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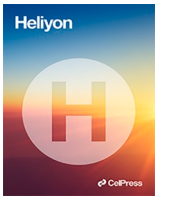

Review article

Endothelial cell dysfunction and targeted therapeutic drugs in sepsis

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ABSTRACT

Sepsis is a life-threatening organ dysfunction caused by an abnormal host response to microbial infections. During its pathogenesis, vascular endothelial cells (ECs) play a pivotal role as essential components in maintaining microcirculatory homeostasis. This article aims to comprehensively review the multifaceted physiological functions of vascular ECs, elucidate the alterations in their functionality throughout the course of sepsis, and explore recent advancements in research concerning sepsis-related therapeutic drugs targeting ECs.

1. Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Endothelial cells (ECs), which line the inner surface of various segments of the circulatory system, play a pivotal role in oxygen and nutrient transport, blood flow regulation, immune cell transportation, and tissue homeostasis maintenance [2]. During sepsis, vascular endothelial cell injury can lead to a cascade of events, including excessive inflammatory responses, increased microvascular permeability, reduced vascular tone, and microthrombus formation [2,3]. These events significantly contribute to the initiation and progression of the disease. In this review, we aim to summarize the key functional alterations of vascular endothelium in physiological as well as in septic pathological states, and explore the potential therapeutic drugs targeting ECs as approaches for managing sepsis.

2. ECs in physiological condition

Vascular ECs exhibit intricate and finely-tuned physiological functions. Under homeostatic conditions, these cells play a multi-faceted function, including the regulation of vascular tone, control of the growth of new vessels, and facilitation of cell and nutrient transport [4]. ECs are central to the vascular endothelial barrier, regulating the contraction and relaxation of blood vessels while maintaining vascular permeability [5]. This is indispensable for circulatory system stability. Additionally, ECs finely modulate

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immune cell activation and intravascular coagulation, contributing to the delicate balance within the vascular microenvironment (Fig. 1) [6]. Key biomarkers related with endothelial function in normal situation were shown in Table 1.

2.1. Components of the vascular endothelial barrier

The vascular endothelial barrier consists of vascular ECs, the glycocalyx, intercellular junction complexes, and the extracellular matrix, collectively responsible for regulating solute exchange across blood vessels and modulating vascular permeability [6]. i. ECs: Within the vascular system, ECs are situated between the blood and surrounding tissue, maintaining local blood environment homeostasis and promptly receiving signals from the vascular microenvironment. ECs can autonomously regulate their functions through specific endothelial receptors, such as vascular endothelial growth factor receptors (VEGFRs) and the angiopoietin-Tie (ANG-Tie) receptors [7–11]. ii. Glycocalyx: The glycocalyx is a complex mesh-like structure anchored to ECs [12]. It primarily consists of heparan

