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REVIEW ARTICLE

Biology of the endothelium: literature review

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Abstract

Extensive research has been dedicated to elucidating the intricate pathophysiological mechanisms underlying endothelial dysfunction. Restoration of endothelial integrity is primarily achieved via two mechanisms: local endothelial cell proliferation and migration, and the adhesion and incorporation of circulating endothelial progenitor cells. Historically, the endothelium was regarded as a quiescent monolayer; however, evidence accumulated over the past two decades has revealed its multifaceted role in modulating coagulation, fibrinolysis, vascular tone, and vascular remodeling. In addition, the endothelium is instrumental in orchestrating the interactions between platelets, leukocytes, and the vascular wall. This literature review synthesizes recent advancements in endothelial biology, with a particular emphasis on the functions of the glycocalyx, the cellular stress response, angiogenic processes, thrombosis, and the pathogenesis of pre-eclampsia.

Keywords: *Endothelium. Biology. Glycocalyx.*

Introduction

The endothelial glycocalyx (GC) is the layer that covers the endothelium; it is made up of glycosaminoglycans (GAG), proteoglycans (PG), and adsorbed plasma proteins. This structure regulates the mechanotransduction of the vascular wall, its permeability and cell adhesion, mainly of leukocytes[1]. Increasing age is associated with a greater risk of suffering from chronic diseases, thus, the aging of the vascular system is evidently related to the development of many diseases and syndromes. The endothelial GC plays an important role in homeostasis and protection of various organ functions[2].

Hyaluronan (HA), a ubiquitous extracellular matrix glycosaminoglycan, is present in the endothelial GC that covers the apical surface of endothelial cells (EC). HA plays a central role in numerous functions of the endothelial surface layer, protecting EC, regulating barrier permeability, and ensuring mechanosensing, which is essential for nitric oxide (NO) production and vasodilation. During acute injury, inflammatory or pathological conditions, the endothelial GC is damaged and its

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degradation is accompanied by the elimination of one or more components of the GC into the systemic circulation. Syndecan-1, heparan sulfate (HS), and HA are the main components whose elimination has been documented and could be used as markers of the state of damage to the endothelium and GC[3].

This review focuses on endothelial biology and its key roles in the functions of the endothelial GC in several conditions, such as stress, angiogenesis, thrombosis, and pre-eclampsia related.

Figure 1 presents a summary of functions of the endothelium in physiological conditions, which are lost in different ways in very variable scenarios.

Methods

The research team convened to systematically organize the content of the manuscript for discussion. The academic article was developed, encompassing key thematic areas, including glycocalyx, endothelial function and stress, angiogenesis, thrombosis, and pre-eclampsia. A targeted literature search was conducted using the keywords "endothelium," "glycocalyx," and "biology," with a publication timeframe spanning 2000-2024. Querying the PubMed database yielded 114 results, from which the 34 most relevant articles prioritizing biological aspects and the mechanistic explanation of related physiological processes were selected for inclusion.

The endothelial GC: composition and functions

The apical plasma membrane of EC carries the site for the GC, a complex junction of macromolecules. GC has a multilayer structure that limits EC contact with cellular and molecular blood elements. GC is formed by glycoproteins and PG. Its composition and shape fluctuate with variation due to shear forces from turbulent blood flow, leading to loss and re-synthesis of GC elements of its constitution. The synthesis of GC is a very complex, and multiple enzymatic pathways working harmoniously are necessary. Various factors are responsible for regulating its renewal or detachment, these include, among others, local pH and mechanical stimuli, for example, HA synthase produces a 240 kDa HA molecule every 5 min. Various authors consider that the endothelium is generally capable of producing enough HA to reestablish a hemodynamically relevant layer in 24 h. Furthermore, HA clearance is very effective, with an estimated half-life between 2 and 6 min and a turnover of 10 mg/day to 100 mg/day in an average 70 kg adult[4-6].

The GC forms a luminal meshwork that provides the EC with a binding structure to plasma proteins and soluble GAG. The GC becomes physiologically active once plasma constituents bind to it or are immersed in it. The side chains that make up GAGs that are negatively charged bind to the core protein of PG. PGs are differentiated by the size of their core proteins and the number of GAG side chains, in addition to their binding to the cell membrane. Between 50% and 90% of GAG are HS[6]. In addition to HS, it also has other GAGs such as hyaluronic acid and chondroitin sulfate, dermatan, and keratan. The HS core proteins are perlecans, glypicans, and syndecans. Perlecan is a PG found in the basement membrane. Glypicans are cell surface HS PG, these have a glycosylphosphatidylinositol anchor. Syndecans are found at the transmembrane level; they are eliminated in soluble form when the GC is altered[7].

Each syndecan consists of an extracellular domain with GAG binding sites, a single-pass transmembrane domain, and a cytoplasmic domain with phosphorylation sites. There are also central proteins; decorines, biglycans, versicans, and mimecanos, these are PG containing dermatan and/or chondroitin sulfate[8]. Hyaluronic acid is the only non-sulfated GAG without a protein core. The GC participates in different vascular functions. Barrier formation, it has a charged mesh structure that acts as a macromolecular sieve. The negative charge repels negatively charged molecules, such as white blood cells, red blood cells, and platelets. Molecules larger than 70 kDa cannot pass through the tight mesh structure of GC, while albumin (67 kDa), despite its overall negative charge at neutral pH, does bind firmly to the GC, due to its amphoteric character. This union reduces hydraulic conductivity across the vascular barrier[9].

The GC, through its intracellular protein domain, can act as a mechanotransducer, allowing the EC to detect mechanical stress. Conformational changes, the detachment of microparticles induced by blood flow, signal for the regulation of vasomotor tone and, thus, the release of NO. In this way, the GC contributes to the maintenance of homeostasis[10]. Figure 2 summarizes the endothelial and GC biology.

