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REVIEW

# Research Progress and Molecular Mechanisms of Endothelial Cells Inflammation in Vascular-Related Diseases

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**Abstract:** Endothelial cells (ECs) are widely distributed inside the vascular network, forming a vital barrier between the bloodstream and the walls of blood vessels. These versatile cells serve myriad functions, including the regulation of vascular tension and the management of hemostasis and thrombosis. Inflammation constitutes a cascade of biological responses incited by biological, chemical, or physical stimuli. While inflammation is inherently a protective mechanism, dysregulated inflammation can precipitate a host of vascular pathologies. ECs play a critical role in the genesis and progression of vascular inflammation, which has been implicated in the etiology of numerous vascular disorders, such as atherosclerosis, cardiovascular diseases, respiratory diseases, diabetes mellitus, and sepsis. Upon activation, ECs secrete potent inflammatory mediators that elicit both innate and adaptive immune reactions, culminating in inflammation. To date, no comprehensive and nuanced account of the research progress concerning ECs and inflammation in vascular-related maladies exists. Consequently, this review endeavors to synthesize the contributions of ECs to inflammatory processes, delineate the molecular signaling pathways involved in regulation, and categorize and consolidate the various models and treatment strategies for vascular-related diseases. It is our aspiration that this review furnishes cogent experimental evidence supporting the established link between endothelial inflammation and vascular-related pathologies, offers a theoretical foundation for clinical investigations, and imparts valuable insights for the development of therapeutic agents targeting these diseases.

**Keywords:** endothelial cells, endothelial inflammation, vascular-related diseases, atherosclerosis, diabetes mellitus, cardiovascular diseases

## Introduction

Endothelial cells (ECs), residing as the innermost layer of blood vessel walls, serve as a critical interface between circulating blood components and the vessel wall itself.[1] These cells interact with substances in the flowing blood while participating in numerous physiological and pathological processes, including metabolism, antioxidant reduction state, inflammation, and immune response.[1,2] As principal regulators of vascular homeostasis, ECs fulfill various functions, such as modulating vascular tension and managing hemostasis and thrombosis.[3] Positioned at the nexus of blood and tissue, ECs are particularly vulnerable to alterations in blood flow and its constituents.[3] Consequently, exposure to specific cytokines or pro-inflammatory

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stimuli may prompt a transition from an anti-thrombotic, anti-inflammatory, and vasodilatory state to one predisposed to coagulation, inflammation, and vasoconstriction.[4]

Inflammation refers to a complex set of biological response processes triggered by various stimulation, including biological, chemical, or physical factors.[5,6] As pivotal effector cells in initiating inflammation, ECs orchestrate the body's response to systemic inflammation, modulate vascular function, and contribute to the pathogenesis of vascular diseases.[7] Although inflammation functions as a self-protective mechanism, dysregulated inflammatory responses can ultimately give rise to various inflammatory disorders, including obesity, hypertension, atherosclerosis (AS), autoimmune diseases, neurodegenerative conditions, diabetes mellitus (DM), sepsis, cardiovascular disease (CVD), and cancer.[6,8–10] Hence, a deeper understanding of the interplay between ECs and inflammation is essential. In recent years, reports have highlighted the central position of ECs in inflammatory processes and the involvement of inflammation in the onset and progression of diverse diseases.[4,11,12] This review delineates the role of ECs in inflammatory processes, the signaling pathways associated with AS, DM, and related complications, respiratory diseases (RD), sepsis, and CVD, and corresponding therapeutic effects. The objective is to enhance researchers' comprehension of vascular-related diseases and provide a foundation for future in-depth investigations and clinical interventions involving ECs and inflammation.

There are reports suggesting that with increasing age, the vascular endothelium may develop into a pro-inflammatory state, potentially leading to vascular endothelial dysfunction and CVD.[13] Some findings demonstrate that aging is associated with the development of a proinflammatory phenotype in the vascular endothelium of healthy adults, which may be caused in part by a reduction in IκB-mediated NF-κB activation. The elevated nuclear content of NF-κB in ECs of healthy older adults with impaired vascular endothelial function, compared to younger healthy subjects, offers compelling evidence suggesting that NF-κB might be involved in the molecular mechanisms contributing to age-related vascular inflammation, endothelial dysfunction, and CVD in humans.[13] Moreover, some findings support the hypothesis that serum 25-hydroxyvitamin D status is associated with vascular endothelial function in middle-aged and elderly patients without clinical disease. Scholars' research findings indicate that reduced levels of 25-hydroxy vitamin D are linked to higher expression of NF-κB and IL-6, along with increased NF-κB-associated suppression of vascular endothelial function. Additionally, it could be linked to the decrease in the expression of vitamin D receptors and 1-hydroxylase in vascular ECs.[14] Furthermore, in a randomized crossover experimental design, scholars discovered that habitual aerobic exercise training may enhance vascular endothelial function in older adults through targeting the NF-κB signaling pathway, which mediates age-related endothelium-dependent dilation in humans. The study also suggests that improving endothelial function in sedentary older individuals can potentially reduce the risk of CVD.[15]

## Literature Inclusion and Exclusion Criteria

Employing the keywords "endothelial cells", "endothelium", and "inflammation", we systematically searched for English-language literature published between 2000, 2012, 2016 and 2022 within the Web of Science and PubMed databases. The initial phase involved screening article titles and abstracts, which was followed by a comprehensive full-text assessment of the articles. Ultimately, 102 papers that fulfilled the inclusion and exclusion criteria were selected.

The inclusion criteria for articles comprised clinical studies and fundamental research focusing on endothelial inflammation, as well as animal models, cell models, therapeutics, inducers, and signaling pathways. The exclusion criteria encompassed non-English studies and those deemed unsuitable for endothelial inflammation research. The investigations retrieved from the literature spanned five disease areas: atherosclerosis (AS), cardiovascular disease (CVD), diabetes mellitus (DM), respiratory disease (RD), and sepsis.

## Endothelial Cells and Inflammation

Under physiological conditions, ECs maintain vascular health by regulating blood flow and distributing nutrients, hormones, and other essential substances.[16–18] They possess the ability to modulate vascular tension, manage hemostasis and thrombosis, inhibit leukocyte adhesion, and control vascular inflammation through vasoconstriction or relaxation.[3,16,19–22] Inflammation constitutes a vital component of innate immunity, safeguarding the host from infection.[23]

As the innermost layer of blood vessels, ECs not only furnish a dynamic interface between circulating blood components and adjacent tissues but also play a crucial role in preserving blood homeostasis and preventing tissue damage.[24] ECs serve as potential targets for lipids, bacterial endotoxins, inflammatory cytokines (tumor necrosis factor

(TNF)-α, ILs, interferon-γ), and microbial agents, with alterations in their functions eliciting inflammatory responses in tissues and organs. Concurrently, vascular inflammation provokes abnormal activation of ECs, leading to dysfunction and structural abnormalities in blood vessels.[25]

Since ECs continuously perceive the extracellular environment, inflammatory stimuli can compromise their barrier function, making them indicative of systemic inflammation.[7] ECs not only safeguard human health but also operate as inflammation mediators, influencing the progression and outcomes of vascular inflammatory diseases.[26] Dysregulated EC activation or dysfunction is considered the initial step in the pathogenesis of vascular inflammatory disorders.[27] Inflammation lies at the core of vascular-related diseases, and endothelial inflammation contributes to a wide variety of diseases, such as highly prevalent conditions such as AS, DM, end-stage renal disease, CVD, etc.[28–32] Therefore, EC inflammation warrants attention and thorough investigation. With a deeper understanding of the mechanism of vascular inflammation, we hope to find relevant disease markers or novel therapeutics to assist clinical diagnosis and improve treatment effectiveness.

## The Role of Endothelial Cells Inflammation in Different Diseases

### Atherosclerosis

Atherosclerosis (AS) arises from the excessive accumulation of lipids and other substances within the arterial intima.[33] This vascular disease, characterized by endothelial inflammation, serves as a major underlying cause of CVD.[34,35] The pathological process of AS is typified by chronic inflammatory reactions, resulting from excessive inflammatory responses to various forms of damage.[31] ECs not only constitute the interface between blood and the arterial intima but also represent the site of AS initiation.[33] Experimental findings indicate that inflammation participates in AS development, with lipids and other traditional risk factors linked to AS via numerous pathways facilitated by inflammatory reactions.[36,37]

Under homeostatic conditions, thrombo regulatory proteins and heparan sulfate proteoglycans on the EC surface, as well as nitric oxide and prostacyclin produced by ECs, contribute to the anticoagulant and anti-thrombotic properties of the normal endothelium.[33,38,39] However, in pathological contexts, inflammatory stimuli activate ECs, leading to the up-regulation of cell adhesion molecules such as E-selectin, intercellular adhesion molecules (ICAM), and vascular cell adhesion molecules (VCAM). This process triggers leukocyte exudation following their rolling on the endothelial surface.[39–41] In summary, EC inflammation is implicated in the progression of AS, and the suppression of inflammation also constitutes an effective treatment for AS.[42,43]

