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Role of endothelial glycocalyx in septic acute lung injury

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Abstract: Septic acute lung injury (SALI) is one of the common complications of sepsis, with a high incidence and closely related to the high mortality of patients in the intensive care unit. The pathophysiological mechanism of SALI is complex and involves multiple aspects such as dysfunction of the pulmonary vascular endothelial barrier. Endothelial glycocalyx (EG), a polysaccharide-protein complex covering the surface of vascular endothelial cells, plays a key role in maintaining vascular integrity, regulating inflammatory responses and coagulation functions. Recent studies have demonstrated that the damage of EG plays an important role in the occurrence and progression of SALI. This article reviews the structural and functional basis of EG, and focuses on discussing the molecular mechanism of EG damage in sepsis and its role in SALI, aiming to provide a theoretical basis for the exploration of therapeutic targets and the development of related drugs for SALI.

Keywords: Endothelial glycocalyx; Sepsis; Acute lung injury; Hyaluronic acid; Inflammatory response; Syndecan; Degradation enzyme

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Sepsis is a life-threatening organ dysfunction caused by the dysregulated host response to infection, and it is one of the leading causes of death among patients in intensive care units (ICUs) globally[1]. The core of its pathophysiological mechanism lies in uncontrolled systemic inflammatory response, coagulation dysfunction, and microcirculatory disturbance, which ultimately lead to multiple organ failure[2]. Acute lung injury (ALI) is a common complication of sepsis. Statistics show that more than 40% of sepsis patients develop ALI, whose main features include diffuse alveolar damage, increased pulmonary vascular permeability, neutrophilic inflammatory response, and severe hypoxemia[3]. Once ALI occurs, the clinical prognosis of patients deteriorates significantly, and the ICU mortality rate can rise from 11% to 38%[3].

One of the main pathological changes in septic acute lung injury (SALI) is impaired pulmonary vascular endothelial barrier function, and its regulatory mechanism is complex[3]. The endothelial glycocalyx (EG) is a dynamic polysaccharide-protein complex covering the luminal surface of vascular endothelial cells (ECs), which plays a key role in maintaining vascular integrity, regulating inflammatory responses, and maintaining the balance between coagulation and anticoagulation[4]. Studies have shown that EG damage may be involved in the development and recurrence of SALI[4], but its specific molecular mechanism is not yet fully clear. This article reviews the research progress on the molecular mechanism of EG damage in sepsis and its role in SALI, aiming to provide potential safe and effective therapeutic targets for the treatment strategies and drug research and development of SALI.

1 Structural and functional basis of EG

EG is a complex gel-like structure covering the surface of ECs, with a thickness of 0.5 to 4.5 μm. Its composition and thickness vary depending on the type of blood vessel, its distribution location in the body, and physiological state[5]. EG is mainly composed of membrane-bound proteoglycans, glycosaminoglycan (GAG), glycoproteins, and adsorbed plasma proteins. The main categories of GAG include heparan sulfate (HS), chondroitin sulfate, dermatan sulfate, keratan sulfate, and hyaluronic acid (HA). Among them, HS has the highest content, accounting for 50% to 90% of the total GAG. These GAG carry negative charges due to sulfation modification, and can adsorb positively charged plasma proteins through electrostatic interaction, thereby maintaining the stable colloid osmotic pressure in blood vessels[6]. In addition, EG also contains a variety of functional plasma proteins and glycoproteins, such as albumin, E-selectin, P-selectin, intercellular adhesion molecule (ICAM), and vascular cell adhesion molecule (VCAM). These proteins not only constitute important components of EG, but also participate in the regulation of its biological functions[4,6].

With its unique structure and molecular composition, EG plays multiple key roles in maintaining vascular homeostasis: (1) Through its gel-like structure and negative charge barrier effect, EG effectively restricts the passage of macromolecular substances, thereby maintaining the balance of colloid osmotic pressure inside and outside blood vessels, and preventing the leakage of fluid and proteins from blood vessels into the tissue space; (2) EG regulates the synthesis and release of nitric oxide (NO) by converting blood flow shear stress into biochemical signals of ECs, thereby maintaining the normal regulation of vascular tone[7]; (3) EG maintains the anticoagulant state of the endothelium and inhibits the formation of microthrombi by adsorbing anticoagulant proteins such as antithrombin III and thrombomodulin[8]; (4) EG shields

adhesion molecules (such as ICAM-1 and VCAM-1) expressed on the surface of ECs through its intact "sugar coat" structure, thereby preventing non-specific adhesion of circulating leukocytes and platelets to ECs[9].

2 Molecular mechanisms of EG damage in sepsis

2.1 Role of inflammatory factors

In the early stage of sepsis, monocytes/macrophages are stimulated by pathogens and release a large number of inflammatory factors, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-1β, and IL-10. These cytokines can bind to corresponding receptors on the surface of ECs and activate downstream signaling pathways, thereby inducing the expression and activation of EG-degrading enzymes. A study by Wiesinger *et al.*[10] found that after treating human umbilical vein ECs with TNF-α or lipopolysaccharide (LPS) *in vitro*, the thickness of EG was reduced by approximately 50%. In addition, another study has confirmed that there is a significant association between IL-6 and its downstream signaling pathways and EG damage[11].

2.2 Regulatory role of angiopoietin (Ang)

The Ang/tyrosine kinase receptor (Tie) 2 signaling pathway plays a key role in regulating vascular stability and permeability[12]. Under physiological conditions, Ang-1 binds to the Tie2 receptor and inhibits the activity of the transcription factor forkhead box O1 (FOXO1), thereby maintaining the stable state of ECs[12]. However, in sepsis, the expression and release of Ang-2 are significantly upregulated[13]. As an endogenous antagonist of Ang-1, Ang-2 can competitively block the binding of Ang-1 to Tie2, thereby relieving the inhibition of FOXO1, which in turn triggers EG degradation, EC activation, and increased vascular permeability[13]. Therefore, the imbalance of the Ang/Tie2 signaling pathway is one of the important mechanisms of EG damage and vascular barrier function destruction in sepsis.