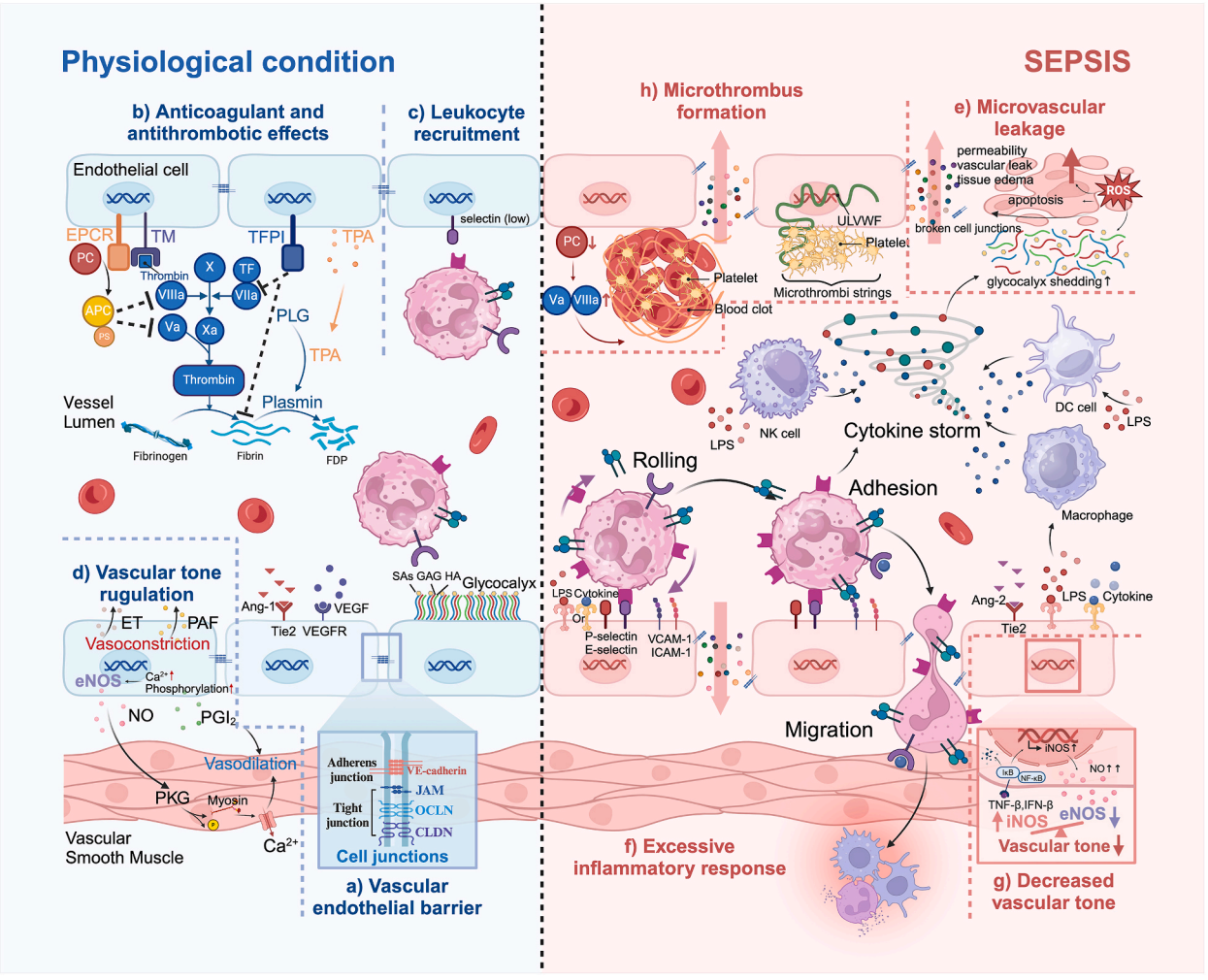

Fig. 1. The role of endothelial cells under normal physiological conditions and during sepsis. **Left (homeostatic condition):** a) Vascular endothelial barrier: consists of vascular ECs, glycocalyx, intercellular junction complexes (adherens junction and tight junction), and the extracellular matrix. b) Anticoagulant and antithrombotic effects: ECs express tPA, TFPI, and TM. c) Leukocyte recruitment: Leukocyte tethering, rolling, activation, arrest, spreading and crawling on the endothelium, and finally migration across the endothelium. d) Regulation of vascular tone: NO mediated by eNOS, activating PKG in smooth muscle cells, leading to reduced intracellular free calcium stores and inhibiting vascular contraction. **Right (during sepsis):** e) Excessive inflammatory response: ECs activated by bacterial products or pro-inflammatory cytokines enhance the expression of adhesion molecules (P-selectin, E-selectin, ICAM-1, and VCAM-1) facilitating WBC recruitment and migration, leading to a cytokine storm and organ dysfunction. f) Microvascular leakage: Glycocalyx shedding, ECs apoptosis, and intercellular junction structures disruption, leading to increased vascular permeability. g) Decreased vascular tone: Upregulation of the iNOS gene increased and the excessive NO production result in decreased vascular tone. h) Microthrombus formation: VWF mediates platelet adhesion to damaged ECs, forming platelet-ULVWF complexes, known as "microthrombi" strings. ECs: endothelial cells; eNOS: endothelial nitric oxide synthase; ICAM-1: intercellular adhesion molecule-1; NO: nitric oxide; PKG: protein kinase G; TFPI: tissue factor pathway inhibitor; tPA: tissue-type plasminogen activator; TM: thrombomodulin; VCAM-1: vascular cell adhesion molecule-1; VWF: Von Willebrand factor; WBC: white blood cells.

Table 1
Key biomarkers related with endothelial function in both normal and septic situations.

Category	Biomarkers related with endothelial function	Normal situation	Septic situation	Reference
Vascular endothelial barrier	1) vascular endothelial growth factor receptor (VEGFR)	Promote endothelial permeability, endothelial cell proliferation and migration, process new blood vessel formation, and regulate inflammation and coagulation	The level of VEGF increases, immunosuppression, VEGFR-3 attenuated proinflammatory cytokine production and may protects against endotoxin shock	[8,9,11]
	2) angiopoietin-Tie (ANG-Tie) receptors	Vascular development, angiogenesis, and remodeling, regulate vascular permeability, homeostasis, quiescence, and stability	Under conditions of enhanced Tie1 shedding, the increase in Ang2/Tie2 binding blocks Tie2 activation and contributes to the destabilization of the endothelium.	[7]
	3) Glycocalyx: heparan sulfate rich glycoproteins, membrane-bound proteoglycans, glycosaminoglycan (GAG) and hyaluronic acid	Preserve endothelial barrier function, regulate leukocyte migration, transmit endothelial shear stress, mediate anti-inflammatory and antioxidant responses, and inhibit thrombus formation	GAG and hyaluronic acid degradation, as well with core proteoglycans cleavage, induce capillary leakage and edema, progressive inflammation, platelet aggregation, coagulopathy and loss of vascular tone	[12–15,41]
	4) Sphingosine-1-phosphate (S1P)	Responsible for conveying intercellular information as a first messenger, participate in the migration, proliferation, differentiation, and clearance of immune cells	Inhibit glycocalyx shedding and degradation, maintain the integrity of vascular ECs, promote lymphocyte circulation, prevent hyperinflammation in sepsis	[12,88]
	5) Adherens junction: cadherin-catenin complex and the nectin-afadin complex	Maintain endothelial integrity, control the movement of solutes between bloodstream and tissues	The phosphorylation of VE-cadherin, dissociation from catenin and its endocytosis induce gaps between ECs, result in increased permeability	[16,17]
	6) Tight junction: occludin (OCLN), claudin (CLDN), and junctional adhesion molecule (JAM)	Regulate the transport of water, ions, and molecules through the paracellular pathway, an important barrier in blood vessels, maintain vascular homeostasis	The levels of occludin and zonula occludens-1 reduced, disrupt the tight junctions of endothelial cells	[17,18]
	7) Reactive oxygen species (ROS)	Pathogen defence, stimulation of angiogenesis and proliferation and in myofibroblasts	The endothelial production of ROS evaluated, ultimately lead to endothelial barrier injury	[38,77]
Anticoagulant and antithrombotic effects	1) Tissue-type plasminogen activator (tPA)	Promote fibrinolysis within the blood vessels	Inflammatory cytokines and PAMPs can enhance tPA expression, leading to an increase of plasmin generation and so modulate tolerogenic or immunogenic status of DCs	[21,22]
	2) Tissue factor pathway inhibitor (TFPI)	Regulate tissue factor (TF), limiting fibrin deposition and inhibiting the TF-factor VIIa complex	The level and activity of TFPI are significantly reduced; decrease TF-initiated thrombin generation and thereby dampen intravascular coagulation signaling mediated by thrombin	[20,24]
	3) Thrombomodulin (TM)	Bind to thrombin, APC, and restrain the coagulation response	The reduced expression of TM on endothelial cell leads to the compromised activation of protein C procoagulant changes	[20]
	4) Activate protein C	Restrict endothelial permeability and limit coagulation amplification	Down-regulation, promotes fibrinolysis and suppresses thrombus and inflammation	[20,23,46,52]
	5) Von Willebrand factor (VWF)	Mediate platelets adhesion to damaged ECs	Active the ultra-large von Willebrand factor (ULVWF) path and form platelet-ULVWF complexes	[2,46,47]
Leukocyte recruitment	1) Chemokines: CCL2, CCL8, CXCL10	Regulate the recruitment of leukocytes to sites of inflammation	Up-regulation, E-selectin, ICAM-1, and VCAM-1 are cleaved from the cell surface and circulate as a soluble form of the receptor	[25,29]
	2) Adhesion molecules: ICAM-1, VCAM-1, intergrins, selectin	Orchestrate leukocyte adhesion, rolling, and crawling	Up-regulation, facilitate the recruitment of leukocyte by promoting their adherence to ECs and mediating their migration from the vascular system to the site of inflammation	[25,28]