The impacts of specific key molecules on inflammation and AS are detailed below. In mouse aortic endothelial cells (MAECs) and human umbilical vein endothelial cells (HUVECs) stimulated by interleukin-1β (IL-1β) and tumor necrosis factor α (TNF-α), it has been demonstrated that Krüppel-like factor 14 (KLF14), a transcription factor linked to coronary artery disease (CAD), mitigates inflammation by inhibiting the NF-κB signaling pathway.[44] Similarly, in Ox-LDL-mediated HUVECs, silencing circular RNA circ_0003645 can mitigate inflammation and apoptosis by suppressing the NF-κB signaling pathway.[45] Moreover, in TNF-α-induced HUVECs, the cordycepin derivative IMM-H007—an activator of AMP-Activated Protein Kinase (AMPK)—can inhibit the inflammatory response by modulating NF-κB and JNK/AP1 signaling pathways.[46] In Ox-LDL-induced HUVECs, Kruppel-like factor 2 (KLF2) knockdown also abrogates the activation of the AMPK/SIRT1 signaling pathway elicited by protein tyrosine phosphatase 1B (PTP1B) knockdown, which can reduce inflammatory directional injury and dysfunction, thus ameliorating AS.[47] In Ox-LDL-induced human aortic endothelial cells (HAECs) models, overexpressed microRNA-20a attenuates the inflammatory response by inhibiting TLR4 and TXNIP signaling pathways, emerging as a potential therapeutic target for anti-AS development.[48] Some researchers have discovered that in Ox-LDL-induced MAECs, overexpressed C1q/tumor necrosis factor-related protein-3 (CTRP3) inhibits the inflammatory response and endothelial dysfunction by activating the PI3K/AKT/eNOS signaling pathway, suggesting that this may be an effective anti-AS strategy.[49] Additionally, in TNF-α-induced HUVECs, apolipoprotein M and sphingosine-1-phosphate (ApoM-S1P) activate the PI3K/AKT signaling pathway by binding to S1PR2, thereby reducing EC injury, inflammatory response, and pyrosis.[50] In the Ox-LDL-induced HUVECs model, overexpressed Vestigial-like 4 (VGLL4) ameliorates apoptosis, oxidative stress, inflammation, and EC dysfunction by

activating the Hippo-YAP/TEAD1 signaling pathway.[51] Similarly, in Ox-LDL-treated HUVECs, cytoplasmic polyadenylation element binding protein 1 (CPEB1) deletion may suppress oxidative stress, inflammatory response, and apoptosis by modulating the SIRT1/LOX-1 signaling pathway.[52] It has also been demonstrated that in Ox-LDL-induced HUVECs, the biomarker Galectin-3 promotes endothelial dysfunction through the LOX-1-mediated LOX-1/ROS/p38/NF-κB signaling pathway, exacerbating AS.[53] In the AS rat model, overexpression of MiR-181b could alleviate inflammation and protect vascular endothelial function by inhibiting the Notch1 signaling pathway.[54] Another researcher found that in a mouse model of coronary AS, upregulated microRNA-107 (MiR107) activated the Notch signaling pathway by suppressing KRT1, thereby inhibiting the inflammatory response and endoplasmic reticulum stress of vascular ECs.[55] In the high-fat diet (HFD)-fed rabbit AS model, myosin light chain kinase inhibitor 7 (ML7) improves vascular endothelial dysfunction and permeability through the mitogen-activated protein kinase (MAPK) signaling pathway.[56] In the aging model of HUVECs, overexpressed MicroRNA-216a, acting as an endogenous inhibitor of the Smad3/IκBα pathway, accelerates the aging and inflammatory response of ECs, emerging as a potential target for aging-related AS.[57] Studies have shown that in LPS-induced rats and ECs models, the JAK/STAT pathway could inhibit the increase of endothelial adenosine deaminase (eADA) activity, attenuate the activation and inflammation of ECs, and thereby improve AS.[58] Collectively, these findings suggest that overexpression of key molecules can reduce endothelial inflammation in IL-1β, TNF-α, Ox-LDL, or LPS-induced cell and animal models.

The following sections discuss the fundamental research on small molecules and drugs in AS models. Studies have demonstrated that in HUVECs and ApoE$^{-/-}$ mice models, exosomes derived from mature dendritic cells can exacerbate AS by increasing endothelial inflammation through the membrane TNF-α-mediated NF-κB signaling pathway.[59] In IL-1β-induced HUVECs and LPS-induced acute inflammatory mice models, chrysin mitigates vascular EC inflammation by suppressing the NF-κB signaling pathway, potentially emerging as a promising drug candidate for the treatment of inflammatory vascular diseases, such as AS.[60]

Likewise, in IL-1β-induced HUVECs and LPS-induced acute inflammatory mouse models, neferine attenuates inflammatory injury by inhibiting the NF-κB signaling pathway, making it a promising candidate for AS treatment.[61] In Ox-LDL-induced HUVECs, triptolide counteracts EC inflammation by impeding the activation of the oxidative stress-dependent NF-κB pathway, contributing to AS prevention.[62] In LPS-induced HUVECs, the anti-inflammatory effect of *Lactococcus lactis*-fermented spinach juice is mediated through the inhibition of the NF-κB signaling pathway, providing a potential treatment for AS.[63]

Moreover, in TNF-α-induced HUVECs and LPS-induced C57BL/6 mice models, the peptide lycosin-I ameliorates the inflammatory response by modulating the IκB/NF-κB signaling pathway, potentially emerging as a new drug candidate for treating inflammatory diseases.[64] In LPS-induced HUVECs, hyperoside hinders EC inflammation and apoptosis by suppressing the activation of the TLR4/NF-κB signaling pathway, potentially reducing the risk of AS.[65] Additionally, in LPS-induced human coronary endothelial cells (HCAECs) models, ficus deltoidea (FD) obstructs EC activation, inflammation, monocyte adhesion, and oxidative stress via NF-κB and eNOS pathways, thereby exerting anti-AS effects.[66]

Previous research indicates that in homocysteine-induced HAECs, catalpol inhibits reactive oxygen species (ROS) production, oxidative stress, endoplasmic reticulum stress, inflammation, and apoptosis by suppressing the Nox4/NF-κB and GRP78/PERK pathways, potentially providing a therapeutic approach for AS prevention and treatment.[67] Similarly, in Ox-LDL-induced human vascular smooth muscle cells (hVSMCs) and HUVECs, myristicin inhibits cell proliferation, apoptosis, and inflammatory cytokine expression by modulating the PI3K/AKT/NF-κB signaling pathway, consequently suppressing AS development.[68]

Furthermore, in LPS-induced human microvascular endothelial cells-1 (HMEC-1), hypaphorine curbs inflammatory responses by regulating TLR4 and PPAR-γ, which rely on the PI3K/AKT/mTOR signaling pathway, potentially serving as a therapeutic agent for endothelial inflammatory diseases, such as AS.[69] In hyperhomocysteinemia-induced HUVECs and mice models, picroside II may decrease EC injury in AS by inhibiting oxidative stress, inflammatory responses, and apoptosis through regulation of the SIRT1/LOX1 signaling pathway.[70] In LPS or Ox-LDL-induced cell models, active polypeptides from Hirudo may prevent AS onset by modulating the LOX-1/LXR-α/ABCA1 signaling pathway, inhibiting THP-1 cell adhesion to HUVECs, reducing the inflammatory response, and suppressing ROS production and apoptosis in

RAW264.7 cells.[34] In Ox-LDL-induced HUVECs, naringin mitigates apoptosis and inflammatory responses by inhibiting the Hippo-YAP signaling pathway, thereby decreasing the formation and progression of AS plaques.[71]

Previous findings suggest that in rat models of cigarette smoke extract (CSE)-induced HAECs and carotid artery injury exposed to cigarette smoke, melatonin reduces ROS generation and cell pyroptosis via the Nrf2/ROS/NLRP3 signaling pathway, preventing smoking-induced vascular injury and AS.[72] Additionally, in Ox-LDL-induced HUVECs and ApoE$^{-/-}$ mice, dihydrohomoplantagin and homoplantaginin minimize EC injury, ROS overproduction, and apoptosis by activating the Nrf2 antioxidative signaling pathway, thereby controlling AS development.[73]

In the in vitro experimental HUVECs model, the choline-derived metabolite trimethylamine N-oxide (TMAO) induces oxidative stress and activates the ROS-TXNIP-NLRP3 inflammasome signaling pathway, resulting in EC inflammation and endothelial dysfunction, thereby increasing AS risk.[74] Intriguingly, in Ox-LDL-induced HUVECs, rapamycin abates the inflammatory response by suppressing the mTORC2/PKC/c-Fos pathway, thus exerting an anti-AS function.[75] Researchers have discovered that in Ox-LDL-induced HUVECs, nintedanib (a multityrosine kinase receptor inhibitor) downregulates arginase II by inhibiting the p53/p21 signaling pathway, improving endothelial inflammation, oxidative stress, and cellular senescence, potentially serving as a therapeutic agent for AS.[76]

In HUVECs and Tlr4$^{mut}$ mice models, disordered blood flow locally activates the TLR4 signaling pathway in ECs by upregulating fibronectin containing the extra domain A in the subendothelial extracellular matrix, leading to endothelial inflammation and AS onset.[77] Significantly increased expression of NDRG1 was found in cytokine-stimulated ECs as well as in human and mouse models of AS, and the findings suggest that NDRG1 is a key signal influencing endothelial inflammation and vascular remodeling, and that inhibiting NDRG1 may be a potential clinical therapeutic target for the treatment of inflammatory vascular diseases such as AS.[78] In an AS model of HFD-fed ApoE $^{-/-}$ mice, a significant increase in plaque formation was observed in the model group; in the LPS-treated HUVECs and RAW264.7 inflammation models, isorhynchophylline reduced LPS-induced inflammatory responses through inhibition of the NF-κB/NLRP3 pathway and promoted the cell migration ability.[79]

From the aforementioned findings, it is evident that AS frequently develops in medium and large arteries composed of ECs, vascular smooth muscle cells (VSMCs), and other vascular cells.[80] These vascular ECs in the table may serve as a valuable model for investigating the molecular mechanisms of vascular diseases (Table 1). AS is a chronic inflammatory vascular disease driven by both traditional and non-traditional risk factors.[31,81] Several inflammation-related signaling pathways are involved in the regulation of AS pathogenesis, including the NF-κB signaling pathway, Toll-like receptor signaling pathway, and PI3K/AKT signaling pathway. These pathways hold significant implications for the progression of AS. Targeting inflammation-related signaling pathways may present a novel and effective approach for treating AS.[31] Consequently, we have summarized the cell models, animal models, and associated signaling pathways related to AS and introduced corresponding research findings. These studies collectively highlight the impact of EC inflammation on the onset and progression of AS.