2.3 Damage caused by oxidative stress and reactive oxygen species (ROS)

Oxidative stress is another key link in the pathological process of sepsis. During this process, activated immune cells and mitochondrial dysfunction can lead to the generation of a large amount of ROS[14]. ROS cause damage to EG through multiple pathways: First, ROS can directly oxidize the main components of EG, such as proteoglycan and GAG, thereby destroying its structural integrity. Second, as important signaling molecules, ROS can activate a variety of transcription factors, which in turn upregulate the expression of inflammatory factors and EG-degrading enzymes, forming a positive feedback cycle[15]. In addition, ROS can also consume endogenous antioxidants, weakening the body's antioxidant defense capacity and making EG more susceptible to oxidative damage[15].

2.4 Core role of enzymatic degradation

2.4.1 GAG-degrading enzyme: heparanase (HPSE)

HPSE-1 is an endo-β-glucuronidase whose main function is to specifically cleave HS chains[16]. In sepsis, inflammatory factors and ROS can induce ECs to express and secrete HPSE-1. Activated HPSE-1 can degrade the most abundant HS component in EG, thereby destroying the structural integrity and physiological function of EG[17]. In a mouse model of sepsis, LPS upregulates the expression of HPSE-1 through the Toll-like receptor 4 (TLR4)/high mobility group box 1 protein (HMGB1) signaling pathway[18]. Activated HPSE-1 not only degrades HS, but its degradation products can also act as damage-associated molecular patterns (DAMPs), further activating the immune response and exacerbating the loss of EG components[19]. In addition, the activity of HPSE-1 is regulated by its homologous protein HPSE-2. Studies have shown that HPSE-2 can inhibit the TLR4 pathway and reduce the expression levels of TNF-α and IL-6, thereby alleviating LPS-induced HS shedding[20].

2.4.2 Proteoglycan-cleaving enzymes: matrix metalloproteinase (MMP) and a disintegrin and metalloproteinase (ADAM)

In sepsis, the expression levels and enzyme activities of multiple MMPs (such as MMP-2, MMP-7, and MMP-9) are significantly increased. These proteases can directly cleave core proteoglycans in EG (such as Syndecan-1), promoting their shedding from the cell surface[21]. A study by Yang *et al.*[22] found that ADAM15, a CD44 epitope lyase, can cleave the extracellular domain of CD44 and release soluble inflammatory signal fragments, thereby weakening the connection between EG and the EC cytoskeleton and leading to impaired vascular endothelial barrier function. In addition, ADAM17 and ADAM10 can also mediate the cleavage of Syndecan-1, promoting the progression of the systemic inflammatory response[23]. The above studies indicate that the expression of ADAM family members is upregulated during sepsis, and their expression levels are closely related to disease severity and clinical prognosis.

2.4.3 Other degrading enzymes: hyaluronidase and lysosomal enzymes

Hyaluronidase can degrade HA in EG, destroying the structural stability of EG[24]. In addition, lysosomal enzymes can also induce the degradation of EG. Studies have found that EG undergoes patchy degradation only 10–15 minutes after exposure to LPS, which is related to the release of hydrolases from lysosomes[25]. This indicates that lysosomal enzymes may play a role in the early stage of EG damage, providing a new perspective for understanding the mechanism of rapid EG degradation.

3 Pathophysiological association between EG damage and SALI

3.1 Destruction of pulmonary vascular endothelial barrier function

The integrity of the alveolar-capillary barrier is the basis for maintaining normal gas exchange. As a key component of this barrier, the integrity of EG is of great significance for maintaining the stability of pulmonary vascular permeability[3]. Under physiological conditions, the dense and structurally intact EG layer can effectively prevent plasma proteins (especially albumin) from infiltrating the pulmonary interstitium and alveolar space, thereby maintaining a normal colloid osmotic pressure gradient[6]. However, in sepsis, massive degradation of EG occurs, destroying its structure that functions as both a physical barrier and a charge barrier, leading to increased vascular permeability. As a result, a large amount of protein-rich plasma components extravasate and accumulate in the pulmonary interstitium and alveolar space, forming non-cardiogenic pulmonary edema[3,26]. Both clinical studies and animal experiments have shown that the degree of EG degradation is significantly positively correlated with the severity of pulmonary edema[27]. In addition, EG damage not only promotes fluid extravasation but also allows fibrinogen to enter the pulmonary interstitium. The extravasated fibrinogen is converted into fibrin under the action of tissue factor (TF), thrombin and other substances, and deposits in the pulmonary interstitium and alveolar space, forming the characteristic "hyaline membrane", which is one of the typical pathological changes of acute respiratory distress syndrome (ARDS)[26]. The above pathological changes significantly impair lung compliance and gas exchange function, becoming a key factor leading to respiratory failure and even death in patients.

3.2 Exacerbated inflammatory response and immune cell infiltration

The intact EG layer covers the adhesion molecules on the surface of ECs through its physical barrier effect, effectively preventing the adhesion of leukocytes such as circulating neutrophils to ECs[9]. When EG is degraded, these adhesion molecules are exposed on the surface of ECs, providing binding sites for the rolling and firm adhesion of leukocytes. In addition, the degradation products of EG (such as HS fragments) can act as endogenous chemokines, inducing leukocytes to migrate and accumulate at the site of inflammation. This enhanced interaction between leukocytes and ECs is the initial link in the infiltration of inflammatory cells into lung tissue, and also one of the important mechanisms causing lung tissue damage[3].

In recent years, the role of neutrophil extracellular traps (NETs) in sepsis-induced organ damage has received widespread attention. NETs are reticular structures composed of DNA, histones and granular proteins, which have the function of capturing pathogens, but their excessive formation may lead to host tissue damage[28]. Studies have shown that EG damage is closely related to the formation of NETs. Degradation of EG can create conditions for the release of NETs, while components in NETs (such as histones) can further aggravate the damage of EG and ECs, thus forming a vicious cycle[29-30].

3.3 Coagulation dysfunction and microthrombosis

EG plays a key role in maintaining the anticoagulant properties of the vascular endothelium, and its damage can trigger the activation of the coagulation system, thereby leading to the formation of microthrombi[5]. The anticoagulant proteins adsorbed on the surface of EG (such as antithrombin III and thrombomodulin) shed into the blood circulation after EG degradation, resulting in a significant decrease in local anticoagulant capacity[31]. Meanwhile, under the stimulation of inflammatory factors, ECs can express TF, a potent procoagulant substance that can activate the exogenous coagulation pathway, promote the generation of a large amount of thrombin, convert fibrinogen into fibrin, and form widely distributed microthrombi in the pulmonary microvessels[32]. These microthrombi can block blood vessels, cause pulmonary tissue perfusion disorders, and aggravate ventilation/perfusion mismatch, thereby further exacerbating hypoxemia. In addition, the formation process of microthrombi consumes a large number of coagulation factors and platelets, leading to a bleeding tendency, and ultimately causing disseminated intravascular coagulation (DIC), which further worsens and complicates the condition[33].

