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Cell-Cell Communication Breakdown and Endothelial Dysfunction

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I. Introduction

Winding and twisting over 100,000 miles, a vascular network composed of over one trillion stitched together endothelial cells (EC) represents the functionally largest organ system within the human body. Operating as a dynamic semi-selective barrier, endothelial-lined vessels are geared for different roles with smooth muscle bound arteries delivering pulsatile oxygen rich blood, capillaries serving as distribution sites for nutrients and oxygen before up taking waste, and the venous system, managed by a series of valves, facilitating vascular return of oxygen poor blood. Within this maze, endothelial cells are geared for organ specific functions and *cell-cell communication* with continuous endothelial boundaries found in skeletal muscle, heart, lung and brain tissue, fenestrations between endothelial cells in endocrine glands, the gastrointestinal mucosal and renal glomeruli, and discontinuous endothelium in the liver and spleen[1]. As such, this diverse and heterogeneous organ system serves as a delivery system and first line of defense in disease processes.

Orchestrated from migrating primitive embryonic splanchnic mesoderm[2], angioblast derived blood islands guided by growth factor gradients such as vascular endothelial growth factor (VEGF) and placental growth factor (PGF), merge together forming vasculogenic lumens while sprouting angioblast activated by VEGF, guides sensitive tip-cells to extend from endothelial stalk cells to form angiogenic extensions[3]. Coalesce of these branching networks, pruned by remodeling, are directed by distinctive environmental cues creating a tissue-specific vascular bed designed to meet the diverse needs of each organ. A fundamental requirement for endothelium in normal organ development and maturation[4–6] suggests that distinct environmental cues within the developing tissues guide endothelial cell

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function. Indeed, recent studies using unbiased transcriptional profiling through single cell analysis of EC from different organs identified distinct organ-specific endothelial genetic profiles that not only define EC heterogeneity, but also suggests that epigenetic footprints control basal expression of EC specific genes[7–11]. Guided by metabolic needs of the tissue[12], endothelial cells are the vascular building blocks essential for embryogenesis, organ development, and tissue regeneration. Disruption in the foundation of the endothelial network contributes to the evolution of pathologic disease processes such as hypo-perfusion, sepsis, vasculopathies associated with diabetes and atherosclerosis and myocardial infarction.

II. Characteristics of the normal endothelium

Tissue homeostasis of the human body requires an adequate flow of blood for not only immune cell surveillance and nutrients but also oxygen delivery. To meet the demands, an elaborate vasculature lined by endothelium develop through the following nuanced processes: (1) *vasculogenesis*; (2) *angiogenesis*; (3) *arteriogenesis*; (4) and the lesser-known *lymphoangiogenesis*. Beginning from vasculogenesis, the angioblast-derived blood islands are specified through precisely timed and spatially coordinated networks of signaling pathways not only between themselves but also among other types of cells, which is collectively referred to as *cell-cell communication*.

The first two of the four processes are typically described in normal physiology while altered mechanisms can occur in pathology due to *endothelial dysfunction*. *Vasculogenesis* is a two-step sequential process of blood vasculature that grow anew from the primitive embryonic splanchnic mesoderm: first, fate determination of the endothelium and differentiation of endothelial progenitor cells that range from hemangioblast to the differentiated endothelial cell; second, the organization that occurs into primitive angioblast-derived blood islands[13,14]. Fate determination is largely genetically determined by transcription factors (e.g., ETS transcription factor variant 2, ETV2; ER71) that it responds to factors secreted from neighboring endoderm such as fibroblast growth factors (e.g. FGF2) and bone morphogenic proteins (e.g. BMP4). As fate is assigned, VEGF signaling regulates endothelial organization into blood islands and tubular formation, a process that has been documented to be both genetically pre-patterned and self-organizing[15]. *Angiogenesis* is the remodeling and emerging of vessels from the existing vasculature, which can be further sub-divided into two types: sprouting and non-sprouting[16,17]. Sprouting refers to the migration, proliferation, and three-dimensional organization of endothelial cells into tubes while non-sprouting is the division and re-modeling of existing vessels by transluminal invagination. Following tubular formation and cardiovascular development, the resulting blood flow creates vectors of physical force that can activate other forms of vascular growth[18,19].