## Cardiovascular Diseases

Cardiovascular disease (CVD) encompasses a range of conditions affecting blood vessels and the heart, including coronary heart disease (CHD), stroke, and peripheral vascular disease.[82,83] CVD is a leading cause of mortality in numerous countries and a common endpoint for various chronic diseases.[84] Multiple potential causes of CVD have been identified, with inflammation being one of them.[85] Clinical and epidemiological studies have established a close link between EC function and CVD risk, revealing that the onset, progression, and alleviation of CVD are intimately associated with the inflammatory response.[43,86] Chronic inflammation plays a pivotal role in the pathogenesis of CVD during its pathological process.[11] Consequently, mitigating endothelial inflammation has emerged as a crucial strategy in treating CVD. A thorough investigation of the connection between inflammation and disease could offer novel insights and approaches for the prevention and treatment of such conditions. In this section, we will discuss the significance of inflammation in the initiation and progression of CVD, as well as basic research methodologies aimed at drug-targeted ECs to enhance vascular function.[85]

**Table 1** Endothelial Inflammation in Atherosclerosis

| Ref. | Drug/Targets | Models (Cells or Animals) | Mechanisms of Protection | Diseases | Pathways |
|---|---|---|---|---|---|
| [44] | KLF14 | IL-1β and TNF-α-induced HCAECs, HUVECs, THP-1 cells, Klf14 KO mice | Inflammation | Atherosclerosis | NF-κB signaling pathway |
| [45] | Circ_0003645 | Ox-LDL-induced HUVECs | Inflammation and apoptosis | Atherosclerosis | NF-κB signaling pathway |
| [46] | IMM-H007 | TNF-α-induced HUVECs, THP-1 cells | Endothelial inflammation | Atherosclerosis | NF-κB and JNK/AP1 signaling pathway |
| [47] | PTP1B | Ox-LDL-induced HUVECs | Endothelial function, inflammation, apoptosis, oxidative stress | Atherosclerosis | AMPK/SIRT1 signaling pathway |
| [48] | MiR-20a | Ox-LDL-induced HAECs | Inflammation | Atherosclerosis | TLR4 and TXNIP signaling pathways |
| [49] | CTRP3 | Ox-LDL-induced MAECs, $ApoE^{-/-}$ mice | Endothelial dysfunction, inflammation | Atherosclerosis | PI3K/AKT/eNOS signaling pathway |
| [50] | ApoM-S1P | TNF-α-induced HUVECs, THP-1 cells | Endothelial cell injury and inflammation, pyroptosis | Atherosclerosis | PI3K/AKT signaling pathway |
| [51] | VGLL4 | Ox-LDL-induced HUVECs | Apoptosis, oxidative stress, inflammation and dysfunction | Atherosclerosis | Hippo-YAP/TEAD1 signaling pathway |
| [52] | CPEB1 | Ox-LDL-induced HUVECs | Oxidative stress, apoptosis, and inflammation | Atherosclerosis | SIRT1/LOX-1 signaling pathway |
| [53] | Galectin-3 | Ox-LDL-induced HUVECs | Endothelial dysfunction | Atherosclerosis | LOX-1/ROS/p38/NF-κB signaling pathway |
| [54] | MiR-181b | $(ApoE)^{-/-}$ male rats | Atherosclerotic inflammation | Atherosclerosis | Notch1 signaling pathway |
| [55] | KRT1, microRNA-107 | SPF Kunming mice | Inflammation, apoptosis, and endoplasmic reticulum stress | Coronary atherosclerosis | Notch signaling pathway |
| [56] | ML7 | HFD-fed Rabbits | Endothelial dysfunction and permeability | Atherosclerosis | MAPK signaling pathway |
| [57] | MicroRNA-216a | Replicative senescence model of HUVECs | Endothelial senescence and inflammation | Atherosclerosis and CAD | Smad3/IκBα signaling pathway |
| [58] | eADA | LPS-induced HAECs, SC, VSMC, LPS-induced Wistar rats, $IL\text{-}6^{-/-}$ mice | Inflammation | Atherosclerosis | JAK/STAT signaling pathway |
| [59] | GW4869 | BMDCs, LPS-treated DCs, DC-exos-stimulated HUVECs; $ApoE^{-/-}$mice | Endothelial inflammation | Atherosclerosis | NF-κB signaling pathway |
| [60] | Chrysin | IL-1β-induced HUVECs, THP-1 cells, LPS-induced C57BL/6J mice | Endothelial inflammation | Atherosclerosis | NF-κB signaling pathway |
| [61] | Neferine | IL-1β-induced HUVECs, THP-1cells, LPS-induced C57BL/6 mice | Inflammation | Atherosclerosis | NF-κB signaling pathway |
| [62] | Triptolide | Ox-LDL-induced HUVECs | Endothelial Inflammation | Atherosclerosis | NF-κB signaling pathway |
| [63] | S.juice | LPS-induced HUVECs | Inflammation | Atherosclerosis | NF-κB signaling pathway |
| [64] | Lycosin-I | TNF-α-induced HUVECs, THP-1 cells, LPS-induced C57BL/6 mice | Inflammation | Atherosclerosis | IκB/NF-κB signaling pathway |
| [65] | Hyperoside | LPS-induced HUVECs | Inflammation and apoptosis | Atherosclerosis | TLR4/NF-κB signaling pathway |
| [66] | FD | LPS-induced HCAECs | Endothelial activation, inflammation, monocytes adhesion and oxidative stress | Atherosclerosis | NF-κB and eNOS signaling pathways |

(*Continued*)

**Table 1** (Continued).

| Ref. | Drug/Targets | Models (Cells or Animals) | Mechanisms of Protection | Diseases | Pathways |
|---|---|---|---|---|---|
| [67] | Catalpol | Homocysteine-induced HAECs | Oxidation, inflammation, apoptosis, ROS | Hyperhomocyst-einemia | Nox4/NF-κB and GRP78/PERK signaling pathways |
| [68] | Myristicin | Ox-LDL-induced HUVECs and hVSMCs | Proliferation and apoptosis | Atherosclerosis | PI3K/AKT and NF-κB signaling pathway |
| [69] | Hypaphorine | LPS-induced HMEC-1 | Inflammation | Atherosclerosis | PI3K/AKT/mTORI signaling pathway |
| [70] | Picroside II | Hyperhomocysteinemia-induced HUVECs and C57BL mice | Inflammation, oxidative stress, apoptosis | Atherosclerosis | SIRT1/LOX-1 signaling pathway |
| [34] | Active polypeptides from Hirudo | LPS or Ox-LDL-induced HUVECs, RAW264.7, THP-1 cells | Inflammation, ROS, foam cell apoptosis | Atherosclerosis | LOX-1/LXR-α/ABCA1 signaling pathway |
| [71] | Naringin | Ox-LDL-induced HUVECs | Inflammation and apoptosis | Atherosclerosis | Hippo-YAP signaling pathway |
| [72] | Melatonin | CSE-induced HAECs | Vascular injury, ROS, pyroptosis | Atherosclerosis | Nrf2/ROS/NLRP3 signaling pathway |
| [73] | Dihydrohomopla-ntagin and Homoplantaginin | Ox-LDL induced HUVECs, $ApoE^{-/-}$ mice | Endothelial cell injury, ROS, apoptosis | Atherosclerosis | Nrf2 Anti-Oxidation signaling pathway |
| [74] | TXNIP | TMAO induced HUVECs | Endothelial dysfunction, inflammation, oxidative stress | Atherosclerosis | ROS-TXINP-NLRP3 signaling pathway |
| [75] | Rapamycin | Ox-LDL-induced HUVECs | Inflammation | Atherosclerosis | mTORC2/PKC/c-Fos signaling pathway |
| [76] | Nintedanib | Ox-LDL-induced HUVECs | Inflammation and cellular senescence, oxidative stress | Atherosclerosis | p53/p21 signaling pathway |
| [77] | TLR4 | LPS-induced HUVECs, HEK293FT, THP-1 cells, C57BL/6J mice, $Tlr4^{mut}$ WT Mice | Inflammation | Atherosclerosis | TLR4 signaling pathway |
| [78] | NDRG1 | Cytokine-stimulated ECs, human and mouse models of AS | Endothelial inflammation and vascular remodeling | Atherosclerosis | NDRG1 pathway |
| [79] | Isorhynchophylline | HFD-fed $ApoE^{-/-}$ mice, LPS-treated HUVECs and RAW264.7 | Inflammation, cell migration ability | Atherosclerosis | NF-κB/NLRP3 pathway |

**Abbreviations**: HUVECs, human umbilical vein endothelial cells; BMDCs, Bone marrow dendritic cells; DC, Dendritic cells; TNF-a, Tumour necrosis factor-a; KLF14, Krüppel-like factor 14; THP-1, Tohoku Hospital Pediatrics-1; HCAECs, Human coronary artery endothelial cells; Ox-LDL, Oxidized low-density lipoprotein; PTP1B, Protein tyrosine phosphatase 1B; HAECs, Human aortic endothelial cells; CTRP3, C1q/tumor necrosis factor-related protein-3; MAECs, Mouse aortic endothelial cells; VGLL4, Vestigial-like 4; CPEB1, Cytoplasmic polyadenylation element binding protein 1; miR-181b, Micro ribonucleic acid-181b; SPF, specific-pathogen-free Kunming mice; ML7, Myosin light chain kinase inhibitor 7; HFD, high-fat diet; CAD, Coronary artery disease; eADA, Ecto-adenosine deaminase; LPS, Lipopolysaccharide; ROS, Reactive oxygen species; SC, Monocyte/macrophage cells; VSMC, Vascular smooth muscle cells; DC-exos; dendritic cells-derived exosomes; $IL\text{-}6^{-/-}$ mice, IL-6 knock-out mice; FD, Ficus deltoidei; hVSMCs, Human vascular smooth muscle cell; HMEC-1, Human microvascular endothelial cells-1; CSE, cigarette smoke extract; TXNIP, thioredoxin-interactive protein; TMAO, Trimethylamine-N-oxide; $Tlr4^{mut}$, Toll-like receptor 4 mutant HeJ mice; WT mice, wild type Heou J mice.