4 Clinical application of EG degradation markers

Since there are technical challenges in directly measuring the thickness and structure of EG in vivo, detecting its components released into the blood after degradation has become the main clinical method for evaluating the degree of EG damage. As a key component of EG core proteoglycans, the plasma concentration of Syndecan-1 is currently the most widely studied biomarker for EG injury[21]. Multiple clinical studies have confirmed that in patients with sepsis, the plasma level of Syndecan-1 is significantly elevated, and the magnitude of its elevation is significantly positively correlated with disease severity and poor prognosis[34-36]. A retrospective study including 262 patients with severe sepsis showed that the plasma level of Syndecan-1 was significantly correlated with the development of ARDS, the occurrence of other organ dysfunctions, and in-hospital mortality[34]. Particularly importantly, the level of Syndecan-1 is an independent risk factor for predicting patient mortality. Even after adjusting for confounding factors such as age and Acute Physiology and Chronic Health Evaluation II (APACHE II) score, its predictive efficacy remains significant[27]. In addition to Syndecan-1, other degradation products of EG, such as HS and HA, have also been confirmed to be usable as biomarkers of endothelial injury, which are correlated with the severity of sepsis and the degree of organ dysfunction[37-40].

5 Therapeutic strategies: protection, repair and replacement of EG

5.1 Clinical strategies for protecting EG integrity

Improper application of various conventional clinical interventions may cause further damage to the already impaired vascular EG. Therefore, optimizing relevant clinical management strategies is of great significance for protecting the structure and function of EG, and is a key link in preventing secondary damage to EG.

5.1.1 Optimization of fluid resuscitation strategy: restrictive fluid administration and avoidance of high volume overload

Fluid resuscitation is the cornerstone of sepsis treatment. However, high volume overload has been confirmed as one of the important factors leading to vascular EG damage[5]. Infusion of a large amount of crystalloid solution can dilute plasma proteins, reduce intravascular colloid osmotic pressure, and simultaneously increase intravascular hydrostatic pressure. The above dual effects jointly promote the exudation of fluid through the damaged EG into the interstitial space, thereby aggravating tissue edema[41]. In addition, some studies suggest that high-volume crystalloid solution itself may have a direct damaging effect on EG structure through mechanical shear force or dilution effect[42]. Therefore, after achieving hemodynamic stability, timely adoption of a restrictive fluid management strategy, including stopping or slowing down the infusion rate and avoiding persistent positive fluid balance, is of great significance for protecting EG integrity and reducing pulmonary edema[43]. Although resuscitation with colloids (such as albumin) may be more beneficial for maintaining colloid osmotic pressure, its direct protective effect on EG remains to be further confirmed by research[44].

5.1.2 Use of vasoactive drugs: restriction of catecholamine application and alternative options

Catecholamines (such as norepinephrine) are commonly used vasoactive drugs during septic shock, but high-dose or long-term application may have adverse effects on vascular EG[45]. High concentrations of catecholamines can activate ECs, leading to increased vascular permeability, and may indirectly cause EG damage by increasing cardiac afterload and vascular wall tension. Therefore, the principle of "minimum effective dose" should be followed in clinical application to avoid excessive blood pressure elevation so as to reduce potential harm. In recent years, some non-catecholamine vasoactive drugs, such as vasopressin and its analogs, have attracted attention because of their potential protective effect on EG. Vasopressin mainly mediates vasoconstriction by activating V1 receptors, and its mechanism of action is different from that of catecholamines, which may cause less interference to endothelial barrier function[45]. However, the above results still need to be further verified by more high-quality clinical studies.

5.1.3 Blood glucose control: prevention of vascular EG damage caused by hyperglycemia

Hyperglycemia is a common type of metabolic disorder in critically ill patients, and it is also an independent risk factor for endothelial dysfunction and vascular EG damage[29]. Hyperglycemia can mediate EG damage through a variety of mechanisms, which mainly include: (1) inducing oxidative stress and promoting the generation of a large amount of ROS; (2) activating signaling pathways such as protein kinase C to increase vascular permeability; (3) promoting the accumulation of advanced glycation end products, leading to protein cross-linking and abnormal structure and function. Therefore, implementation of strict blood glucose management (usually referring to maintaining blood glucose levels at 6–10 mmol/L) is regarded as a key intervention measure to protect EG integrity and improve the prognosis of patients with sepsis[46]. In addition, insulin itself is considered to have direct anti-inflammatory effects and vascular endothelial protective effects, which may have potential benefits for the maintenance of EG structure[45].

5.1.4 Potential protective effect of glucocorticoids

Glucocorticoids have significant anti-inflammatory and immunosuppressive effects. Theoretically, they can indirectly exert a protective effect on vascular EG by inhibiting the release of pro-inflammatory cytokines[47]. Some small-scale clinical studies and animal experiments have shown that low-dose glucocorticoids may help to reduce the degradation process of EG[48]. However, the application of glucocorticoids is still controversial, and its potential adverse reactions (such as hyperglycemia, immunosuppression, muscle weakness, etc.) limit its clinical use to a certain extent. At present, there is no sufficient evidence to confirm whether glucocorticoids can bring clear clinical benefits to patients with sepsis by protecting EG, and its efficacy and safety still need to be further verified by larger-scale randomized controlled trials.

5.2 Therapies targeting EG-degrading enzymes

5.2.1 Application prospects of heparanase inhibitors

Heparanase plays a core role in sepsis-related EG damage. Therefore, heparanase inhibitors are expected to become an intervention strategy with great clinical potential. Multiple studies have shown that unfractionated heparin and the non-anticoagulant heparin derivative N-acetylheparin can effectively inhibit heparanase activity, and their mechanism of action is to directly block the degradation process of HS and Syndecan-1, thereby protecting the structure and function of EG at the source[49-50]. In addition, ulinastatin has also been confirmed to inhibit the expression and activity of heparanase induced by LPS, and has shown the effect of reducing vascular permeability and inhibiting HS degradation in a mouse model of ARDS[51]. However, most heparanase inhibitors are still in the preclinical research stage at present, and their safety, pharmacokinetic

characteristics and efficacy in humans still need to be systematically evaluated. Promoting the translation of these drugs from basic research to clinical application is an important direction for future therapeutic development.