The latter two of the four processes, arteriogenesis and lymphoangiogenesis, are frequently described as compensatory in context of pathology that limit oxygen delivery including, but not limited to, tissue damage and ischemia. As an adaptive response to ischemia, *arteriogenesis*, also known as collateral artery growth, is the proliferation and formation of collateral arteries from pre-existing arterial connections[16]. *Lymphoangioigenesis* is the growth of lymphatic vessels from existing ones[20].

With such a vast network of vessels that cover the human body, the endothelium is influenced by location-specific physiological mechanisms, referred to as endothelial cell (EC) heterogeneity. The location thereby dictates their genetic and phenotypic characteristics along with cell-cell communication. Originally discovered by electron microscopy, EC heterogeneity was defined by structural characteristics like the presence of plasmalemmal vesicles which are now called caveolae[21]. Since then, experimental techniques (e.g. confocal microscopy), have defined the classical markers of the endothelial lineage as follows: hemangioblast ($CD133^+/VEGFR2^+$); neonatal angioblast ($CD34^+/VEGFR2^+/VE\text{-}Cadherin^-$); adult endothelial progenitor cell ($CD34/VEGFR2^+VE\text{-}Cadherin^+$); matured endothelium ($CD34^+/CD31^+/VEGFR2^+/VE\text{-}Cadherin^+$). Technological advances in RNA sequencing at the single cellular level have made it possible to further describe endothelial populations based on antigen composition along with the respective gene expression. Studies utilizing single-cell RNA sequencing further support EC heterogeneity as being organ-specific[8,11,22]. For example, the endothelium in the heart and lung express higher levels of von Willebrand Factor (vWF) than do the kidney and liver[11]. More specifically within the heart, vWF expression is higher in arterioles than capillaries or venules while it is a mosaic pattern within the aorta of the adult heart[22]. These studies support endothelial cell heterogeneity and an organ-specific identity.

The endothelium is not an inert tube-like delivery system functioning in isolation, but rather a metabolically active regulator of adequate blood flow. In constant communication with circulating factors the endothelium can respond dynamically to its (micro) environment, further highlighting the importance of EC location and heterogeneity. Exposed to such a wide range of signals, the collective heterogeneous endothelium selectively process and respond (signal) while minimizing spontaneous activity (noise) thus modulating cell-cell communication with other cells such as pericytes or leukocyte[23]. Emerging evidence supports a dynamic metabolic shift within the endothelium during vessel formation – an important distinction from the dogma that genetic signaling cascades determined these processes. With relatively low mitochondrial counts[24], tip cells of sprouting endothelium *in vitro* rely on changes to glycolytic flux while stalk cells relies on changes to fatty acid oxidation. Therefore, emerging evidence supports the importance of ensuring the availability of essential metabolic components to maintain endothelial cell well-being and vessel stability.

III. Functions of the Endothelium

Governed by mechanical and humoral forces, endothelial cells function as the gatekeeper of fluid, circulating cells and solutes. Functionally, physiologic solutes and fluid transporting is reliant on two mechanisms, the paracellular process based on cell-cell junctions and transcellular vesicle-based pathways[25,26]. Acting as the dominant avenue, paracellular transport is mediated by the cooperation between two junction types, tight junctions and adherens junctions. Tight junctions (TJ), also known as zonulae occludens, are composed of a series of proteins including claudins, occludins, JAMs (junctional adhesion molecules) and ESAM (endothelial cell-selective adhesion molecule) and are responsible for the structural actin cytoskeletal foundation of the EC cell. Varying in amount and organization based on vascular region, a higher concentration of TJs are required for the blood brain barrier, large

arteries and vessels with continuous networks while fewer TJ present are found where EC facilitate transport such as capillaries and venules. Although the TJ are known to be preferential sites for basal transport, they are also susceptible to plasma protein and leukocyte extravasation.

Working in conjunction with TJ, adherens junctions (AJ) are protein complexes linked together by a cytoplasmic actin cytoskeleton that connects the cytoskeleton of one EC to the adjacent EC through an endothelial specific adhesion protein called vascular endothelial (VE) cadherin. Stabilization of the Ca^{2+} dependent extracellular domain of VE cadherin through its binding to the catenin family proteins, results in its maintenance at the juxtamembrane domain providing membrane competence and preventing its destabilizing internalization. Together, TJ and AJ provide EC stability by regulating junctional tension through carefully organized crosstalk between these two interdependent and mechanisms. However, when disruption of this organized cell-cell interface through either disconnection of the junction complexes or through clustering of the junctional complexes forming focal junctional connections occurs, it can create voids between the cells that contribute to vessel permeability.