(*continued on next page*)

Table 1 (*continued*)

Category	Biomarkers related with endothelial function	Normal situation	Septic situation	Reference
Vascular tone regulation	1) Nitric oxide (NO)	Vasodilatory substances, maintain vascular homeostasis, including modulation of vascular dilator tone, regulation of local cell growth, and protection of the vessel from injurious consequences of platelets and cells circulating in blood	Down-regulation,leads to decreased vascular tone	[2]
	2) Endothelial nitric oxide synthase (eNOS)	Under specific circumstances, eNOS can be activated, product NO	The phosphorylation of eNOS leads to vasodilation dysfunction	[2,44]
	3) Inducible nitric oxide synthase (iNOS)	iNOS can be activated, product NO	The Increased transcription of the iNOS gene and the excessive production of NO leads to decreased vascular tone	[2,44]
	4) Adrenomedullin (ADM)	Regulate intracellular cytoskeletal dynamics, bolster endothelial barrier resilience, and mediate vasodilation	An excessive release of ADM permeates into the interstitial space, precipitating unwarranted vasodilation of vascular smooth muscle cells	[102–104]
	5) Prostacyclin (PGI2)	Induces cAMP-PKA-mediated vasodilation, inhibiting the activation and aggregation of platelets to prevent thrombosis	Greatly increased and contributes to vasodilation	[5]
	6) Endothelin (ET)	Vasoconstrictive mediators, activate endothelin A receptors	Activation a number of signalling pathways, increase synthesis of IL-1, IL-6 and TNF-α	[5]
	7) Platelet-activating factor (PAF)	Vasoconstrictive mediators; activates polymorphonuclear leukocytes (PMNs)	Activate inflammatory cascades that eventually results in endothelial dysfunction	[30]

ADM: adrenomedullin; APC: Activate protein C; eNOS: endothelial nitric oxide synthase; ICAM: ntercellular adhesion molecule-1. iNOS: inducible nitric oxide synthase; NO: nitric oxide; ROS: reactive oxygen species; S1P: Sphingosine-1-phosphate; TF: tissue factor; TFPI: tissue factor pathway inhibitor; TM: thrombomodulin; ULVWF: unusually large von Willebrand factor path; VCAM-1: vascular cell adhesion molecule-1; VEGF: vascular endothelial growth factor receptor; VWF: Von Willebrand factor.

sulfate rich glycoproteins, membrane-bound proteoglycans, glycosaminoglycan (GAG) side chains, and long-chain hyaluronic acid [13]. The glycocalyx is indispensable for preserving endothelial barrier function, regulating leukocyte migration, transmitting endothelial shear stress, mediating anti-inflammatory and antioxidant responses, and inhibiting thrombus formation [14]. Current research indicates that the various components of the glycocalyx work synergistically to maintain vascular endothelial integrity and protect organ function [15]. iii. Intercellular Junctional Complexes: The intercellular junctional complexes among vascular ECs form a complex structure, categorized into three types: adherens junctions, tight junctions, and gap junctions. These complexes play a pivotal role in maintaining tissue integrity and regulating vascular permeability [16,17]. The permeability of the endothelial barrier is primarily governed by adherens junctions and tight junctions [2]. Adherens junctions comprise the cadherin-catenin complex and the nectin-afadin complex [16]. Tight junctions are predominantly composed of transmembrane proteins such as occludin (OCLN), claudin (CLDN), and junctional adhesion molecule (JAM), which control the permeability of solutes between the bloodstream and surrounding tissues [17,18].

2.2. Anticoagulant and antithrombotic effects

Under resting conditions, vascular ECs exhibit specific anticoagulant and antithrombotic properties to maintain the circulatory system stability [19]. ECs express various inhibitory molecules, including tissue-type plasminogen activator (tPA), tissue factor pathway inhibitor (TFPI), and thrombomodulin, which exert influence on the synthesis and activity of key enzymes in the coagulation cascade, particularly thrombin [20]. It is the presence of these coagulation inhibitors that empowers vascular endothelium to fulfill its physiological roles in anticoagulation and fibrinolysis. ECs enhance fibrinolysis by synthesizing and releasing tPA, thereby promoting fibrinolysis within the blood vessels [21,22]. Through the production of TFPI, ECs regulate tissue factor (TF), limiting fibrin deposition and inhibiting the TF-factor VIIa complex [23,24]. Furthermore, ECs express thrombomodulin (TM), which, upon binding to thrombin, activates protein C, ultimately leading to the inactivation of FVa and FVIIIa, thus effectively restraining the coagulation response [20].

2.3. Leukocyte recruitment

ECs serve as sentinels that govern the ingress of white blood cells into tissues [25]. The migration of white blood cells between ECs forms the cornerstone of both innate and adaptive immune responses [26,27]. During inflammation, pro-inflammatory cytokines such as TNF-αactivate ECs, inducing the expression of numerous chemokines, including CCL2, CCL4, CXCL2, and adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [28,29]. These molecules facilitate the binding of white blood cells to the activated endothelial cell surface. Additionally, some integrins are involved in these adhesive interactions, serving as homologous ligands for adhesion molecules [28].

2.4. Vascular tone regulation

Under physiological conditions, ECs exhibit dual capabilities, generating both vasodilatory substances, such as nitric oxide (NO) and prostacyclin (PGI2), as well as vasoconstrictive mediators like endothelin (ET) and platelet-activating factor (PAF) [5,30]. The vascular endothelium regulates vascular tone through these mechanisms. Nitric oxide plays a pivotal role in both the physiological and pathological processes of ECs [5,31]. Under physiological conditions, NO is primarily mediated by endothelial nitric oxide synthase (eNOS) and plays a role in vasodilation, inhibiting the expression of adhesion molecules, and inhibiting platelet aggregation [32]. Under specific circumstances, such as increased intracellular calcium and phosphorylation, eNOS can be activated, resulting in the production of nitric oxide from its substrate L-arginine [32]. NO diffuses into the surrounding tissue and activates protein kinase G (PKG) in smooth muscle cells, which reduces intracellular free calcium stores by phosphorylating myosin, consequently inhibiting vascular contraction [33].