Vascular endothelium and angiogenesis

The vascular endothelium is the lining of the internal wall of the blood vessels, which has a basal lamina and EC, which form the vascular intima, with a total surface area of 3000-6000 m^2, fulfilling specialized functions according to their location, among the main ones being

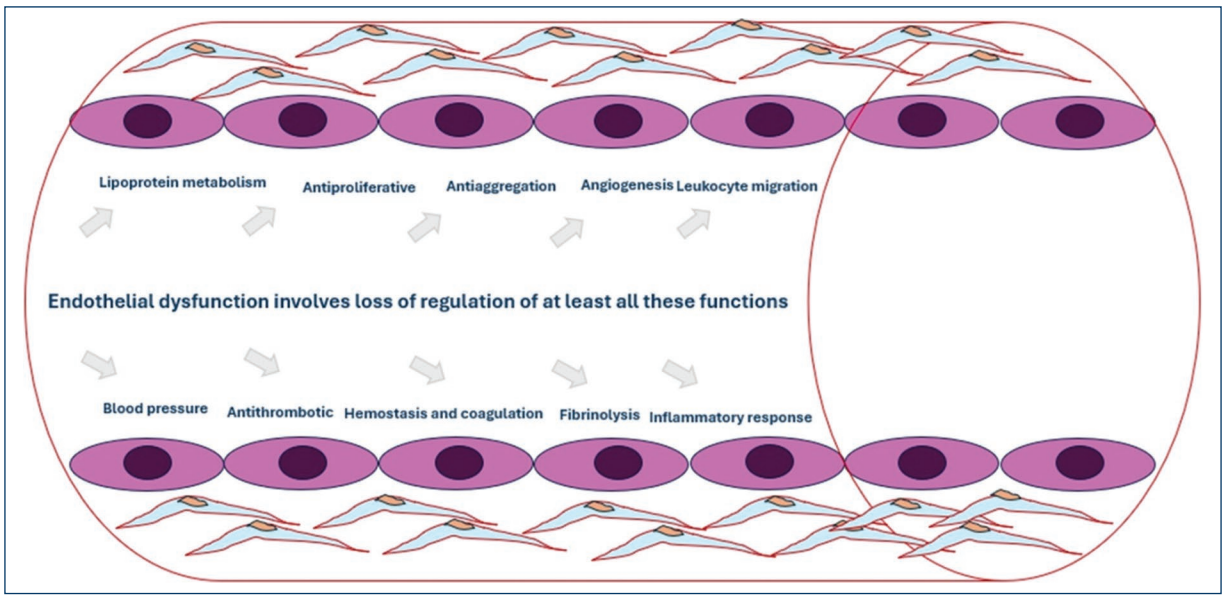


Figure 1. A summary of the functions of the endothelium in physiological conditions is represented, which are lost during various pathological conditions.

the following: Regulation of homeostasis and thrombosis, regulation of leukocyte-endothelium interaction, vasomotor regulation, regulation of smooth muscle growth[11].

Due to the wide variety of cellular components of the vascular endothelium, which have different and complex functions, the term "single inert layer" does not find a place within the new definitions. Furthermore, it is an important component of the vascular system within the diversity of blood vessels, such as arterial vessels (low capacitance or high capacitance) and venous vessels, with a variable permeability capacity considering physiological and/or pathological clinical conditions. On the contrary, blood capillaries are intended to allow an exchange of intra- and extravascular components, whether solutes or liquids, maintaining pressures of 0-25 mmHg, which are variable in the different organs of the body; another function of the capillary is to serve as a reservoir for specific blood cells. Blood vessels thus provide specific homeostasis in each organ. For this reason, the vascular endothelium and blood vessels are more than just ducts that supply oxygen and nutrients. Therefore, when endothelial dysfunction is found due to hypoxic and/or ischemic processes where homeostasis and total or partial restriction of nutritional intake are altered, diseases occur that can compromise life acutely or chronically, thus altering one of the main functions of EC which is angiogenesis[12].

Angiogenesis, defined as the formation of new blood vessels from pre-existing vessels, begins with the specialized function of EC, which can be divided into three subtypes of specialized cells: The tip cells are non-proliferative cells with high migratory capacity responsible for giving the correct direction; the stem cells, with high proliferative capacity, lengthening the new vessel; and the cells of the phalanx, responsible for completing the formation of the new vessel. Vascular endothelial growth factor (VEGF) is the key angiogenic factor released in hypoxic states, to recover oxygenation and nutrient supply for the new sprout of a blood vessel. When two tip cells meet, they are joined by the process of vascular anastomosis and a perfused vessel is formed, with a consequent decrease in VEGF levels and the production of platelet-derived growth factor B (PDGF-B). To recruit PDGF receptors B (PDGF-RB) to express pericytes, which confer stability to the new blood vessel[13].

There is a term used in recent years, which is coalescent angiogenesis that refers to a mechanism of blood vessel formation, whose relationship in embryonic angiogenesis and/or pathological angiogenesis has not yet been accurately determined. Different types of angiogenesis have been studied, which are: Post-natal vasculogénesis, which occurs after embryonic life, in association with tumor or ischemic processes, producing circulating endothelial colony-forming cells, which promote angiogenesis by paracrine factors. Sprouting

