International Journal of General Medicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

The Model of Neutrophil Chemotaxis Participated by the Vascular Endothelial Glycocalyx

Ping Li[1,*], Zhengwang Si[2,*], Yiming Shao[2], Weiwei Wu[1]

[1]Department of Burns Surgery, The First Hospital of Jilin University, Changchun, Jilin, 130000, People's Republic of China; [2]Department of Burns Surgery, Affiliated Hospital of Jining Medical University, Jining Medical University, Jining, Shandong, 272000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Weiwei Wu, Department of Burns Surgery, The First Hospital of Jilin University, Changchun, Jilin, 130000, People's Republic of China, Email jdsswk_www@163.com; Yiming Shao, Department of Burns Surgery, Affiliated Hospital of Jining Medical University, Jining Medical University, Jining, Shandong, 272000, People's Republic of China, Email symlcyb@163.com

Abstract: The vascular endothelial glycocalyx is a critical structural and functional component. It maintains endothelial integrity, orchestrates hemodynamic regulation, enables selective blood component filtration, and mediates mechanotransduction. Existing in a dynamic equilibrium, this glycoprotein-polysaccharide matrix provides an interactive platform for intravascular reactions and actively participates in innate immune responses (eg, neutrophil chemotaxis and adhesion). During localized tissue infection, pathogen-derived chemokines become enriched within the endothelial glycocalyx, establishing a chemotactic gradient that directs neutrophil recruitment. Intriguingly, neutrophil-derived proteolytic enzymes and reactive oxygen species released during degranulation reciprocally degrade the glycocalyx architecture, thereby amplifying chemokine liberation and creating a self-reinforcing feedback loop that potentiates neutrophil extravasation and directional migration. This review systematically analyzes two distinct mechanistic models elucidating the dual role of the endothelial glycocalyx in neutrophil chemotaxis. These conceptual frameworks advance our understanding of the spatiotemporal regulation of innate immune responses at the vascular interface while highlighting potential therapeutic targets for inflammatory disorders associated with glycocalyx dysfunction.

Keywords: neutrophil, chemokines, endothelial glycocalyx

Introduction

The endothelial glycocalyx (eGC) is a gel-like layer on the luminal surface of endothelial cells, composed of membrane-bound proteoglycans, glycoproteins, glycosaminoglycans (GAGs), and adherent plasma proteins.[1,2] By maintaining endothelial permeability and microvascular tone, it stabilizes transendothelial osmotic gradients and modulates neutrophil chemotaxis and adhesion.[2] Multiple factors can damage the eGC, including shear stress, infection, and pathological stress. And vascular endothelial injury is implicated in various diseases.[3–5]

Disruption of the eGC during inflammation does not merely result in the release of shielded cytokines that mediate further pathological responses—it also liberates bioactive cleavage products from core eGC components, which actively amplify inflammatory signaling and serve as critical biomarkers of endothelial injury. The eGC's proteoglycan and glycosaminoglycan (GAG) constituents, including syndecan-1 and hyaluronic acid (HA), undergo enzymatic degradation by sheddases (heparanase-1, matrix metalloproteinases/MMPs, hyaluronidases) activated during inflammatory states such as sepsis, trauma, or COVID-19.[6,7] For instance, syndecan-1, a transmembrane proteoglycan anchoring heparan sulfate and chondroitin sulfate to the endothelial surface, is cleaved by MMPs (eg, MMP-7, −9) and ADAM17, releasing its ectodomain into the circulation. This fragment not only disrupts endothelial adherens junctions by interfering with VE-cadherin localization but also acts as a damage-associated molecular pattern (DAMP) to enhance leukocyte adhesion and proinflammatory cytokine secretion.[8] HA, a non-sulfated GAG forming the eGC's structural scaffold, is degraded into low-molecular-weight fragments (<500 kDa) by hyaluronidases (eg, HYAL2, TMEM2) and reactive oxygen species

Received: 26 June 2025
Accepted: 4 November 2025
Published: 17 November 2025

(ROS). These HA fragments bind to toll-like receptor 4 (TLR4) on endothelial cells and immune cells, triggering NF-κB activation and the production of IL-6, TNF-α, and CXCL8—further exacerbating vascular inflammation and permeability.[6] Clinically, circulating levels of syndecan-1 and HA fragments correlate with disease severity: in septic patients, plasma syndecan-1 >898 ng/mL and HA >441 ng/mL predict 90-day mortality, while in COVID-19, elevated HA and syndecan-1 are associated with ICU admission and multi-organ dysfunction.[6,7] Notably, these cleavage products also exert organ-specific effects: hippocampal penetration of heparan sulfate fragments (liberated from eGC degradation) inhibits brain-derived neurotrophic factor (BDNF), contributing to septic cognitive dysfunction, while urinary HA and syndecan-1 levels serve as early markers of renal injury in sepsis and chronic kidney disease.[8] Together, these findings highlight that eGC disruption's consequences extend far beyond cytokine release, with its cleavage products acting as both active mediators of inflammation and clinically relevant biomarkers of endothelial and organ dysfunction.

During infections, neutrophils migrate along chemokine concentration gradients by rolling on the vascular endothelium toward the infection site, while releasing cytokines such as myeloperoxidase (MPO), matrix metalloproteinases (MMPs), and heparin-binding protein (HBP) to mediate anti-inflammatory responses. Recent studies have reported that these cytokines can damage the eGC, thereby exacerbating vascular leakage.[9] Neutrophil extracellular traps (NETs) are capable of degrading the glycocalyx structure on the surface of vascular endothelial cells.[10] In this review, we explore the reciprocal interactions between the eGC and neutrophils during chemotaxis and synthesize existing models of chemotactic regulation. And we emphasize that in infectious diseases, neutrophil chemotaxis disrupts the eGC integrity, thereby promoting vascular leakage.

Despite extensive research on eGC biology and neutrophil chemotaxis, three critical knowledge gaps remain unaddressed in the current literature. First, most studies focus on either eGC degradation by neutrophils (eg, via degranulation or NETs)[6,8] or chemokine gradient maintenance by intact eGC,[9] but few synthesize the reciprocal regulatory relationship between eGC degradation and chemokine gradient dynamics—ie, how eGC breakdown modulates chemokine distribution, and in turn, how altered chemokine gradients influence neutrophil-mediated eGC damage. Second, existing models of eGC-chemokine interactions (the "bridge model" and "cloud model") are often discussed in isolation, with limited systematic comparison of their context-dependent applicability (eg, in acute vs chronic inflammation).[10,11] Third, while eGC degradation products (eg, syndecan-1 fragments, hyaluronic acid fragments) are recognized as biomarkers of endothelial injury,[7] their direct role in regulating neutrophil chemotaxis—beyond amplifying inflammation—has not been comprehensively summarized. This review addresses these gaps by: (1) synthesizing the bidirectional crosstalk between eGC degradation and chemokine gradient maintenance, integrating findings from studies on neutrophil-derived mediators (MPO, MMPs)[6,8] and eGC structural biology;[5] (2) systematically comparing the "bridge model" and "cloud model" to clarify their respective scenarios (acute vs chronic inflammation) using evidence from in vivo chemokine activity assays;[10,11] (3) summarizing the dual role of eGC degradation products as both inflammatory mediators and regulators of neutrophil recruitment, drawing on clinical and preclinical data.[7,9] By filling these gaps, this review provides a comprehensive framework for understanding the eGC's central role in orchestrating neutrophil chemotaxis and identifies unresolved questions for future research".