With the ongoing progress of clinical trials and experimental research, our understanding of the pathophysiological mechanisms of sepsis continues to deepen. The role of endothelial cells in vascular development, maintenance of homeostasis and immune responses is increasingly emphasized. In parallel, a growing body of research is exploring the mechanisms by which endothelial cells maintain physiological functions and their interactions with the peripheral physiological environment.

3. Vascular ECs responses during sepsis

Vascular ECs continuously sense changes in the external environment and respond promptly to microbial invasion. During sepsis, microbial pathogens can cause damage to vascular ECs, resulting in a series of adverse consequences, including excessive inflammatory responses, microvascular leakage, decreased vascular tone, and microthrombus formation (Fig. 1) [34]. The evidence supporting the role of ECs during sepsis is continuously growing [35]. Key biomarkers related with endothelial function in septic situation were shown in Table 1.

3.1. Excessive inflammatory response

When ECs are activated by bacterial products or pro-inflammatory cytokines, they enhance the expression of adhesion molecules on their surface, such as P-selectin, E-selectin, VCAM-1, and ICAM-1 [36]. As mentioned earlier, these adhesion molecules facilitate the recruitment of white blood cells by promoting their adherence to ECs and mediating their migration from the vascular system to the

site of inflammation [29]. During sepsis, damaged ECs recruit a large number of innate immune cells, such as macrophages, natural killer cells, neutrophils, dendritic cells, etc., which release pro-inflammatory mediators, triggering a cytokine storm and contributing to organ dysfunction [36,37]. In this intense inflammatory state, almost all cellular components of the microcirculation become disrupted [2]. This excessive inflammatory response not only disrupts the body through a cytokine storm but also inflicts further damage to the endothelial microenvironment, such as abnormal expression of eNOS and the generation of reactive oxygen species (ROS) [38].

3.2. Microvascular leakage

During sepsis, factors like excessive production of inflammatory mediators and ROS exacerbate the damage to the vascular