5.2.2 Exploration of MMP and ADAM inhibitors

Under the condition of sepsis, multiple MMPs (such as MMP-2, MMP-7, and MMP-9) are often activated simultaneously, and there is certain functional redundancy among them[21]. Therefore, broad-spectrum MMP inhibitors may have more clinical application potential than specific inhibitors. Some marketed drugs, such as doxycycline, have broad-spectrum MMP inhibitory effects in addition to antibacterial activity. Animal experimental studies have shown that doxycycline can effectively reduce EG shedding and reduce the severity of lung injury[52]. In addition, small peptide inhibitors targeting ADAM17-mediated cleavage of Syndecan-1 and Syndecan-4 have also been identified as potential therapeutic drugs[53]. However, long-term or systemic inhibition of MMP and ADAM may interfere with normal tissue remodeling and repair processes, and potential adverse reactions need to be carefully evaluated.

5.3 Repair of EG and replacement therapies

5.3.1 Exogenous supplementation of EG components

Exogenous supplementation of EG components is a direct replacement treatment strategy, among which HA is the most widely studied component at present[54]. As a key structural component of EG, HA has biological functions such as water retention, anti-inflammation and immunomodulation. Baljinnyam *et al.*[55] intraperitoneally injected high-molecular-weight HA into mice, which effectively reduced the lung water content of sepsis mice with Syndecan-1 deficiency and significantly improved their survival rate. The potential mechanisms may include: (1) directly supplementing the damaged EG layer; (2) inhibiting the activation and infiltration of inflammatory cells; (3) promoting the tissue repair process. In addition, studies have shown that supplementing key proteins such as albumin required to maintain EG structure through fresh frozen plasma is helpful for restoring vascular endothelial function[56]. The advantage of this type of strategy is that the components are clear and the safety is relatively high, but its efficacy may be limited by the in vivo half-life of the supplemented substances, tissue distribution characteristics and integration efficiency with endogenous EG.

5.3.2 Drugs promoting endogenous EG synthesis

Promoting endogenous EG synthesis is a more physiological repair strategy. Sulodexide is a compound preparation composed of low-molecular-weight heparin and dermatan sulfate, which has been applied in the clinical treatment of vascular diseases[57]. Studies have shown that sulodexide not only has an anticoagulant effect, but also can promote ECs to synthesize and secrete the main components of EG, thereby accelerating the repair process of EG[58]. In addition, intravenous infusion of liposomal nanocarriers of preassembled glycocalyx (LNPG) is a new method for restoring EG. LNPG rapidly restores EG through fusion with endothelial cell membranes and maintains its integrity thereafter, effectively improving endothelial function[59]. Furthermore, when LNPG is delivered to ECs lacking EG, the therapeutic effect of LNPG has been confirmed both *in vivo* and *in vitro*[60]. The core advantage of this type of strategy is that it activates the body's own repair mechanism, but its onset of effect may be relatively slow, so it needs to be reasonably applied in combination with the stage of disease development.

5.4 Challenges and prospects of translational medicine

Although therapeutic strategies targeting vascular EG have shown great potential in animal models, their translation to clinical application still faces multiple challenges. First, there are species differences between animal models and human diseases, and existing models are often difficult to fully simulate the complex pathophysiological process and high heterogeneity of human sepsis. Second, there is still a lack of real-time, non-invasive techniques for evaluating EG status at present, which limits the dynamic monitoring of therapeutic effects. Clinically, indirect judgment is mainly made by detecting EG degradation products in plasma (such as Syndecan-1, HS fragments), but such methods have lag and non-specificity, and are difficult to accurately reflect the real-time changes of local EG. In addition, treatment timing and patient screening are key factors determining the success of intervention. Since EG damage can occur in the early stage of sepsis, the effective therapeutic window is relatively narrow, and intervention must be implemented in time at the initial stage of the disease. Therefore, identifying the largest potential population that can benefit from EG-targeted therapy is a prerequisite for realizing individualized precision medicine. Despite facing many challenges, as a core regulatory hub connecting inflammatory response, coagulation activation and microvascular barrier function, the scientific value and clinical potential of EG as a therapeutic target cannot be ignored. With the continuous deepening of basic research and the development of clinical translation technology, it is expected that safe and effective EG-targeted treatment regimens will be developed in the future, providing new therapeutic hope for patients with SALI.

6 Summary and prospects

In summary, previous studies have clearly confirmed the core mechanism of EG in SALI. Under physiological conditions, as an important component of the vascular barrier, EG not only maintains vascular integrity and regulates vascular tone, but also exerts key functions of inhibiting thrombosis and regulating inflammatory responses. Under the pathological condition of sepsis, the synergistic effect of excessively activated inflammatory response, oxidative stress and multiple degrading enzymes

leads to extensive degradation and shedding of EG. This damage process is not simply a concomitant phenomenon of pathological changes, but a key initiating link connecting systemic inflammation in sepsis and specific lung injury. EG damage directly leads to increased pulmonary vascular permeability and induces non-cardiogenic pulmonary edema. Meanwhile, the exposure of adhesion molecules on the surface of ECs aggravates the infiltration and activation of inflammatory cells such as neutrophils. In addition, the loss of endothelial anticoagulant properties activates the coagulation system and promotes the formation of microthrombi. These pathophysiological changes are intertwined and jointly constitute the complex pathological mechanism of SALI.

In view of the core role of EG in SALI, protecting, repairing or replacing EG has become a highly promising new therapeutic strategy. At present, multiple therapeutic approaches are being actively studied, ranging from optimizing routine clinical management, developing novel drugs targeting EG-degrading enzymes, to exploring exogenous supplementation of EG components. Although there are still many challenges and controversies in the process of translation from basic research to clinical application, as a multifunctional platform integrating barrier, signal transduction and immunomodulatory functions, the potential of EG as a therapeutic target cannot be ignored. Future research should focus on solving current technical bottlenecks, clarifying key scientific issues, and verifying the safety and efficacy of these new strategies through rigorous clinical trials. With the in-depth understanding of the biological functions of EG, EG-targeted precise therapeutic strategies are expected to provide new treatment directions for improving the prognosis of SALI, a critical disease.