According to the latest research, arterial dysfunction, such as impaired endothelial function like reduced endothelium-dependent dilation (EDD), and large artery stiffening, are key factors in the development of CVD and tend to worsen with age. These are mainly mediated by an overproduction of ROS and an increase in chronic, low-grade inflammation.[87]

In a clinical study, regular aerobic exercise has demonstrated its ability to inhibit oxidative stress and lower inflammatory marker levels, which may effectively improve endothelial dysfunction and large elastic artery stiffening. As a result, this intervention serves as a promising measure for preventing and treating CVD and promoting

cardiovascular health.[88] Interestingly, multiple pilot trials have indicated that Inspiratory Muscle Strength Training (IMST), a high-resistance inspiratory muscle training, can reduce chronic low-grade inflammation and improve cardiovascular function, enhancing compliance among middle-aged and older individuals. This approach addresses the limitations of only a small proportion of adults meeting the aerobic exercise guidelines.[89,90] In addition, in vehicle-treated animals, observations suggest that oral administration of apigenin reverses vascular endothelial dysfunction and large elastic artery stiffening and prevents foam cell formation in an established cell culture model of early AS. These preclinical research findings offer valuable insights into the inhibition of age-related intrinsic mechanical wall stiffening in the aorta and vascular inflammation. They lay the groundwork for future translational studies assessing the potential of apigenin therapy in treating arterial dysfunction and reducing the risk of CVD.[91] It is noteworthy that in a randomized, double-blind, placebo-controlled, single-point parallel group clinical trial, age-related increases in large elastic artery stiffening and systolic blood pressure were found to be associated with oxidative stress, inflammation, and increased vascular smooth muscle tension, leading to the development of CVD. However, the researchers discovered that supplementing with nicotinamide riboside could alleviate the rise in systolic blood pressure and arterial stiffness in middle-aged and older individuals, thereby improving cardiovascular health.[92]

Endothelium-dependent dilation is a prerequisite for CVD. Recently, in a double-blind placebo-controlled study, it was confirmed that inhibiting acute systemic inflammation can improve endothelium-dependent dilation in women with a history of preeclampsia during pregnancy. This finding, based on a cutaneous microcirculation model, suggests that the vascular dysfunction observed during preeclamptic pregnancies may increase the lifelong risk of CVD in these women.[93] Secondly, in an epidemiologic and observational study, it was shown that acute systemic inflammation impairs endothelium-dependent dilatation of human veins in humans, and in this study, it was found that there is a close relationship between infections or inflammation, which is usually considered to be associated with CVD.[94] Notably, in a small open-label study, experts found that short-term treatment with the NF-κB inhibitor salicylate improved nitric oxide (NO)-mediated endothelium-dependent dilatation of the microvasculature in young adults with major depression. Besides, there is substantial evidence that adult major depression is associated with a substantially increased risk of future CVD development. Thus, the development of new therapeutic interventions to prevent or slow the progression of CVD has strong relevance.[95] In addition, two key findings need to be noted in a study. First, in a rat model, inhalation of multi-walled carbon nanotubes induced lung inflammation. Second, the inhalation of multi-walled carbon nanotubes resulted in profound changes in endothelium-dependent dilation of coronary arteries. Taken together, these results are the first report of coronary microvascular dysfunction after multiwall carbon nanotubes.[96] Scientists have also determined in recent years that the effects of pulmonary exposure to particulate matter on endothelium-dependent dilation of systemic microvascular are dependent on pulmonary and/or microvascular inflammation, and that, these systemic inflammations associated with particulate matter exposure have been considered to be linked to impaired cardiovascular function in affected individuals.[97]

In acute arterial wall shear stress-induced saphenous vein ECs, the inflammatory response can be diminished by inhibiting the activation of the NF-κB signaling pathway.[98] Similarly, in TNF-α-induced HAECs, zafirlukast (a cysteinyl leukotriene receptor type 1 (CysLT1R) antagonist) reduces inflammatory injury and ROS by suppressing the NF-κB signaling pathway, potentially serving as a novel therapeutic agent for CVD.[99] Likewise, in angiotensin II–induced C57BL/6 mice and HUVECs, schizandrin B mitigates endothelial to mesenchymal transition, oxidative stress, and inflammation by inhibiting the NF-κB signaling pathway, thereby attenuating vascular remodeling and potentially reducing the progression of CAD.[100] In TNF-α-induced HCAECs, epigallocatechin gallate diminishes the inflammatory response by suppressing the NF-κB signaling pathway, potentially providing a treatment for CAD.[101] Interestingly, in a model of hypoxia-reoxygenation-induced human cardiac microvascular EC injury, overexpressed MicroRNA-106b inhibited B-cell linker (BLNK) by repressing the NF-κB signaling pathway, thereby reducing inflammatory injury in cardiac ECs.[102] Additionally, in a rat model of ischemia-reperfusion-induced SD, Vitamin D hinders the inflammatory response by inhibiting the RhoA/ROCK/NF-κB signaling pathway, thus decreasing myocardial ischemia-reperfusion injury.[103] Intriguingly, in HUVECs subjected to simulated microgravity, endoplasmic reticulum stress activates the iNOS/NO-NF-κB and NLRP3 inflammasome signaling pathways, promoting EC inflammation and apoptosis, ultimately leading to cardiovascular dysfunction.[104] In contrast, under endosulfan (a fat-soluble insecticide)-induced HUVECs, oxidative stress and endoplasmic reticulum stress are reduced by suppressing the

IRE1α/NF-κB signaling pathway, thereby inhibiting EC inflammation and endothelial dysfunction, potentially decreasing the incidence of CVD.[105] Furthermore, in Ox-LDL-induced HUVECs and HASMCs, orexin A ameliorates endothelial inflammation by inhibiting THP-1 cell adhesion to ECs through the suppression of MAPK p38 and NF-κB signaling pathways.[106] Interestingly, in hexavalent chromium-induced THP-1 cells and HUVECs, taxifolin reduces oxidative stress and apoptosis by inhibiting NF-κB and p38 MAPK signaling pathways, thereby preventing CAD.[107] In palmitic acid (PA)-induced HUVECs, adiponectin decreases ROS, endothelial inflammation, and IR by modulating the ROS/IKKβ signaling pathway, providing new insights into the mechanism of cardiovascular protective action.[108] In a mouse model of heart failure with preserved ejection fraction (HFpEF), QiShenYiQi mitigates HFpEF by inhibiting microvascular endothelial inflammation and activating the NO-cGMP-PKG signaling pathway.[109] Additionally, in ApoE$^{-/-}$ mice fed HFD, the cordycepin derivative IMM-H007, an activator of AMP-Activated Protein Kinase (AMPK), suppresses vascular inflammation and improves endothelial dysfunction by regulating the AMPK-PI3K-AKT-eNOS signaling pathway, contributing to cardiovascular protection.[110] Moreover, in Ox-LDL-induced HUVECs, ginsenoside Rg1 attenuates apoptosis, senescence, and oxidative stress by regulating the AMPK/SIRT3/p53 signaling pathway, thus laying the groundwork for the treatment of CHD.[111] In leptin-induced HUVECs, 1.25-dihydroxycholecalciferol ([1,25 (OH)2D3]) reduces oxidative stress and inflammation by activating the Nrf2-antioxidant signaling pathway, thereby decreasing obesity and the risk of CVD and other health problems.[112] Some researchers have observed that in PA-induced SD rats, methotrexate can improve endothelial dysfunction by activating the AMPK/eNOS pathway to inhibit the inflammatory response in perivascular adipose tissue, thereby providing pharmacological evidence for the treatment of CVD.[113]

The significance of vascular endothelial function in the initiation and progression of CVD cannot be understated.[114] Inflammation within the vascular endothelium serves as a primary contributor to CVD development.[115] To gain deeper insights into the amelioration of CVD through inflammation reduction, this section outlines various vascular ECs models and animal models employed to investigate the pathogenesis of CVD. We also present an overview of molecular mechanisms targeted for CVD treatment, encompassing the RhoA/ROCK/NF-κB signaling pathway, iNOS/NO-NF-κB/IκB signaling pathway, NLRP3 inflammasome signaling pathway, IRE1α/NF-κB signaling pathway, and the MAPK p38 signaling pathway (Table 2).

