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Endothelium as A Part of Septic Multiple Organ Dysfunction Syndrome (Mods)-Is Endocan an Answer?

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Abstract

Sepsis is complex syndrome with endothelial barrier integrity compromise, contributing to end-organ dysfunction. Some findings have established that markers of septic endothelial activation are associated with extent of sepsis severity, organ dysfunction and mortality. Endocan is a novel endothelium derived soluble dermatan sulfate proteoglycan and endocan's increased serum levels founded in patients with sepsis were of prognostic value.

Keywords: Sepsis; Endothelium activation; Endothelial barrier permeability; Organ dysfunction

Introduction

The blood vessel lumen is lined by endothelial cells, which are the primary component of the microvascular permeability barrier. Vessel integrity is influenced by the interaction of endothelial cells with the extracellular matrix, glycocalyx and supporting cells. The main inter-endothelial junctions are the tight junction and adherens junction. These junctions interface with the cell's cytoskeleton via specific adaptor proteins. Adherens junctions have been identified in almost all types of vascular beds, especially in the peripheral microvasculature.

Endothelium-a physiological structure and role

The structural component of the adherens junction is Vascular-Endothelial (VE) cadherin, a transmembrane molecule, which is organized in a multimeric protein complex, and connecting neighboring endothelial cells [1]. Intracellulary, VE-cadherin is connected to the actin cytoskeleton via a family of catenin (α-,β-,γ-catenins). Connection to the actin cytoskeleton is stabilized by p120-catenin which binds to protein kinases (Src family kinases) and phosphates. The catenins serve not only as a structural linkage between VE-cadherin and the cytoskeleton, they also transduce signals for cell-cell communication [2]. VE-cadherin is one of the key molecules integrating signals for opening and tightening of cell junctions. The calcium-dependent interaction of endothelial VE-cadherin of the adherens junction is relayed to the actin cytoskeleton by different adaptor proteins. The cytoskeleton is connected with integrin proteins that anchor endothelial cells to the surrounding extracellular matrix [3]. Actin-based structures are found in the spectrin-based skeleton beneath the plasma membrane, and in stress fibres, focal adhesions and the cortical actin ring [3]. The polymerization and depolymerization of actin filaments, and the proportion of filaments devoted to various actin-containing structures is under tight regulation. The actin-based cytoskeleton is regulated by members of the Rho family of GTPases: Rac, Cdc42 and RhoA. Signaling through RhoA which occurs in response to stimulation by thrombin and other inflammatory mediators destabilizes the endothelial junction and increases permeability [4]. The endogenous lipid Sphingosine-1-Phosphate (S1P) decreases vascular permeability, in part, by stimulating endothelial Rac activity and increasing cortical actin [4]. Thrombin disrupts cortical actin and initiates endothelial cell contraction by increasing the inward tension exerted by stress fibres [5]. The endothelial monolayer functions to control the influx and efflux of substances between the interstitium and vessel lumen. The cell-cell/matrix adhesion-based structure is semi-permeable to water and non-lipophilic molecules, providing size-and charge-selectivity for solute transport across the microvessel wall [2]. The permeability properties of the endothelial barrier are critical in the maintenance of fluid homeostasis and in the regulation of physiological functions of tissues and organs [2].

The role of the endothelial glycocalyx

The endothelial glycocalyx is a complex and multicomponent negatively charged layer at the luminal surface of vascular endothelium. The EG consists of endothelial membrane-bound molecules, including glycoproteins with short branched carbohydrate side-chain and proteoglycans with long unbranched Glycosaminoglycan side-chain (GAG), that provide the basis for plasma-endothelial cell interaction [6]. In and on top of this net are plasma and endothelium derived soluble components incorporated. The composition of membrane-bound proteoglycans, glycoproteins, glycoaminoglycans as well as the composition of associated plasma proteins and soluble glycosaminoglycans doesn't create a static picture. The whole layer-endothelial surface layer-is very dynamic, and there is a dynamic equilibrium between this layer of soluble components and flowing blood [7]. The glycocalyx facilitates the red blood cells flow and limits adhesion of platelets and white blood cells to endothelium. Enzymatic removal of any of glycocalyx components significantly changes its properties demonstrating a synergic interaction of all glycocalyx constituents [7].