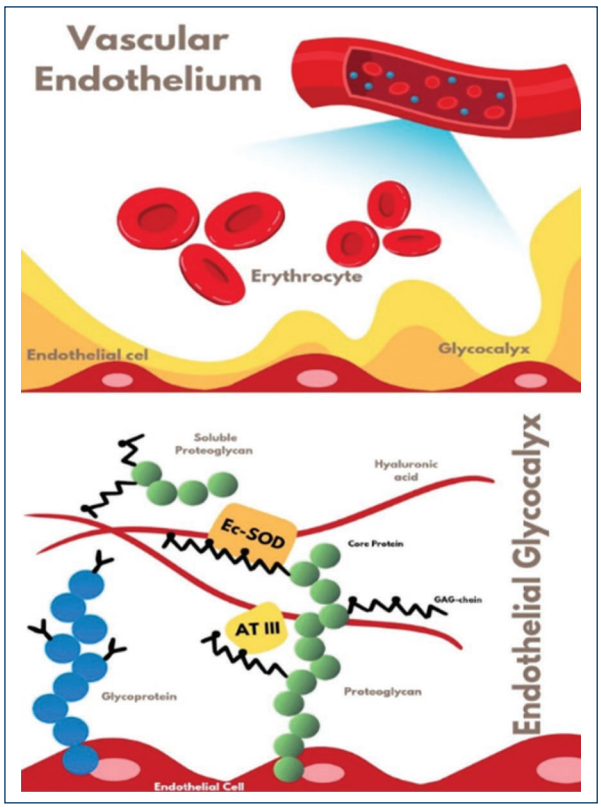


Figure 2. Endothelial glycocalyx illustration. Up: The endothelial glycocalyx can be observed as an area that does not normally come into direct contact with red blood cells. Down: composition of endothelial glycocalyx. PG, with long unbranched glycosaminoglycan side chains (GAG chain), and glycoproteins, with branched carbohydrate side chains, are bound in the endothelial membrane. Within and on top of this structure are plasma- and endothelium-derived components, such as hyaluronic acid and other soluble PG (e.g., thrombomodulin) and other proteins, such as extracellular superoxide dismutase (ec-SOD) and antithrombin III (AT III). All these components make up the endothelial glycocalyx.

angiogenesis is the best-known form of angiogenesis, where a new functional blood vessel is generated after the release of VEGF and fibroblast growth factor by EC; being considered the fastest form of vascularization in a growing tissue. Intussusceptive angiogenesis has a mechanism opposite to coalescent angiogenesis, with the formation of transvascular pillars dividing the vascular wall to form two different blood vessels. Another type of angiogenesis is the co-option of vessels or perivascular invasion, which occurs from existing blood vessels without vascular proliferation. This form of angiogenesis is seen in tumor processes. Both intussusceptive angiogenesis and vessel co-option, to this day, create discussion as to whether or not they should be part of angiogenesis, because both lack vascular proliferation, but share vascular phenotypic and functional changes[14].

Therefore, understand that the endothelium is a highly specialized tissue and that the different complex mechanisms of angiogenesis in its various forms are elementary processes that occur from embryogenesis and even in adult life, also involved in processes, such as wound healing, ischemic, and tumor processes[15]. Figure 3 summarizes the angiogenesis mechanisms.

Endothelium and stress

The configuration of the GC can be damaged due to pathological situations, such as low shear stress (LSS) of the fluid (LSS since it mediates the synthesis and release of matrix metalloproteinases (MMP) due to its function as a proteolytic enzyme; causing lubrication of matrix metalloproteases 2 and 9 (MMP-2, MMP-9). Otherwise, the tissue inhibitor of metalloproteinase-2 (TIMP-2) acts as an inhibitor of MMP-2, thus preventing the degradation of the extracellular matrix[16].

Autophagy maintains endothelial homeostasis, although stress can alter this process and cause dysfunction in the endothelium. Moderate autophagy is a beneficial process for the GC, since it degrades and reuses macromolecules and organelles under stress, favoring the integrity and proper functioning of the GC and EC; However, this process can be affected by excessive autophagy, causing alterations in the synthesis of MMP and NO, caused by endothelial shear, and this in turn leads to lower production of HS and consequently endothelial dysfunction[16].

Autophagy markers have been studied, such as the proteins LC2, Beclin-1, and p62, which can be negatively modified by stress that causes endothelial dysfunction. However, to measure the proper functioning of the endothelium, specifically the GC, LSS can be assessed, since this can positively induce the synthesis of MMP-2 and MMP-9 and which translates into GC dysfunction[16]. EC are continually exposed to various mechanical forces derived from blood flow, maintaining vascular homeostasis when there is cellular integrity, in addition to generating an anticoagulant and anti-inflammatory environment that maintains both the permeability of the basement membrane and vascular tone[17].

The fluid shear stress (FSS) is a tangential vector of the force exerted by the blood flow, that is, it is the friction force of the blood flow per unit area parallel to the vessel wall (dynes/cm^2 or Pascals, Pa). The FSS organizes the growth of blood vessels, their