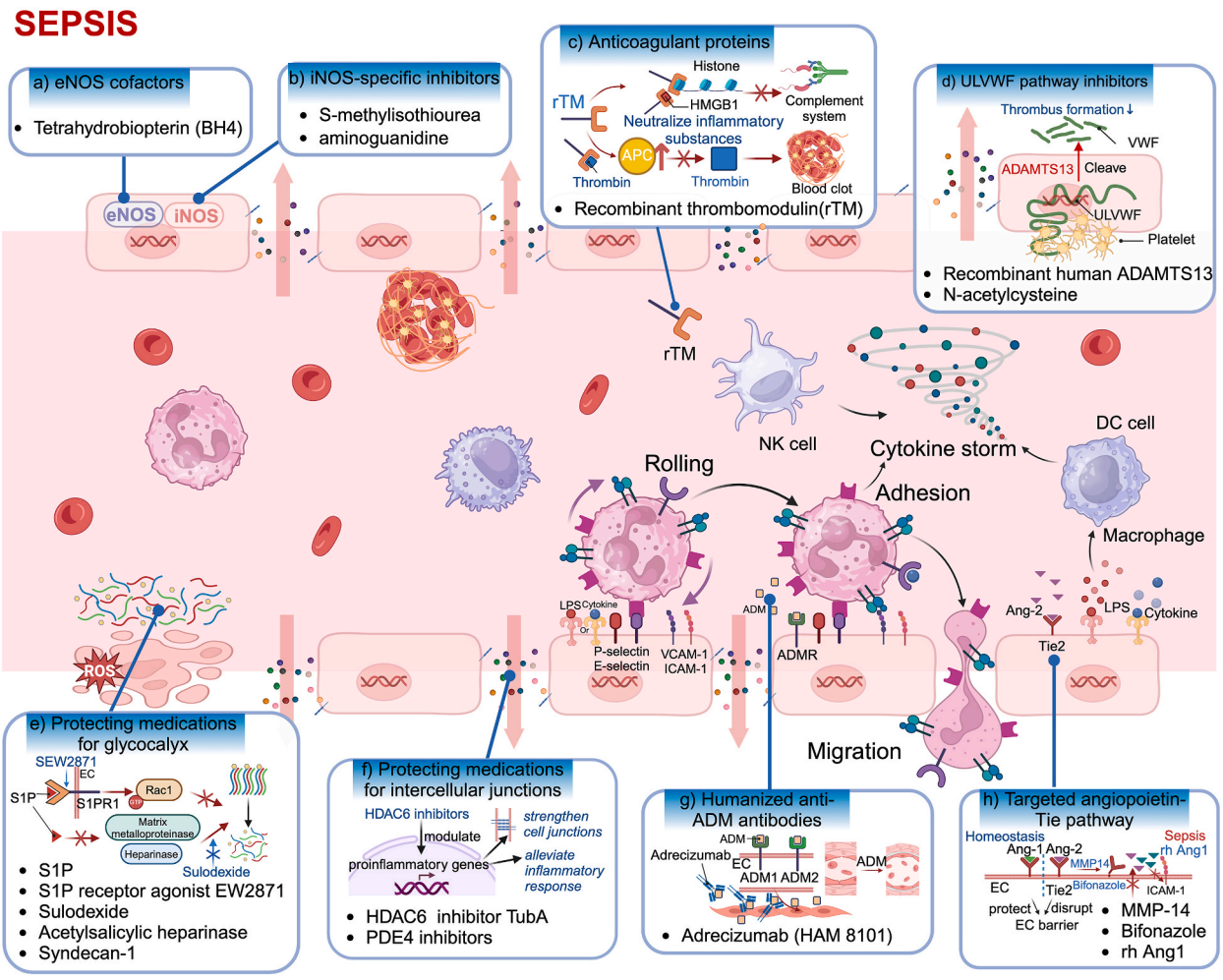

Fig. 2. Potential targets and targeted therapeutic drugs for endothelial dysfunction in sepsis. a) eNOS cofactors: BH4, regulates eNOS and restores endothelial function. b) iNOS-specific inhibitors: S-methylisothiourea sulfate and aminoguanidine, inhibit iNOS and maintains vascular tone. c) Anticoagulant proteins: rTM, generates APC upon binding to thrombin, limiting coagulation amplification. d) ULVWF pathway inhibitors: ADAMTS13, and N-acetylcysteine (NAC), cleaves ULVWF multimers into smaller VWF, reducing thrombus formation in vascular injury. e) Protecting medications for glycocalyx: S1P receptor agonists, activate S1PR1 and inhibit glycocalyx shedding; Sulodexide: counteracts the degrading effects of heparinase, promoting endothelial glycocalyx regeneration; Acetylsalicylic heparinase, reduce glycocalyx loss; Syndecan-1, prevent glycocalyx degradation. f) Protecting intercellular junctions: HDAC6 inhibitors TubA, strengthen cell-cell connections and protect the endothelial barrier; PDE4 inhibitors: prevent the disruption of endothelial barrier structure. g) Humanized anti-ADM antibody: Adrecizumab (HAM 8101), constrict the dissemination of ADM into the interstitium. h) Therapeutic targeting of the angiopoietin-Tie pathway: MMP-14, facilitates the extracellular domain shedding of Tie2, upholding the integrity of the endothelial barrier; Bifonazole, enhance vascular barrier function by curtailing the release of Angpt-2; rh Ang1, stabilizes endothelial barrier function and dampens the inflammatory response by inhibiting ICAM-1 expression. ADM: adrenomedullin; APC: activated protein C; BH4: tetrahydrobiopterin; eNOS: endothelial nitric oxide synthase; HDAC6: Histone deacetylase 6; PDE: Phosphodiesterase; iNOS: inducible nitric oxide synthase; MMP: matrix metalloproteinase; rh Ang1: recombinant human angiopoietin-1; rTM: recombinant thrombomodulin; S1P: Sphingosine-1-phosphate; ULVWF: Ultralarge von Willebrand factor; VWF: Von Willebrand factor.

endothelial barrier [38]. This includes shedding of the glycocalyx, apoptosis of ECs, and disruption of intercellular junction structures, leading to increased vascular permeability, extravasation of blood constituents, and tissue organ edema [2,39–41]. The accumulation of fluid within the body promotes increased diffusion distances between capillaries and tissue cells, affecting microvascular perfusion and ultimately mediating organ dysfunction [42]. Therefore, endothelial barrier dysfunction and the resulting microvascular leakage may be at the core of the pathogenesis of organ failure in sepsis [43].

3.3. Decreased vascular tone

During sepsis, inducible nitric oxide synthase (iNOS) becomes the major source of NO [5]. Various molecules involved in sepsis-induced inflammation, such as TNF-β and IFN-β, can activate the degradation of IκB and increase the transcription of the iNOS gene [44]. The excessive production of NO leads to decreased vascular tone. Additionally, in ischemic tissues, iNOS expression varies in different regions of blood vessels, ultimately resulting in pathological shunting of blood and exacerbating tissue perfusion impairment [45].

3.4. Microthrombus formation

During sepsis, the anticoagulant properties of ECs can be compromised [20]. Von Willebrand factor (VWF) stored within Weibel-Palade bodies in ECs is a multimeric glycoprotein that can mediate platelets adhesion to damaged ECs [46]. Sepsis-induced diffuse endothelial cell damage leads to the formation of elongated structures anchored to the damaged endothelial cell membrane, mediated by the unusually large von Willebrand factor path (ULVWF) [47]. This structure recruits activated platelets, ultimately forming platelet-ULVWF complexes, known as "microthrombi" strings [48,49]. These "microthrombi" strings block the vascular lumen, impeding blood flow in arterioles and capillaries, exacerbating tissue hypoxia [50,51]. Another reason for the procoagulant state in sepsis is the downregulation of protein C [52]. When thrombin binds to thrombomodulin, protein C is converted to activated protein C (APC), which dissociates from endothelial protein C receptor (EPCR) and binds to protein S, resulting in the inactivation of factors Va and VIIIa, thereby interrupting the coagulation cascade [23,53].

Table 2
Targeted therapeutic drugs for endothelium dysfunction in sepsis.

Types of agents	Names of agents	The function of agents	Reference
eNOS cofactors	1) Tetrahydrobiopterin (BH4)	Restore endothelial function, improve microcirculatory perfusion ratios and enhance functional capillary density	[78]
iNOS-specific inhibitors	1) S-methylisothiourea sulfate	Inhibit iNOS, maintain vascular tone	[79]
	2) Aminoguanidine	Inhibit iNOS, maintain vascular tone	[80,81]
Anticoagulant proteins	1) Recombinant thrombomodulin (rTM)	Inhibit thrombin generation, antagonize inflammatory and reduce histone H3 levels	[20,82,83]
	2) Activated protein C (APC)	Restrict endothelial permeability and limit coagulation amplification	[20,84]
Ultra-large von Willebrand factor (ULVWF) pathway inhibitors	1) Recombinant human ADAMTS13	Cleave ULVWF multimers into smaller Von Willebrand factor (VWF), and reduce thrombus formation	[87]
	2) N-acetylcysteine	Similar to recombinant human ADAMTS13, inhibit the ULVWF pathway	[48]
Protecting Medications for glycocalyx	1) Sphingosine-1-phosphate (S1P) and its receptor agonists	Inhibit the glycocalyx shedding and degradation; reduce microvascular permeability, and improve vascular perfusion	[34,42, 88–90]
	2) Sulodexide	Counteract the degrading effects of heparinase and promote the regeneration of glycocalyx	[91,92]
	3) Acetylsalicylic heparinase	Reduce glycocalyx loss	[93]
	4) Syndecan-1	Prevent glycocalyx degradation	[94]
Protecting medications for intercellular junctions	1) Histone deacetylase 6 (HDAC6) inhibitors	Modulate the transcription of pro-inflammatory genes, strengthen cell-cell connections	[96,97]
	2) Phosphodiesterase 4 (PDE4) inhibitors	Prevent the disruption of endothelial barrier structure	[99,100]
Humanized anti- adrenomedullin (ADM) antibodies	1) Adrecizumab	Curb exaggerated interstitial vasodilation and extend the half-life of ADM	[102,104]
Therapeutic targeting of the angiopoietin-Tie pathway	1) Matrix metalloproteinase-14 (MMP-14)	Facilitate the extracellular domain shedding of Tie2	[107]
	2) Bifonazole	Curtail the release of Angpt-2	[108]
	3) Recombinant human angiopoietin-1 (rh Ang1)	Inhibit the expression of ICAM-1	[109]
	4) Angiopoietin-2-binding and Tie2-activating antibodies (ABTAA)	Constrict Angpt-2 activity while concurrently activating Tie2	[110]

ADM: adrenomedullin; APC: Activated protein C; eNOS: endothelial nitric oxide synthase; ICAM: ntercellular adhesion molecule-1. iNOS: inducible nitric oxide synthase; S1P: Sphingosine-1-phosphate; ULVWF: unusually large von Willebrand factor path; VWF: Von Willebrand factor.