Conflict of interest None

Reference

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·脓毒症专题·研究进展·

内皮细胞糖萼在脓毒症性急性肺损伤中的作用

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摘要：脓毒症性急性肺损伤(SALI)是脓毒症常见的并发症，具有较高的发病率，并与重症监护病房患者高死亡率密切相关。SALI的病理生理机制复杂，涉及肺血管内皮屏障功能障碍等多个方面。内皮细胞糖萼(EG)是一种覆盖于血管内皮表面的多糖—蛋白质复合物，在维持血管完整性、调节炎症反应及凝血功能中发挥关键作用。近年来的研究表明，EG的损伤在SALI的发生与发展过程中具有重要作用。本文综述了EG的结构与功能基础，重点探讨了脓毒症中EG损伤的分子机制及其在SALI中的作用，旨在为SALI的治疗靶点探索和相关药物的研发提供理论依据。

关键词：内皮细胞糖萼；脓毒症；急性肺损伤；透明质酸；炎症反应；黏结蛋白聚糖；降解酶

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Role of endothelial glycocalyx in septic acute lung injury

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Abstract: Septic acute lung injury (SALI) is one of the common complications of sepsis, with a high incidence and closely related to the high mortality of patients in the intensive care unit. The pathophysiological mechanism of SALI is complex and involves multiple aspects such as dysfunction of the pulmonary vascular endothelial barrier. Endothelial glycocalyx (EG), a polysaccharide-protein complex covering the surface of vascular endothelial cells, plays a key role in maintaining vascular integrity, regulating inflammatory responses and coagulation functions. Recent studies have demonstrated that the damage of EG plays an important role in the occurrence and progression of SALI. This article reviews the structural and functional basis of EG, and focuses on discussing the molecular mechanism of EG damage in sepsis and its role in SALI, aiming to provide a theoretical basis for the exploration of therapeutic targets and the development of related drugs for SALI.

Keywords: Endothelial glycocalyx; Sepsis; Acute lung injury; Hyaluronic acid; Inflammatory response; Syndecan; Degradation enzyme

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脓毒症是由于宿主对感染反应失调所引发的一种危及生命的器官功能障碍，是全球范围内重症监护病房(intensive care unit, ICU)患者死亡的主要原因之一[1]。其病理生理机制的核心在于失控的全身性炎症反应、凝血功能紊乱以及微循环障碍，最终导致多器官功能衰竭[2]。其中，急性肺损伤(acute lung injury, ALI)是脓毒症常见的并发症。据统计，超过40%的脓毒症患者并发ALI，其主要特征包括弥漫性肺泡损伤、肺血管通透性增加、中性粒细胞性炎症反应以及严重的低氧血症[3]。一旦发生ALI，患者的临床预后显著恶化，ICU死亡率可由11%上升至38%[3]。

脓毒症性急性肺损伤(septic acute lung injury, SALI)的主要病理变化之一是肺血管内皮屏障功能受损，其调控机制复杂[3]。内皮细胞糖萼(endothelial glycocalyx, EG)是覆盖于血管内皮细胞(endothelial cells, ECs)管腔表面的一种动态的多糖-蛋白质复合物，在维持血管完整性、调控炎症反应及维持凝血与抗凝平衡中发挥着关键作用[4]。研究表明，EG损伤可

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能参与了SALI的发生与发展过程[4]，但其具体分子机制尚不完全明确。本文综述了脓毒症中EG损伤的分子机制及其在SALI中的作用研究进展，旨在为SALI的治疗策略和药物研发提供潜在的安全有效治疗靶点。

1　EG的结构与功能基础

EG是覆盖于ECs表面的一层复杂的凝胶状结构，厚度为0.5~4.5 μm，其成分与厚度因血管类型、在机体内的分布位置以及生理状态的不同而有所差异[5]。EG主要由膜结合的蛋白聚糖、糖胺聚糖（glycosaminoglycan，GAG）、糖蛋白以及吸附性血浆蛋白共同组成。主要的GAG类别包括硫酸乙酰肝素（heparan sulfate，HS）、硫酸软骨素、硫酸皮肤素、硫酸角质素和透明质酸（hyaluronic acid，HA）。其中，HS含量最高，占GAG总量的50%~90%。这些GAG由于硫酸化修饰而带有负电荷，能够通过静电吸附带正电荷的血浆蛋白，从而维持血管内的胶体渗透压稳定[6]。此外，EG中还包含多种功能性血浆蛋白和糖蛋白，如白蛋白、E-选择素、P-选择素、细胞间黏附分子（intercellular adhesion molecule，ICAM）以及血管细胞黏附分子（vascular cell adhesion molecule，VCAM），这些蛋白不仅构成了EG的重要组成部分，还参与调控其生物学功能[4,6]。

EG凭借其独特的结构与分子组成，在维持血管稳态方面发挥着多重关键作用：（1）EG通过其凝胶状结构及负电荷屏障作用，有效限制大分子物质的通过，从而维持血管内外胶体渗透压平衡，防止液体和蛋白质从血管渗漏到组织间隙；（2）EG通过将血流剪切力转化为ECs的生化信号，调控一氧化氮（nitric oxide，NO）的合成与释放，从而维持血管张力的正常调节[7]；（3）EG通过吸附抗凝蛋白如抗凝血酶Ⅲ和血栓调节蛋白，维持内皮的抗凝状态，抑制微血栓的形成[8]；（4）EG通过其完整“糖衣”结构遮蔽ECs表面表达的黏附分子（如ICAM-1和VCAM-1），从而阻止循环中的白细胞和血小板与ECs发生非特异性黏附[9]。

2　脓毒症中EG损伤的分子机制

2.1　*炎症因子的作用*　在脓毒症早期，单核/巨噬细胞受到病原体刺激后释放大量炎症因子，例如肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）、白细胞介素（interleukin，IL）-6、IL-1β和IL-10等。这些细胞因子可与ECs表面的相应受体结合，并激活下游信号通路，从而诱导EG降解酶的表达及活化。Wiesinger等[10]研究发现，在体外环境中使用TNF-α或脂多糖（lipopolysaccharide，LPS）处理人脐静脉ECs后，其EG厚度可减少约50%。此外，另有研究证实，IL-6及其下游信号通路与EG损伤之间存在显著关联[11]。

