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Endothelial Cells: Role in Infection and Inflammation

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Abstract. Infection and resulting sepsis continue to be important causes of morbidity and mortality in surgical patients. Although much has been learned about the pathogens and the leukocyte responses to these pathogens, we are only beginning to understand the role of the host in these pathologies. The endothelium is a dynamic participant in cellular and organ function rather than a static barrier as it was once believed. Emerging evidence implicates the endothelium as a central effector in the inflammatory response. Through the expression of surface proteins and secretion of soluble mediators, the endothelium controls vascular tone and permeability, regulates coagulation and thrombosis, and directs the passage of leukocytes into areas of inflammation. Derangements in these normal functions may contribute significantly to a maladaptive inflammatory response leading to systemic inflammation and multiple organ failure.

Inflammation is the mechanism by which the body heals. Physiologically, it operates in a restricted environment to eradicate infected or devitalized tissue. Although usually beneficial to the host, inflammation is intrinsically destructive to the immediate surroundings. If the inflammatory response escapes local control, it induces a generalized systemic response. Excessive or prolonged activation of macrophages and neutrophils results in inappropriate production of cytokines. These substances potentiate the inflammatory response by activating inflammatory and endothelial cells in vascular compartments remote from the initial sites of inflammation. The increasingly dysregulated and misdirected immune response leads to whole-body inflammation, coagulopathy, and organ injury associated with the systemic inflammatory response syndrome (SIRS). If persistent, the host enters the spiral of increasing organ dysfunction, eventually leading to death [1, 2]. Although the pathogenic mechanisms of SIRS are not yet clear, investigations suggest that the endothelium is a central effector in the process rather than a mere victim of neutrophil-mediated damage.

Vascular endothelial cells form an interface between tissues and inflammatory cells. This unique location allows localization of the inflammatory reaction to sites of injury or infection while protecting adjacent healthy tissues. Endothelial cells mediate the local inflammatory response through modulation of vascular tone and local blood flow, increases in vascular permeability, induction of a prothrombogenic surface, and stimulation of leukocyte extravasation [3]. Given their central role in the initiation and coordination of the local inflammatory response, it is likely that the endothelium plays a primary role in the pathogenesis of systemic inflammation.

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Vascular Tone

Early during the development of the inflammatory response, vasodilatation leads to increased blood flow and transport of plasma proteins and leukocytes to sites of inflammation. Most vasodilators act indirectly, stimulating endothelial cells to release mediators that cause relaxation of underlying vascular smooth muscle cells [4]. The arachidonic acid metabolite prostacyclin (PGI_2) is a vasodilator synthesized by endothelial cells in response to thrombin, histamine, superoxide radicals, and leukotriene C_4 (LTC_4) [5, 6]. Tumor necrosis factor (TNF)- and interleukin-1 (IL-1)-stimulated endothelial cells release markedly more PGI_2 in response to the same degree of thrombin or histamine than do untreated cells [7] due to induction of enzymes involved in the arachidonic acid pathway. Another vasodilator produced by endothelial cells is endothelial-derived relaxing factor (EDRF), of which nitric oxide (NO) is the principal component. NO is generated by the same agonists as prostacyclin [4]. Endothelial cells synthesize vasoconstrictors such as endothelin-1 and platelet-derived growth factor (PDGF) [4]. Cytokine-stimulated endothelial cells also release platelet-activating factor (PAF), which relaxes or constricts vascular smooth muscle in a dose-dependent manner [8]. Although endothelial cells produce both constrictors and dilators, endothelial cell activation causes overall vasodilatation, and TNF and IL-1 enhance this vasodilatory effect.

The characteristic hemodynamic features of septic shock include elevated cardiac output and reduced peripheral vascular resistance due to systemic vasodilatation. This reduction in peripheral vascular resistance occurs despite elevated levels of circulating catecholamines and is relatively unresponsive to vasopressor agents [1]. Vascular insufficiency results from a functional defect that depresses the contractile response of smooth muscle cells, leading to a predominantly vasodilatory tone. Vascular hypocontractility has been described in arteries excised from septic animals and arteries incubated with endotoxin [9, 10]. These hemodynamic derangements are associated with distributive changes in systemic and microcirculatory blood flow leading to impaired oxygen utilization and organ dysfunction.