3.5. The contribution of different immune cells and components leading to endothelial cell dysfunction during sepsis

i. Monocyte-Macrophages: In the progression of sepsis, there is a complex interplay between monocytes and endothelial cells. Tissue factor expression on monocytes significantly increases, leading to sepsis-associated coagulation disorders [54]. Furthermore, endothelial cell-derived extracellular vesicles (EVs) with elevated levels of VCAM-1 interact with and reprogram monocytes, exacerbating sepsis-associated acute lung injury (ALI) [55]. Macrophages also contribute to endothelial dysfunction by releasing exosomes, which mediate sepsis-associated acute kidney injury by impacting glomerular endothelial cells [56]. Additionally, macrophages can augment lipopolysaccharide (LPS)-induced endothelial cell apoptosis via the Ang1 and NF-κB pathways [57]. Moreover, migration inhibitory factor (MIF) from macrophages can induce excessive endothelial permeability, leading to sepsis vascular leakage [58].

ii. Neutrophils: Neutrophils serves as the frontline defense of innate immune against sepsis. Besides traditional mechanisms like phagocytosis and the release of inflammatory cytokines, reactive neutrophils secrete myeloperoxidase (MPO), neutrophil elastase (NE), and proteinase G at the site of infection, and they also release nuclear DNA to form neutrophil extracellular traps (NETs) [59]. Although NETs effectively eliminate pathogens, they can also directly harm endothelial cells via cytotoxic effects, resulting in tissue damage and organ failure [3,60,61].

iii. Lymphocytes: Lymphocytes are integral to immune response, with specific subgroups playing distinct roles during sepsis. Natural killer T cells (NKT), exhibiting characteristics of both conventional T cells and NK cells, can be activated by endothelial cells during sepsis [62]. This activation increases the proportion and activity of $CD4^+$ NKT cells in the blood, participating in the regulation of downstream immune cascade reactions in septic patients. The role of natural killer cells (NK) in sepsis is debated. While dysregulation of inflammatory factors can lead to abnormal NK cell activation, triggering a cytokine storm and severe organ damage, NK cells also possess certain endothelial protective functions [63]. NK cell therapy can be shown to reduce levels of NO, IL-10, and VEGF in septic mice, thus maintaining vascular endothelial barrier stability. Additionally, innate lymphoid cells (ILC) play a crucial role in the innate immune response to sepsis. ILC2, a key mediator of sepsis inflammatory response, promptly to signals from infected tissues by producing Th2-type cytokines, thereby mediate the sepsis inflammatory response [64]. HMGB1 promotes type 2 inflammation induced by ILC2 via the RAGE receptor, exacerbating lung injury [65]. Furthermore, ILC2 can inhibit caspase-1 activation and reduce endothelial cell pyroptosis by secreting IL-9 [66].

3.6. Differential impact of sepsis pertaining to endothelial cells across sexes

Sex is increasingly recognized as a crucial factor in sepsis. Women tend to exhibit lower susceptibility to sepsis, leading to higher post-sepsis survival rates, while male patients often experience more severe organ dysfunction [67,68]. This disvergence may be attributed to several factors: 1) Protective effects of estrogen on endothelial cell function [69]: Estrogen activates eNOS to produce NO, decreases ET-1 levels, enhances sensitivity to vasodilatory factors, and promotes endothelial-dependent vasodilation [70]; It reduces the secretion of pro-inflammatory cytokines and chemokines, inhibits the expression of adhesion molecules, and diminishes white blood cells (WBC) binding, thereby attenuating the inflammatory response. [71]; Estrogen induces cell proliferation and migration to facilitate endothelial healing and protect the endothelial barrier integrity [72]; It activates the VEGF/Akt/NO pathways, promoting angiogenesis both in vitro and in vivo [73]. Progesterone functions similarly to estrogen. 2) Transcriptomics and proteomics analyses reveal that sex, independently of sex hormones, significantly influences transcriptomic variation in endothelial cells. 3) Higher angiogenic potential in female compared to male endothelium: Inflammatory agents and VEGF increase endothelial programmed cell death 1 ligand 1 (PD-L1) expression in a sex-specific manner, fostering angiogenesis and regulating excessive immune response in females [74]. Despite the stronger protective functions observed in female endothelial cells, their exact role in the sepsis remains incompletely understood. Estrogen, estrogen receptor agonists, and dehydroepiandrosterone (DHEA) hold potential as adjunctive drugs for sepsis treatment, but current clinical trials are insufficient to support their therapeutic efficacy [73]. It is essential to acknowledge that individual studies present diverse perspectives on the sex-specific response to sepsis [75]. Therefore, further research is needed to investigate the influence of sepsis on endothelial cells based on sex disparities.

In summary, the normal structure and function of endothelial cells are compromised during sepsis, resulting in the impaired endothelial barrier function, coagulation abnormalities, impaired microcirculatory function and ultimately organ failure. While the importance of endothelial cells in sepsis is increasingly recognized, the potential pathophysiology of the septic endothelial barrier remains poorly understood. Further research is needed to investigate the endothelial cell metabolism, mediators of endothelial injury, and the role of abnormal neuroexcitation in endothelial injury during sepsis.

4. Targeted therapeutic drugs for endothelium dysfunction in sepsis

As previously discussed, the vascular endothelium plays a crucial role in the development of sepsis. Targeted therapies aimed at the vascular endothelium hold significant promise for sepsis treatment. In this section, we will delve deeper into sepsis-related therapeutic agents that specifically target the vascular endothelium (Fig. 2, Table 2) [76].