Transcellular transport is dependent on vesicle-based mechanisms where macromolecules and fluid navigate across the EC through endocytosis, fusion and vesiculo-vacuolar transport. For example, endocytosis of proteins such as albumin via its receptor clusters requires direct interaction with caveolin-1, resulting in caveolae-mediated albumin transport while fusion of albumin-containing vesicles to the basal membrane utilizes SNARE proteins. Vesiculo-vacuolar organelles, predominately found in the capillary venules of tumors, form a transendothelial highway from plasma extravasation through interconnecting vesicles and vacuoles that span the luminal to abluminal surface. An alternative mechanism of transport is the paracellular transportation at the cell-cell junctions called transcellular diapedesis. This method allows for the extravasation of leukocytes and tumor cells at sites of endothelial cell adhesion molecules including intracellular adhesion molecule-1 (ICAM-1) and platelet-endothelial cell adhesion molecule-1 (PECAM-1), CD99, or junctional adhesion molecule (JAM)-A. These finely regulated mechanisms are vital in the maintenance of vascular integrity and when inflammation or injury occurs, yield to movement of vessel contents into surrounding tissue.

Vascular injury to the endothelial cell barrier triggers a cascading chain reaction through a combination of inflammatory and wound healing processes in an attempt to regain hemostasis that in part is regulated by the disrupted endothelium[27]. Within intact vessels quiescent EC hold transmembrane tissue factor (TF), a major initiator of hemostatic clot formation, inactive. Following EC disturbance, the extrinsic coagulation cascade is initiated through TF activation of factor (F) VII significantly augmenting the proteolytic activity of FVIIa that contributes to conversion of FX to FXa. FXa promotes transformation of prothrombin to thrombin whose function as a protease activates fibrinogen to the protein polymer fibrin. Once initiated, an amplification of the process ensues with circulating platelet aggregation while the propagation phase results in the production of large amounts of insoluble fibrin that when crosslinked forms an organized clot or thrombus, sealing the site of injury[27–30]. While vital in the repair process, TF also contributes to pathogenic

processes such as atherosclerotic plaques and thromboembolisms. Once a wound is repaired, EC regulate vessel recanalization through release of pro-fibrinolytic molecules such as tissue plasminogen activator (t-PA) and urokinase-type plasminogen activator (uPA) and platelet cleaving metalloproteases resulting in clot degradation.

Beyond barrier and integrity, the endothelium is positioned as a pivotal regulator of vascular contractile forces. Through the release of vasodilator substances, EC modulate the state of adjacent smooth muscle by way of endothelium-derived relaxing factor (EDRF) also known as nitric oxide (NO). Regulated by circulating neurohumoral mediators such as histamine, acetylcholine, bradykinin, thrombin and growth factors, endothelial L-arginine is enzymatically converted by nitric oxide synthase to produce NO. Counteracting the relaxing effects of NO, "physiologic stimuli such as physical forces, circulating hormones (catecholamines, melanocortin, vasopressin) platelet derived substances (serotonin, adenosine diphosphate), and autacoids (histamine, bradykinin, prostacyclin, prostaglandin E_4) share with acetylcholine[31]" the ability to mediate endothelial release of vasoconstrictor substances called endothelium-derived contracting factors resulting in perivascular smooth muscle cell contraction. While NO release can be chronically upregulated through exercise, dietary factors and estrogen, similarly it can be downregulated in response to oxidative stress, vascular diseases such as diabetes and hypertension, and aging. As a result of endothelial-dependent dysregulation of vascular contractile forces, it contributes to progression of disease processes associated with aged individuals and patients with hypertension and diabetes[31].

IV. Endothelial development and cell-cell communication

The clinical importance of signaling networks that coordinate the heterogenous endothelium regulation of cardiovascular activity, and its dependence on endothelial cell-cell communication is enormous. With such a key role as an effector, the endothelium must detect and process the numerous local and circulating cues presented from an average of six neighboring cells[32]. Exposed to such a wide range of signals, the collective of EC heterogeneity selectively process and respond (signal) while minimizing spontaneous activity (noise). Thereby modulating input with a coordinated signaling output with other neighboring cells is fundamental to maintain vessel homeostasis.