2.2　*血管生成素（angiopoietin，Ang）的调控作用*　Ang/酪氨酸激酶受体（tyrosine kinase receptor，Tie）2信号通路在调控血管稳定性和通透性方面发挥关键作用[12]。在生理状态下，Ang-1通过与Tie2受体结合，抑制转录因子叉头框蛋白O1（forkhead box O1，FOXO1）的活性，从而维持ECs的稳定状态[12]。然而，在脓毒症中，Ang-2的表达和释放显著上调[13]。作为Ang-1的内源性拮抗剂，Ang-2可竞争性阻断Ang-1与Tie2的结合，从而解除对FOXO1的抑制，进而引发EG降解、ECs活化以及血管通透性增加[13]。因此，Ang/Tie2信号通路的失衡是脓毒症中EG损伤及血管屏障功能破坏的重要机制之一。

2.3　*氧化应激与活性氧（reactive oxygen species，ROS）的损伤*　氧化应激是脓毒症病理进程中的另一个关键环节，在该过程中，活化的免疫细胞以及线粒体功能障碍可导致大量ROS的生成[14]。ROS对EG的损伤具有多方面作用：首先，ROS可以直接氧化EG的主要组成成分，如蛋白聚糖和GAG，从而破坏其结构完整性；其次，ROS作为重要的信号分子，能够激活多种转录因子，进而上调炎症因子及EG降解酶的表达，形成正反馈循环[15]。此外，ROS还可消耗内源性抗氧化剂，削弱机体的抗氧化防御能力，使EG更易遭受氧化损伤[15]。

2.4　*酶促降解的核心作用*

2.4.1　GAG降解酶——乙酰肝素酶（heparanase，HPSE）　HPSE-1是一种内切-β-葡萄糖醛酸酶，其主要功能是特异性切割HS链[16]。在脓毒症中，炎症因子和ROS可诱导ECs表达并分泌HPSE-1。活化的HPSE-1可降解EG中最丰富的HS成分，从而破坏EG的结构完整性与生理功能[17]。在脓毒症小鼠模型中，LPS通过Toll样受体4（Toll like receptor 4，TLR4）/高迁移率族蛋白B1（high mobility group box 1 protein，HMGB1）信号通路上调HPSE-1的表达[18]。活化的HPSE-1不仅降解HS，其降解产物还可作为损伤相关分子模式（damage-associated molecular patterns，DAMPs），进一步激活免疫反应，加剧EG成分的丢失[19]。此外，HPSE-1的活性受到其同源蛋白HPSE-2的调控。研究表明，HPSE-2可通过抑制TLR4通路并降低TNF-α和IL-6的表达水平，从而减轻LPS诱导的HS脱落[20]。

2.4.2　蛋白聚糖切割酶——基质金属蛋白酶（matrix metalloproteinase，MMP）与解整合素金属蛋白酶（a disintegrin and metalloproteinase，ADAM）　在脓毒症中，多种MMP（如MMP-2、MMP-7、MMP-9）的表达水平和酶活性显著升高，这些蛋白酶可直接切割EG中的核心蛋白聚糖［如黏结蛋白聚糖（Syndecan）-1］，促使其从细胞表面脱落[21]。Yang等[22]研究发现，ADAM15是一种CD44表位裂解酶，可通过裂解CD44的胞外结构域，释放可溶性炎症信号片段，从而削弱EG与ECs骨架之间的连接，导致血管内皮屏障功能受损。此外，ADAM17和ADAM10也可介导Syndecan-1的裂解，促进全身性炎症反应的进展[23]。以上研究说明ADAM家族成员在脓毒症期间表达上调，其表达水平与疾病严重程度及临床预后密切相关。

2.4.3　其他降解酶——透明质酸酶与溶酶体酶　透明质酸酶能够降解EG中的HA，破坏EG的结构稳定性[24]。此外，溶酶体酶也可以诱导EG的降解。研究发现，EG在暴露于LPS后仅10~15 min，就会出现斑片状降解，这一现象与溶酶体内水解酶的释放有关[25]。这表明溶酶体酶可能在EG损伤的早期阶段就发挥作用，这为理解EG快速降解的机制提供了新视角。

3　EG损伤与SALI的病理生理联系

3.1　*肺血管内皮屏障功能破坏*　肺泡—毛细血管屏障的完整

性是维持正常气体交换的基础，而EG作为该屏障的关键组成部分，其完整性对于维持肺血管通透性稳定具有重要意义[3]。在生理状态下，致密且结构完整的EG层能够有效阻止血浆蛋白（尤其是白蛋白）渗入肺间质和肺泡腔，从而维持正常的胶体渗透压梯度[6]。然而，在脓毒症中，EG发生大量降解，破坏了其兼具物理屏障与电荷屏障功能的结构，导致血管通透性增加，富含蛋白质的血浆成分因此大量外渗并积聚于肺间质和肺泡腔内，形成非心源性肺水肿[3,26]。临床研究和动物实验均表明，EG降解程度与肺水肿的严重程度呈显著正相关[27]。此外，EG的损伤不仅促进液体外渗，还使纤维蛋白原进入肺间质。外渗的纤维蛋白原在组织因子（tissue factor，TF）及凝血酶等物质的作用下转化为纤维蛋白，并沉积于肺间质和肺泡腔，形成特征性的“透明膜”，这是急性呼吸窘迫综合征（acute respiratory distress syndrome，ARDS）的典型病理改变之一[26]。上述病理变化显著损害了肺的顺应性和气体交换功能，成为导致患者发生呼吸衰竭乃至死亡的关键因素。

3.2 *炎症反应加剧与免疫细胞浸润* 完整的EG层通过物理屏障作用覆盖于ECs表面的黏附分子之上，有效阻止了循环中的中性粒细胞等白细胞与ECs之间的黏附[9]。当EG发生降解，这些黏附分子暴露于ECs表面，为白细胞的滚动及牢固黏附提供了结合位点。此外，EG的降解产物（如HS片段）可作为内源性趋化因子，诱导白细胞向炎症部位迁移并聚集。这种白细胞与ECs之间相互作用的增强，是炎症细胞向肺组织浸润的起始环节，也是引发肺组织损伤的重要机制之一[3]。