Vascular Permeability

Tissue edema secondary to increased vascular permeability is a classic sign of inflammation. Alterations in endothelial cell morphology and resultant increased fluid permeability are affected by inflammatory agents, cytokines, and the direct action of neutrophils. Agonists that increase intracellular calcium, such as fibrin, thrombin, and histamine, cause endothelial cell contraction and separation [11]. Cellular contraction is rapid and short-lived, leading to extravasation of fluid and proteins but not cells. Fluid leak leads to blood stasis, reducing shear forces and favoring leukocyte adherence to the endothelial surface. Cytokines, such as TNF, IL-1, and interferon-γ (INFγ) produce vascular leak by cytoskeletal reorganization within endothelial cells resulting in delayed but persistent increases in vascular permeability [12]. In this context, recombinant human cytokines used for cancer therapy have been limited by the complication of significant edema [13]. In animal studies, TNF or INFγ injection resulted in focal swelling of microvascular endothelial cells and the presence of amorphous material in the vessel wall indicating increased vascular permeability [14]. Similarly, incubation with lipopolysaccharide (LPS) results in direct morphologic changes in bovine endothelial cells, including dilation of intracellular junctions, cell contraction, and ruffling of the surface membrane [15].

It has been found that endothelial cells respond to neutrophil contact by increasing intracellular calcium, a second messenger involved in endothelial cell contraction and separation. According to this model, endothelial cells not only play a role in the adhesion of neutrophils to their surface but actively modulate their transmigration and extravasation [6, 16]. One theory suggests that neutrophil–endothelial cell interactions can become pathologic when activated neutrophils, adherent to the endothelium, prematurely degranulate, releasing toxic oxygen radicals and proteolytic enzymes. The resulting endothelial cell damage or lysis leads to vascular leakage. Proof of direct involvement of neutrophils alone in this process is lacking. In cases of severe injury, endothelial cells can retract from the underlying basement membrane [6]. Electron microscopic studies of vessels isolated from septic animals have revealed endothelial injury with separation of the endothelium from the internal elastic lamina and an increase in interendothelial gaps [17]. This mechanism of endothelial cell damage is also thought to cause pulmonary leak in patients with adult respiratory distress syndrome (ARDS), a frequent complication of SIRS [18].

Thrombosis and Coagulation

The syndrome of disseminated intravascular coagulation (DIC) and microvascular thrombosis are complications of SIRS. These derangements involve endothelium-derived signals that affect thrombin generation, fibrinolysis, and platelet activation.

Postmortem studies of SIRS have revealed fibrin microthrombi adjacent to intact microvascular endothelial cells, suggesting a dysregulation of normal endothelial cell anticoagulant function [19]. Quiescent endothelial cells provide three anticoagulant mechanisms that limit intravascular thrombosis. First, cell surface expression of thrombomodulin and secretion of protein S provide negative feedback to thrombin generation through the activation of protein C [20]. In addition, activated protein C degrades tissue plasminogen activator (tPA) inhibitor, promoting plasmin formation and subsequently activating fibrinolysis [21]. Second, heparin sulfate associated with the endothelial cell surface catalyzes the inactivation of serine proteases by antithrombin III [22]. Finally, endothelial cells inhibit platelet aggregation through synthesis of prostacyclin and adenosine [23].

Tumor necrosis factor was first identified by virtue of its ability to produce hemorrhagic necrosis of tumors [24] and has since been implicated as a significant proximal mediator in the pathogenesis of SIRS [25]. Exposure of intact endothelial cells to TNF and related cytokines such as IL-1 results in a loss of basal anticoagulant activity and induction of new procoagulant and prothrombogenic functions [26]. TNF and IL-1 inhibit the expression of thrombomodulin and the generation of activated protein C, leading to unopposed coagulation [26, 27]. Animal studies have shown that activated protein C protects baboons from lethal *Escherichia coli* infusion, and monoclonal blockade of protein C causes death at sublethal doses [28]. TNF and IL-1 decrease endothelial synthesis of tPA while increasing synthesis of tPA inhibitor. In addition, the lack of protein C results in unopposed tPA inhibitor activity. The net effect of these derangements are reduced plasmin formation and minimal fibrinolysis [29]. In addition, these cytokines induce synthesis and surface expression of tissue factor, enabling the intact endothelium to initiate the extrinsic coagulation cascade [26, 27]. These changes potentiate unopposed and uncontrolled procoagulant activity.