Proteoglycans

Proteoglycans consist of a core protein to which one or more glycosaminoglycan chain are linked and a one core protein can

contain different types of glycosaminoglycan chains. There is a variation among proteoglycan core protein depending on their size, number of attached glycosaminoglycan chains and fact if they are or not bound to the cell membrane. There are five types of glycosaminoglycan chains: heparin sulfate, chondroitin sulfate, dermatan sulfate, keratin sulfate and hyaluronan (or hyaluronic acid). They are linear polymers disaccharides with variable lengths that are modified by sulfation and/or (de)acetylation to a variable extent [7]. In vasculature heparin sulfate proteoglycans are its dominant structural component and represent 50-90% of all proteoglycans present in glycocalyx. The second common in the endothelial glycocalyx is galactosaminoglycan chondroitin sulfate/dermatan sulfate. The typical ratio for the vascular endothelium for heparin sulfate and chondroitin sulfate is 4:1. Heparan sulfate and chondroitin sulfate/dermatan sulfate containing proteoglycans are produced in endoplasmic reticulum and Golgi apparatus of the endothelial cell [8]. Another glycosaminoglycan-hyaluronan is a long polymeric molecule (up to 10^4 kDa) and in contrast to others glycosaminoglycans is not linked to a core protein [7]. Hyaluronan has no negatively charged sulfate groups and is capable of forming viscous solutions. The structural diversity is linked to functional diversity of glycosaminoglycans. The diversity of GAG sulfation patterns and small chain modifications may have functional consequences. Conditions that change glycocalyx thickness or modulate GAG sulfation pattern and charge are likely to influence vascular permeability.

Glycoproteins

Glycoproteins are regarded as structural molecules connecting the glycocalyx to the endothelial cell membrane. The group of glycoproteins playing an important role in cell recruitment from the blood stream and in cell signaling are the endothelial cell adhesion molecules. There are three families of cell adhesion molecules present in the endothelial glycocalyx: the selectins, the integrins, and the immunoglobulin superfamily. Selectin located on the vascular endothelium are E-selectin and P-selectin. E-selectins are expressed on the activated endothelium, P-selectins are expressed on platelets and the endothelium, and L-selectins are constitutively expressed on leucocytes [9]. Integrins are heterodimers comprising of an α and a β chain and can recognize multiple ligands including proteins of extracellular matrix, cell surface glycoproteins, complement factors and soluble components of the haemostatic and fibrynolytic cascade [10]. The endothelial glycocalyx may function as a fluid shear-stress sensor, which may regulate the production of Nitric Oxide (NO). This finding was dependent on the heparin sulfate and hyaluronic acid constituents of the glycocalyx. The released NO derived from endothelial NO synthase may stabilize the endothelial barrier through activation of focal adhesion kinase and recruitment of additional focal adhesion complexes to the basal endothelial surface [10]. Endothelium is continuously exposed to fluid shear force at its apical side and this force differs along the length of a single vessel, it is evident that mechanical stress represents an extrinsic factor modifying regional barrier properties [10].

Endotoxin influence on the endothelium

Endotoxin (LPS) the component of outer membrane of Gram-negative bacteria triggers the systemic inflammatory response and in various models *in vivo* induces profound vascular leakage. An LPS-induced increase in endothelial permeability occurs as the result of endothelial contraction caused by RhoA-dependent increase in MLC phosphorylation, reorganization of actin filaments, and protein tyrosine phosphorylation [11]. LPS influence on the endothelium results from release of mediators such as TNF-α, IL-1, IL-8. TNF-α results in the upregulation of endothelial adhesion molecules ICAM-1 and E-selectin, there by promoting neutrophil adhesion to endothelium and ROS generation resulting in increase of endothelial permeability [12]. It has been shown that changes in endothelial barrier integrity are related to β_2 integrin signaling, leading to changes in endothelial cytosolic free calcium and reorganization of actin filaments [12]. Participation of β_2 integrins causes release of heparin-binding protein promoting neutrophil adhesion to endothelial cells *via* upregulation of ICAM-1 and causing endothelial cytoskeletal reorganization, CD11b/CD18 is one of such β_2 integrin [13].