**Table 2** Endothelial Inflammation in Cardiovascular Diseases

| Ref. | Drug/Targets | Models (cells or animals) | Mechanisms of protection | Diseases | Pathways |
|---|---|---|---|---|---|
| [88] | Regular aerobic exercise | \ | Oxidative stress, inflammation | Endothelial dysfunction, large elastic artery stiffening, CVD | \ |
| [89,90] | IMST | \ | Inflammation, cardiovascular function | CVD | \ |
| [91] | Apigenin | Vehicle-treated animals | Endothelial dysfunction and large elastic artery stiffening | AS and CVD | \ |
| [92] | Nicotinamide riboside | \ | Large elastic artery stiffening, oxidative stress, inflammation | CVD | \ |
| [93] | Women with a history of preeclampsia during pregnancy | Cutaneous microcirculation model | Endothelium-dependent dilation; inflammation | CVD | \ |
| [94] | Salmonella typhi vaccine | Salmonella typhi vaccine-induced Inflammatory response | Endothelium-dependent dilatation, infections, or inflammation | CVD | \ |
| [95] | Salicylate | Nitric oxide (NO)-mediated | Endothelium-dependent dilatation, ROS | CVD | \ |

(*Continued*)

**Table 2** (Continued).

| Ref. | Drug/Targets | Models (cells or animals) | Mechanisms of protection | Diseases | Pathways |
|---|---|---|---|---|---|
| [96] | MWCNT | SD rats | Impairment of Coronary Arteriolar Endothelium-Dependent Dilation; inflammation | CVD | \ |
| [97] | Particulate Matter | Male SD rats | Pulmonary/ microvascular inflammation | CVD | \ |
| [98] | BAY11-7085 | Acute shear stress-induced HUVECs | Endothelial inflammation | Ischaemic heart disease | NF-κB signaling pathway |
| [99] | Zafirlukast | TNF-α-induced HAECs | Endothelial inflammation, ROS | Cardiovascular diseases | NF-κB signaling pathway |
| [100] | Schizandrin B | Angiotensin II–induced HUVECs, C57BL/6 mice | Inflammation, oxidative stress | Vascular remodeling | NF-κB signaling pathway |
| [101] | Epigallocatechin gallate | TNF-α-induced HCAECs | Inflammation | Cardiovascular disease | NF-κB signaling pathway |
| [102] | MicroRNA-106b, BLNK | Hypoxia-reoxygenation-induced HCMECs and CMECs | Inflammation injury | Endothelial cells dysfunction | NF-κB signaling pathway |
| [103] | Vitamin D | Ischemia-reperfusion-induced SD rats | Inflammation | Cardiovascular diseases | RhoA/ROCK/NF-κB signaling pathway |
| [104] | 4-PBA, TUDCA | ER stress-induced HUVECs, HMECs | Inflammation and apoptosis | Cardiovascular dysfunction | iNOS/NO-NF-κB/IκB and NLRP3 inflammasome pathways |
| [105] | NAC, STF-083010 | Endosulfan-induced HUVECs | Inflammation, dysfunction, oxidative stress, endoplasmic reticulum stress | Cardiovascular diseases | IRE1α/NF-κB signaling pathway |
| [106] | Orexin A | Ox-LDL-induced HUVECs and HASMCs; THP-1 cells | Inflammation | Cardiovascular diseases | MAPK p38 and NF-κB signaling pathways |
| [107] | Taxifolin, Cr (VI) | Hexavalent chromium-induced HUVECs, THP-1 cells | Oxidative stress, apoptosis | Cardiovascular diseases | NF-κB and p38 MAPK signaling pathways |
| [108] | Adiponectin | PA-induced HUVECs | Endothelial inflammation, IR, ROS | Cardiovascular and related diseases | ROS/IKKβ signaling pathway |
| [109] | QiShenYiQi | HFD fed C57BL/6N mice | Inflammation, oxidative stress | HFpEF | NO-cGMP-PKG signaling pathway |
| [110] | IMM-H007 | TNF-α-induced C57BL/6 mice, HFD fed ApoE$^{-/-}$mice, HUVECs | Endothelial dysfunction, inflammation | Cardiovascular diseases | AMPK-PI3K-AKT-eNOS signaling pathway |
| [111] | Ginsenoside Rg1 | Ox-LDL-induced HUVECs | Apoptosis, senescence, oxidative stress | Coronary heart disease | AMPK/SIRT3/p53 signaling pathway |
| [112] | [1,25 (OH)2D3] | Leptin-induced HUVECs | Oxidative stress and inflammation | Obesity | Nrf2-antioxidant signaling pathway |
| [113] | Methotrexate | PA-induced SD rats, 3T3-L1 cells | Inflammation | Cardiovascular diseases | AMPK/eNOS signaling pathway |

**Abbreviations**: IMST, Inspiratory Muscle Strength Training; HCMECs, Human cardiac microvascular endothelial cells; CMECs, cardiac microvascular endothelial cells; SD rats, Sprague-Dawley rats; 4-PBA, 4-phenylbutyric acid; TUDCA, tauroursodeoxycholic acid; ER, endoplasmic reticulum; HMECs, human microvessel endothelial cells; NAC, N-acetylcysteine; PA-induced, Palmitic acid-induced; HFpEF, Heart failure with preserved ejection fraction; Cr (VI), Chromium (VI); 1.25 (OH)2D3, 1.25-dihydroxycholecalciferol; IR, Insulin resistance; HASMCs, Human airway smooth muscle cells; NO, nitric oxide; MWCNT, multi-walled carbon nanotube.

## Diabetes Mellitus and Its Complications

Diabetes mellitus (DM) is a metabolic disorder characterized by persistent hyperglycemia resulting from inadequate insulin action, insufficient insulin secretion, or a combination of both.[116] Vascular complications associated with DM are the primary drivers of morbidity and mortality in affected individuals.[117] Hyperglycemia initially impairs blood vessels, with ECs considered the primary targets of hyperglycemic injury. Endothelial damage and inflammation play crucial roles in the pathogenesis of type 2 diabetes mellitus (T2DM) and its vascular complications.[32,117,118] Recent evidence also indicates that vascular EC dysfunction is present during the pre-DM stage, contributing significantly to the development and progression of both macrovascular and microangiopathic complications.[119] Chronic inflammation is a prevalent feature of T2DM.[120] Besides, the connection between inflammation and DM has sparked interest in targeting inflammation as a means to improve DM and its related complications.[121] This section provides an overview of recent treatments and preventive measures, which target different signaling pathways to help reduce inflammation and manage diabetes.

The following research highlights advancements in mitigating inflammatory responses in DM by modulating key molecular players. In high glucose (HG)-induced HUVECs, silencing long noncoding RNA MALAT1 has been shown to alleviate apoptosis and inflammatory responses by inhibiting the NF-κB signaling pathway.[122] Similarly, in HG-induced human retinal endothelial cells (HRCECs) and streptozotocin-induced diabetic retinopathy model mice, depletion of SOX4, a transcription factor expressed in the pancreas, inhibited endothelial inflammatory responses, migration, and angiogenesis via the NF-κB signaling pathway.[123] Studies have demonstrated that in HG-induced HUVECs, overexpression of cystic fibrosis transmembrane conductance regulator (CFTR) reduces ROS, oxidative stress, and inflammatory response by regulating NF-κB and MAPK signaling pathways, thereby mitigating diabetic CAD.[124] In HG-induced HUVECs, downregulation of hsa_circ_0068087 could inhibit endothelial dysfunction and inflammatory response by suppressing the TLR4/NF-κB/NLRP3 inflammasome signaling pathway.[125] In a human retinal endothelial cells model, soluble gp-130 fused chimera (sgp130-Fc) attenuated endothelial inflammation, apoptosis, and endothelial barrier disruption through inhibition of the IL-6 trans-signaling pathway, thereby reducing diabetic retinopathy.[126] In HG-induced HUVECs, overexpressed malignant fibrous histiocytoma amplified sequence 1 (MFHAS1) inhibits the inflammatory response by activating the AKT/HO-1 signaling pathway, thus controlling the development of diabetes.[127] In diabetic db/db mice and HUVECs models, overexpressed transcription factor EB (TFEB) attenuated vascular endothelial inflammation by inhibiting the IKK (IκB kinase)-p65 signaling pathway.[128] In HG-induced HUVECs, overexpression of microRNA-9-5p reduced apoptosis and inflammatory responses by inhibiting CXC chemokine receptor-4 (CXCR4) to suppress the mitogen-activated protein kinase (MAPK)/ERK and PI3K/AKT/mTOR signaling pathways.[129]

The following studies showcase the research advancements involving small molecule compounds and drugs in diabetes models. In HG-induced HUVECs, ketamine has been shown to inhibit EC inflammation by attenuating ROS production, reducing phosphorylation of PKC βII Ser660, and deactivating PKC and NF-κB.[130] Interestingly, in db/db mice and HG and palmitate-induced MAECs, circulating metabolites of strawberries may improve vascular inflammation and endothelial dysfunction by inhibiting the NF-κB signaling pathway, thereby preventing diabetes-related vascular complications.[131] In advanced glycation end products (AGEs)-induced HUVECs, salidroside reduces EC inflammation and oxidative stress by modulating the AMPK/NF-κB/NLRP3 signaling pathway.[132] Among palmitate-induced HUVECs and SD rats, the ethyl acetate extract of C. chinense (CCE) reduces endothelial inflammation and IR by inhibiting TLR4-mediated NF-κB and MAPK signaling pathways, suggesting its potential as a therapeutic agent for treating IR and DM-related endothelial dysfunction.[133] In mouse models of diabetic nephropathy and AGEs-induced mouse glomerular endothelial cells (mGECs) injury, catalpol improved endothelial dysfunction and inflammatory response by inhibiting the RAGE/RhoA/ROCK signaling pathway, thereby ameliorating the pathological injury of diabetic kidneys.[134] In HG-induced HUVECs, sodium hydrosulfide (NaHS) reduces endothelial injury and inflammation by inhibiting the p38 MAPK signaling pathway, thus treating vascular complications of DM.[135] In palmitate and insulin-induced HUVECs and HFD fed mice models, spinosin improves IR and reduces ROS production and inflammation by modulating the PI3K/AKT/eNOS signaling pathway.[136] Albiflorin exerts a potential therapeutic effect on diabetes vascular complications by inhibiting HG-induced apoptosis and inflammatory response in HUVECs through the suppression of the PARP1/ NF-κB signaling pathway.[137]

In light of these studies, our understanding of the inflammatory mechanisms associated with DM and its vascular complications has significantly advanced (Table 3). This section offers a comprehensive overview of the methodologies, experimental progress, and related pathways involved in DM treatment. Collectively, these studies underscore the crucial role of inflammation in ECs during the pathological process of DM and provide valuable insights for future research aimed at treating DM through anti-inflammatory approaches.