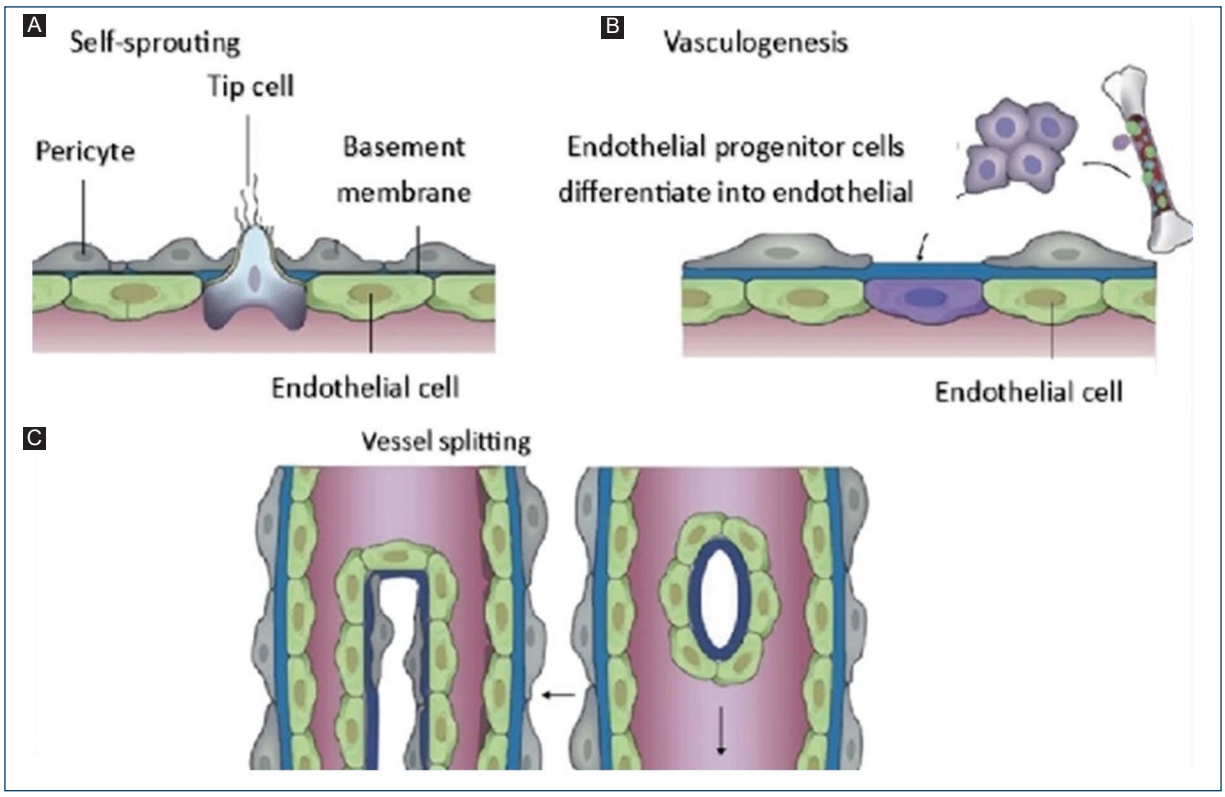


Figure 3. Normal tissues mechanisms of angiogenesis: sprouting angiogenesis (**A**), vasculogenesis (**B**), and intussusception (**C**). There are 3 methods of blood vessel formation in normal tissues: **A:** vessel formation can occur by sprouting angiogenesis; **B:** by the recruitment of bone-marrow-derived and/or vascular-wall-resident endothelial progenitor cells that differentiate into endothelial cells; **C:** by a process of vessel splitting known as intussusception.

homeostasis, and the phenotype of EC, which collaborates in vasoregulation after sudden changes in blood flow, in addition, it also regulates the remodeling of the vascular wall secondary to a chronic hemodynamic modification[17].

Mechanotransduction refers to the process by which fluid shear stress is detected and converted into a biological response. Endothelial cells possess a diverse array of mechanosensors including ion channels, tyrosine kinase receptors, G protein-coupled receptors, and integrins that translate hemodynamic variations into biochemical signals. These signals regulate gene expression, cellular behavior, morphology, and phenotype, ensuring the adaptive response of endothelial cells to mechanical stimuli. Through specialized mechanosensitive signaling pathways, the physiological characteristics of FSS fluctuate based on blood vessel size and the properties of the vascular bed, undergoing dynamic modifications throughout the cardiac cycle[17].

The change in the hemodynamic environment generates certain heterogeneity in the vascular phenotype, in the endothelium of the arteries and veins, generating a specific microenvironment with a specific content of oxygen, growth factors, adhesion molecules, and shear stress levels. This means that in the absence of vascular pathological processes, laminar and unidirectional FSS will occur more commonly, thus generating blood flow that presents a continuous tangential force on the lumen of the endothelium in an anterograde manner[17].

The endothelium plays a crucial indirect role in tissue function and metabolic regulation by governing transendothelial transport and secreting metabolic factors that influence growth, differentiation, and cellular activity. Through these mechanisms, it maintains homeostasis and vascular tone, ensuring optimal physiological balance[18].

Various causes can alter the functioning and structure of the endothelium, the main ones being oxidative stress, high blood pressure or a metabolic cause such as diabetes, which can generate the presence of inflammation and oxidative stress, which will ultimately lead to endothelial dysfunction with initial vasoconstriction and subsequent vasodilation with an increased risk

of thrombosis and a pro-inflammatory state secondary to the inactivation of endothelial NO synthase (eNOS), and the decrease in NO, as well as the upregulation of the expression of NO molecules. Adhesion and the increase in chemokines, in addition to an increase in leukocyte adhesion, cell permeability, platelet activation, oxidation of low-density lipoproteins, and finally the proliferation and migration of vascular smooth muscle cells[18]. Fatty acids can generate endothelial dysfunction due to increased inflammation, activation of the renin-angiotensin system, apoptosis, and increased production of NO when they are in excess, which will also generate oxidative stress in EC[18]. Similarly, severe trauma, secondary coagulopathy that causes an increase in sympatho-adrenal activation that increases catecholamines in perivascular sympathetic nerves with the consequent release of tissue plasminogen activator (tPA) will cause endothelial dysfunction with injury to the GC, leak capillary, and hyperfibrinolysis[19].

Endothelial dysfunction can affect the systemic circulation, including the renal and coronary circulation as well as the pulmonary circulation, which is why physiological processes derived from neurotransmitters and hormones will also be affected, in addition to the normal coagulation process[20].

Figure 4 summarizes the interaction of the endothelium with multiple stress mechanisms.

Endothelium and thrombosis

The maintenance of blood fluidity is controlled by the inner lining of the circulatory system, a thin layer of cells, the endothelium. EC cover the entire vasculature of vertebrates, and thus, form a hemocapatible blood container with a large surface. EC act by promoting anti-coagulant properties and counteracting platelet activation and aggregation. However, if activated by vasoactive agents, they release VWF that promotes binding of platelets and t-PA that enhances control by fibrinolysis[21].