Endothelium in sepsis

Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection [14]. It is devastating syndrome that can progress to severe sepsis with the development of organ dysfunction, next to septic shock with hypotension unresponsive to fluid resuscitation, and finally to multiple organ failure [15]. An important element involved in sepsis pathophysiology is the vascular endothelial barrier. Local and systemic effects of infection and host response lead to a breakdown of endothelial barrier integrity [1]. Endothelial surface pays a pivotal role in the progression of sepsis. Under physiological conditions, endothelial cells modulate vascular homeostasis. In sepsis the endothelial injury is the result of the production of variety of substances as oxygen free radicals, arachidonic acid metabolites, and products of anaerobic metabolism [16]. The endothelial damage is also mediated by complement and neutrophil activation, platelet aggregation and monocytes production of cytokines. As a result of these mechanisms, endothelium generates inflammatory mediators itself changing into a procoagulant surface, producing vasoactive substances and inflammatory agents and expressing adhesion molecules [16]. This activated state may be considered dysfunctional when an overactive endothelium disturbs the homeostatic state instead of restoring it. In this context, endothelial dysfunction involves combination of increased leukocyte adhesion and transmigration, increased permeability, a shift in the hemostatic balance towards the procoagulant side, and an alteration in vasomotor tone [17]. A common final pathway for many inflammatory stimuli is the activation of an endothelial-specific myosin light chain kinase and the cascading activation of signaling that results in actin stress fiber formation and endothelial cell contraction that opens cell–cell junctions, resulting in enhanced permeability [12]. Tissue oxygenation is impaired by the loss of barrier function of the endothelium caused by a loss of function of vascular endothelial cadherin, changes in endothelial cell-to-cell junctions, high levels of angiopoietin 2 and inbalance between sphingosine-1 phosphate receptor 1 (S1P1) and S1P3 within the vascular wall [18].

Microvascular leak

During sepsis, increased microvascular leak appears due to combination of endothelial damage: cellular apoptosis, loss of intercellular junctional integrity, or remodeling of the cellular cytoskeleton. Microvascular leak is one of the critical determinants of the pathophysiology of endothelial septic changes [16]. Inflammatory mediators (thrombin, VEGF) induce endothelial leak by promoting the internalization of VE-cadherin. VEGF initiates a signaling cascade

involving Src kinase, Vav2 and Rac that triggers the serine phosphorylation of VE-cadherin, leading to the recruitment of β-arrestin2 and culminating in the endocytosis of VE-cadherin [19]. Cell-cell junctional complexes link to the cellular cytoskeleton causes that junctional forces and cell shape are coordinated. The cytoskeleton itself plays the role in regulation of permeability. Cytoskeleton remodeling leads to rapid changes in cell shape and could introduce gaps in the endothelial monolayer being a reason for microvascular leak. Activation of RhoA in response to thrombin, VEGF, IL-1 regulates effector molecules such as the actin-severing enzyme cofilin. This enzyme disrupts actin cytoskeleton, which in turn destabilizes VE-cadherin at endothelial junction and increases membrane permeability [17].

Next mechanism of endothelial leak is excessive endothelial cells activation. Normally NF-κB is kept in the cytosol by its inhibitor, I-κB. I-κB degradation through inflammatory mediators allows for NF-κB nuclear translocation leading to endothelial activation. Some degree of endothelial activation is required for host defense, excessive activation causes endothelial damage and vascular leak [20]. Some barrier-enhancing agent exerts their effect in part by blocking NF-κB. An example of endogenous barrier-protective agent is the secreted growth factor Ang1 (Angiopoietin) [21]. Binding of Ang1 to its receptor Tie2 leads to suppression of NF-κB-directed gene expression and signaling mediated by the A20-binding inhibitor of NF-κB activator-2 (ABIN-2) protein [20]. Ang1 binding also induces translocation of Tie2 to the endothelial junction where multimeric Ang1 functions as a bridge between Tie2 receptors at the junction associate with Vascular Endothelial Protein Tyrosine Phosphatase (VE-PTP) which has been shown to inhibit paracellular permeability [20]. Li et al. has shown that Ang1 inhibits thrombin-induced activation of Rho^{-} and $Ca2^{+}$ dependent pathway, together with protein kinase C (PKC) [21]. This effect of Ang1 is counterbalanced by Ang2-related growth factor released by activated endothelial cells. Ang2 by binding Tie2 inhibits ang1-mediated signaling [21]. Parikh et al. demonstrated in his study, that circulating Ang2 level was increased in septic patients and correlated with the ability to induce endothelial leak in cell culture monolayer [22].