## Sepsis

Sepsis is a life-threatening systemic inflammatory response syndrome resulting from infection.[138] It is characterized by organ dysfunction stemming from the host's dysregulated response to infection.[139] However, the host's inflammatory response also contributes to the pathological and physiological changes observed in sepsis.[140,141] At least 19 million people globally are affected by this condition annually.[142,143] Research into the pathogenesis of sepsis has revealed that both inflammation and

**Table 3** Endothelial Inflammation in Diabetes Mellitus

| Ref. | Drugs/Targets | Models (Cells or Animals) | Mechanisms of Protection | Diseases | Pathways |
|---|---|---|---|---|---|
| [122] | MALAT1 | HG-induced HUVECs | Inflammation and apoptosis | Diabetes mellitus | NF-κB signaling pathway |
| [123] | SOX4 | HG-induced HRCECs, streptozotocin-induced DB mice | Inflammation | Diabetic retinopathy | NF-κB signaling pathway |
| [124] | CFTR | HG-induced HUVECs | ROS, inflammation, and apoptosis | Diabetic cardiovascular diseases | NF-κB and MAPK signaling pathways |
| [125] | hsa_circ_0068087 | HG-induced HUVECs | Endothelial dysfunction, inflammation | Diabetes mellitus | TLR4/NF-κB/NLRP3 signaling pathway |
| [126] | Sgp130 | HRECs | Inflammation and apoptosis | Diabetic retinopathy | IL-6 trans-signaling pathway |
| [127] | MFHAS1 | HG-induced HUVECs | Inflammation | Diabetes mellitus | AKT/HO-1 signaling pathway |
| [128] | TFEB | IL-1β-induced HUVECs, db/db mice | Inflammation | Vascular complications of diabetes | IKK (IκB Kinase)-p65 signaling pathway |
| [129] | microRNA-9-5p | HG-induced HUVECs | Inflammation and apoptosis | Diabetes mellitus | (MAPK)/ERK and PI3K/AKT/mTOR signaling pathways |
| [130] | Ketamine | HG-induced HUVECs | Endothelial inflammation, ROS | Perioperative hyperglycemia | NF-κB signaling pathway |
| [131] | Circulating metabolites of strawberry | db/db mice, HG and palmitate-induced MAECs, WEHI78/24 cells | Endothelial dysfunction, inflammation | Diabetes | NF-κB signaling pathway |
| [132] | Salidroside | AGEs-induced HUVECs | Endothelial inflammation, oxidative stress, apoptosis | Diabetic conditions | AMPK/NF-κB/NLRP3 signaling pathway |
| [133] | CCE | PA-induced HUVECs and SD rats | Endothelial inflammation | Insulin resistance | NF-κB and MAPK signaling pathways |
| [134] | Catalpol | AGEs-induced MGECs, DN mice | Endothelial dysfunction, inflammation | Diabetic nephropathy | RAGE/RhoA/ROCK signaling pathway |
| [135] | NaHS | HG-induced HUVECs | Injury and inflammation | Diabetes mellitus | p38 MAPK signaling pathway |
| [136] | Spinosin | PA and insulin-induced HUVECs, HFD fed mice | ROS and inflammation | Diabetes mellitus | PI3K/AKT/ eNOS signaling pathway |
| [137] | Albiflorin | HG-induced HUVECs | Apoptosis and inflammatory response | Diabetes vascular complications | PARP1/NF-κB signaling pathway |

**Abbreviations**: HRCECs, human retinal endothelial cells; CFTR, Cystic fibrosis transmembrane conductance regulator; sgp130Fc, Soluble gp-130 fused chimera; HRECs Human retinal endothelial cells; MFHAS1, Malignant fibrous histiocytoma amplified sequence 1; TFEB, Transcription factor EB; HG-induced, High-glucose induced; AGEs, advanced glycation end products; CCE, C. chinense.

anti-inflammatory responses are triggered during the early stages of infection. Inflammatory mediators can also induce infection, leading to abnormal EC activation, endothelial barrier injury, and an imbalance between pro-inflammatory and anti-inflammatory responses. This imbalance results in an inflammatory cell storm that causes extensive cellular damage.[143,144] Persistent and repeated inflammatory damage has been implicated in EC injury during sepsis.[145] ECs typically serve as crucial physical barriers that maintain vascular intima integrity. However, in sepsis, the release of substantial amounts of endotoxins and inflammatory cytokines directly contributes to vascular EC injury.[146]

Numerous sepsis models are induced by LPS. For instance, in LPS-induced HUVECs, upregulation of hnRNPA2/B1 has been shown to inhibit EC injury by suppressing NF-κB and VE-cadherin/β-catenin signaling pathways.[147] Likewise, in LPS-induced endotoxemia animal models and mouse lung microvascular endothelial cells, endothelial calpain knockout mitigates acute kidney injury and apoptosis in mice by inhibiting the p38-iNOS signaling pathway.[148] Moreover, in LPS-induced endotoxemia mouse models, HPMECs, and HUVECs, yes-associated protein (YAP, a transcriptional coactivator) attenuates the inflammatory response by blocking tumor necrosis factor receptor-associated factor 6 (TRAF6)-mediated NF-κB activation.[149] Furthermore, in LPS-induced lung epithelial cells, HUVECs, and sepsis mice, downregulation of programmed death ligand 1 (PD-L1) reduces the inflammatory response and apoptosis by inhibiting the HIF-1α signaling pathway.[150] Intriguingly, researchers discovered in an LPS-induced sepsis mouse model that rigosertib improved the inflammatory response by inhibiting the MEK1-ERK signaling pathway.[151] In LPS-treated HUVECs and a mouse cecum ligation (CLP)-induced sepsis model, findings suggest that the upregulation of PCSK9 activates the TLR4/MyD88/NF-κB and NLRP3 pathways, inducing inflammation and resulting in endothelial dysfunction. Therefore, inhibiting PCSK9 may represent a novel strategy to improve vascular endothelial function in sepsis.[152]

This section presents an overview of ECs' role in sepsis development (Table 4). ECs undergo morphological and functional changes during infection or tissue damage, a process known as EC activation.[3] Activated ECs produce various pro-inflammatory cytokines. The studies mentioned above suggest that blocking inflammatory signaling pathways can diminish the inflammatory response in sepsis. Experiments have also demonstrated that LPS-induced endothelial inflammation is a well-established cell model of sepsis. Targeting hnRNPA2/B1, endothelial calpain, yes-associated protein (YAP), programmed cell death receptor (PD)-L1, PCSK9 and rigosertib may be effective in inhibiting the inflammatory response and, consequently, reducing sepsis. This section holds significant value for gaining a deeper understanding of vascular EC inflammation in sepsis treatment.

## Respiratory Diseases

Respiratory diseases (RD), particularly non-communicable chronic inflammatory diseases of the airways, are among the leading causes of mortality worldwide.[153] Persistent inflammation in the respiratory tract underlies all respiratory

**Table 4** Endothelial Inflammation in Sepsis

| Ref. | Drugs/Targets | Models (Cells or Animals) | Mechanisms of Protection | Diseases | Pathways |
|---|---|---|---|---|---|
| [147] | hnRNPA2/B1 | LPS-induced HUVECs | Endothelial injury | Sepsis | NF-κB and VE-cadherin/β-Catenin pathways |
| [148] | LPS | LPS-induced PMECs, C57BL/6 mice, TEK/Capn4$^{-/-}$, LYZ/Capn4$^{-/-}$ | Apoptosis, ROS | Acute kidney injury | p38-iNOS signaling pathway |
| [149] | TRAF6 | LPS-induced HUVECs, HLMVECs, YAP-deficient mice | Endothelial dysfunction, inflammation | Sepsis and organ failure | NF-κB signaling pathway |
| [150] | PD-L1 | BEAS-2B cells, LPS-induced HUVECs, mice | Inflammation, apoptosis | Sepsis | HIF-1α signaling pathway |
| [151] | Rigosertib | LPS-induced C57BL/6 mice | Inflammation | Sepsis | MEK1-ERK signaling pathway |
| [152] | PCSK9 | LPS-treated HUVECs, CLP-induced sepsis model | Inflammation and endothelial dysfunction | Sepsis | TLR4/MyD88/NF-κB and NLRP3 pathways |

**Abbreviations**: TRAF6, Tumor necrosis factor receptor-associated factor 6; PMECs, Pulmonary microvascular endothelial cells; HLMVECs, Human lung microvascular endothelial cells; TEK/Capn4$^{-/-}$, Transgenic mice with endothelial-specific Capn4 knockout; LYZ/Capn4$^{-/-}$, myeloid-specific Capn4 knockout; CLP, Cecum ligation.

diseases and is the primary characteristic of all chronic respiratory diseases.[154,155] This section reviews RDs associated with endothelial inflammation, including asthma, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), and acute lung injury (ALI). Asthma is a chronic RD characterized by airway inflammation with clinical manifestations such as dyspnea, wheezing, chest tightness, and cough.[156–158] COPD, characterized by irreversible airflow restriction, is an inflammatory disease affecting both the airway and lung tissue, particularly associated with an abnormal inflammatory response to cigarette smoke.[159] ALI and ARDS represent two different stages of a disease caused by direct lung injury and indirect systemic inflammatory reactions.[160]

Previous research results have shown that in ovalbumin induced asthma mouse models and in vitro cell models, the deletion of ECs Sox17 (endothelium-specific transcription factor) could inhibit the adhesion of IL-33 stimulated THP-1 cells to HUVECs and HPMECs by inhibiting ERK and STAT3 signaling pathways, as well as allergic airway inflammation in mice.[161] Furthermore, in cigarette smoke extract-induced HUVECs, the antioxidant mitoquinone (MitoQ) reduces ROS, autophagy, endothelial barrier damage, and inflammation by inhibiting NF-κB and NLRP3 inflammasome signaling pathways, thereby mitigating COPD.[162] Studies have demonstrated that in LPS-induced HPMECs, inhibition of microRNA-92a targets integrin α5 (ITGA5) through the PI3K/AKT signaling pathway, reducing endothelial barrier dysfunction and thus improving ALI/ARDS.[163] Similarly, in LPS-induced ARDS mouse models and EA.hy 926 HUVECs, ghrelin inhibits EC damage and apoptosis by regulating the PI3K/AKT signaling pathway.[164] In LPS-induced HPMECs, ripaudil, a novel ROCK2 inhibitor, suppresses apoptosis and inflammatory response by regulating the ROCK2/eNOS signaling pathway, making it a potential drug for the clinical treatment of ALI.[165] Likewise, in LPS-induced acute lung injury mouse models and alveolar epithelial cells, simvastatin inhibits apoptosis by upregulating the Survivin/NF-κB/p65 signaling pathway.[166] In LPS-induced rat pulmonary microvascular endothelial cells (PMVECs) and a rat model of ARDS, overexpression of Sema3A can inhibit the ERK/JNK signaling pathway, thereby improving ECs apoptosis and angiogenesis in the ARDS model, ultimately reducing lung injury and inflammation in rats.[167]

In conclusion, this section highlights the unique role of EC inflammation in the pathogenesis of RD. Additionally, we summarize the key signaling pathways that initiate different mechanisms and propagate the inflammatory response, including NF-κB and NLRP3 inflammasome signaling pathways, ERK and STAT3 signaling pathways, PI3K/AKT signaling pathways, Survivin/NF-κB/p65 signaling pathways, ERK/JNK signaling pathway and ROCK2/eNOS signaling pathways. Research advances in RD and endothelial inflammation may serve as a reference for the development of new drugs to prevent or treat these RDs (Table 5).