Composition and Functions of the eGC

In the 1940s, the eGC was first proposed by Chambers et al who suggested that a thin layer covers the luminal surface of vascular endothelial cells.[12] Desjardins et al demonstrated that enzymatic removal of specific proteoglycans from the eGC resulted in a twofold increase ($P < 0.05$) in microvascular hematocrit.[11] Pries et al conducted in vitro simulations of blood flow in large microvessels and found that microvessels with a diameter of 30μm exhibited significantly higher flow resistance compared to glass tubes of the same diameter, indirectly confirming the existence of the eGC.[13] By applying dye exclusion methods, Vink et al detected a distinct gap between FITC-dextran plasma tracers and endothelial cells, and further estimated the in vivo thickness of this layer.[14]

The surface of the eGC is composed of negatively charged complex polysaccharide chains, primarily consisting of GAGs such as hyaluronic acid (HA), heparan sulfate(HS), chondroitin sulfate, and sialic acid.[15,16] Together, these components create a tightly packed, negatively charged mesh-like structure.[17] Plasma proteins, enzymes, enzyme inhibitors, growth factors, and cytokines interact with the negatively charged mesh structure of the eGC through cationic

binding sites within their molecular structures, cationic amino acids, free cations, and water.[18] The interactions between the eGC and proteins are highly dependent on the local microenvironment, including factors such as cation content, cation concentration, and pH.[18] In recent years, Fan et al utilized stochastic optical reconstruction microscopy to observe the ultrastructure of the eGC. Their findings revealed that HA forms elongated molecular chains that are interwoven into a network covering the luminal surface of endothelial cells, where it plays a dominant role in mechanosensing. In contrast, HS consists of shorter molecules oriented perpendicular to the cell surface. Furthermore, HA plays a predominant role in the molecular sieve function of the eGC.[19]

The base of the eGC is predominantly composed of syndecans, which account for 50% to 90% of its total composition.[5,20] Its surface harbors binding sites for polysaccharide chains, and the specific polysaccharide species bound to these sites differ across various organs. Under physiological conditions, the eGC exists in a dynamic equilibrium in vivo, where its degradation and synthesis occur concurrently, maintaining a relatively stable thickness on the vascular surface.[21] Following acute degradation of the eGC, its thickness can be restored to the original level within 5–7 days in vivo.[22] Some studies suggest that this dynamic equilibrium allows the eGC to influence its surrounding environment, while the environment also determines the state of the glycocalyx.[23,24]

The eGC serves as a platform for diverse vascular reactions. Proteins such as albumin, fibrinogen, fibronectin, thrombomodulin, antithrombin III, superoxide dismutase, and cell adhesion molecules interact with it, while its dynamic equilibrium concurrently participates in other intravascular processes.[2,25] In addition, it acts as a buffer against oxidants, cytokines, and circulating immune cells from the plasma, which otherwise directly interact with endothelial cells.[26]

Under normal physiological conditions, the eGC is maintained at a certain thickness, which shields specific cellular molecules—such as platelet endothelial cell adhesion molecule (PECAM), vascular cell adhesion molecule (VCAM), and intercellular adhesion molecule (ICAM)—beneath its structure.[27] Studies have demonstrated that selectins are shielded by the eGC under physiological conditions, preventing their interaction with neutrophils.[28,29] Endothelial cells exposed to laminar shear stress develop a thicker glycocalyx on their surface, which plays a pivotal role in reducing vascular permeability and enhancing endothelial anti-inflammatory, antithrombotic, and anti-angiogenic properties.[30] Numerous diseases lead to eGC disruption, including sepsis, trauma, inflammation, ischemia-reperfusion injury (IRI), shock, hypervolemia, hypertension, hyperglycemia, hypernatremia, diabetes mellitus, and atherosclerosis,[21] leading to the release of shieled cytokines, which subsequently mediate further pathological responses.

The eGC plays a critical role in regulating blood flow, filtering blood components, and sensing and transducing mechanical signals.[31] Inflammatory tissues release mediators such as bradykinin and histamine, inducing vasodilation in adjacent vessels, which slows blood flow and lowers shear stress, but may increase total blood flow depending on vascular context. Studies suggest that hemodynamic shear stress can be transduced from the bloodstream to the cytoplasm via core proteins without requiring direct interaction with the eGC. Alterations in blood flow velocity may activate signaling pathways by changing conformational in glycan structures.[31] A study demonstrated that both in vitro and in vivo, elevated laminar shear stress increases HA expression on the endothelial surface.[30] In animal models, Fan Jie demonstrated that the eGC plays a central role in mechanosensing, while HA primarily mediates the molecular sieving function.[19] The eGC has been extensively validated as a mechanosensor for hemodynamic forces by numerous studies.[32–35] The eGC senses fluid shear stress and regulates vascular tone through nitric oxide (NO).[36–38]

The eGC Maintains Chemokine Gradients

Neutrophil recruitment is a central event in inflammatory responses, where chemokines direct the precise localization of neutrophils to sites of inflammation,[39,40] but the detailed mechanisms of this process are not yet fully elucidated. Early studies suggested that chemokines released by inflamed cells into the bloodstream are rapidly diluted under free-flow conditions, failing to establish a stable, high-concentration gradient in specific regions necessary to guide leukocyte adhesion.[41] Consequently, models of chemokine immobilization on the vascular endothelium have been progressively established. Recent advancements in endothelial glycocalyx (eGC) research have revealed that the eGC serves as a platform for chemokine anchoring, functioning as a foundational scaffold that dynamically and intensely interacts with diverse plasma components in vivo.[42,43] The differential interactions between the eGC and distinct chemokines determine the spatial gradients of these chemokines in specific vascular regions (eg, microvasculature of inflamed

tissues), thereby establishing chemotactic specificity within the inflamed vascular region.[44] Studies have demonstrated that the eGC forms robust bounds with chemokines, facilitating their concentration on the vascular endothelium of inflamed tissues and the establishment of chemokine gradients.[45] HS has been demonstrated to immobilize chemokines on the luminal surface of endothelial cells.[46] Notably, MIP-2/CXCL2 binds to endothelial cells via HS, a process critical for neutrophil intraluminal crawling and transmigration of endothelial cells.[45] Sandra Li employed chlorite-oxidized oxyamylose to mimic the interactions between the eGC and chemokines, thereby modulating leukocyte migration and aggregation during inflammation in vivo.[47]

General Process of Neutrophil Chemotaxis

Over the past two decades, leukocyte recruitment has been extensively studied and established as a model widely depicted in most pathology and immunology textbooks (Figure 1). Following the onset of tissue inflammation, inflammatory cells secrete mediators that induce vasodilation in the surrounding vasculature. Dilated blood vessels exhibit slowed blood flow, enabling leukocytes to disengage from the axial flow and undergo margination along the vascular endothelium. Simultaneously, inflammatory cytokines such as IL-4 and TNF induce the expression of endothelial adhesion molecules, including selectins.[48] Under the action of adhesion molecules, particularly selectins, leukocytes form initial adhesive interactions with the vascular endothelial surface.[49,50] Under the hemodynamic forces of axial blood flow, primary adhesive bonds undergo cycles of engagement and disengagement, enabling leukocytes to roll along the vascular endothelial surface.[48,51,52] Following chemokine engagement, rolling leukocytes activate surface-expressed integrins, which mediate more stable secondary adhesive interactions with endothelial ligands.[53] As chemokine density gradually increases, leukocytes upregulate surface adhesion molecules, causing their rolling velocity along the vascular endothelium to decelerate. Ultimately, leukocytes arrest at sites of maximal chemokine concentration (inflammatory foci), extend pseudopods, and undergo transendothelial migration to infiltrate inflamed tissues. The eGC, primarily