The endothelium heterogeneity of a vascular bed acquires specialization by adapting to environment-specific variance in shear stress and cues. Early experimental approaches, particularly in isolation such as organ baths or vessel isolation studies, had supported the notion that the endothelium was relatively homogenous in its function. In order for specialization to occur, it dictates that there is an expression of specific receptors that sense transdifferential cues. For example, postcapillary venules highly express surface protein markers for classical leukocyte adhesion such as E-cadherin, P-selectin, VCAM1, whereas it does not express the endothelial protein C receptor that is found on large vessels.

Extracellular cues are sensed through their respective receptors, which are then transmitted as broadly defined to be either functional or proliferative-migratory signals. The breadth of signals for cell-cell communication is extensive yet growing. In addition to classical growth

factors such as VEGF and PDGF isoforms, lipids such as sphingosine-1-phosphate (S1P) or ceramide-1-phosphate (C1P) metabolites secreted such as succinate and exosomes have been found to dictate signaling in the endothelium[32–39].

The cell-cell communication that exists between endothelium and neighboring cells are transmitted through the following ways: endocrine, neurotransmitter, paracrine, and autocrine. Historically, Bayliss and Starling who showed a substance secreted into the bloodstream from the jejunum evoked a response in the pancreas first illustrated endocrine signaling in 1902. Neurotransmitter signaling was then described where an extracellular cue was directly exerted by the nervous system onto effector tissue. Methods to initiate transmission of local signaling occur through paracrine signaling to neighboring cells or self-activating autocrine signaling. Many cues such as the ligands VEGF, PDGF, S1P, C1P are distributed in a concentration gradient that are recognized by their respective receptors and signal through multiple transmission methods in a context-dependent manner. For example, gradients of autocrine VEGF isoforms are essential for vascular homeostasis while paracrine VEGF isoforms guide tip formation[40–42].

Ligands bind to receptors that are generally classified into the following 3 types: G protein-coupled, ion channel-linked, or enzyme-linked. G protein-coupled receptors (GPCRs) are named for the heterotrimeric guanosine triphosphate (GTP)-binding proteins that mediate their cellular actions; they contain seven membrane-spanning alpha helices and a cytosolic C-terminal tail that is involved in receptor de-sensitization. Ligands binding to ion channel-linked receptors cause an open conformation to a channel that allows specific ions to pass through. Finally, enzyme-linked receptors bound to their respective ligand activate an intracellular enzyme, typically a kinase including, but not limited to, receptor tyrosine kinase (RTK) and receptor guanylyl cyclases. The time-dependent consequences of the ligand-receptor binding can be grouped as follows: (1) short-term, functional; (2) long-term, proliferative signaling. The same ligand-receptor binding can result in more than one output and are thereby context-dependent. Take S1P binding to one of its five GPCRs, S1PR1–5, as an example. S1P levels in plasma range from 0.1 – 1 μM[43,44]. Mid-range levels of S1P secreted by the endothelium can bind to S1PR1 on leukocytes to mediate their short-term homing[34]. However, increased amounts over time are needed for vascular maintenance by inducing proliferation[33]. In the following section, examples of various important cell-cell communications are described.

A. Mural cell (i.e., pericyte, vascular smooth muscle cells)-endothelium

Critical to vascular foundation, mural cells are essential for development and homeostasis of blood vessels. Alterations or disruption in mural cells contribute to endothelial dysfunction. Comprised of pericytes and vascular smooth muscle cells (vSMC), similar to EC heterogeneity, the heterogeneity of mural cells is found through various vascular beds and tissue, differing by morphology and antigen expression. Whereas pericytes associate with blood vessels of smaller diameter, vSMCs associate with those of larger diameter vessels to directly control vasodilation and vasoconstriction. The ratio of pericyte to endothelium can range between 1:1, found in neural tissue, to 1:10, found in skeletal muscle[45].

During angiogenesis, sprouting endothelium secrete PDGF-B to chemoattract pericytes that express the respective receptor PDGFR-β, stimulate proliferation of vSMCs, and initiate maturation of undifferentiated mesenchymal cells. Conversely, pericytes secrete angiopoietin-1 (Ang1) that binds to Tie2 and VEGF that binds to VEGFR2[40] found on endothelium in a paracrine manner to promote its survival and attachment to mural cells. Recent studies describe exosomes secreted from vSMCs to endothelium increased its permeability and worsened atherosclerosis progression[38].

