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Functions of the endothelium and its role in hematopoietic cell transplantation

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ABSTRACT

The endothelium is a single-layered structure that responds to physical and chemical signals with various factors it synthesizes. In the early days of its discovery, as the inner wall of the vessels, the endothelium was thought to be a simple barrier that lays on the surface. Over time it is discovered that endothelium maintains body homeostasis with the molecules it synthesizes, despite its simple single-layer structure. It has been accepted as an important organ that contributes to the maintenance of vascular tone, cell adhesion, inflammation, vascular permeability and coagulation. Any imbalance in these physiological and pathological events causes endothelial dysfunction. This can cause many diseases such as atherosclerosis, hypertension, diabetes, or it can occur because of these. Endothelial related disorders may also complicate hematopoietic stem cell transplantation (HSCT), which is used to treat various hematologic and neoplastic diseases. These life-threatening complications include graft-versus-host disease, hepatic veno-occlussive disease, transplant-associated thrombotic microangiopathy and diffuse alveolar hemorrhage. They share a similar pathophysiology involving endothelial cells with different clinical presentations. Therefore, current researche on the issue is putting the endothelium under the spotlight for novel markers and treatment options that should be used to monitor or treat at least some of these complications following HSCT.

1. Introduction

The endothelium is the cell layer that covers the inner surface of the vessel wall and is necessary for the normal functioning of the vascular system. It acts as a physical and functional filter between circulating erythrocytes, liquid blood components and tissue metabolic products [1, 2] During the development of the vascular system, it regulates cellular adhesion and vessel wall generation in addition to maintaining vasculogenesis and angiogenesis [3].

Endothelial cells (EC) respond heterogeneously to exogenous stimuli and play an important role in regulating homeostasis of the vascular system [4]. ECs often remain silent throughout adolescence; however, they also retain the capacity to rapidly initiate new vessel formation in response to injury or pathological conditions [5]. Endothelium-derived vasodilator and vasoconstrictor factors can regulate vascular tone, permeability, coagulation, and inflammation through regulation of various mediators such as cell adhesion molecules, cytokines, and chemokines. In addition to vascular tone and coagulation, it regulates leukocyte traffic and intake of nutrients and electrolytes, and neovascularization of hypoxic tissue [6]. To ensure hemostasis by endothelial cells certain mediators are secreted. These are nitric oxide (NO), which provides vasodilation, endothelin-1 (ET-1), platelet activation factor (PAF), which causes vasoconstriction with prostacyclin (PGI2) and angiotensin II [6–12].

The vascular endothelium plays a pathogenic key role in the onset of atherosclerosis and cardiovascular disease, and conversely, vascular injuries from conditions such as angioplasty, stenting, diabetes, hypertension, and immunological damage can also lead to endothelial dysfunction and damage to the endothelium [7–12].

This article aims to understand the endothelial physiology and to explain the role of endothelium in homeostasis in the healthy, as well as to explain the endothelial damage-related complications that occur in hematopoietic stem cell transplantation (HSCT).

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2. Physiological functions of the endothelium

2.1. Endothelium as a barrier

Like other functions of the endothelium, its role in vascular permeability depends on the type and location of the vessel. Capillaries and post-capillary venules act as exchange vessels of the circulation. Lipophilic and low molecular weight hydrophilic substances can move between blood and tissues without being hindered. But vessels can be selectively permeable for macromolecules. This semi-selective barrier is necessary to maintain intravascular and extravascular fluid balance. For the initiation and maintenance of events such as inflammation, immune response and wound healing, the passage of antibodies, hormones, cytokines molecules into the interstitial space is necessary [13–15].

During inflammation, the binding of neutrophils to the endothelium causes damage to endothelial cells and formation of oxidants and results in increased permeability [16]. Recently, it has been shown that the binding of neutrophils to the endothelium triggers the signaling mechanism mediated by leukocyte CD18, releasing neutrophil cationic protein. Another inflammatory mediator, thrombin, can increase endothelial permeability through several mechanisms (transcellular vesicular permeability, increase in paracellular permeability, change in glycocalyx negative charge, etc.) by activating receptors on endothelial cells [17]. One of the hypothesized mechanisms for increased permeability in inflammatory conditions is related to pericyte contractility [18].

2.2. Control of vascular tonus

Endothelial cells are located on the intima of all vessels but display different structures and phenotypes depending on vessel type [19]. The control of vascular tone is mainly based on the vasodilators produced by the endothelium, such as NO, PGI2 and endothelium-derived hyperpolarizing factor (EDHF) and the balance between vasoconstrictors-endothelin-1 and superoxide is important [20]. Besides the inhibition of platelet aggregation, NO and PGI2 also act as vasodilators. Another important factor regulating vascular tone is superoxide ions. The source of these free radicals such as endothelium or inflammatory cells that are damaged or collected in the inflammation area. The interaction between superoxide radicals and NO causes the formation of peroxy-nitrite and a decrease in NO concentration [21]. Peroxy-nitrite causes oxidation of low-density lipoproteins and adverse modification of other proteins, thereby causing endothelial dysfunction. The increased superoxide formation inhibits PGI2 synthesis but does not affect TxA2 synthesis. In addition to NO, endothelial function is regulated by other bioactive substances many of which interact [22].