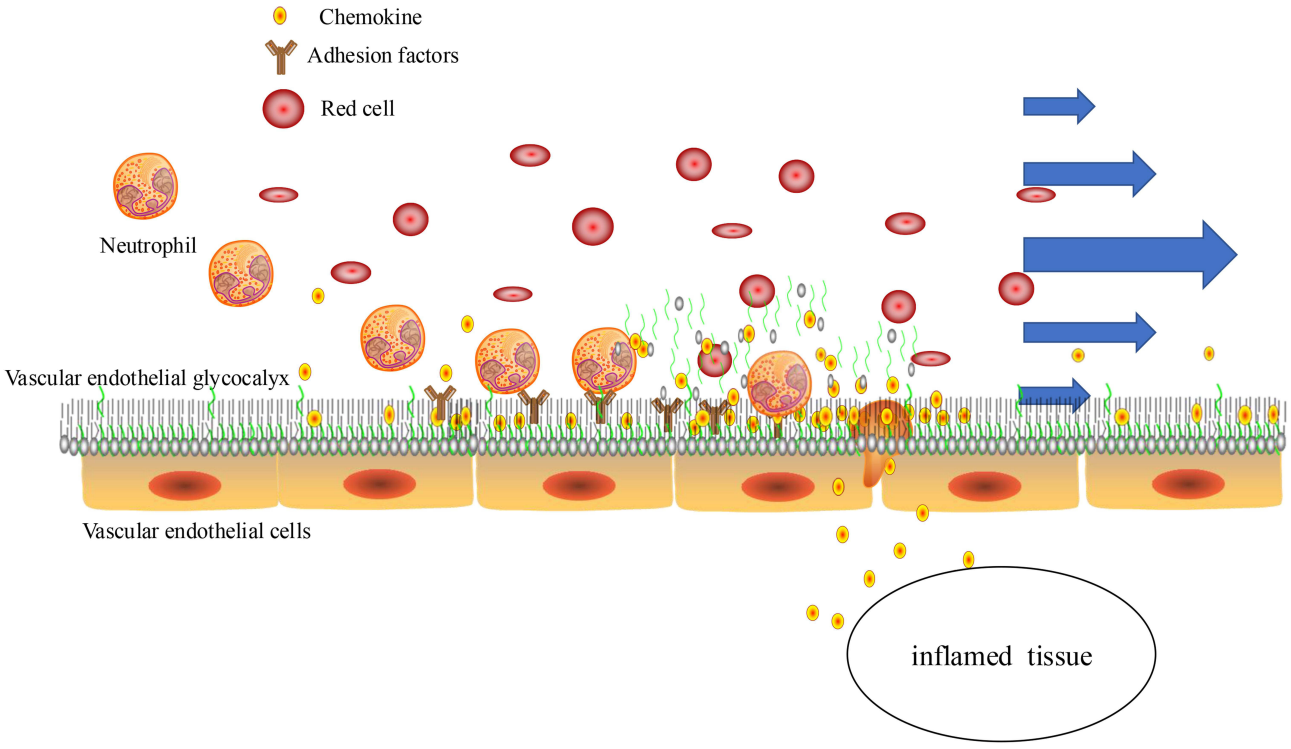

Figure 1 Canonical Neutrophil Chemotaxis Model. Schematic illustration of the initial stages of neutrophil chemotaxis regulated by the vascular endothelial glycocalyx. It depicts neutrophils interacting with the vascular endothelial glycocalyx layer. Chemokines (yellow dots) are shown forming a gradient, guiding neutrophils toward the inflammatory tissue. Red blood cells flow through the vessel, and adhesion factors on the endothelial surface facilitate neutrophil-endothelium interactions during the process of leukocyte recruitment.

secreted by endothelial cells, is a gel-like layer that plays critical physiological roles, including antithrombotic and anti-inflammatory effects, as well as the regulation of vascular permeability.[43,54]

Neutrophil Degranulation Damages the eGC

MPO, the most abundant enzyme in neutrophil granules, binds to the vascular wall upon release into the vascular lumen. It accumulates along endothelial cells, translocates into the subendothelial space, oxidizes extracellular matrix components,[55] and reduces the bioavailability of NO.[56] Due to its abundance of arginine and lysine residues, MPO carries a high cationic charge at physiological pH.[57,58] Kashish Manchanda's study demonstrated that the positive charge of MPO neutralizes the negatively charged layer of the eGC, reducing repulsion between endothelial cells and leukocytes,[59] and damaging the eGC directly. Both in vitro and in vivo studies have demonstrated that alterations in charge distribution can modulate the thickness and function of the eGC.[60,61]

Sheddases, a family of enzymes that cleave extracellular domains of membrane proteins and glycosaminoglycans (GAGs), play a central role in eGC degradation during inflammation—their dysregulation drives eGC structural collapse and vascular dysfunction, while targeted inhibition emerges as a promising therapeutic strategy. Key sheddases include matrix metalloproteinases (MMPs), ADAM17, hyaluronidases, and heparanase-1, each with distinct mechanisms of eGC damage and therapeutic potential. MMPs (eg, MMP-2, −9, −14) directly degrade eGC components: MMP-9 cleaves syndecan-1 and heparan sulfate (HS) chains, while MMP-14 activates pro-MMP-2 to amplify HS and hyaluronic acid (HA) breakdown.[62] Selective MMP inhibitors (eg, ND-336) that cross the blood-brain barrier have entered preclinical trials for vascular and neurological disorders, avoiding off-target toxicity of early broad-spectrum inhibitors. ADAM17, a metalloproteinase critical for TNF-α shedding, also cleaves syndecan-1's ectodomain—recent drug repurposing studies show FDA-approved ceftolozane binds ADAM17's active site, inhibiting eGC degradation and TNF-α release.[63] Hyaluronidases (eg, HYAL1, HYAL2) degrade HA, a major eGC structural component: HYAL2-mediated HA fragmentation generates pro-inflammatory low-molecular-weight HA (LMW-HA), which activates TLR4/NF-κB signaling.[64] PEGylated hyaluronidase inhibitors (eg, PEGPH20) reduce tumor-associated eGC damage and enhance immunotherapy efficacy. Heparanase-1, the only enzyme cleaving HS, releases HS-bound chemokines and disrupts eGC integrity—small-molecule inhibitors (eg, OGT2115) restore eGC barrier function in sepsis models.[65] Notably, MMP-mediated eGC degradation involves multi-cellular sources and regulatory networks that further define its pathological significance. During inflammation, MMPs are directly secreted by endothelial cells, compromising components of the eGC.[66–68] MMP15 knockdown in endothelial cells significantly reduces LPS-induced shedding of the glycocalyx marker CD44.[69] Similarly, MMP15 knockout mice exhibited significantly reduced CD44 shedding following the cecal ligation and puncture procedure. MPO acts as a regulatory molecule for MMPs in vivo,[70] and its enzymatic activity positively enhances MMP activity.[71] Studies have confirmed that MMP-mediated shedding of Syndecan-4 is a mechanism contributing to glycocalyx injury in glomerular endothelial cells in vitro, resulting in increased endothelial permeability.[72] Neutrophils can simultaneously secrete MPO and MMPs, which act synergistically on the eGC.