Thrombosis reflects an imbalance between procoagulant and anticoagulant mechanisms. In some cases, thrombotic lesions are precipitated by gross changes in blood flow, vascular wall integrity, or systemic levels of coagulation factors. In other cases, thrombosis is induced by functional changes within the endothelium. EC express a wide variety of factors that contribute to hemostasis, including procoagulants, anticoagulants, cell adhesion molecules, vasomotor substances, and cell survival signals. Because the endothelium displays a remarkable diversity of structure and function, the relative contribution of any one of these factors to the hemostatic balance varies between different vascular beds. Once formed, a thrombus feeds back on surrounding EC to induce altered expression of adhesion molecules, changes in the expression of procoagulants-anticoagulants, and alterations in vasomotor tone. The resulting phenotype may either be adaptive or compound the thrombogenicity of the local environment. The molecular mechanisms underlying these alterations are partially elucidated by the impact of activated coagulation factors on endothelial function[22].

Once EC become activated, they play an essential role to the generation of thrombin through the expression of pro-coagulant factors that contribute to both initiation and propagation of thrombin generation. Platelet-endothelium interactions play an integral role in the activation and regulation of platelets. While an intact endothelium inhibits the adhesion of platelets, through the release of NO and prostaglandin I_2, activated EC express a variety of molecules and receptors that increase platelet adhesion to the site of injury.

Under physiological conditions, the endothelium prevents thrombosis by providing a surface that discourages the attachment of cells and clotting proteins. When stressed beyond a certain threshold, the quiescent endothelium initiates numerous mechanisms to induce clotting (e.g. by expression of TF and fVIII) and anticoagulation (Fig. 4). Concomitantly, activated EC recruits platelets to the site of injury (e.g. by expression of VWF), where it serves as a support surface for the formation of pro-coagulant complexes and platelet aggregation[23].

The endothelium plays a crucial role in providing the proper hemostatic balance. The function of EC far exceeds that of providing a non-thrombogenic inner layer of the vascular wall that helps to maintain blood fluidity. Under physiological conditions, EC prevent thrombosis by means of different anticoagulant and antiplatelet mechanisms (Fig. 4). These cells are involved in all main hemostatic pathways triggered upon vascular injury and limit clot formation to the areas where hemostasis is needed to restore vascular integrity. One important way in which EC control the clotting system is by regulating the expression of binding sites for anticoagulant and procoagulant factors on the cell surface. In the quiescent state, EC maintain blood fluidity by promoting the activity of numerous anticoagulant pathways, including the protein C/protein S pathway. After activation, as can be brought about by cytokines, the balance of endothelial properties can be tipped in favor of clot formation through the coordinated induction of procoagulant and suppression of anticoagulant