It has been observed that neutropenic mice cannot initiate DIC in response to endotoxin, suggesting a pathogenic role of neutrophils in the coagulopathy associated with SIRS [30]. Neutrophils adhere to activated endothelial cells expressing E-selectin and PAF. Activated neutrophils release oxygen radicals, which inactivate α_1-proteinase inhibitor and α_2-macroglobulin, potent leukocyte elastase inhibitors. This situation facilitates elastase-induced damage of endothelial cells within the inflammatory focus. The damaged endothelium expressing tissue factor initiates the extrinsic coagulation cascade [31]. Therefore in the face of a procoagulant endothelial surface, neutrophil-mediated endothelial damage sets into motion uncontrollable coagulation.

Although the effects of TNF and IL-1 on the endothelial cells are procoagulant, their effects on platelets are unclear. Both cytokines increase endothelial synthesis of PGI_2, an inhibitor of platelet activation and adhesion, while also increasing the synthesis of PAF, an activator of platelet adhesion and degranulation [32–34]. Several inflammatory agents provoke endothelial degranulation of von Willebrand factor (vWf), an important mediator of platelet adhesion and aggregation [35–40]. Studies have shown that LPS or TNF infusion into healthy humans causes a significant increase in plasma vWf levels accompanied by local intravascular platelet aggregation and erythrostasis in the absence of tissue factor and fibrin deposits [41–44]. Elevated plasma vWf has been reported in several inflammatory conditions including rheumatologic disease [45], SIRS [46, 47], and ARDS [46, 48, 49]. Several investigators have sought to establish the predictive value of serum vWf levels in the development of ARDS, but its utility as an early biochemical marker has not been shown. These studies were based on the premise that elevated serum levels were derived from local damage to the pulmonary vasculature. In SIRS patients elevated plasma vWf levels were associated with decreased endothelial vWf content in the dermal microvasculature, suggesting diffuse endothelial activation in vascular beds uninvolved in the primary insult [47]. Regardless of its origin, excess plasma vWf predisposes the formation of platelet microthrombi in the pres-

ence of an intact endothelium. These microthrombi may lodge in capillaries, causing areas of local tissue ischemia and hypoperfusion, ultimately leading to the organ failure associated with SIRS.

Endothelial Cell Adhesion Molecules

Leukocyte adhesion to postcapillary venular endothelium is a critical step in the inflammatory process subject to multiple biologic regulators that serve to maximize the defensive capacity of leukocytes while limiting damage to the host. Cytokine and chemotactic signals generated at sites of inflammation result in the ordered expression of complementary adhesion molecules that support the sequential steps of leukocyte margination, rolling, and transmigration.

Selectins

The selectins are a group of surface glycoproteins essential to leukocyte margination and rolling along the vascular endothelium. Its members include endothelial E- and P-selectins and L-selectin expressed on neutrophils. The proteins are structurally homologous, containing the amino-terminal C-type lectin domain important for mediating the adhesion of these proteins via a carbohydrate ligand [50]. P-selectin is stored in α-granules of platelets [51, 52] and Wiebel-Palade bodies of endothelial cells [53, 54]. It is not constitutively expressed but is rapidly redistributed to the cell surface upon activation by TNF [55], histamine, thrombin [56], complement [57], oxygen radicals [58], and leukotrienes. Expression is maximal within 20 minutes of stimulation and begins to decline within 1 hour. E-selectin is expressed on activated endothelial cells [14, 59]. Expression requires de novo mRNA and protein synthesis and is induced by LPS [14] and TNF and IL-1 [59, 60]. Consequently, E-selectin expression is not observed until 2 hours after stimulation and is no longer detectable at 24 hours [14, 59]. In vitro, INFγ potentiates the expression of E-selectin in response to TNF or IL-1 but does not induce up-regulation when administered alone [61].

The ligand for P-selectin, P-selectin glycoprotein ligand-1 (PSGL-1), is distributed on monocytes, neutrophils [62], natural killer cells, and memory T lymphocytes [63]. COS cells transfected with PSGL-1 cDNA yield a biologically active ligand that binds P-selectin, and polyclonal antibodies to PSGL-1 inhibit the binding of P-selectin to neutrophils [64]. The sialylated glycans Lewis x (Le^x) antigen and sialic acid are components of PSGL-1 and are required for P-selectin interaction on cell surfaces [65–67]. The Le^x antigen expressed on cells of the myeloid lineage is also thought to serve as a ligand for E-selectin [68, 69]. L-selectin has been postulated to serve as a ligand for both E- and P-selectin [70–72].