Endothelin (ET) is a vasoconstrictor which is expressed in the body in three isoforms, ET-1, ET-2, and ET-3 [23]. Endothelial cells only release ET-1. Regulation of ET-1 production as well as its release is stimulated by inflammatory cells such as interleukins and TNF-α and decreased by NO and PGI_2 [19,23,24].

Activation of endothelial receptors and the subsequent increase in Ca2+ levels cause K + efflux by the cell. The smooth muscle cell responds to changes in extracellular K + levels and releases K + out of the smooth muscle cell, causing hyperpolarization. The change in the membrane potential of the smooth muscle cell reduces intracellular Ca2+ levels, resulting in relaxation [25].

Gap junctions are intercellular channels that can transfer signals from the endothelial cells to the smooth muscle cells. In particular, gap junctions can transfer K^+ ions from the smooth muscle cells into the endothelial cell [26].

2.3. Endothelium as an anti-coagulation surface

Endothelial cells have an important place in the mechanism of hemostasis and thrombosis (Fig. 1). Under physiological conditions, the endothelium forms an anticoagulant surface with the functions of inhibition of platelet aggregation, inhibition of coagulation activation and fibrinolysis. Conversely, the endothelium become procoagulant when damaged or under inflammatory conditions [27].

Prostacyclin is synthesized by vascular endothelial and smooth muscle cells as a product of arachidonic acid metabolism. Prostacyclin inhibits platelet activation, secretion, and aggregation, as well as the interaction of monocytes with the endothelium. NO similarly inhibits platelet adhesion, activation and aggregation. A significant portion of the NO released from the endothelial cell causes vasodilation by acting on the smooth muscle under the endothelium. Some NO passes into the lumen and affects platelets [28].

Four mechanisms play a role in inhibition of coagulation by endothelial cells:

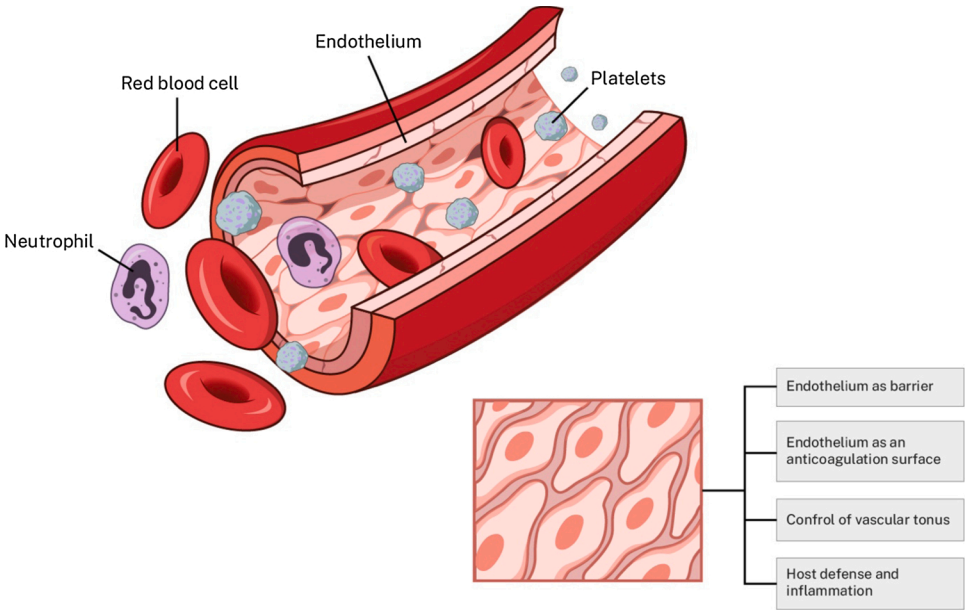

Fig. 1. Schematic representation of endothelial histology and normal physiological functions.

1) Thrombomodulin on the surface of endothelial cells binds thrombin. This complex inhibits the coagulant property of thrombin and increases its affinity for protein C and activates protein C [29,30].
2) Protein S, thought to be synthesized by endothelial cells, acts as a cofactor of protein C. It also has anticoagulant properties without activated protein C and interacts directly with factors Va and VIIIa [30].
3) Heparan sulfate proteoglycans are released into the luminal surface and subendothelial regions of the endothelium. Heparan sulfate binds to antithrombin and activates it. Thus, thrombin, which is a procoagulant, accelerates activation of factor Xa and factor IXa [31,32].
4) Tissue factor pathway inhibitor (TFPI) has been shown to be found in and secreted from the apical granules of endothelial cells. The tissue factor-factor VIIa-factor-Xa complex inhibited by TFPI [33].