Endothelium in sepsis-should it be monitoring?

One of the largest organ-endothelial system having a central role in homeostasis of organ functions-is not monitoring in daily clinical routine. Sepsis is a complex syndrome with various clinical manifestations in patients. During sepsis, the release of pro-inflammatory cytokines initiates an activation cascade of endothelial cells. Septic endothelial activation and dysfunction are critical determinants of the host response and one the factors responsible for the complex sepsis pathophysiology [16]. Endothelial dysfunction is referred to an imbalance of vasoconstriction and vasodilation, vascular leakage and edema formation. The endothelial injury is highly associated with mortality. Some studies results confirming that markers of endothelial activation are associated with sepsis severity, organ dysfunction and mortality, supports the hypothesis that endothelial function should be routinely monitoring during the course of sepsis [16,23-26].

Endocan-a biomarker for endothelial damage monitoring?

Human endocan is a product a unique gene called *esm*1.This gene spans 12-15 kb long, located in a long arm of the chromosome 5, and contained 3 exons. Endocan is a proteoglycan secreted by vascular endothelium. Endocan is stable at low levels in the blood of healthy subjects and can be measured in serum. Endocan contains a protein core and saccharide moiety covalently linked to it. The protein core is composed of 165 amino acids. During posttranslational modification endocan acquires one dermatan sulfate side chain linked to serine residue at position 137 of protein core. The protein core possesses two distinct domains: N-terminal cysteine rich domain of 110 aminoacids and C-terminal domain of 55 aminoacids free of cysteine. The N-terminal 110 aminoacids also contain an endothelial growth factor (EGF)-like domainand a phenyloalanine rich region. Endocan is basically a secretory molecule, rather than extracellular matrix component for providing structural support to cells. The dermatan sulfate of endocan consists of about 32 disaccharide units. Both nonsulfated and disulfated units are present in higher proportion in endocan than other DS proteoglycans [27]. The protein core glycosaminoglycan of endocan have been implicated in interactions with extracellular matrix components, cell surface proteins, intracellular molecules, as well as soluble mediators which in turn regulate cell differentiation, migration and adhesion. Endocan is secreted specifically by endothelial cells and overexpressed in specialized tip cells [28]. It belongs to a set of 6 genes specifically overexpressed during the angiogenic switch, while low expression of endocan appears to characterize dormant tumors [27]. In human tumors, endocan is overexpressed by endothelial cells from various cancers like non-small lung cancer (NSCLC), hepatocarcinoma (HCC), kidney cancer, glioblastoma, and bladder cancer [29]. Multiple studies indentified endocan expression as part of molecular signatures defining a poor prognosis in NSCLC, breast cancer, glioblastoma and HCC [26]. In addition, endocan shows a poteniat anti-inflammatory activity through inhibition of the LFA-1-dependent leucocyte functions, which could contribute to its net protumoral activity [30].

The expression of endocan is up-regulated by VEGF-A, VEGF-C, TNF-α, IL-1, transforming growth factor-β1 and phosphatidylinositide 3-kinases (PI3K) and interferon-γ cause down-regulation.

In acute infection vascular endothelium and leucocytes express adhesion molecules playing a major role in leucocyte migration to the site of infection. TNF-α and IL-1 stimulate expression of E- and P-selectins and integrin ligands like ICAM-1 on endothelium of small blood vessels, adjacent to the inflamed site. In response to infection, during activation, leukocytes acquire E- and P-selectins and high affinity integrins-LFA-1 (CD11a/CD18). Binding of LFA-1 to ICAM-1 initiates the process of leukocytes transmigration and movement toward site of infection in peripheral tissues. The binding of protein core of endocan with LFA-1 has negative effect on LFA-1 interaction with endothelial ICAM-1, so endocan inhibits leukocytes migration and homing [31].