4.1. eNOS cofactors

In sepsis, dysfunctional eNOS can result in adverse consequences, including reduced vascular tone and excessive ROS production [44,77]. Tetrahydrobiopterin (BH4) serves as a pivotal cofactor for eNOS. BH4-regulated eNOS plays a vital role in maintaining

vascular tone under physiological conditions. Several experiments have confirmed BH4's ability to restore endothelial function, improve microcirculatory perfusion ratios, and enhance functional capillary density [78].

4.2. iNOS-specific inhibitors

Multiple studies have suggested that non-selective inhibition of nitric oxide synthase (NOS) may worsen organ dysfunction in sepsis patients [79]. Conversely, specific inhibition of iNOS has shown promise in improving sepsis outcomes. S-methylisothiourea sulfate is an iNOS-specific inhibitor that has demonstrated increased survival rates in rodent models of septic shock [80]. Another iNOS-specific inhibitor, aminoguanidine, has been reported to attenuate circulatory failure in a septic shock rodent model and improve survival rates [81].

4.3. Anticoagulant proteins

Recombinant thrombomodulin (rTM) is an anticoagulant protein similar to endogenous thrombomodulin, which can generate activated protein C (APC) upon binding to thrombin, thereby limiting coagulation amplification. Research suggests that rTM can inhibit thrombin generation, ameliorating microcirculatory disturbances in sepsis [20,82]. Beyond its anticoagulant effect, rTM exhibits robust anti-inflammatory properties, neutralizing various inflammatory substances, including histones and high mobility group box 1 (HMGB1), while suppressing excessive activation of the complement system [83]. Experiments conducted by Nakahar and colleagues have demonstrated that rTM significantly reduces histone H3 levels, mitigates renal damage, and substantially increases the survival rate of rats in the rTM-treated group [83]. Additionally, APC stands as a potential endothelial protective therapy, it can restrict endothelial permeability by influencing protease-activated receptor-1 (PAR-1) and limit coagulation amplification [84,85].

4.4. ULVWF pathway inhibitors

Traditional anticoagulants targeting the TF pathway have shown limited efficacy in treating microthrombosis in sepsis, primarily because they do not inhibit the generation of ULVWF [86]. ADAMTS13, a zinc metalloproteinase, cleaves ULVWF multimers into smaller VWF, reducing thrombus formation in vascular injury. Recombinant human ADAMTS13 can replicate the effects of ADAMTS13, inhibiting microthrombus formation through the ULVWF pathway, and it has demonstrated promising results in animal models [87]. Chen J et al. have shown that N-acetylcysteine (NAC), a compound similar to recombinant human ADAMTS13, can also inhibit the ULVWF pathway [48].

4.5. Protecting medications for glycocalyx

i. Sphingosine-1-phosphate (S1P) receptor agonists: S1P is a phospholipid that inhibits glycocalyx shedding by activating Sphingosine-1-phosphate receptor 1 (S1PR1) on ECs [34,88]. Additionally, S1P can inhibit matrix metalloproteinases or block heparinase, reducing the degradation of endothelial glycocalyx [88,89]. S1P receptor agonists can help restore endothelial barrier function, reduce microvascular permeability, and improve vascular perfusion [43]. For instance, the S1P receptor agonist SEW2871 has been shown to decrease renal microvascular permeability in a murine sepsis model, thereby enhancing capillary perfusion around renal tubules [90]. ii. Sulodexide: Sulodexide is a compound similar to heparin sulfate, which can counteract the degrading effects of heparinase, thus promoting the regeneration of endothelial glycocalyx. Sulodexide has demonstrated favorable results in glycocalyx restoration among patients with endothelial cell damage [91,92]. Furthermore, acetylsalicylic heparinase can also reduce glycocalyx loss in a murine sepsis model and lower mortality rates. iii. Syndecan-1: Syndecan-1 is a mixture of glucosamine and glycocalyx shedding inhibitors [93]. It can prevent glycocalyx degradation and improve the survival rate of septic mice. The application of Syndecan-1 can maintains the integrity of the endothelial barrier and alleviate inflammation-induced glycocalyx loss [94].

4.6. Protecting medications for intercellular junctions

i. Histone deacetylase 6 (HDAC6) inhibitors: HDAC6, a class IIb deacetylase, regulates the functionality of non-nuclear proteins through deacetylation and ubiquitination [95]. HDAC6 is widely expressed in ECs and modulates late-stage histone deacetylation, potentially resulting in increased endothelial barrier permeability [96]. HDAC6 inhibitors can modulate the transcription of pro-inflammatory genes, strengthen cell-cell connections, and thereby protect the endothelial barrier. TubA is an efficient and highly selective HDAC6 inhibitor, and research has indicated that TubA can prolong the survival of septic mice by inhibiting apoptosis in pulmonary vascular ECs, alleviating the inflammatory response, and restoring endothelial cell barrier function [97]. ii. Phosphodiesterase 4 (PDE4) inhibitors: PDE4 is a specific isoenzyme responsible for the degradation of cyclic adenosine monophosphate (cAMP) and is highly expressed in inflammatory cells and ECs [98]. Inhibiting PDE4 can effectively prevent the disruption of endothelial barrier structure induced by LPS and cecal ligation and puncture (CLP) in septic rats, thereby protecting renal function in CLP-induced septic mice [99,100]. Consequently, PDE4 inhibitors emerge as potential therapeutic options for preventing visceral failure in sepsis.

4.7. Humanized anti-adrenomedullin (anti-ADM) antibody

Adrenomedullin (ADM) is a pivotal hormone primarily produced and secreted by vascular ECs, playing a crucial role in modulating vascular tone and preserving endothelial barrier integrity [101]. ADM binds to ADM1 and ADM2 receptors, thereby regulating intracellular cytoskeletal dynamics, bolstering endothelial barrier resilience, and mediating vasodilation through receptor interaction with endothelial and vascular smooth muscle cells [102,103]. In sepsis, an excessive release of ADM permeates into the interstitial space, precipitating unwarranted vasodilation of vascular smooth muscle cells. Notably, the circulating ADM concentration is independently linked to organ failure and unfavorable clinical outcomes in sepsis [103]. Adrecizumab (HAM 8101), a humanized antibody designed to target the N-terminal domain of ADM, exerts its therapeutic effect by constricting the dissemination of ADM into the interstitium [104]. This antibody effectively curbs exaggerated interstitial vasodilation, extends the half-life of ADM, and acts as a sentinel for preserving endothelial cell barrier integrity [102].