IRI has been demonstrated to induce eGC damage. A study confirmed that ROS and calcium ions (Ca^2+) generated during IRI contribute to vascular endothelial injury, ROS production occurs upstream of calcium signaling, but the glycocalyx damage mediated by ROS is ultimately dependent on calcium-dependent pathways.[73] Hyperglycemia induces eGC dysfunction by increasing ROS generation and activating Toll-like receptor TLR-2/4 pathways.[74] Although SOD bound to the eGC surface provides antioxidant protection,[75] numerous studies have demonstrated that excessive ROS can directly degrade the eGC.[21,76,77] The use of antioxidants can significantly ameliorate eGC damage under infectious conditions.[78] During infections, the respiratory burst of neutrophils releases substantial amounts of ROS, which may serve as one of the primary contributors to eGC damage in infectious diseases. In inflammatory diseases, contact between neutrophils and the eGC activates IL-β2 integrin signaling, which induces the release of HBP from neutrophils, increasing vascular permeability significantly.[79] In burn patients, neutrophils secrete substantial amounts ofHBP. A clinical study demonstrated that the early increase in vascular permeability in these patients is associated with HBP.[80] In another animal study, HBP secreted by neutrophils accumulated on the vascular endothelium, promoting monocyte adhesion and arrest.[81] This phenomenon is likely attributable to HBP-induced disruption of the eGC, which leads to the exposure of adhesion molecules and subsequent interaction with monocytes.

Neutrophil elastase (NE) directly disrupts the pulmonary eGC in LPS-induced mouse models.[82] In type 2 diabetic mouse models, the formation of neutrophil extracellular traps (NETs) also contributes to eGC damage.[83] Other neutrophil-associated cytokines, including IL-1β, IL-6, and TNF-α, also contribute to eGC damage.

In addition to degranulation-derived factors (eg, MPO, MMPs), neutrophil extracellular traps (NETs)—another key mediator of neutrophil-induced tissue damage—also contribute to eGC degradation. NETs are web-like filamentous extracellular structures released by neutrophils in response to supernumerary or oversized pathogens.[84] NETs entrap pathogens in a network of DNA, histones, proteases, and other cytotoxic and highly inflammatory compounds, including myeloperoxidase (MPO), NE, MMPs and pentraxin3.[84] NETs act as a double-edged sword, where persistent inflammation or chronic stimulation may lead to excessive NET formation, thereby exacerbating tissue damage during inappropriate inflammatory responses. Furthermore, NET formation has been observed under non-pathological conditions, including but not limited to sterile inflammation, autoimmune diseases, metabolic dysregulation, vasculitis, thrombosis, and carcinogenesis in contexts of dysregulated homeostasis.[85] The majority of NET-associated diseases are mechanistically linked to their capacity to disrupt vascular endothelial cells.[10] Studies have demonstrated that circulating DNA levels positively correlate with vascular endothelial injury in pediatric patients, with this association primarily attributed to syndecan-1, a key component of the endothelial glycocalyx.[86]

Multiple intragranular enzymes anchored to NETs-DNA contribute to vascular endothelial and glycocalyx injury. However, experimental evidence indicates that DNA can suppress the enzymatic activity of myeloperoxidase (MPO) and other proteases, thereby mitigating their damaging effects on healthy tissues.[87] Similarly, a separate line of investigation has revealed that elevated DNase levels at lesional sites in inflammatory bowel disease (IBD) patients degrade NETs-DNA scaffolds, resulting in liberation of NET-associated cytotoxic enzymes and subsequent aggravation of localized vascular endothelial damage.[88]

Models of eGC-Driven Neutrophil Chemotaxis

Two conceptual models—the ‘bridge model” and “cloud model”—have been proposed to explain the interaction between eGC and chemokines during neutrophil chemotaxis. Notably, neither the “bridge model” nor the “cloud model” is an original contribution of this review; both are established conceptual frameworks adapted from prior foundational studies.

Early models proposed that chemokines bound to the eGC could simultaneously engage leukocyte surface receptors, triggering leukocyte expression of integrins. However, studies have confirmed that soluble glycocalyx components compete with chemokine receptors for binding sites.[89] In the molecular structure of chemokines, the binding sites for receptors overlap with those for the glycocalyx.[90,91] Some chemokine residues are involved in both GAG and receptor binding, but the overlap is not always complete. For instance, CXCL1/MGSA binds GAGs via distinct domains that do not interfere directly with receptor engagement.[91] This partial overlap allows chemokines to interact with eGC GAGs while maintaining the ability to activate leukocyte receptors, a key feature of chemotactic regulation. Chemokines can exist in low oligomeric states and exert physiological functions in vivo.[92] The “bridge model” remains widely accepted, which proposes that the chemokines that trigger leukocyte activation are oligomerized and anchored to the eGC and the free end of oligomeric chemokines binds to chemokine receptors.

A recent study targeting the chemokine CXCL10 as a therapeutic focus investigated related antibodies and found that antibodies inhibiting free chemokines were effective in vivo, while inhibiting glycoprotein-bound chemokines exhibited minimal efficacy in vivo, however, in vitro experiments confirmed that both antibody types were functional.[93] These findings demonstrate that in vivo chemokine activity primarily originates from the free state, thereby challenging the validity of the “bridge model”. Graham, G. J. has also challenged the “bridge model”, proposing a novel “cloud model” (Figure 2). The “cloud model” proposes that the primary role of the eGC is to concentrate chemokines at the site of infection. The interaction between chemokines and the eGC is hypothesized to be dynamic. Chemokines undergo multiple cycles of binding, dissociation, and rebinding to the eGC, forming a “chemokine cloud” that transitions efficiently between bound and free states. The reversible binding kinetics of chemokines allow them to become readily accessible after being released from the eGC, thereby facilitating interactions with receptors on passing leukocytes.[94] The “cloud” model provides a dynamic perspective on chemokine-eGC interactions, but it faces experimental challenges. For example, quantifying the binding-dissociation kinetics of chemokines with the eGC in vivo is technically difficult, as it requires real-time tracking of individual