近年来，中性粒细胞胞外诱捕网（neutrophil extracellular traps，NETs）在脓毒症所致器官损伤中的作用受到广泛关注。NETs是由DNA、组蛋白及颗粒蛋白组成的网状结构，具有捕获病原体的功能，但其过度形成则可能导致宿主组织损伤[28]。已有研究表明，EG损伤与NETs的形成密切相关，EG的降解可为NETs的释放创造条件，而NETs中的成分（如组蛋白）又可进一步加剧EG和ECs的损伤，从而形成一个恶性循环[29-30]。

3.3 *凝血功能紊乱与微血栓形成* EG在维持血管内皮抗凝特性方面发挥关键作用，其损伤可触发凝血系统的激活，进而引发微血栓的形成[5]。EG表面吸附的抗凝蛋白（如抗凝血酶Ⅲ和血栓调节蛋白）在EG降解后脱落进入血液循环，导致局部抗凝能力显著下降[31]。与此同时，在炎症因子的刺激下，ECs可表达TF，这是一种强效的促凝物质，能够激活外源性凝血途径，促进大量凝血酶生成，使纤维蛋白原转化为纤维蛋白，并在肺微血管内形成广泛分布的微血栓[32]。这些微血栓可堵塞血管，造成肺组织灌注障碍，加重通气/血流比例失调，从而进一步加剧低氧血症。此外，微血栓的形成过程会消耗大量凝血因子和血小板，导致出血倾向，最终引发弥散性血管内凝血（disseminated intravascular coagulation，DIC），使病情进一步恶化并趋于复杂化[33]。

4 EG降解标志物的临床应用

由于在体内直接测量EG的厚度与结构存在技术挑战，检测其降解后释放入血的组分已成为评估EG损伤程度的主要临床方法。Syndecan-1作为EG核心蛋白聚糖的关键成分，其血浆浓度是目前研究最为广泛的EG损伤生物标志物[21]。多项临床研究证实，在脓毒症患者中，血浆Syndecan-1水平显著升高，且其升高幅度与疾病严重程度及不良预后呈显著正相关[34-36]。一项纳入262例重症脓毒症患者的回顾性研究显示，血浆Syndecan-1水平与是否发展为ARDS、是否并发其他器官功能障碍以及住院死亡率均具有显著相关性[34]。尤为重要的是，Syndecan-1水平是预测患者死亡的独立危险因素，即使在校正年龄和急性生理学与慢性健康状况评分系统Ⅱ（Acute Physiology and Chronic Health Evaluation Ⅱ，APACHE Ⅱ）评分等混杂因素后，其预测效能仍保持显著[27]。除Syndecan-1外，EG的其他降解产物，如HS和HA，亦被证实可作为内皮损伤的生物标志物，与脓毒症的病情严重程度及器官功能障碍程度相关[37-40]。

5 治疗策略：保护、修复与替代EG

5.1 *保护EG完整性的临床策略* 多种常规临床干预措施若应用不当，可能对已受损的血管EG造成进一步损伤。因此，优化相关临床管理策略对于保护EG结构与功能具有重要意义，是防止其继发性损害的关键环节。

5.1.1 液体复苏策略的优化——限制性液体与避免高容量负荷 液体复苏是脓毒症治疗的基石，然而高容量负荷已被证实为导致血管EG损伤的重要因素之一[5]。大量晶体液的输注可稀释血浆蛋白，降低血管内胶体渗透压，同时升高血管内静水压，上述双重效应共同促进液体经受损EG向组织间隙渗出，进而加重组织水肿[41]。此外，部分研究提示，高容量晶体液本身可能通过机械剪切力或稀释性效应对EG结构产生直接损伤作用[42]。因此，在实现血流动力学稳定后，及时采取限制性液体管理策略，包括停止或减缓输液速度，避免持续性的液体正平衡，对于保护EG完整性、减轻肺水肿具有重要意义[43]。尽管使用胶体液（如白蛋白）进行复苏可能更有利于维持胶体渗透压，但其对EG的直接保护作用仍有待进一步研究证实[44]。

5.1.2 血管活性药物的使用——儿茶酚胺类药物的应用限制与替代选择 儿茶酚胺类药物（如去甲肾上腺素）是脓毒症休克期间常用的血管活性药物，但高剂量或长期应用可能对血管EG产生不利影响[45]。高浓度儿茶酚胺可激活ECs，导致血管通透性增加，并可能通过升高心脏后负荷及血管壁张力，间接造成EG损伤。因此，在临床应用中应遵循“最低有效剂量”原则，避免过度提升血压以减少潜在危害。近年来，一些非儿茶酚胺类血管活性药物，如血管加压素及其类似物，因其可能对EG具有保护作用而受到关注。血管加压素主要通过激活V1受体介导血管收缩，其作用机制与儿茶酚胺不同，可能对内皮屏障功能的干扰更小[45]。然而，上述结果仍需更多高质量的临床研究进一步验证。

5.1.3 血糖控制——预防高血糖对血管EG的损伤 高血糖是危重患者普遍存在的代谢紊乱类型，也是导致内皮功能障碍及血管EG损伤的独立危险因素[29]。高血糖可通过多种机制介导EG损害，主要包括：（1）诱导氧化应激，促进大量ROS生成；（2）激活蛋白激酶C等信号通路，增加血管通透

性;(3) 促进晚期糖基化终末产物的积累,引发蛋白质交联及结构功能异常。因此,实施严格的血糖管理(通常指将血糖水平维持在6~10 mmol/L)被视为保护EG完整性、改善脓毒症患者预后的关键干预措施[46]。此外,胰岛素本身被认为具有直接的抗炎作用和血管内皮保护效应,可能对EG结构的维护具有潜在益处[45]。

5.1.4　糖皮质激素的潜在保护作用　糖皮质激素具有显著的抗炎与免疫抑制效应,理论上可通过抑制促炎细胞因子的释放,间接发挥对血管EG的保护作用[47]。部分小规模临床研究及动物实验表明,低剂量糖皮质激素可能有助于减轻EG的降解过程[48]。然而,糖皮质激素的应用仍存在争议,其潜在不良反应(如高血糖、免疫抑制、肌无力等)在一定程度上限制了其临床使用。目前尚无充分证据证实糖皮质激素在脓毒症患者中是否能通过保护EG而带来明确的临床获益,其疗效与安全性仍需通过更大规模的随机对照试验进一步验证。