4.8. Therapeutic targeting of the angiopoietin-Tie pathway

Under physiological conditions, angiopoietin-1 (Angpt-1) activates the endothelial tyrosine kinase receptor Tie2, thereby fostering endothelial barrier stability and fortifying the actin cytoskeleton within ECs [105]. Conversely, angiopoietin-2 (Angpt-2) disrupts endothelial barrier stability by promoting the activation of β1-integrin [106]. Presently, research has illuminated the role of matrix metalloproteinase-14 (MMP-14) in facilitating the extracellular domain shedding of Tie2, thereby upholding the integrity of the endothelial barrier [107]. The pharmacological agent Bifonazole demonstrates the ability to enhance vascular barrier function by curtailing the release of Angpt-2 [108]. Furthermore, the administration of recombinant human angiopoietin-1 (rh Ang1) stands as a potent intervention, stabilizing endothelial barrier function in CLP murine models, consequently averting pulmonary capillary leakage and dampening the inflammatory response through the inhibition of ICAM-1 expression [109]. Pioneering research has underscored the superiority of angiopoietin-2-binding and Tie2-activating antibodies (ABTAA) in comparison to conventional Angpt-2 antibodies. These innovative agents effectively constrict Angpt-2 activity while concurrently activating Tie2, ultimately culminating in superior preservation of the endothelial barrier [110].

4.9. Potential molecules in or associated with endothelial cell that can improve prognosis of sepsis

In addition to the aforementioned targets and corresponding therapeutic agents, several potential molecules associated with endothelial cells could be targeted to improve the prognosis of sepsis. Acid sphingomyelinase (ASM), a lysosomal hydrolase, regulates the secretion of macrophage exosomes, thereby inducing endothelial cell damage. Deletion of the ASM gene in mice reduces both exosome secretion in renal glomeruli and endothelial cell damage [56]. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a member of the proprotein convertase family. Inhibits PCSK9 can mitigate the decline in endothelium-dependent vasodilation function in septic mice, thereby enhancing the survival rate [111]. TRIM47, a prominently expressed E3 ubiquitin ligase in vascular endothelial cells, functions as a novel activator of endothelial cells and promotes LPS-induced acute lung injury through potentiating the k63-linked ubiquitination of TRAF2. Inhibiting TRIM47 expression suppresses the transcription of various pro-inflammatory cytokines in endothelial cells, thereby alleviating endothelial cell inflammation [112]. Moreover, ATP-citrate lyase (ACLY) promotes EC gluco-lipogenic metabolism and proinflammatory response through acetylation-mediated MYC transcription. Inhibition of ACLY significantly improves lipopolysaccharide-induced endothelial cell inflammation and organ injury [113]. These molecules mediate endothelial dysfunction in sepsis, indicating that inhibiting their expression can alleviate endothelial cell damage in sepsis. They may serve as potential therapeutic targets for treating sepsis-associated endothelial dysfunction and organ injury.

Although there are emerging treatments for sepsis that target endothelial cells, most studies have focused on isolated and specific mechanisms, underestimating the complexity of the body's internal immune response. Therefore, future drug development for sepsis must take into account the interactions between different cell types, inflammatory mediators and signaling pathways.

5. Limitations of the previous studies and prospects for future research

Despite numerous studies on endothelium cell function in sepsis, several limitations persist. Firstly, the heterogeneity of endothelial cells is often overlooked in previous studies. This heterogeneity manifests in two main aspects: a) Diseases can induce transcriptomic changes in endothelial cells. Single-cell sequencing and spatial transcriptomic analysis have confirmed significant heterogeneity among endothelial cells in conditions such as idiopathic pulmonary fibrosis and pulmonary arterial hypertension [114,115]. Novel candidate drugs targeting endothelial cell gene targets associated with specific diseases hold potential application prospects [114]. b) Endothelial cells exhibit organs-specific heterogeneity [79]. Single-cell sequencing has revealed distinct transcriptomic profiles of organ-specific endothelial cells in acute lung and kidney injuries in sepsis [56,116,117]. These findings suggest that targeting specific endothelial cell subtypes in particular organs may offer potential therapeutic benefits for improving organ dysfunction in sepsis. Secondly, most researchers primarily focus on investigating the therapeutic effects of single molecules on sepsis, with limited exploration of combined interventions targeting multiple pathways to preserve endothelial function [118]. Developing combined therapeutic strategies aimed at endothelial dysfunction presents a promising new direction for sepsis treatment. Lastly, current research predominantly relies based on animal studies, which have inherent limitations [27]. Translating experimental findings from animal models to clinical practice remains highly challenging.

6. Conclusion

In sepsis, endothelial cell damage plays a central role, triggering various pathological processes such as vascular leakage, tissue edema, disrupted vascular tone, and microvascular thrombosis. These processes ultimately culminate in microcirculatory dysfunction and multi-organ failure among septic patients.

Exploring the functionality of ECs in sepsis offers a deeper understanding of the pathophysiology of this grave condition and provides a foundation for innovative treatment approaches. Protecting the endothelial barrier and maintaining its function are of paramount importance in preventing the worsening of septic patients' conditions. Targeted therapeutic medications designed to mitigate endothelial damage in sepsis present promising prospects. They contribute to stabilizing the endothelial barrier, mitigating inflammatory responses, and enhancing the overall prognosis of septic patients.

However, despite the potential significance of these treatment modalities in sepsis management, further research is necessary to authenticate their safety and efficacy. Future investigations will continue in unraveling the intricate interplay between sepsis and ECs, with the aim of discovering superior therapeutic strategies that can improve the survival rates and quality of life for individuals afflicted by sepsis.

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Data availability statement

Data sharing is not applicable. No data was used for the research described in the article.

Ethics statement

Review or approval by an ethics committee was not needed for this study because no data on patients or experimental animals was used in the article. Informed consent was not required for this study because no clinical data was produced in the review article.

CRediT authorship contribution statement

Kunwei Chen: Writing – original draft, Visualization. **Dongdong Wang:** Writing – original draft, Visualization. **Minyue Qian:** Writing – review & editing, Investigation. **Mengcao Weng:** Writing – review & editing, Investigation. **Zhongteng Lu:** Writing – review & editing. **Kai Zhang:** Writing – review & editing, Conceptualization. **Yue Jin:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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