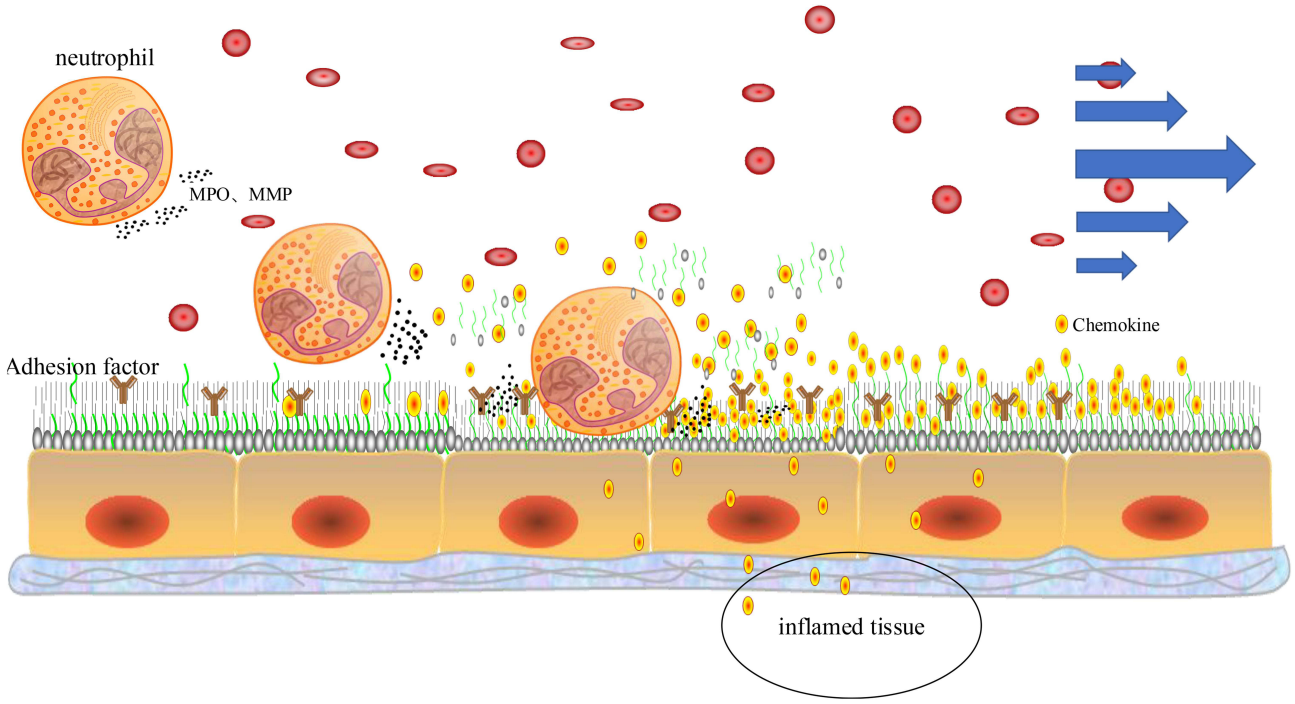

Figure 2 The "Cloud" Model of Neutrophil Chemotaxis. Schematic representation of neutrophil-mediated damage to the vascular endothelial glycocalyx during inflammation. Neutrophils are shown releasing factors like myeloperoxidase (MPO) and matrix metalloproteinases (MMP), which degrade the vascular endothelial glycocalyx. This degradation leads to increased exposure of adhesion factors and altered chemokine (yellow dots) distribution, impacting the chemotactic gradient and interactions between neutrophils and the endothelium, with the ultimate direction of neutrophil movement toward the inflammatory tissue.

chemokine molecules. Additionally, the model does not fully explain how chemokine gradients are maintained in regions with high blood flow, where rapid dissociation of chemokines from the eGC might disrupt gradient stability.

Emerging data suggest that free chemokines are more biologically active in vivo, but this does not fully invalidate the bridge model. Instead, it is more accurate to state that chemokine activity primarily originates from the free state, which limits the applicability of the bridge model in certain contexts. For example, in acute inflammation, free CXCL8 (IL-8) is the main driver of neutrophil recruitment, while the bridge model may be more relevant in chronic inflammatory conditions where eGC-anchored chemokines maintain long-term gradients. To further clarify the distinguishing features of the two eGC-chemokine interaction models—the "bridge model" and the "cloud model"—and provide a intuitive comparison for readers, A table systematically contrasts their key characteristics across three critical dimensions: receptor accessibility, binding dynamics, and experimental support (Table 1). This tabular summary not only distills the core mechanisms

Table 1 Comparison of the "Bridge Model" and "Cloud Model" of eGC-Mediated Chemokine Regulation

Comparison Criterion	Bridge Model	Cloud Model
Receptor Accessibility	Chemokine receptors bind to the free end of oligomerized chemokines anchored to eGC; limited accessibility due to fixed anchoring	Chemokines dissociate from eGC dynamically, enabling direct and flexible binding to receptors; high accessibility
Binding Dynamics	Stable, long-term binding of chemokines to eGC; low dissociation rate	Transient, reversible binding of chemokines to eGC; high dissociation rate (cycles of binding-dissociation)
Experimental Support	Supported by in vitro studies on oligomeric chemokine-eGC binding (eg, Proudfoot et al, 2003)	Supported by in vivo studies on free chemokine activity (eg, Bonvin et al, 2017) and dynamic binding assays
Applicable Inflammatory Context	Chronic inflammation (maintains long-term chemokine gradients)	Acute inflammation (rapid chemokine release and neutrophil recruitment)

https://doi.org/10.2147/IJGM.S549797

discussed earlier but also highlights the context-dependent applicability of each model, reinforcing the understanding of how eGC regulates chemokine-mediated neutrophil chemotaxis under different inflammatory conditions.

Conclusion

The eGC plays a pivotal role in regulating blood flow, filtering blood components, and sensing and transducing mechanical signals. Additionally, it serves as a dynamic platform for physicochemical reactions involving various vascular factors. During infections, neutrophils are recruited to inflammatory sites and the eGC contributes to in mediating the release and concentration of chemokines. Chemokines and the eGC maintain a dynamic equilibrium between their bound state and their free state, thereby enabling interaction with receptors on passing leukocytes.

During inflammation, chemokines released into the bloodstream are captured and anchored by the eGC on the vascular surface, where they become concentrated (this localized concentration can occur either as individual chemokine molecules bound to the eGC or as oligomeric clusters of chemokines attached to the glycocalyx). During leukocyte rolling, chemokines are "released" from their bound or oligomeric states. As the leukocytes approach the inflammatory tissue, the density of this release gradually increases, causing their rolling to slow down and ultimately anchor them at the site of inflammation.

While neutrophil degranulation drives eGC degradation via MPO, MMPs, and HBP, monocytes/macrophages-secreted TNF-α and IL-1β act as early proinflammatory mediators in inflammatory vascular injury, contributing to permeability through multiple pathways including eGC degradation.[95] IL-1β induces vascular leakage via TF-dependent extrinsic coagulation: it upregulates endothelial TF, triggering thrombin production that disassembles VE-cadherin junctions and contracts F-actin cytoskeletons, forming gaps.[96] It also upregulates HGF and ROS-generating enzymes to further damage eGC.[95] TNF-α disrupts vascular integrity by inducing PECAM1 phosphorylation, altering its cytoskeleton associations and weakening junctions.[97] It upregulates sheddases like MMPs to accelerate eGC degradation and can alone induce vascular leak syndrome (VLS) in vivo.[98] Together, TNF-α and IL-1β complement neutrophil-mediated damage as early triggers of eGC dysfunction.[99] Their omission overlooks sequential inflammatory vascular injury, weakening pathophysiological overview. These cytokines also create a microenvironment enhancing neutrophil recruitment, linking early inflammation to subsequent eGC degradation.

Extensive research has confirmed that the degradation of the eCG is closely associated with neutrophils. Neutrophils release cytokines such as MPO, MMPs, ROS, and HBP, which directly damage the eCG. This damage may facilitate the dissociation and exposure of chemokines from the eCG. Future studies should focus on: (1) identifying specific therapeutic targets within the eGC-chemokine-neutrophil axis (eg, sheddase inhibitors, GAG mimetics); (2) validating the cloud model in vivo using intravital imaging techniques; (3) exploring the role of eGC degradation products as diagnostic biomarkers for inflammatory diseases. These efforts could advance the development of targeted therapies for disorders associated with eGC dysfunction, such as sepsis and acute lung injury.

Data Sharing Statement

Data is available from the corresponding authors (Dr. Weiwei Wu: jdsswk_www@163.com; Dr. Yiming Shao: shaoyiming_jnmu@163.com) upon reasonable request.