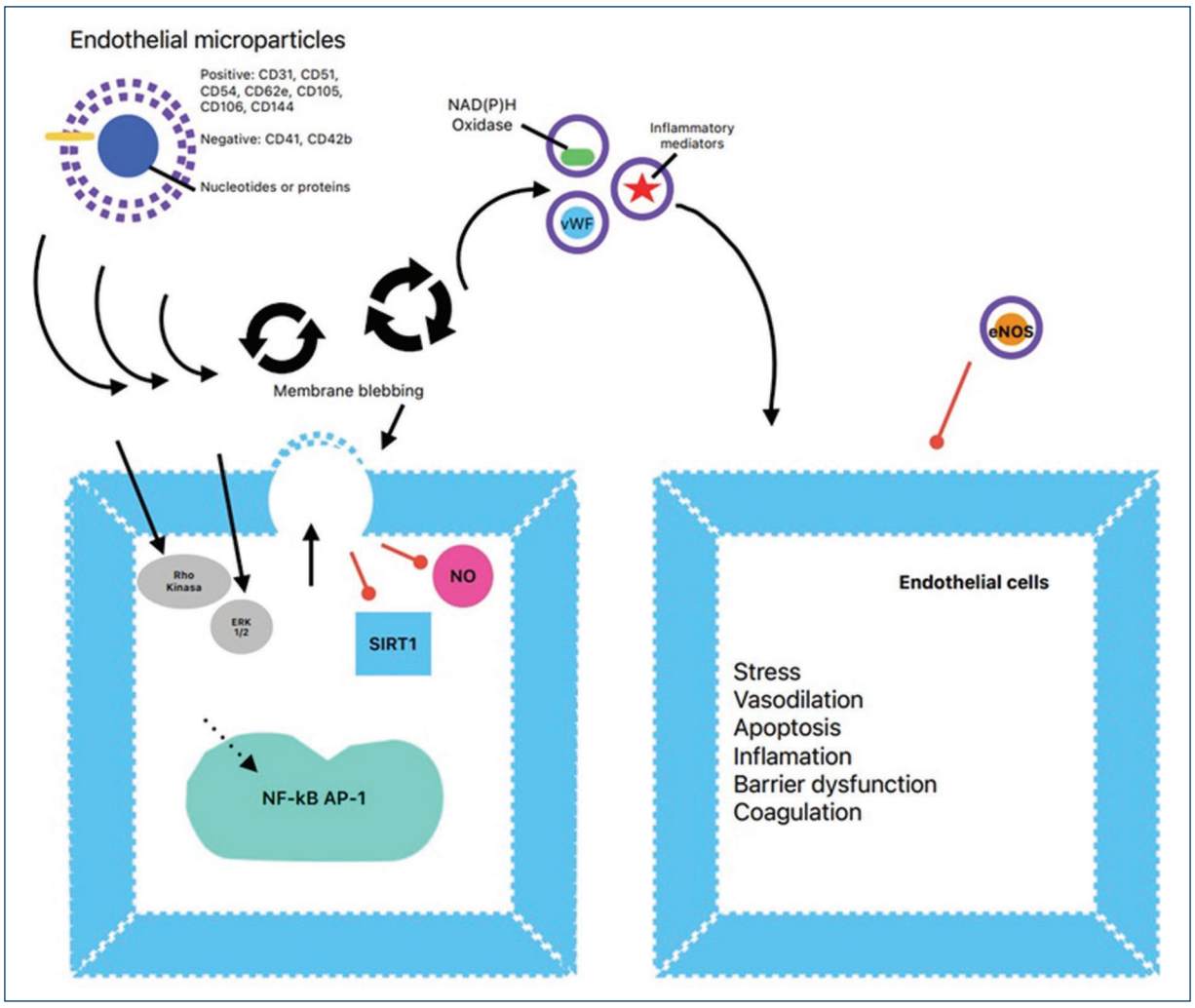


Figure 4. Illustration showing potential causes of endothelial dysfunction. Release of endothelial microparticles that increase and alter the activation of the Rho kinase, NF-b and AP-1 pathways under shear stress, or through the inhibition of Sirtuin 1 (SIRT1) and nitric oxide (NO). These microparticles are identified by endothelial markers and, due to the lack of markers on the platelet surface, functional proteins are transported, including Von Willebrand factor (vWF), Nicotinamide adenine dinucleotide phosphate or NAD(P)H oxidase, inflammatory mediators, and NO synthase. These same microparticles will damage adjacent endothelial cells, stimulating apoptosis and triggering vascular endothelial dysfunction.

mechanisms. Tumor necrosis factor suppresses the formation of thrombomodulin, an endothelial anticoagulant cofactor, and induces the expression of tissue factor, which is at procoagulant cofactor[24].

The endothelium is a widely distributed organ system that plays an important role in both physiology and the pathophysiology of many diseases. The endothelium has many functions, over and above its well-recognized role in mediating vascular tone. One of these critical activities is the maintenance of blood fluidity and the repair of injured blood vessels. The endothelium is remarkably heterogeneous in structure and function. Indeed, EC regulate hemostatic balance by site-specific formulas of anticoagulants and procoagulants. These different equations are sufficient to explain why systemic imbalances in coagulation factors invariably lead to local thrombotic phenotypes. The propensity to develop clots in specific vascular beds is further accentuated by local endothelial dysfunction. An important goal for the future is to identify diagnostic markers that reflect phenotypic changes at the level of individual vascular beds, and to develop therapies that target one or another site of the vasculature[25]. Figure 5 summarizes the properties related to thrombosis and procoagulation of the endothelium, procoagulation properties of EC[26].