P-selectin plays a role in inflammation and thrombogenesis [73] by mediating the interaction of leukocytes with platelets [74] and endothelial cells [65]. Using purified P-selectin incorporated into phospholipid membranes, it has been demonstrated that P-selectin mediates leukocyte rolling [75]. In mutant mice lacking the P-selectin gene, initial leukocyte rolling and extravasation are defective [76], and anti-P-selectin antibodies decrease neutrophil recruitment in a rat model of acute lung injury [77]. The role of E-selectin is to mediate neutrophil rolling under conditions of flow. Human neutrophils adhere and roll on monolayers transfected with human E-selectin cDNA under physiologic shear stress [72]. Adhesion and rolling was almost completely blocked by anti-E-selectin monoclonal antibodies.

In addition, P-selectin is responsible for macrophage recruitment during prolonged tissue injury. In a peritonitis model using P-selectin null mice, peritoneal macrophages in wild-type mice increased threefold after 48 hours, whereas macrophages in mutant mice remained near baseline levels [78]. In patients with inflammatory bowel disease, resected bowel showed more P-selectin in inflamed areas than in adjacent areas of normal gut [79]. The observation that, after surface expression, P-selectin can be cycled back to Wiebel-Palade bodies where it is available for reexpression [80] is consistent with the postulated role of P-selectin in chronic inflammatory processes.

Immunoglobulin Supergene Family

Another group of cell adhesion molecules involved in endothelial cell–leukocyte interactions is the immunoglobulin supergene family. This group comprises intercellular adhesion molecules-1 and -2 (ICAM-1, ICAM-2), vascular cell adhesion molecule-1, (VCAM-1) and platelet–endothelial cell adhesion molecule-1 (PECAM-1). The most well studied of these molecules is ICAM-1, an integral membrane glycoprotein, constitutively expressed on numerous cell types including endothelial cells [81]. In vitro ICAM-1 expression is up-regulated in response to IL-1, TNF, and INFγ [60]. In a baboon model up-regulation of ICAM-1 was detected within 6 to 9 hours of TNF injection, and expression reached a plateau within 24 hours [59]. ICAM-1 is the ligand for members of the β_2-integrin family of adhesion molecules. Specifically, it binds leukocyte function associated antigen-1 (LFA-1) [82, 83], expressed on all leukocytes, and Mac-1 [84, 85], a cell adhesion molecule expressed on monocytes and neutrophils.

ICAM-1 plays a critical role in events subsequent to initial leukocyte margination. An in vitro model under conditions of flow demonstrated that anti-ICAM-1 antibodies markedly inhibited neutrophil transmigration but had no effect on the number of rolling neutrophils [86]. PECAM-1 is localized at the surface borders of adjacent endothelial cells and may be required for neutrophil transmigration [87].

Soluble Adhesion Molecules

Soluble forms of E-selectin have been found in supernatants of cytokine-stimulated endothelial cells in culture [88, 89]. Low serum levels are present in healthy subjects, and elevated levels were detected in patients with septic shock [89]. The molecular weight of the soluble form is consistent with its generation by cleavage of the cytoplasmic domain. Circulating E-selectin is biologically active. P-selectin mRNA exists in a alternately spliced form, lacking the transmembrane domain, suggesting the existence of a shed form [90]. A biologically active form of P-selectin has also been reported to circulate in plasma [91]. A soluble form of ICAM-1 has been reported in the supernatant of cytokine-activated endothelial cells and in human serum [88, 92, 93].

Soluble adhesion molecules may have several potential functions. Down-regulation of surface expression may be a prerequisite for the transition from leukocyte adhesion to extravasation. The soluble forms may function as competitive inhibitors of membrane-bound forms, thereby regulating cell adhesion [94]. Alternatively, the soluble forms may have cytokine-like functions.

For instance, it has been demonstrated that soluble E-selectin has chemoattractant properties [95]. In the clinical setting, monitoring soluble adhesion molecule levels may have diagnostic or prognostic utility in diseases associated with endothelial pathology. E-selectin is a particularly attractive candidate in this regard as it is expressed only by vascular endothelial cells and not by any other cell types.