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.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Balistreri CR, Di Giorgi L, Monastero R. Focus of endothelial glycocalyx dysfunction in ischemic stroke and Alzheimer's disease: possible intervention strategies. *Ageing Res Rev*. 2024;99:102362. doi:10.1016/j.arr.2024.102362
2. Uchimido R, Schmidt EP, Shapiro NI. The glycocalyx: a novel diagnostic and therapeutic target in sepsis. *Crit Care*. 2019;23(1):16. doi:10.1186/s13054-018-2292-6
3. Lu Z, Fang P, Li S, et al. Lactylation of histone H3k18 and Egr1 promotes endothelial glycocalyx degradation in sepsis-induced acute lung injury. *Adv Sci*. 2025;12(7):e2407064. doi:10.1002/advs.202407064
4. Pesonen E, Passov A, Andersson S, et al. Glycocalyx degradation and inflammation in cardiac surgery. *J Cardiothorac Vasc Anesth*. 2019;33(2):341–345. doi:10.1053/j.jvca.2018.04.007
5. Harding IC, Mitra R, Mensah SA, Nersesyan A, Bal NN, Ebong EE. Endothelial barrier reinforcement relies on flow-regulated glycocalyx, a potential therapeutic target. *Biorheology*. 2019;56(2–3):131–149. doi:10.3233/BIR-180205
6. Sullivan RC, Rockstrom MD, Schmidt EP, Hippensteel JA. Endothelial glycocalyx degradation during sepsis: causes and consequences. *Matrix Biol Plus*. 2021;12:100094. doi:10.1016/j.mbplus.2021.100094
7. Patterson EK, Cepinskas G, Fraser DD. Endothelial glycocalyx degradation in critical illness and injury. *Front Med Lausanne*. 2022;9:898592. doi:10.3389/fmed.2022.898592
8. Suzuki A, Tomita H, Okada H. Form follows function: the endothelial glycocalyx. *Transl Res*. 2022;247:158–167. doi:10.1016/j.trsl.2022.03.014
9. Liu L, Shao Y, Zhang Y, et al. Neutrophil-derived heparin binding protein triggers vascular leakage and synergizes with myeloperoxidase at the early stage of severe burns (with video). *Burns Trauma*. 2021:9:tkab030. doi:10.1093/burnst/tkab030
10. Zhang H, Wang Y, Qu M, et al. Neutrophil, neutrophil extracellular traps and endothelial cell dysfunction in sepsis. *Clin Transl Med*. 2023;13(1):e1170. doi:10.1002/ctm2.1170
11. Desjardins C, Duling BR. Heparinase treatment suggests a role for the endothelial cell glycocalyx in regulation of capillary hematocrit. *Am J Physiol*. 1990;258(3 Pt 2):H647–54. doi:10.1152/ajpheart.1990.258.3.H647
12. Chambers R, Zweifach BW. Intercellular cement and capillary permeability. *Physiol Rev*. 1947;27(3):436–463. doi:10.1152/physrev.1947.27.3.436
13. Pries AR, Secomb TW, Gessner T, Sperandio MB, Gross JF, Gaehtgens P. Resistance to blood flow in microvessels in vivo. *Circ Res*. 1994;75(5):904–915. doi:10.1161/01.res.75.5.904
14. Vink H, Duling BR. Identification of distinct luminal domains for macromolecules, erythrocytes, and leukocytes within mammalian capillaries. *Circ Res*. 1996;79(3):581–589. doi:10.1161/01.res.79.3.581
15. Foote CA, Soares RN, Ramirez-Perez FI, et al. Endothelial glycocalyx. *Compr Physiol*. 2022;12(4):3781–3811. doi:10.1002/cphy.c210029
16. Zhang J, Kong X, Wang Z, et al. AMP-activated protein kinase regulates glycocalyx impairment and macrophage recruitment in response to low shear stress. *FASEB J*. 2019:fj201801869RRR. doi:10.1096/fj.201801869RRR
17. Rostgaard J, Qvortrup K. Electron microscopic demonstrations of filamentous molecular sieve plugs in capillary fenestrae. *Microvasc Res*. 1997;53(1):1–13. doi:10.1006/mvre.1996.1987
18. Weinbaum S, Tarbell JM, Damiano ER. The structure and function of the endothelial glycocalyx layer. *Annu Rev Biomed Eng*. 2007;9:121–167. doi:10.1146/annurev.bioeng.9.060906.151959
19. Fan J, Sun Y, Xia Y, Tarbell JM, Fu BM. Endothelial surface glycocalyx (ESG) components and ultra-structure revealed by stochastic optical reconstruction microscopy (STORM). *Biorheology*. 2019;56(2–3):77–88. doi:10.3233/BIR-180204
20. Becker BF, Jacob M, Leipert S, Salmon AH, Chappell D. Degradation of the endothelial glycocalyx in clinical settings: searching for the sheddases. *Br J Clin Pharmacol*. 2015;80(3):389–402. doi:10.1111/bcp.12629
21. Cao RN, Tang L, Xia ZY, Xia R. The endothelial glycocalyx as a potential theriapeutic target in organ injuries. *Chin Med J*. 2019;132:963–975. doi:10.1097/CM9.0000000000000177
22. Potter DR, Jiang J, Damiano ER. The recovery time course of the endothelial cell glycocalyx in vivo and its implications in vitro. *Circ Res*. 2009;104(11):1318–1325. doi:10.1161/CIRCRESAHA.108.191585
23. Wang G, Tiemeier GL, van den Berg BM, Rabelink TJ. Endothelial glycocalyx hyaluronan: regulation and role in prevention of diabetic complications. *Am J Pathol*. 2020;190(4):781–790. doi:10.1016/j.ajpath.2019.07.022
24. Wang G, de Vries MR, Sol W, et al. Loss of endothelial glycocalyx hyaluronan impairs endothelial stability and adaptive vascular remodeling after arterial ischemia. *Cells*. 2020;9(4):824. doi:10.3390/cells9040824
25. Liu HQ, Li J, Xuan CL, Ma HC. A review on the physiological and pathophysiological role of endothelial glycocalyx. *J Biochem Mol Toxicol*. 2020;34:e22571. doi:10.1002/jbt.22571
26. Machin DR, Phuong TT, Donato AJ. The role of the endothelial glycocalyx in advanced age and cardiovascular disease. *Curr Opin Pharmacol*. 2019;45:66–71. doi:10.1016/j.coph.2019.04.011
27. Drost CC, Rovas A, Kusche-Vihrog K, et al. Tie2 activation promotes protection and reconstitution of the endothelial glycocalyx in human sepsis. *Thromb Haemost*. 2019;119(11):1827–1838. doi:10.1055/s-0039-1695768
28. Sundd P, Pospieszalska MK, Cheung LS, Konstantopoulos K, Ley K. Biomechanics of leukocyte rolling. *Biorheology*. 2011;48(1):1–35. doi:10.3233/BIR-2011-0579
29. Lipowsky HH. The endothelial glycocalyx as a barrier to leukocyte adhesion and its mediation by extracellular proteases. *Ann Biomed Eng*. 2012;40(4):840–848. doi:10.1007/s10439-011-0427-x
30. Wang G, Kostidis S, Tiemeier GL, et al. Shear stress regulation of endothelial glycocalyx structure is determined by glucobiosynthesis. *Arterioscler Thromb Vasc Biol*. 2020;40(2):350–364. doi:10.1161/ATVBAHA.119.313399
31. Jiang XZ, Lu Y, Luo KH, Ventikos Y. Understanding endothelial glycocalyx function under flow shear stress from a molecular perspective. *Biorheology*. 2019;56(2–3):89–100. doi:10.3233/BIR-180193
32. Pikoula M, Tessier MB, Woods RJ, Ventikos Y. Oligosaccharide model of the vascular endothelial glycocalyx in physiological flow. *Microfluid Nanofluidics*. 2018;22(2):21. doi:10.1007/s10404-018-2037-5
33. Cooper S, Emmott A, McDonald KK, Campeau MA, Leask RL. Increased MMP activity in curved geometries disrupts the endothelial cell glycocalyx creating a proinflammatory environment. *PLoS One*. 2018;13(8):e0202526. doi:10.1371/journal.pone.0202526