**Table 5** Endothelial Inflammation in Respiratory Diseases

| Ref. | Drug/Targets | Models (Cells or Animals) | Mechanisms of Protection | Diseases | Pathways |
|---|---|---|---|---|---|
| [161] | IL-33, Sox17 | Ovalbumin-induced HUVECs, HPMECs, WT mice, Sox17$^{i\Delta EC}$ mice, U937 and THP-1 cells | Allergic airway inflammation | Asthma | ERK and STAT3 signaling pathways |
| [162] | The Antioxidant MitoQ | CSE-induced, HUVECs | Mitochondrial damage, ROS, autophagy, endothelial barrier injury, inflammation | COPD | NF-κB and NLRP3 inflammasome pathways |
| [163] | microRNA-92a | LPS-induced, HPMECs | Endothelial damage inflammatory | ARDS | PI3K/AKT signaling pathway |
| [164] | Ghrelin | LPS-induced Mice, EA.hy 926 cells | Inflammation, apoptosis | ARDS | PI3K/AKT signaling pathway |
| [165] | Ripasudil | LPS-induced PMVECs | Inflammation and apoptosis | ALI | ROCK2/eNOS signaling pathway |
| [166] | Simvastatin | LPS-induced AECs, Wistar rats | Apoptosis, inflammation | ALI | Survivin/NF-κB/p65 signaling pathway |
| [167] | Sema3A | LPS-induced PMVECs, rat model of ARDS | Lung injury and inflammation; apoptosis and angiogenesis | ARDS | ERK/JNK signaling pathway |

**Abbreviations**: CSE, Cigarette smoke extract; COPD, Chronic obstructive pulmonary disease; MitoQ, Mitoquinone; HPMECs, Human pulmonary microvascular endothelial cells; ARDS, Acute Respiratory Distress Syndrome; PMVECs, Pulmonary microvascular endothelial cells; ALI, Acute Lung Injury; AECs, Alveolar epithelial cells; WT mice, wild-type mice; Sox17$^{i\Delta EC}$ mice, Sox17 knockout mice.

## Clinical Researches

A recent clinical study revealed that an aqueous extract of Terminalia chebula considerably diminished endothelial dysfunction and oxidative stress, thereby reducing CVD risk in patients with type 2 diabetes mellitus (T2DM).[168] In a randomized, double-blind, placebo-controlled clinical investigation, a standardized aqueous extract of Phyllanthus emblica fruits significantly improved endothelial dysfunction, oxidative stress, inflammation, and lipid profiles in individuals with metabolic syndrome.[169] According to a randomized, double-blind clinical trial, moderate supplementation with docosahexaenoic acid (DHA)-rich fish oil significantly enhanced PPARγ activity in patients with T2DM, potentially mitigating cardiovascular complications in DM patients.[170] Likewise, a double-blind randomized controlled trial demonstrated that omega-3 fatty acids could improve vascular inflammation and decrease AS.[171] Intriguingly, a pilot study found that oral supplementation with L. plantarum 299v (Lp299v) improved vascular endothelial function and reduced systemic inflammation in men with CAD.[172] Small clinical studies have discovered that the anti-inflammatory properties of Tongmai Yangxin pill (TMYX) could enhance patients' serum biochemical markers, subsequently reducing the risk of coronary heart disease (CHD).[173] Following a randomized, double-blind, parallel, placebo-controlled trial involving 100 hemodialysis patients, the combined administration of pomegranate peel extract (PPE) and vitamin E (Vit E) was found to mitigate endothelial inflammation and bolstering vascular endothelial function, thus preventing CVD development.[174] In a single-blind, two-group, prospective randomized controlled trial for cardiac rehabilitation with 120 eligible participants (70 men and 50 women) suffering from chronic heart failure, group-based high-intensity aerobic interval training substantially improved the inflammatory status.[175] In a clinical trial including 46 patients with stable CAD and chronic obstructive pulmonary disease (COPD), ticagrelor alleviated symptoms by reducing systemic inflammation and oxidative stress.[176] Lastly, a double-blind, placebo-controlled, randomized clinical trial showed that nanocurcumin (NC) supplementation for patients with severe sepsis diminished the inflammatory response and protected endothelial function.[177]

EC injury is a crucial factor contributing to the inflammatory response, making the protection of vascular endothelial function essential for preventing and treating inflammatory vascular diseases. Consequently, the investigation of medications to maintain vascular health has become pivotal in managing vascular inflammatory diseases (Table 6).[178] Among the drugs currently in clinical use, statin lipid-lowering medications, herbal formulations, traditional Chinese

**Table 6** Clinical Study of Endothelial Inflammation-Related Diseases

| Ref. | Drugs | Dosing Concentrations | Periodicities | SAMPLE SIZES | Diseases | Treatment Effects |
|---|---|---|---|---|---|---|
| [173] | TMYX | 40 pills/time, 2 times/day | 8 weeks | 8 | CHD | TMYX improves serum biochemical parameters of patients and effectively suppresses inflammation |
| [170] | DHA-enriched fish oil | 2400 mg/d | 8 weeks | 50 | T2DM | Short-term supplementation with DHA-rich fish oil will protect the cardiovascular system from atherosclerotic lesions and exert its anti-inflammatory effects |
| [172] | Lp299v | 20 billion CFU | 6 weeks | 20 | CAD | Lp299v improves vascular endothelial function and reduces inflammation in patients with CAD |
| [169] | PEE | 500 mg twice daily | 8 and 12 weeks | 65 | MetS | PEE improved endothelial function, oxidative stress, systemic inflammation, and lipid profiles |
| [174] | PPE and Vit E | 225 mg PPE and 400 IU Vit E | 8 weeks | 100 | HD | PPE and vit E improve inflammatory status and endothelial function in HD patients |
| [168] | TC | 250/500 mg twice daily | 12 weeks | 60 | T2DM | TC improves endothelial dysfunction, systemic inflammation, and lipid profile, thereby reducing cardiovascular risk factors in patients with T2DM |

(*Continued*)

**Table 6** (Continued).

| Ref. | Drugs | Dosing Concentrations | Periodicities | SAMPLE SIZES | Diseases | Treatment Effects |
|---|---|---|---|---|---|---|
| [177] | NC | 160 mg twice daily | 10 days | 40 | Sepsis | NC has protective effects on inflammation, endothelial function, oxidative stress and biochemical factors in sepsis patients |
| [175] | CR | 6MWT | 12 weeks | 120 | CHF | CR improve the inflammatory status of patients with CHF |
| [176] | Ticagrelor | n=23 | 1-month | 46 | CAD/COPD | Ticagrelor reduces systemic inflammation and oxidative stress in CAD/COPD patients |
| [171] | O3FAs | 4g daily of either EPA, DHA, fish oil (2:1 EPA: DHA) | 30 days | 40 | Atherosclerosis | O3FAs improve vascular inflammation and reduce the development of atherosclerosis |

**Abbreviations**: TMYX, Tongmai Yangxin Pill; CHD, Coronary heart disease; T2DM, Type 2 diabetes mellitus; Lp299v, Lactobacillus Plantarum 299v; CAD, Coronary artery disease; CFU, Colony forming unit; MetS, Metabolic syndrome; PEE, P. emblica aqueous extract; HD, Hemodialysis PPE, Pomegranate peel extract; Vit E, Vitamin E; IU, International unit; TC, Terminalia chebula; NC, nano curcumin; CHF, Chronic heart failure; CR, Cardiac rehabilitation; 6MWT, 6-minute walk test; COPD, Concomitant chronic obstructive pulmonary disease; O3FAs, Omega-3 fatty acids; EPA, Eicosapentaenoic acid; DHA, Docosahexaenoic acid.

medicines, fruit and plant extracts, and antiplatelet agents have demonstrated effectiveness in improving vascular inflammation.[26] These medications exert protective effects on vascular endothelial function through indirect mechanisms.[179] Furthermore, adopting a healthy diet and engaging in regular physical exercise can also contribute to preserving endothelial function.

## Discussion and Summary

Preserving the integrity of ECs is vital for maintaining human health and preventing diseases. ECs serve as the natural lining of blood vessels, regulating vascular and organ integrity, and playing a critical role in the inflammatory response.[180] Under physiological conditions, ECs prevent the infiltration of inflammatory cells into tissues by regulating vascular tension and controlling hemorrhage and thrombosis.[3,16,22] Endothelial inflammation is a key initiating event under pathological conditions and an early indicator of disease.[4] Comprehending the various functions of ECs and elucidating inflammatory regulatory mechanisms can provide insight into disease progression and enhance treatment outcomes.