5.2　靶向EG降解酶的治疗

5.2.1　肝素酶抑制剂的应用前景　肝素酶在脓毒症相关性EG损伤中发挥核心作用,因此,肝素酶抑制剂有望成为极具临床潜力的干预策略。多项研究表明,普通肝素和非抗凝活性的肝素衍生物N-乙酰肝素能够有效抑制肝素酶活性,其作用机制是通过直接阻断HS和Syndecan-1的降解过程,从而在源头上实现对EG结构与功能的保护[49-50]。此外,乌司他汀也被证实能够抑制LPS诱导的肝素酶表达和活性,在小鼠ARDS模型中显示出降低血管通透性和抑制HS降解的作用[51]。然而,目前大多数肝素酶抑制剂仍处于临床前研究阶段,其在人体中的安全性、药代动力学特征及疗效尚需系统评估。推动该类药物由基础研究向临床转化,是未来治疗开发的重要方向。

5.2.2　MMP与ADAM抑制剂的探索　在脓毒症状态下,多种MMP(如MMP-2、MMP-7、MMP-9)常被同时激活,且功能上存在一定的冗余性[21],因此广谱MMP抑制剂可能较特异性抑制剂更具临床应用潜力。部分已上市药物,如多西环素,除具备抗菌活性外,还具有广谱MMP抑制作用。动物实验研究表明,多西环素可有效减少EG脱落,降低肺损伤的严重程度[52]。此外,针对ADAM17介导的Syndecan-1和Syndecan-4裂解的小肽抑制剂也被识别为潜在治疗药物[53]。然而,长期或全身性抑制MMP与ADAM可能干扰正常的组织重塑与修复过程,需对潜在不良反应进行谨慎评估。

5.3　EG的修复与替代疗法

5.3.1　外源性补充EG组分　外源性补充EG组分是一种直接的替代性治疗策略,其中HA是目前研究最为广泛的成分[54]。HA作为EG的关键结构组分,具有保水、抗炎及免疫调节等生物学功能。Baljinnyam等[55]通过给小鼠腹腔注射高分子量HA,有效降低了脓毒症Syndecan-1缺陷小鼠的肺含水量,并显著提高其存活率。其潜在机制可能包括:(1) 直接补充受损的EG层;(2) 抑制炎症细胞的活化与浸润;(3) 促进组织修复过程。此外,研究表明,通过新鲜冰冻血浆补充维持EG结构所需的白蛋白等关键蛋白,有助于恢复血管内皮功能[56]。该类策略的优势在于成分明确、安全性较高,但其疗效可能受到补充物质在体内的半衰期、组织分布特性以及与内源性EG整合效率的限制。

5.3.2　促进内源性EG合成的药物　促进内源性EG合成是一种更具生理性的修复策略。舒洛地特是一种由低分子量肝素与硫酸皮肤素组成的复合制剂,已应用于血管性疾病的临床治疗[57]。研究表明,舒洛地特不仅具有抗凝作用,还可促进ECs合成并分泌EG主要组分,从而加速EG的修复过程[58]。此外,静脉输注预组装糖萼脂质体纳米载体(liposomal nanocarriers of preassembled glycocalyx,LNPG)是一种恢复EG的新方法,LNPG通过与内皮细胞膜融合快速恢复EG,并在此后保持其完整性,有效改善内皮功能[59]。其次,当LNPG递送至缺乏EG的ECs时,LNPG的治疗效果在体内和离体均得到证实[60]。该类策略的核心优势在于激活机体自身的修复机制,但其作用起效可能相对较慢,需结合病情发展阶段进行合理应用。

5.4　转化医学的挑战与前景　尽管针对血管EG的治疗策略在动物模型中展现出巨大潜力,但其向临床应用的转化仍面临多重挑战。首先,动物模型与人类疾病之间存在种属差异,现有模型往往难以全面模拟人类脓毒症的复杂病理生理过程及其高度异质性。其次,目前尚缺乏实时、无创评估EG状态的技术手段,导致治疗效应的动态监测受限。临床上主要依赖检测血浆中EG降解产物(如Syndecan-1、HS片段)进行间接判断,但此类方法具有滞后性和非特异性,难以准确反映局部EG的实时变化。此外,治疗时机与患者筛选是决定干预成败的关键因素。由于EG损伤在脓毒症早期即可发生,有效的治疗窗口期较窄,必须在疾病初期及时实施干预。因此,识别能够从EG靶向治疗中获益的最大潜在人群,是实现个体化精准医疗的前提条件。尽管面临诸多挑战,EG作为连接炎症反应、凝血激活与微血管屏障功能的核心调控枢纽,其作为治疗靶点的科学价值和临床潜力不容忽视。随着基础研究的不断深入以及临床转化技术的发展,未来有望开发出安全、有效的EG靶向治疗方案,为SALI患者提供新的治疗希望。

6　总结与展望

综上所述,既往研究已明确证实EG在SALI中的核心作用机制。在生理状态下,EG作为血管屏障的重要组成部分,不仅维持血管完整性、调节血管张力,还具有抑制血栓形成和调控炎症反应的关键功能。在脓毒症病理状态下,过度激活的炎症反应、氧化应激及多种降解酶的协同作用,导致EG发生广泛降解和脱落。这一损伤过程并非单纯病理改变的伴随现象,而是连接脓毒症系统性炎症与肺部特异性损伤的关键始动环节。EG损伤直接导致肺血管通透性增加,诱发非心源性肺水肿;同时,ECs表面黏附分子的暴露加剧了中性粒细胞等炎症细胞的浸润与活化;此外,内皮抗凝特性的丧失激活了凝血系统,促进微血栓形成。这些病理生理改变相互交织,共同构成了SALI的复杂病理机制。

鉴于EG在SALI中的核心作用,保护、修复或替代EG已成为极具前景的治疗新策略。目前,从优化临床常规管理到

开发靶向EG降解酶的新型药物，再到探索外源性补充EG组分，多种治疗途径正在积极研究中。尽管从基础研究向临床转化过程中仍面临诸多挑战与争议，但EG作为一个整合了屏障、信号传导和免疫调节功能的多功能平台，其作为治疗靶点的潜力不容忽视。未来研究应着重解决当前技术瓶颈，阐明关键科学问题，并通过严谨的临床试验验证这些新策略的安全性与有效性。随着对EG生物学功能的深入认识，以EG为靶点的精准治疗策略有望为改善SALI这一危重疾病的预后提供新的治疗方向。

利益冲突　无

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