in response to hypoxia), and serotonin (released during platelet aggregation) [17]. Therefore, NO plays

a key role in normal vascular physiology to maintain the vascular wall in a quiescent state by inhibiting inflammation cellular proliferation, and thrombosis. ED is primarily characterized by the impaired regulation of vascular tone caused by a lack of NO bioavailability. No one single mechanism can explain ED: rather, a complex interplay of multiple regulatory pathways leads to this condition. An imbalance between the endothelial-derived relaxation and contraction factors, as well as defects in their downstream signaling cascades could contribute to the development of ED [18]. This could be a result of reduced eNOS activity, lack of cofactors for nitric oxide synthesis, attenuated nitric oxide release, or increased nitric oxide degradation, depletion of tetrahydrobiopterin, increase of endogenous nitric oxide synthesis inhibitors, an imbalance in the ubiquitin-proteasome system modulating the endothelial (dys)function by interaction with several essential regulatory pathways, and several other mechanisms [18-21]. The known risk factors such as hypercholesterolemia, hypertension, cigarette smoke, and diabetes, as well as other inflammatory conditions may induce chronic dysregulation of NO and the production of the reactive oxygen species [22]. All of these environmentally driven mechanisms of endothelial activation are likely to be modulated by genetic factors. ED should therefore more appropriately be considered as the endothelial activation that represents a switch from a quiescent phenotype to one that involves the host's defense response [23,24].

ED may be detected functionally as changes in the vasomotor responses, cell proliferation, platelet adhesion/aggregation, vascular permeability, or leucocyte/endothelial interactions. Circulating markers of endothelial function/integrity include the metabolites of NO, plasma levels of endothelin 1, markers of inflammation (intercellular adhesion molecules, selectins, cytokines), or markers of fibrinolysis (tissue plasminogen activator and plasminogen activator inhibitor), apoptotic microparticles of endothelial origin, circulating endothelial progenitors, circulating endothelial cells, etc. Usually, experimental and clinical studies evaluate ED as alterations in the endothelium-dependent relaxations.

The measurement of flow-mediated dilation represents a simple method of examining vasodilator function [25]. Flow-mediated dilation induced by reactive hyperemia has been known to be endothelium dependent; however, this technique has an advantage as it mimics a fundamental physiological process of NO production, which is the activation of eNOS in response to changes in shear stress. Thijssen et al. [26] has presented one of the latest comprehensive methodological and physiological guidelines for the assessment of flow-mediated dilation in humans. As outlined in this paper, flow-mediated dilation reflects the endothelium-dependent and largely nitric oxide-mediated arterial function and has been used as a surrogate marker of vascular health.

There is no doubt that the structural and functional integrity of the endothelium is crucial to the maintenance of vascular homeostasis. The endothelium is increasingly becoming a surrogate end-point of the therapeutic approach to cardiovascular risk, inflammation and tumor diseases.

The pharmacological approach in improving/reversal of ED was shown to be beneficial in clinical trials which have investigated the actions of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, statins and other lipid

lowering agents, calcium channel blockers, some β -receptor blockers (nebivolol), thiazolidinediones, erythropoietin, L-arginine, antioxidants, vitamins, tetrahydrobiopterin, or stimulators of endothelial progenitor cells [19,20,27]. The search and the creation of new drugs that can restore endothelial function, open up new prospects for the treatment of innumerable diseases.

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