Additionally, von Willebrand factor (vWF), essential for coagulation and platelet function, is derived from the endothelium [34].

2.4. Host defense and inflammation

ECs produce regulators of inflammation and host defense mechanisms and play a key role in recruiting leukocytes and adhesion and chemo-attractants to sites of inflammation (Fig. 1) [35]. Important adhesion molecules expressed on ECs include P-selectin, E-selectin, intracellular cell adhesion molecule 1 (ICAM 1) and vascular cell adhesion molecule (VCAM) [36–39]. The endothelial cell layer serves as the gateway for the entry of leukocytes into tissue in response to inflammatory stimuli using a transmigration process termed extravasation [36–39]. Therefore, the endothelium plays an important role in the regulation of immune responses and inflammation (Fig. 1).

3. Pathophysiology of endothelial dysfunction

Endothelial dysfunction (ED) is a pathological condition that occurs due to the imbalance between vasodilation and vasoconstriction provided by the endothelium. Under normal conditions, the vascular endothelium regulates vasodilation, provides a non-adhesive surface for circulating leukocytes and inhibits vascular smooth muscle proliferation, platelet aggregation thrombus formation. While platelet and leukocyte adhesion are important for the healing of inflammatory cells in injured areas, induction of procoagulant factors is important in the creation of fibrin formation [1,40].

In various disease states, including atherosclerosis, the endothelium emits signals that reduce NO bioavailability with consequent expression of adhesion molecules that promote the “homing”and atheroma infiltration of leukocytes and other blood-derived cells, so leading to a noxious imbalance between vasodilatation and vasoconstriction, inhibition and stimulation of smooth muscle cell proliferation and migration, and thrombogenesis and fibrinolysis [41].

Endothelial dysfunction is one of the earliest signs and an important event in the onset of the atherosclerotic process and insulin resistance [42,43]. The reduction in NO activity caused by 1) decreased eNOS expression, 2) insufficient substrate (L-arginine) or co-factors (tetrahydrobiopterin or BH4) for eNOS or the presence of antagonists, 3) impaired eNOS activation (due to increased caveolin), and 4) increased degradation rate of NO [41].

Over the past 40 years, hematopoietic stem cell transplantation has ceased to be an experimental treatment and is now widely used in many malignant and nonmalignant diseases. As it is known, stem cell transplantation is an effective treatment method that can cure many diseases. However, approximately one-third of the patients die within 1 year after transplantation, especially due to problems encountered during or after allogeneic transplantation [44,45].

4. Clinical conditions related to endothelial dysfunction in hematopoietic stem cell transplantation

There are many factors that can cause endothelial damage in patients undergoing HSCT. Additionally, myeloma, lymphoma, and leukemia can cause ED independent of transplantation [46,47]. Chemotherapeutic drugs used for the conditioning regimen during transplantation activate endothelial cells and inflammatory processes [48]. Total body irradiation (TBI) also induces endothelial cell apoptosis and upregulates ICAM levels [49]. Many studies indicate a relationship between the intensity of the conditioning regimen, type of transplant and endothelial damage [50].

During engraftment, cytokines secreted from damaged tissues exaggerated endothelial damage [51]. Additionally, infections and immunosuppressive agents potentiate endothelial damage [52,53]. A correlation was found between high doses of tacrolimus after stem cell transplantation and an increase in complications due to endothelial damage [53].

When the literature is reviewed, many risk factors are mentioned for complications due to endothelial dysfunction after HSCT. Conditioning regimen, use of TBI, type and number of transplants, lower performance, older age, degree of HLA mismatch, the presence of pretransplant comorbidities, and donor type are the most defined risk factors [45,47].

There are many clinical disorders reported in the literature associated with endothelial dysfunction: graft-versus-host disease, posterior reversible encephalopathy syndrome, early fluid retention, early bilirubinemia, hepatic veno-occlusive disease, transplant-associated thrombotic microangiopathy and diffuse alveolar hemorrhage [45,47,54–56]. Among these, four important clinical conditions described in detail below are graft-versus-host disease, hepatic veno-occlusive disease, transplant-associated thrombotic microangiopathy and idiopathic pneumonia syndrome/diffuse alveolar hemorrhage.

4.1. Graft-versus-host disease

Graft-versus-host disease (GvHD) is a disorder resulting from the immune-attack of donor T lymphocytes to the recipient’s tissues [57]. The incidence of acute GvHD following allogeneic HSCT is around 30 %–50 % and overall mortality ranges between 16 % and 92 % varying by GvHD grade [57,58].