B. Monocyte/Macrophage-endothelium

Monocytes/macrophages are an important cellular source of hallmark-secreted factors, such as VEGF-A, that are essential for blood vessel growth. During vascular growth, cell-cell communications from tissue-resident macrophages regulate interlock sprouting of angiogenic vessels through direct cell-to-cell contact[46,47]. The classical view of monocyte egression in an injury context will be described (Chapter 4: Platelet activation and endothelial dysfunction; Chapter 5: Role of antithrombin III and tissue factor pathway; Chapter 17: Coagulation disorders in HLH/Macrophage activation syndrome). The regulation of the sources of cytokine secretion is important to be understood. For example, in tissue repair macrophages that are matured from recruited $CCR2^{+}Ly6\text{-}c^{+}$ monocytes are essential for secreting VEGF-A, contributing to vessel growth[48].

Yet controversial is the notion that macrophages are a source of circulating endothelial progenitors through transdifferentiation. On one hand, evidence supporting the transdifferentiation of macrophage-endothelium is through overlapping gene expression profiles of leukocyte subpopulations and endothelium; as certain monocyte populations express the classical endothelial marker CD31[49,50]. On the other hand, studies suggest that the monocyte sub-populations defined to express classical endothelial markers are rather simply a sub-population of macrophages, which are also highly plastic and known to acquire markers in its environment. Further studies are necessary to define the contribution of macrophages to vascular endothelium.

C. Endothelial to Mesenchymal (EndMT) Transition

Endothelial-to-Mesenchymal Transition (EndMT) is a process where matured endothelium undergoes signaling cascades to acquire characteristics of mesenchymal cells (e.g., myofibroblasts); it is analogous to its corollary counterpart, epithelial-to-mesenchymal transition that has been described to a much greater and deeper extent. This phenomenon has become highlighted recently for its involvement in endothelial dysfunction and subsequent adult cardiovascular disease pathogenesis[51]. Whether it is causative in disease pathology remains unclear due to discrepancies and lack of standardization in experimental approaches to study EMT. Secreted transforming growth factor (TGF)-β is a potent factor for EndMT. An alteration in the signaling leads to endothelial dysfunction and contributes several pathogeneses as seen in the retina, where pericyte-derived TGF-β maintains endothelial integrity and stabilizes the structure[52,53].

The functions of the endothelium through signaling processes of cell-cell communication are clearly complex yet interconnected. With the development of highly sensitive and specific

techniques and assays such as single cell RNA sequencing, the identity of endothelial heterogeneity has become apparent; it also has allowed for experimental approaches to consider the cell-to-cell variability and the signaling networks there within. The heterogeneity contributes to the impaired cell-cell communication that results in endothelial dysfunction. Ultimately, the clinician's perspective to alter blood flow to meet the metabolic demands remains a daunting task that may be improved through a deeper appreciation of the endothelial heterogeneity and targeting to improve outcomes of the disrupted signaling machineries that lead to diseases.

V. Mechanisms of endothelial dysfunction contributing to disease progression

Guardian of vascular homeostasis and tone, endothelial cells (EC) are the first line regulators of the pro-inflammatory and immune responses while in tissue repair, they govern the reparative vessel rebuilding process of neovascularization. As the body ages, cellular components including the endothelium are also declining with EC morphology and functionality tightly coupled with self-imposed risk factors such as smoking, obesity, and diabetes driving this process. Recent studies highlight the pathophysiologic changes associated with the aging endothelium. For example, endothelial cell aging or senescence plays a key role in arterial stiffing and hypertension[54]. As cells age, they lose their ability to replicate, are prone to apoptosis, and demonstrate reduced regenerative ability. This in part is due to irreversible cell cycle arrest where in the G1 phase, they no longer respond to cyclin-dependent kinase regulated cell growth stimuli[54]. Mediated in part by activity of p53, telomere dysfunction and DNA damage contribute to cell senescence while p16/retinoblastoma gene product pathways are associated more with chromatin disruptions and mitogenic stress and are associated with atherosclerotic plaques[55–57].