Juxtacrine Signals and Neutrophil Transmigration

Stimulated endothelial cells release a variety of fluid-phase inflammatory mediators that act as paracrine and autocrine signals. They include cytokines IL-1, IL-6, and IL-8; granulocyte/macrophage colony-stimulating factors GM-CSF, G-CSF, and M-CSF; and chemotactic factors gro-α and monocyte chemotactic protein (MCP) [23]. These factors have pleiotropic effects on hemostasis, vascular tone, leukocytes, and endothelial cells themselves. Increasingly, the importance of juxtacrine mediators, such as PAF, in leukocyte–endothelial cell activation is recognized. When expressed on the cell surfaces, juxtacrine mediators exert their effects by tethering specific effector cells and inducing functional activation. Often the tethered cells activate each other, a process termed cross-cellular activation. During the inflammatory process, as neutrophils and endothelial cells interact they activate each other via paracrine signals, allowing leukocyte adhesion and activation to be maximized at areas of inflamed endothelium while minimizing damage to tissues [96, 97].

Mediators generated in the inflammatory environment activate the endothelium to up-regulate E-selectin, P-selectin, and PAF. The selectins, capable of supporting neutrophil rolling, recruit neutrophils under physiologic conditions of flow. The selectins tether the neutrophil to the endothelium without causing activation. This facilitates interaction with PAF, which primes the adherent neutrophil via activation of specific neutrophil receptors. Neutrophils respond with increased cytosolic Ca^{2+}, which causes up-regulation and increased binding affinity of surface integrins and shedding of L-selectin. These surface changes allow the cell to stop rolling and become firmly adherent to the endothelium. In addition, the neutrophil becomes polarized and primed for enhanced degranulation. Neutrophil binding to endothelial E-selectin may in turn cause further endothelial activation through increases in endothelial Ca^{2+}. ICAM-1 expression is increased, so integrin-mediated neutrophil adhesion to the vessel wall is strengthened. Endothelial cells retract, resulting in gap formation and increased vascular permeability, which facilitates the movement of neutrophils from the intravascular to the extravascular environment. Thus through paracrine stimulation and cross-cellular activation both the neutrophil and the endothelial cell are essential to the process of cellular adhesion and extravasation.

Role of Endothelial Cells in the Pathogenesis of SIRS

The intimate relationship between endothelial cells and leukocytes during the inflammatory response renders the endothelium susceptible to neutrophil-mediated damage. Aberrant adhesion molecule expression may cause pathologic interactions between endothelium and activated granulocytes at sites remote from the initial infection. Adherent neutrophils can then degranulate prematurely and destroy underlying endothelial cells. The endothelial cell and basement membrane damage that ensues allows fluid and protein accumulation in the extravascular space, ultimately resulting in organ damage.

The endothelial cell injury seen in severe inflammatory states has been attributed to damage by activated neutrophils, although evidence now suggests that the endothelial cell is an active participant in its own demise. One study found that endothelial cell activation is a far more significant determinant of endothelial cell toxicity than is neutrophil activation. Using unstimulated human endothelial cells, neutrophils from SIRS patients were significantly more adherent that control neutrophils. Endothelial cells activated with TNF and IL-1 showed a marked increase in neutrophil adherence and cytotoxicity in both the SIRS and control groups, irrespective of neutrophil activation [98]. The specific adhesion molecules implicated in increased adherence and cytotoxicity have yet to be clearly defined, although ICAM-1 and E-selectin are likely involved. In vitro, ICAM-1 expression has been shown to promote, and be sufficient for, neutrophil-mediated cytotoxicity [99]. Animal studies have indicated that ICAM-1 plays a significant role in the organ damage resulting from septic shock. ICAM-1-deficient mice were resistant to the lethal effects of gram-positive and gram-negative sepsis [100]. Monoclonal antibodies directed against E-selectin on cytokine-stimulated endothelial cell monolayers inhibit polymorphonuclear leukocyte (PMN) adhesion and subsequent migration [101, 102]. These data suggest that therapeutic blockade of adhesion molecules expressed on endothelial cells or prevention of their expression is more likely to produce positive results than blockade of neutrophil adhesion molecules.

A study of endothelial adhesion molecule expression in the dermal microvasculature of SIRS patients provides insight into the state of generalized endothelial cell activation. Although baseline adhesion molecule expression did not differ between SIRS patients and controls, differences were observed in response to a subcutaneous TNF challenge. E-selectin expression was increased in SIRS patients but not in controls, indicating that SIRS patients are primed to up-regulate this molecule, perhaps due to previous activation. In contrast, SIRS patients did not up-regulate P-selectin in response to a TNF challenge, whereas control subjects did. Thus with SIRS the endothelium is activated at sites remote from the initial inflammatory insult, responding differently to cytokine stimulation than do the controls. This factor may play a role in aberrant neutrophil–endothelial cell interactions and the distant organ failure that eventually ensues [103].