During transplantation, damage to the recipient’s tissue after conditioning causes pro-inflammatory cytokine release and activates antigen presenting cells of the host. Host antigens are presented to the donor T lymphocytes and alloreactivity develops resulting in further tissue damage [59], endothelial cells are not recognized by T cells, but continuous exposure to the pro-inflammatory cytokines induce endothelial injury and, paradoxically, endothelial damage in GvHD contributes to steroid resistance and treatment failure [59]. There are reports of circulating endothelial factors like angiopoietin and VEGF studied as biomarkers of GvHD development [60].

4.2. Hepatic veno-occlusive disease

Hepatic veno-occlusive disease (VOD) is an obliterative venulitis caused by the damage of endothelial cells lining hepatic sinusoids and it results in coagulative necrosis of hepatocytes [61]. According to the European Society for Blood and Marrow Transplantation (EBMT) reports, the rates for VOD following autologous and allogeneic HSCT are 3% and 9% respectively [62]. The mortality rate is about 80 % and it is mostly associated with the development of multiorgan failure following VOD [63].

The clinical manifestations of VOD arise from post-sinusoidal hypertension owing to the obstruction of sinusoidal flow. There are many factors with a role in the progress of sinusoidal obstruction, but the first trigger is endothelial injury that happens after chemotherapy (especially busulphan and cyclophosphamide) or radiation [64]. Endothelial injury

results in the release of vWF and tissue factor which in turn causes platelet aggregation and coagulation [65]. There are also inflammatory mediators, matrix metalloproteinases and heparinase secreted because of endothelial injury and these make a further damage to the cytoskeletal structure and then gaps occur in the endothelial lining resulting in leakage into the space of Disse and embolize sinusoids [66].

4.3. Transplant-associated thrombotic microangiopathy

Transplant-associated thrombotic microangiopathy (TA-TMA) is a complication of allogeneic transplantation occurring when endothelial injury causes microangiopathic hemolytic anemia with platelet consumption resulting in microvascular thrombosis and organ dysfunctions [67]. The precise incidence of TA-TMA is debatable and ranges between 0.5 %–76 %, but it usually occurs within 100 days of transplantation [68].

The exact pathogenesis remains unknown and vascular endothelial injury in TA-TMA is multifactorial [69]. However, the natural procoagulant state of TA-TMA directly damages the endothelium and the level of vWF is elevated in TA-TMA, are markers of endothelial injury like thrombomodulin, plasminogen activator inhibitor-1, ICAM-1, VCAM-1, E-selectin, IL-1, TNF- α, IFN- γ, and IL-8 [70]. However, endothelial activation results in generation of microparticles that contributes to the progression of TA-TMA [71].

4.4. Idiopathic pneumonia syndrome/diffuse alveolar hemorrhage

Idiopathic pneumonia syndrome (IPS) is a disorder characterized by alveolar damage in the absence of any etiology for pulmonary disease like infection, cardiac failure or fluid overload [72]. It may be a complication of both autologous and allogeneic HSCT and the incidence range is 2 %–15 % during the first 120 days after transplantation [73,74]. Diffuse alveolar hemorrhage occurs in about 10 % of patients with IPS and the mortality rate is as high as 80 % [73,74].

Although the exact pathophysiology of IPS is not fully understood, TNF-α, is reported to contribute to the evolution of IPS via different mechanisms. It increases MHC expression, facilitates the migration of leukocytes, eases cell-mediated toxicity and cytokine-related direct toxicity and leads to the apoptosis of pulmonary vascular endothelial cells [75]. Endothelial injury in IPS is clinically presented as pulmonary edema and elevated bronchoalveolar fluid protein levels due to endothelial leak [76.]. The reported biomarkers in IPS patients are elevated ICAM-1 and VCAM-1, which act as evidence for endothelial activation [75,76].

5. Future directives

The endothelium originates from the mesoderm, which is located in the cardiovascular system and surrounds the inner walls of the vessels. A human adult has approximately ten billion ECs that constitute about 1.5 % of body mass. Composed of single-layered squamous epithelial cells and synthesized by these cells through various factors, the tissue plays an important role in the regulation of vascular tone, cell adhesion, inflammation, vascular permeability and coagulation control.

As studies have increased to understand the physiology of the intact endothelium and the roles of endothelium in acute inflammation, our knowledge of the pathogenesis of many diseases has increased. However, the number of patients and diseases undergoing allogeneic stem cell transplantation is increasing due to the better definition of the factors affecting the transplant results and the widespread use of low-intensity conditioning regimens. However, post-transplant complications still have a high rate of morbidity and mortality. The common role of endothelium in the pathophysiology of these events makes ECs a promising target for therapeutic intervention for stem cell transplantation complications.

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