Cellular production of reactive oxygen species (ROS) such as hydrogen peroxide and hydroxyl radicals contribute to EC oxidative stressors that are deleterious to DNA transcription and redox sensitive signaling pathways. Not limited to classic ROS alone, EC are also vulnerable to uncoupled forms of NO that gives rise to damage inducing peroxynitrites. When free radical scavengers such as glutathione synthase and superoxide synthases balance cellular ROS, premature EC senescence is avoided. Unchecked ROS expression contributes to inflammation, organ dysfunction and inhibition of NO-dependent relaxation. In conjunction with ROS, circulating inflammatory biomarkers promote EC dysfunction. From prolonged low-grade inflammation arising from sustained venous hypertension and valvular incompetence of chronic venous disease[58] to life-threatening sepsis, recruitment of leukocytes perpetuates the inflammatory cascade[59–61]. As the interface between circulating pro-inflammatory mediators such as IL-6, TNF-α and monocyte chemoattractant protein-1 and body tissues, EC function as innocent bystanders as activated inflammatory pathways triggered by release of inflammatory cytokines promote vascular injury. Not limited to bacterial and viral etiologies, chronic inflammatory and oxidative states have also been identified in dysregulated endocrine and paracrine states such as obesity where adipocyte-derived factors and adipo-cytokines contribute to adipose tissue

inflammation, reduction of NO bioavailability, insulin resistance and oxidized low-density lipoproteins[62].

In conjunction with the release of cytokines, microthrombosis is induced. Stemming from exocytosis of large amounts of von Willebrand factor multimers (ULVWF) and platelet activation, they form platelet-ULVWF complexes resulting in disseminated intravascular microthrombosis, a reduction in microcirculation, and tissue hypoxia. This circular amplification process of inflammation, microthrombosis, hypoxia and oxidative stress gives rise to the "two-activation theory of the endothelium" where the endotheliopathy of sepsis promotes the activation of the two independent endothelial pathways: inflammatory and microthrombotic[63,64].

While disruption of the microcirculation due to collaboration between inflammatory and microthrombotic processes is a hallmark of immune regulated sepsis, EC also secrete a gel-like substance called endothelial glycocalyx that supports healthy microvascular flow. Found on the luminal surface of vascular endothelium, glycocalyx is composed of glycosaminoglycans, glycoproteins, and glycolipids where they modulate "vascular resistance to maintain homogeneity in microcirculation, mechanotransducing fluid shear stress to endothelium, modulating vascular permeability, and buffering endothelial cells from plasma oxidants, cytokines, and circulating immune cells[65]." However, during the aging process, glycocalyx deteriorates contributing to microvascular dysfunction and cardiovascular disease. When combined with dysregulation of endothelial NO and altered redox states, recruitment of proper endothelial progenitor cells and modulation of the inflammatory process begins to become unbalanced leading to endothelial dysfunction and pathologic progression of disease processes[66].

In contrast to vessel maintenance, tumor growth and progression are dependent on vessel formation. Influenced by tumor metabolic needs vascular growth, extension and remodeling actively guide tumor neovascularization. Previously quiescent EC are recruited into hypoxic and necrotic regions where there is a disregard for immune surveillance and vessel growth occurs in a sea of hypoxia, inflammation and ROS. As a result of this volatile environment, tumor vasculature has increased amounts of leakage and anergy. Stabilization of the endothelium through use of anti-angiogenic therapy allows for improvement in vessel stability, perfusion, oxygen delivery, and importantly distribution of tumor targeting drugs. Therefore, normalization of the EC barrier within tumors is a critical in cancer therapy[67].

VI. Conclusions and Perspectives:

Complex partners in the maintenance of vascular integrity, endothelial cells in conjunction with supporting mural cells are an essential foreman guiding the egress of circulating cells, oxygen, and nutrients to meet tissue metabolic needs. Interference in endothelial-endothelial cell-cell communication and signaling contributes to progression of pathologic disease processes. Expanding our understanding of those factors that modulate this diverse and heterogenous endothelial cell population is critical to improving our understanding of disease progression and the identification of novel therapeutic approaches.

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Key points:

- Metabolism and organ-specific signaling steer endothelial cell heterogeneity.
- Disruption of the vascular endothelial cell lining contributes to disease progression.
- The endothelium has an active role in local inflammatory and thrombotic response.

Synopsis:

Guided by organ-specific signals in both development and disease response, the heterogeneous endothelial cell population is a dynamic member of the vasculature. Functioning as the gatekeeper to fluid, inflammatory cells, oxygen, and nutrients, endothelial cell communication with its local environment is critical. Impairment of endothelial cell-cell communication not only disrupts this signaling process, but also contributes to pathologic disease progression. Expanding our understanding of those processes that mediate endothelial cell-cell communication is an important step in the approach to treatment of disease processes.