In his study, related to sepsis, Scherpereel et al. observed that circulating endocan level in blood was related to the severity of sepsis and reflected outcome of the patient [32]. De Freitas Caires et al. have described elevated blood levels of cathepsin G-cleaved endocan in patients with sepsis. This 14 kDa circulating protein (p14) is the fragment of endocan specifically cleaved by cathepsin G, a neutrophil-derived serine protease. De Freitas Caires et al. have found that 20 out of 55 severe septic patients had increased plasma levels of p14, whereas in the control subjects p14 was undetectable [33]. Palmiere et al. investigated endocan, procalcitonin and C-reactive protein in postmortem serum from femoral blood in a series of sepsis-related fatalities and control individuals who underwent medicolegal investigations. The sepsis-related fatalities group consisted of sixteen

forensic autopsy cases with documented clinical diagnosis of sepsis *in vivo*. The control group consisted of sixteen forensic autopsy cases with various non-infectious causes of death. Post-mortem serum endocan concentrations were significantly higher in the sepsis group, with values ranging from 0.519 ng/ml to 6.756 ng/ml. In the control group, endocan levels were undetectable in eleven out of sixteen cases. Palmiere concluded that endocan can be considered a suitable biological parameter for the detection of sepsis-related deaths in forensic pathology routine [34]. Kao et al. investigated differential changes in plasma levels of ESM-1(endocan) before and after antibiotic treatment in hospitalized adult patients with community-acquired pneumonia. The authors concluded that ESM-1(endocan) is able to play a role in the diagnosis and clinical assessment of the severity of CAP [35]. In one part of Lee's studies serum endocan levels were measured in healthy volunteers and in patients with sepsis. Median serum endocan levels in healthy volunteers cohort were 0.75 ng/mL in comparison to median levels of 1.55 ng/mL, 2.402 mg/mL, and 6.07 ng/mL in sepsis, severe sepsis, and septic shock respectively. Difference between groups was statistically siqnificant ($p<0.000001$) suggesting that endocan levels can be used to predict the level of severity of sepsis and as monitoring marker of progression of sepsis [36,37]. In summary all these results suggest that in septic patients endocan blood level is related to severity of sepsis and outcome of patient. Mihajlovic et al. searched for association of endocan levels at 24 hours after the onset of sepsis with organ failure and mortality. The concentration of endocan was found to be higher in patients with sepsis-induced organ failure than in those with less severe forms of sepsis 2.05 ± 0.74 ng/mL vs 1.19 ± 0.59 ng/mL. Endocan levels were also correlated with mortality and higher levels were found in non-survivors than in survivors 2.18 ± 0.77 ng/mL vs 1.62 ± 0.75 ng/mL [36,38]. Parmentier et al. in a large, prospective observational clinical trial measured endocan levels in 125 septic ICU's patients and correlated survival at day 10 of admission to levels at day 2 and day 7. Preliminary results for 39 patients showed that endocan levels were higher at admission in patients with poor prognosis. In this group of patients endocan levels at day 2 and day 7 were increased and deceased by day 10. Conversely, endocan levels fell as early as day 2 in patients who survived to day 10 of admission [39]. Tang et al. has demonstrated that patients with endocan levels above 4.96 ng/mL were more likely to develop into septic shock and renal failure, and the AUROC of endocan was 0.772 for septic shock and 0.714 for renal failure. By contrast, PCT, CRP, and WBC did not show discriminative power for an early prediction of organ failure and sepsis severity [40].

Conclusions

Endothelium is one of the largest organs and the vascular endothelial barrier is an important element of septic response. The local and systemic effects of infection cause endothelial activation, and breakdown of microvascular integrity results in septic multiple organ dysfunction syndrome. According to some studies results, in sepsis, one of elements of its complex clinical picture, endothelial septic activation, should be routinely monitoring. Starting from 2006 Sherpereel's publication concerning endocan- the endothelial activity biomarker, many studies suggest that in septic patients, endocan blood level is related to severity of sepsis and outcome of patient. It is possibly that measurement of endocan as assessment of septic endothelial activity could potentially guide the development of sepsis treatment strategies and improvement of sepsis treatment results.

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