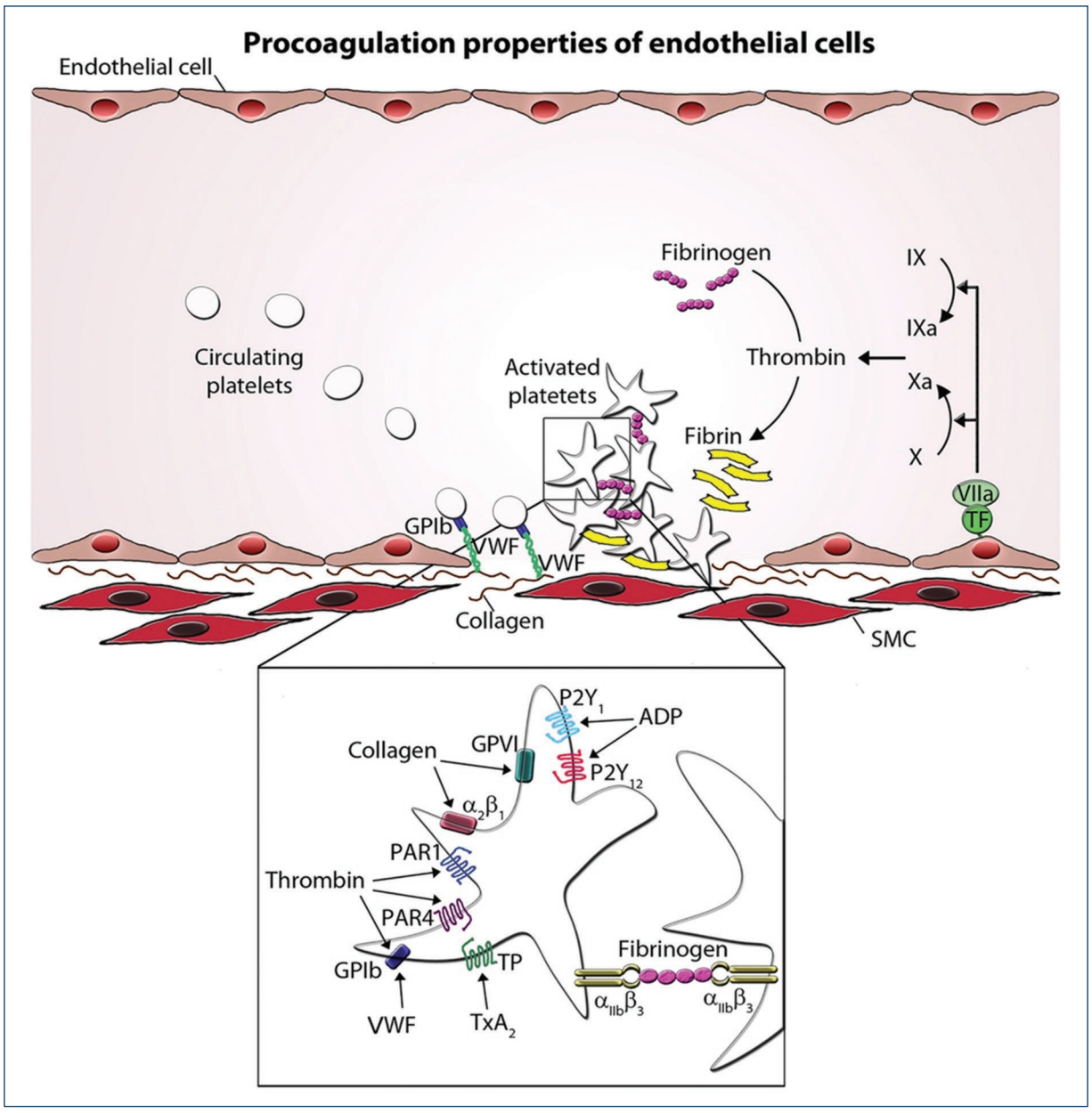


Figure 5. Procoagulation properties of endothelial cells. "At sites of vascular injury, Von Willebrand factor (VWF) binds to the exposed subendothelial collagen. VWF then captures platelets from the circulation through the interaction of the VWF with GPIb on the platelet. The binding of GPVI with collagen leads to further platelet activation. This results in the integrin-mediated adhesion of platelets and cellular activation releasing mediators. Selected platelet agonists and their receptors are indicated. Thrombin binds to GPIb and activates protease-activated receptor 1 and 4 (PAR1 and PAR4, respectively), ADP activates P2Y1 and P2Y12 receptors, and thromboxane A2 (TxA2) activates the thromboxane receptor (TP). Agonist stimulation results in integrin αIIbβ3 activation and the transition to an active conformation, which binds fibrinogen and mediates platelet aggregate formation. SMC smooth muscle cell" (*from Neubauer and Zieger*[26]).

Endothelium and pre-eclampsia

Placentation is a complex process, which involves an adaptation between trophoblastic cells and maternal immune cells, to establish an adequate blood supply between the mother-fetus binomials, through endometrial invasion by the fetal trophoblast[27].

For the above to happen, the fetal trophoblast invades the maternal decidua, promoting the remodeling of the spiral arteries, replacing their EC, muscles and