34. Cooper S, McDonald K, Burkat D, Leask RL. Stenosis hemodynamics disrupt the endothelial cell glycocalyx by MMP activity creating a proinflammatory environment. *Ann Biomed Eng*. 2017;45(9):2234–2243. doi:10.1007/s10439-017-1846-0
35. Liu J, Kang H, Ma X, et al. Vascular cell glycocalyx-mediated vascular remodeling induced by hemodynamic environmental alteration. *Hypertension*. 2018;71(6):1201–1209. doi:10.1161/HYPERTENSIONAHA.117.10678
36. Francekovic P, Gliemann L. Endothelial glycocalyx preservation-impact of nutrition and lifestyle. *Nutrients*. 2023;15(11):2573. doi:10.3390/nu15112573
37. Dragovich MA, Chester D, Fu BM, et al. Mechanotransduction of the endothelial glycocalyx mediates nitric oxide production through activation of TRP channels. *Am J Physiol Cell Physiol*. 2016;311(6):C846–C853. doi:10.1152/ajpcell.00288.2015
38. Tarbell JM, Pahakis MY. Mechanotransduction and the glycocalyx. *J Intern Med*. 2006;259(4):339–350. doi:10.1111/j.1365-2796.2006.01620.x
39. Liu B, Jin Y, Yang J, et al. Extracellular vesicles from lung tissue drive bone marrow neutrophil recruitment in inflammation. *J Extracell Vesicles*. 2022;11(5):e12223. doi:10.1002/jev2.12223
40. Sigmundsdottir H, Butcher EC. Environmental cues, dendritic cells and the programming of tissue-selective lymphocyte trafficking. *Nat Immunol*. 2008;9(9):981–987. doi:10.1038/ni.f.208
41. Rot A. Endothelial cell binding of NAP-1/IL-8: role in neutrophil emigration. *Immunol Today*. 1992;13(8):291–294. doi:10.1016/0167-5699(92)90039-A
42. Kunnathattil M, Rahul P, Skaria T. Soluble vascular endothelial glycocalyx proteoglycans as potential therapeutic targets in inflammatory diseases. *Immunol Cell Biol*. 2024;102(2):97–116. doi:10.1111/imcb.12712
43. Becker BF, Chappell D, Bruegger D, Annecke T, Jacob M. Therapeutic strategies targeting the endothelial glycocalyx: acute deficits, but great potential. *Cardiovasc Res*. 2010;87(2):300–310. doi:10.1093/cvr/cvq137
44. Sepuru KM, Rajarathnam K. Structural basis of chemokine interactions with heparan sulfate, chondroitin sulfate, and dermatan sulfate. *J Biol Chem*. 2019;294:15650–15661. doi:10.1074/jbc.RA119.009879
45. Massena S, Christoffersson G, Hjertstrom E, et al. A chemotactic gradient sequestered on endothelial heparan sulfate induces directional intraluminal crawling of neutrophils. *Blood*. 2010;116(11):1924–1931. doi:10.1182/blood-2010-01-266072
46. Wang L, Fuster M, Sriramarao P, Esko JD. Endothelial heparan sulfate deficiency impairs L-selectin- and chemokine-mediated neutrophil trafficking during inflammatory responses. *Nat Immunol*. 2005;6(9):902–910. doi:10.1038/ni1233
47. Li S, Pettersson US, Hoorelbeke B, et al. Interference with glycosaminoglycan-chemokine interactions with a probe to alter leukocyte recruitment and inflammation in vivo. *PLoS One*. 2014;9(8):e104107. doi:10.1371/journal.pone.0104107
48. Petri B, Phillipson M, Kubes P. The physiology of leukocyte recruitment: an in vivo perspective. *J Immunol*. 2008;180(10):6439–6446. doi:10.4049/jimmunol.180.10.6439
49. Phillipson M, Heit B, Parsons SA, et al. Vav1 is essential for mechanotactic crawling and migration of neutrophils out of the inflamed microvasculature. *J Immunol*. 2009;182(11):6870–6878. doi:10.4049/jimmunol.0803414
50. Phillipson M, Heit B, Colarusso P, Liu L, Ballantyne CM, Kubes P. Intraluminal crawling of neutrophils to emigration sites: a molecularly distinct process from adhesion in the recruitment cascade. *J Exp Med*. 2006;203(12):2569–2575. doi:10.1084/jem.20060925
51. Ley K, Laudanna C, Cybulsky MI, Nourshargh S. Getting to the site of inflammation: the leukocyte adhesion cascade updated. *Nat Rev Immunol*. 2007;7(9):678–689. doi:10.1038/nri2156
52. Phillipson M, Kubes P. The neutrophil in vascular inflammation. *Nat Med*. 2011;17(11):1381–1390. doi:10.1038/nm.2514
53. Luo BH, Carman CV, Springer TA. Structural basis of integrin regulation and signaling. *Annu Rev Immunol*. 2007;25:619–647. doi:10.1146/annurev.immunol.25.022106.141618
54. Van Teeffelen JW, Brands J, Stroes ES, Vink H. Endothelial glycocalyx: sweet shield of blood vessels. *Trends Cardiovasc Med*. 2007;17(3):101–105. doi:10.1016/j.tcm.2007.02.002
55. Baldus S, Eiserich JP, Mani A, et al. Endothelial transcytosis of myeloperoxidase confers specificity to vascular ECM proteins as targets of tyrosine nitration. *J Clin Invest*. 2001;108(12):1759–1770. doi:10.1172/JCI12617
56. Maiocchi SL, Morris JC, Rees MD, Thomas SR. Regulation of the nitric oxide oxidase activity of myeloperoxidase by pharmacological agents. *Biochem Pharmacol*. 2017;135:90–115. doi:10.1016/j.bcp.2017.03.016
57. Manchanda K, Kolarova H, Kerkenpass C, et al. MPO (Myeloperoxidase) reduces endothelial glycocalyx thickness dependent on its cationic charge. *Arterioscler Thromb Vasc Biol*. 2018;38(8):1859–1867. doi:10.1161/ATVBAHA.118.311143
58. Klebanoff SJ. Myeloperoxidase: friend and foe. *J Leukoc Biol*. 2005;77(5):598–625. doi:10.1189/jlb.1204697
59. Klinke A, Nussbaum C, Kubala L, et al. Myeloperoxidase attracts neutrophils by physical forces. *Blood*. 2011;117(4):1350–1358. doi:10.1182/blood-2010-05-284513
60. Kang H, Fan Y, Sun A, Deng X. Compositional or charge density modification of the endothelial glycocalyx accelerates flow-dependent concentration polarization of low-density lipoproteins. *Exp Biol Med*. 2011;236(7):800–807. doi:10.1258/ebm.2011.011072
61. van Haaren PM, VanBavel E, Vink H, Spaan JA. Charge modification of the endothelial surface layer modulates the permeability barrier of isolated rat mesenteric small arteries. *Am J Physiol Heart Circ Physiol*. 2005;289(6):H2503–7. doi:10.1152/ajpheart.00587.2005
62. Lenci E, Cosottini L, Trabocchi A. Novel matrix metalloproteinase inhibitors: an updated patent review (2014–2020). *Expert Opin Ther Pat*. 2021;31(6):509–523. doi:10.1080/13543776.2021.1881481
63. Sunil AA, Jose D, Karri SK, Pukhraj P, Varughese JK, Skaria T. Biomolecular interactions between the antibacterial ceftolozane and the human inflammatory disease target ADAM17: a drug repurposing study. *J Biomol Struct Dyn*. 2024;42(21):11706–11716. doi:10.1080/07391102.2023.2263895
64. Lu J, Zhao Z, Pan L, et al. Hyaluronidase: structure, mechanism of action, diseases and therapeutic targets. *Mol Biomed*. 2025;6(1):50. doi:10.1186/s43556-025-00299-y
65. Zhang Y, Cui L. Discovery and development of small-molecule heparanase inhibitors. *Bioorg Med Chem*. 2023;90:117335. doi:10.1016/j.bmc.2023.117335
66. Schmidt EP, Yang Y, Janssen WJ, et al. The pulmonary endothelial glycocalyx regulates neutrophil adhesion and lung injury during experimental sepsis. *Nat Med*. 2012;18(8):1217–1223. doi:10.1038/nm.2843
67. Reine TM, Lanzalaco F, Kristiansen O, et al. Matrix metalloproteinase-9 mediated shedding of syndecan-4 in glomerular endothelial cells. *Microcirculation*. 2019;26:e12534. doi:10.1111/micc.12534
68. Ali MM, Mahmoud AM, Le Master E, Levitan I, Phillips SA. Role of matrix metalloproteinases and histone deacetylase in oxidative stress-induced degradation of the endothelial glycocalyx. *Am J Physiol Heart Circ Physiol*. 2019;316(3):H647–H663. doi:10.1152/ajpheart.00090.2018