Antiadhesion Molecule Therapy

Attempts to attenuate neutrophil-mediated endothelial cell damage have been aimed at the blockade of essential adhesion molecule interactions. Oligosaccharides and anti-selectin antibodies have attempted to block interactions of selectins with their receptors. Another approach has been the use of recombinant forms of the selectins and synthetic selectin-derived peptides. Selectin-derived peptides have been shown to inhibit neutrophil infiltration into sites of inflammation in a mouse peritonitis model [104]. In rabbits, selectin blockade attenuated lung injury in response to acid aspiration [105]. In rats, anti-E-selectin antibodies inhibited neutrophil influx in glycogen-induced peritonitis and attenuated neutrophil-mediated lung injury following immune complex deposition [106].

A novel selectin inhibitor is pertussis toxin, which binds oligosaccharide structures similar to those serving as selectin ligands. Pertussis toxin-derived peptides reduce neutrophil binding to activated endothelial cells in vitro and reduce footpad swelling in mice [107].

Other approaches have been aimed at the immunoglobulin supergene family of adhesion molecules. Antibodies to the neutrophil ligand for ICAM-1 decreased lung injury associated with gram-negative sepsis in primates and pigs [108]. Anti-ICAM-1 antibodies have been shown to inhibit leukocyte infiltration and tissue injury in several models of lung inflammatory disease [109, 110]. In rats, antibodies to PECAM-1 blocked the accumulation of neutrophils in the peritoneal cavity following glycogen-induced peritonitis and in the alveolar compartment following immune complex deposition in the lung [111]. The clinical utility of such agents awaits confirmation in clinical trials.

Conclusions

An emerging hypothesis identifies the endothelium as the central effector in the inflammatory response. This organ is ubiquitous and uniquely located to act as an interface between circulating cells, soluble factors, and parenchymal cells. In this position it concentrates and localizes the inflammatory response. When the endothelium fails, smooth muscle dysfunction leads to massive vasodilatation, venous pooling and hypoperfusion of vital tissues. Increases in vascular permeability cause significant generalized tissue edema. The endothelial surface becomes prothrombogenic, precipitating coagulopathy and microthrombus formation. Aberrant adhesion molecule expression leads to neutrophil-mediated cytotoxicity. These manifestations of systemic inflammation result in significant organ injury and eventual organ failure.

Résumé

L'infection et le sepsis qui en résulte continuent d'être une cause importante de morbidité et de mortalité chez les patients en chirurgie. En dépit des progrès acquis concernant les germes pathogènes et la réponse des leucocytes vis-à-vis de ces germes, nous commençons à comprendre à paine le röle de l'höte dans ces pathologies. L'endothélium n'est pas une simple barrière statique comme on le croyait autrefois, mais semble jouer un röle dynamique dans la fonction cellulaire et organique. Il existe de plus en plus de preuves que l'endothélium est un effecteur principal de la réponse inflammatoire. A travers l'expression des protéines de surface et la sécrétion de médiateurs solubles, l'endothélium contröle le tonus et la perméabilité vasculaires, régule la coagulation et la thrombose ainsi que dirige le passage des leucocytes dans les régions d'inflammation. Le dérèglement de ces fonctions normales peut contribuer de façon significativa à la réponse inflammatoire mal adaptée qui mène vers le syndrome d'inflammation systémique et la défaillance polyviscérale.

Resumen

La infección y el consecuente estado séptico siguen siendo causas importantes de morbilidad y mortalidad en los pacientes quirúrgicos. Aunque es mucho lo que se ha progresado en el conocimiento de los patógenos y de las respuestas leucocitarias a ellos, solo ahora comenzamos a entender el rol del huésped en tales estados patológicos. El endotelio es un participante dinámico en la función celular y orgánica, y no una mera barrera estática, como antes se consideraba. Nuevas evidencias implican al endotelio como efector central de la respuesta inflamatoria. Mediante la expresión de proteínas de superficie y la secreción de moduladores solubles, el endotelio controla el tono vascular y la permeabilidad, regula la coagulación y la trombosis y dirige el paso de leucocitos hacia las áreas de inflamación. Las alteraciones de estas funciones normales pueden contribuir en forma significativa a una respuesta inflamatoria inadecuada, lo cual lleva a la inflamación sistémica y la falla multiorgánica.

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