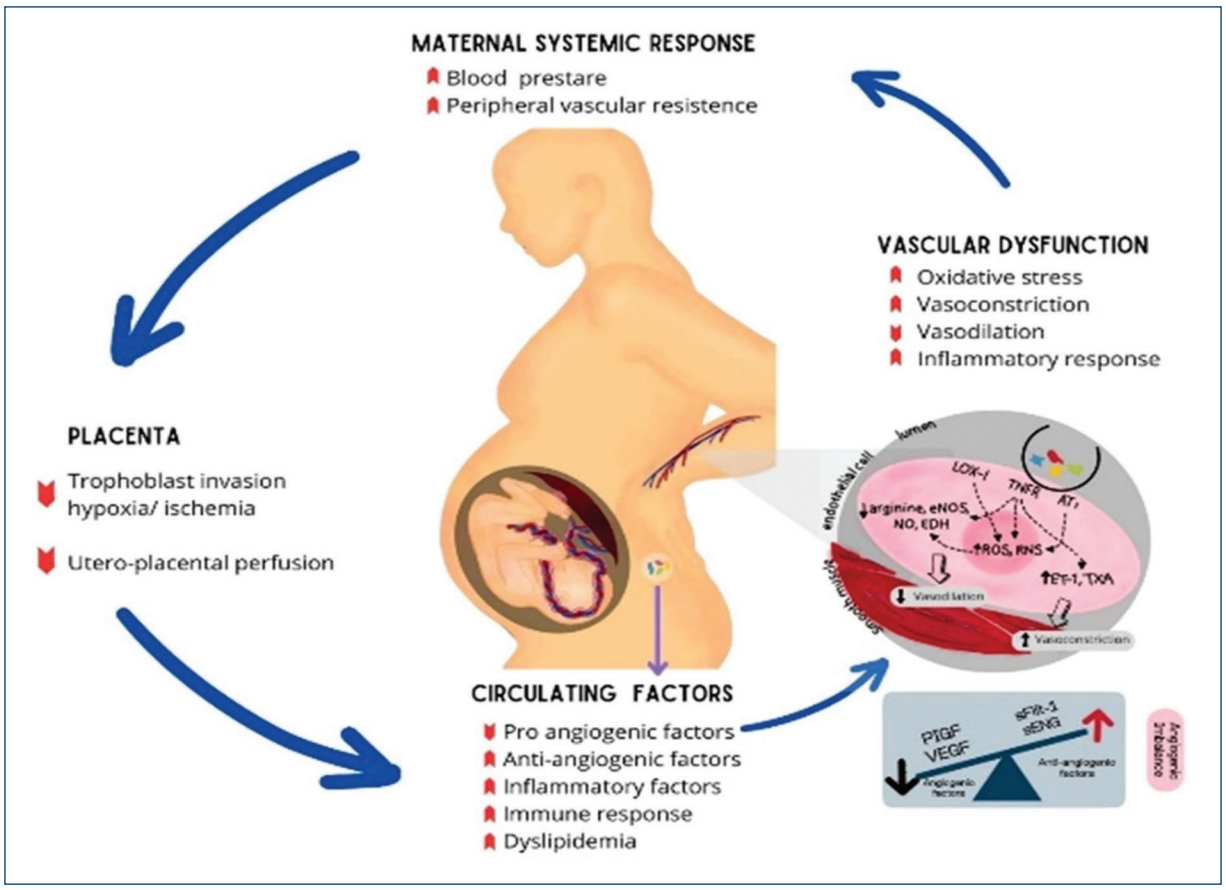


Figure 6. Schematic representation of the factors involved in the development of pre-eclampsia. The anomalous invasion of the trophoblast into the spiral arteries, maintaining a placental state of hypoperfusion, this generates hypoxia-ischemia leads to the release of vasoactive and inflammatory factors into the maternal circulation, including anti-angiogenic factors, inflammatory mediators, and inflammatory cytokines. These mediators cause an exaggerated inflammatory response, with oxidative stress, which, together with the angiogenic imbalance, induces endothelial activation and injury. AT1: Angiotensin type 1 receptor; eNOS: endothelial nitric oxide synthase; EDH: endothelium-dependent hyperpolarization; ET-1: endothelin type 1; IL-6: interleukin 6; LOX-1: lectin-like oxidized low-density lipoprotein receptor 1; NO: nitric oxide; ROS: reactive oxygen species; RNS: reactive nitrogen species; sFlt-1: soluble fms-type tyrosine kinase 1; sEng: soluble endoglin; TNF-a: tumor necrosis factor alpha; TNFR: tumor necrosis factor receptor; TXA: thromboxane.

innervation, converting them into vessels of low resistance and high capacitance. In pre-eclampsia, this trophoblastic invasion is anomalous, resulting in vessels of small caliber, high resistance[28] and low capacitance, maintaining the placenta in a state of hypoperfusion, ultimately resulting in hypoxia and ischemia at this level. This leads to the release of inflammation factors and vasoactive factors that will contribute to the maternal endothelial dysfunction syndrome[29]. The maternal vascular endothelium is one of the main sites of action for the vasoactive factors released in pre-eclampsia. The main function of EC is to maintain vascular function, to regulate blood flow and perfusion in the face of hemodynamic changes, as well as to provide a protective barrier that regulates the movement of proteins, water, ions, and cells from the intravascular space toward the wall of the glass[29].

There are two types of vasoactive factors released in pre-eclampsia: pro-angiogenic and anti-angiogenic factors. Pro-angiogenic factors are responsible for vascular development and maintenance of placental function, the most studied of which are VEGF and PIGF (placental growth factor). VEGF promotes angiogenesis by binding to two specific receptor tyrosine kinases, VEGF type 1 and VEGF type 2. PIGF interacts with VEGF1, functioning independently as a heterodimer, thus facilitating

angiogenesis. On the other hand, anti-angiogenic factors are responsible for inhibiting the formation of new blood vessels from existing vessels, in this case, the most studied are soluble tyrosine kinase 1 type fms (sFlt-1) and soluble endoglin (sEng). sFlt-1 functions as a VEGF1 receptor, preventing interaction with its specific receptors. The sEng member of transforming growth factor beta 1 (TGF-b1) and transforming growth factor beta 3 (TGF-b3), prevents the activity of pro-angiogenic factors, through the inhibition of TGF-b1 signaling and bone morphogenic proteins in turn reduces the activity of eNOS[30]; resulting in hypoxia secondary to ischemia of trophoblastic cells, with significant overexpression of sFlt-1 mediated by the transcription factor hypoxia-inducible factor type 1; causing an imbalance between angiogenic and anti-angiogenic factors with a predominance of the latter; resulting in an inhibition of the vasodilator effect and the genesis of endothelial dysfunction[31].

Furthermore, in pre-eclampsia, there is a pathological release of free radicals and ROS (reactive oxygen species) and (reactive nitrogen species) by the placenta, creating an imbalance between the production of these and its antioxidant mechanisms, leading to oxidative stress, inflammation, and apoptosis of syncytiotrophoblast cells[32].

Abnormal implantation in the patient with pre-eclampsia leads to poor immunological adaptation, with greater activation of nuclear factor kappa light chain enhancer of activated B cells, the complement system, and a variety of immune cells. Elevated levels of many cytokines and chemokines have been identified in the maternal circulation; particularly tumor necrosis factor alpha and interleukin 1 are mediators of endothelial activation and dysfunction. Endothelial dysfunction is the central point for the genesis of hemodynamic alterations in pre-eclampsia. Various markers of endothelial activation, including thrombomodulin, Von Willebrand factor, fibronectin and plasminogen activator inhibitor, as well as platelet EC adhesion molecule type 1, intercellular adhesion molecule type 1 and vascular cell adhesion molecule type 1 are increased in the plasma of women with pre-eclampsia[33].

In women with pre-eclampsia, a reduction and decreased sensitivity to vasodilator agents, including NO and prostacyclin, as well as a reduction in the vasodilator effect mediated by endothelium-dependent hyperpolarization (EDH), the latter associated with reduced levels of PlGF, a known activator of EDH. Elevated levels of oxidized low-density lipoprotein and its receptor lectin-like oxidized low-density lipoprotein receptor 1 have been identified, which promote inflammation through the formation of superoxides. Similarly, increases in the enzyme Arginase have been identified, which produces decoupling of eNOS, contributing to oxidative stress by reducing the production of NO[34].

Figure 6 summarizes the most important mechanisms involved in endothelial dysfunction in pre-eclampsia.

Conclusion

A comprehensive analysis of the vascular endothelium's molecular biology and physiology provides critical insights into the pathophysiological mechanisms underlying syndromes observed in critically ill patients. Under physiological conditions, endothelial guanylate cyclase is a pivotal regulator of microvascular tone, modulating leukocyte adhesion and transendothelial migration, while concurrently limiting intravascular thrombus formation.

Angiogenesis is a multifaceted process governed by a tightly controlled interplay between proangiogenic and antiangiogenic factors. Hypoxemia functions as a key inducer, stimulating vascular endothelial growth factor synthesis and activating genetic pathways essential for neovascularization. Disruption of the delicate balance between these mediators is central to the development of pre-eclampsia syndrome and critically influences the severity of its clinical manifestations.

Ultimately, endothelial dysfunction constitutes a core paradigm in elucidating the pathophysiology of a wide range of acute and chronic diseases, underscoring its fundamental role in both health and disease.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not

apply. data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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