In summary, we have confirmed that ECs are key targets and crucial components of the inflammatory process.[6] Studies suggest that these cells, situated in areas susceptible to vascular endothelial lesions, may be an ideal model for examining the molecular mechanisms of vascular-related diseases (Table 7 and Figure 1). This review also summarizes the inducers of inflammation and the therapeutic agents that inhibit inflammation in these cell types. Concurrently, recent studies have shed light on the key signaling pathways that regulate pro-inflammatory and anti-inflammatory responses in ECs (Figure 2).

**Table 7** Directions for Mechanistic Studies in Different Cell Models

| Cells | Mechanisms of Protection |
|---|---|
| HUVECs | Endothelial inflammation, Oxidative stress, Insulin resistance; ROS, Apoptosis, Endothelial injury, Allergic airway inflammation, Autophagy, Permeability, Cellular senescence, Proliferation, Endoplasmic reticulum stress, Mitochondrial damage |
| HAECs | Inflammation, ROS, Oxidation, Apoptosis, Vascular injury, Pyroptosis |
| THP-1 | Endothelial inflammation, Pyroptosis, Oxidative stress, Apoptosis, ROS |
| HCAECs | Endothelial activation, Inflammation, Monocytes adhesion, Oxidative stress |
| Others | Inflammation, Endothelial dysfunction, Apoptosis, ROS, Endothelial senescence, Proliferation, Allergic airway inflammation |

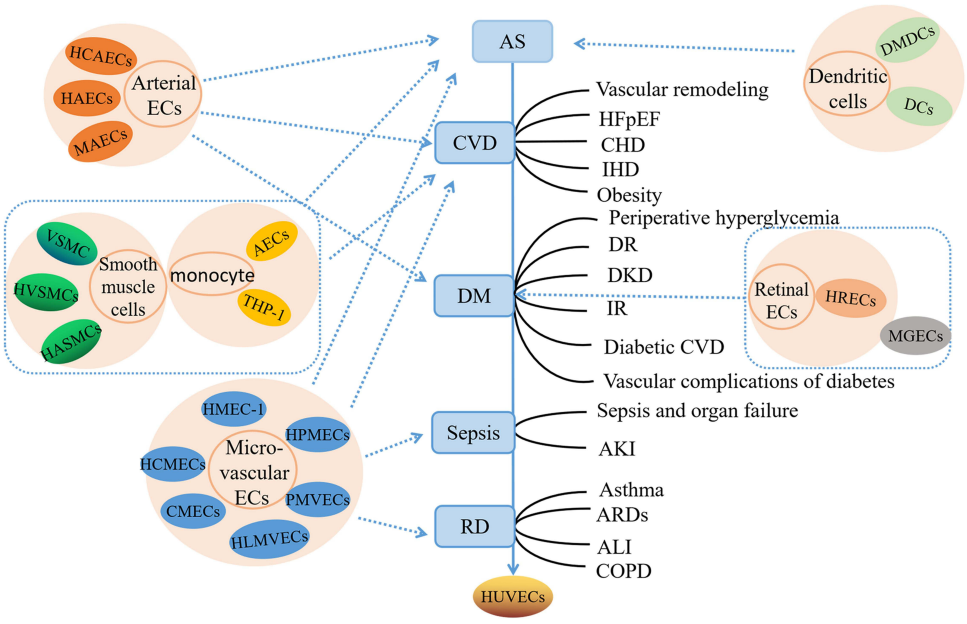


**Figure 1** Relationship between endothelial cells inflammation models and related diseases.

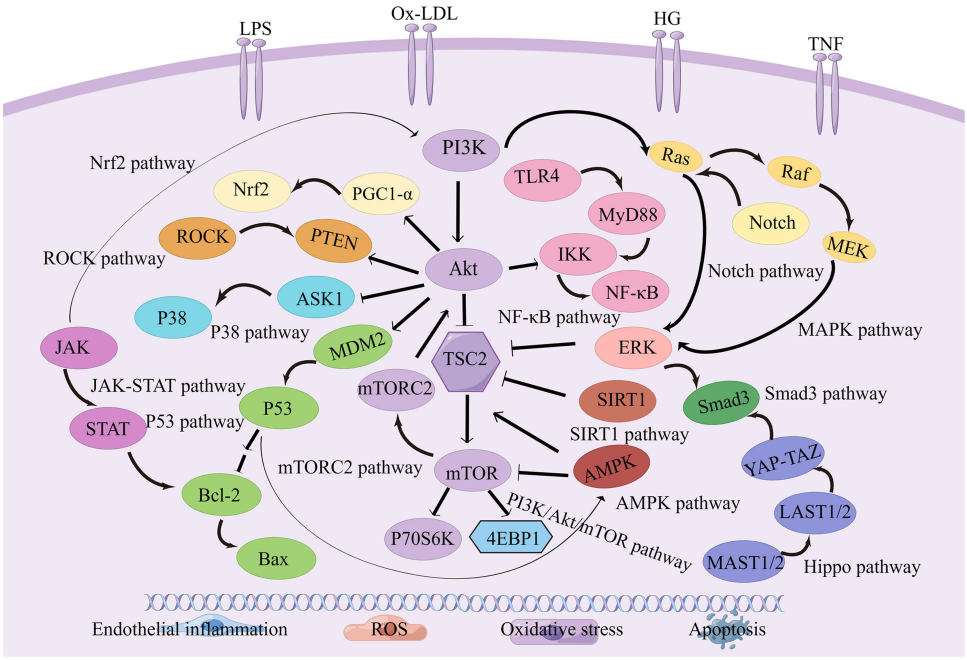


**Figure 2** Signaling pathways involved in the regulation of endothelial cells inflammation.

Despite the comprehensive analysis of the relationship between endothelial inflammation and vascular-related diseases, this study presents certain limitations. Relatively small sample sizes in clinical trials may cause fluctuations in research findings. In clinical practice, numerous anti-inflammatory treatments are available, such as the routine use of

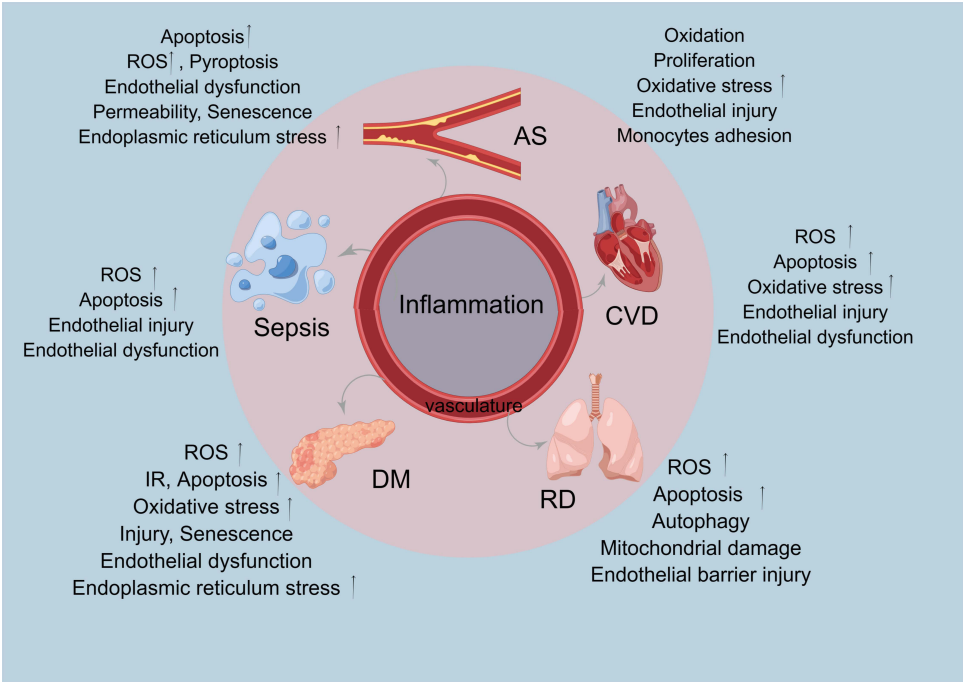


**Figure 3** Inflammation- Vascular- Disease- Pathological States.

antibiotics. However, these therapeutic strategies can only inhibit or eliminate pathogenic microorganisms without reversing the changes in EC function. To thoroughly alleviate inflammation's secondary effects on blood vessels and organs, we propose an approach that combines anti-inflammatory therapy with the restoration of EC function, offering new insights for treating vascular inflammation.

In conclusion, this article not only underscores the significance of endothelial inflammation in vascular-related diseases but also highlights how understanding the molecular interactions and pathways regulating the inflammatory response can improve therapeutic strategies and promote drug development (Figure 3 and Table 8). Nevertheless, individuals should be aware that adopting a healthy and reasonable lifestyle (eg, quitting smoking, losing weight, increasing physical activity) can significantly reduce the occurrence of various risk factors. It is hoped that this review will inspire new perspectives and lay a theoretical foundation for clinical research.

**Table 8** Research Gaps and Future Directions in Endothelial Cells Inflammation in Vascular-Related Diseases

| Issue | Research Gaps | Future Directions |
|---|---|---|
| Transformation | Translation between basic experimental research and clinical research is challenging | Conducting multi-center and diverse clinical trials to further improve endothelial cell inflammation in vascular-related diseases |
| Protection mechanisms | Better understanding of how ECs inflammation is manifested in people with vascular-related diseases (AS, CVD, DM, sepsis, RD) | These mechanisms largely serve as potential targets for the treatment of diseases |
| Propaganda channels | Widely publicize effective interventions for the treatment of vascular-related diseases (AS, CVD, DM, sepsis, RD) | Using the Internet and other means to spread among people with vascular related-diseases and high-risk groups |

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest in this work.

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