69. Yang X, Meegan JE, Jannaway M, Coleman DC, Yuan SY. A disintegrin and metalloproteinase 15-mediated glycocalyx shedding contributes to vascular leakage during inflammation. *Cardiovasc Res*. 2018;114(13):1752–1763. doi:10.1093/cvr/cvy167
70. van der Veen BS, de Winther MP, Heeringa P. Myeloperoxidase: molecular mechanisms of action and their relevance to human health and disease. *Antioxid Redox Signal*. 2009;11(11):2899–2937. doi:10.1089/ARS.2009.2538
71. Zhang Y, Dong H, Seeburg DP, et al. Multimodal molecular imaging demonstrates myeloperoxidase regulation of matrix metalloproteinase activity in neuroinflammation. *Mol Neurobiol*. 2019;56(2):954–962. doi:10.1007/s12035-018-1137-2
72. Ramnath RD, Butler MJ, Newman G, et al. Blocking matrix metalloproteinase-mediated syndecan-4 shedding restores the endothelial glycocalyx and glomerular filtration barrier function in early diabetic kidney disease. *Kidney Int*. 2020;97(5):951–965. doi:10.1016/j.kint.2019.09.035
73. Jackson-Weaver O, Friedman JK, Rodriguez LA, et al. Hypoxia/reoxygenation decreases endothelial glycocalyx via reactive oxygen species and calcium signaling in a cellular model for shock. *J Trauma Acute Care Surg*. 2019;87(5):1070–1076. doi:10.1097/TA.0000000000002427
74. Pahwa R, Nallasamy P, Jialal I. Toll-like receptors 2 and 4 mediate hyperglycemia induced macrovascular aortic endothelial cell inflammation and perturbation of the endothelial glycocalyx. *J Diabetes Complications*. 2016;30(4):563–572. doi:10.1016/j.jdiacomp.2016.01.014
75. Vink H, Constantinescu AA, Spaan JA. Oxidized lipoproteins degrade the endothelial surface layer: implications for platelet-endothelial cell adhesion. *Circulation*. 2000;101(13):1500–1502. doi:10.1161/01.cir.101.13.1500
76. Bashan N, Kovsan J, Kachko I, Ovadia H, Rudich A. Positive and negative regulation of insulin signaling by reactive oxygen and nitrogen species. *Physiol Rev*. 2009;89(1):27–71. doi:10.1152/physrev.00014.2008
77. Gupte SA, Wolin MS. Oxidant and redox signaling in vascular oxygen sensing: implications for systemic and pulmonary hypertension. *Antioxid Redox Signal*. 2008;10(6):1137–1152. doi:10.1089/ars.2007.1995
78. Iba T, Levy JH. Derangement of the endothelial glycocalyx in sepsis. *J Thromb Haemost*. 2019;17(2):283–294. doi:10.1111/jth.14371
79. Gautam N, Olofsson AM, Herwald H, et al. Heparin-binding protein (HBP/CAP37): a missing link in neutrophil-evoked alteration of vascular permeability. *Nat Med*. 2001;7(10):1123–1127. doi:10.1038/nm1001-1123
80. Johansson J, Lindbom L, Herwald H, Sjoberg F. Neutrophil-derived heparin binding protein--a mediator of increased vascular permeability after burns? *Burns*. 2009;35(8):1185–1187. doi:10.1016/j.burns.2009.02.021
81. Soehnlein O, Xie X, Ulbrich H, et al. Neutrophil-derived heparin-binding protein (HBP/CAP37) deposited on endothelium enhances monocyte arrest under flow conditions. *J Immunol*. 2005;174(10):6399–6405. doi:10.4049/jimmunol.174.10.6399
82. Suzuki K, Okada H, Takemura G, et al. Neutrophil elastase damages the pulmonary endothelial glycocalyx in lipopolysaccharide-induced experimental endotoxemia. *Am J Pathol*. 2019;189(8):1526–1535. doi:10.1016/j.ajpath.2019.05.002
83. Hirota T, Levy JH, Iba T. The influence of hyperglycemia on neutrophil extracellular trap formation and endothelial glycocalyx damage in a mouse model of type 2 diabetes. *Microcirculation*. 2020;27. doi:10.1111/micc.12617
84. Adrover JM, McDowell SAC, He XY, Quail DF, Egeblad M. NETworking with cancer: the bidirectional interplay between cancer and neutrophil extracellular traps. *Cancer Cell*. 2023;41(3):505–526. doi:10.1016/j.ccell.2023.02.001
85. Wang H, Kim SJ, Lei Y, et al. Neutrophil extracellular traps in homeostasis and disease. *Signal Transduct Target Ther*. 2024;9(1):235. doi:10.1038/s41392-024-01933-x
86. Russell RT, Christiaans SC, Nice TR, et al. Histone-complexed DNA fragments levels are associated with coagulopathy, endothelial cell damage, and increased mortality after severe pediatric trauma. *Shock*. 2018;49(1):44–52. doi:10.1097/SHK.0000000000000902
87. Kolaczkowska E, Jenne CN, Surewaard BG, et al. Molecular mechanisms of NET formation and degradation revealed by intravital imaging in the liver vasculature. *Nat Commun*. 2015;6:6673. doi:10.1038/ncomms7673
88. Shao Y, Li L, Yang Y, et al. DNase aggravates intestinal microvascular injury in IBD patients by releasing NET-related proteins. *FASEB J*. 2024;38(1):e23395. doi:10.1096/fj.202301780R
89. Proudfoot AE. Chemokines and glycosaminoglycans. *Front Immunol*. 2015;6:246. doi:10.3389/fimmu.2015.00246
90. Lau EK, Paavola CD, Johnson Z, et al. Identification of the glycosaminoglycan binding site of the CC chemokine, MCP-1: implications for structure and function in vivo. *J Biol Chem*. 2004;279(21):22294–22305. doi:10.1074/jbc.M311224200
91. Sepuru KM, Rajarathnam K. CXCL1/MGSA is a novel glycosaminoglycan (GAG)-binding Chemokine: structural evidence for two distinct non-overlapping binding domains. *J Biol Chem*. 2016;291(8):4247–4255. doi:10.1074/jbc.M115.697888
92. Proudfoot AE, Handel TM, Johnson Z, et al. Glycosaminoglycan binding and oligomerization are essential for the in vivo activity of certain chemokines. *Proc Natl Acad Sci U S A*. 2003;100(4):1885–1890. doi:10.1073/pnas.0334864100
93. Bonvin P, Gueneau F, Buatois V, et al. Antibody neutralization of CXCL10 in vivo is dependent on binding to free and not endothelial-bound chemokine: implications for the design of a new generation of anti-chemokine therapeutic antibodies. *J Biol Chem*. 2017;292(10):4185–4197. doi:10.1074/jbc.M116.745877
94. Graham GJ, Handel TM, Proudfoot AEI. Leukocyte adhesion: reconceptualizing chemokine presentation by glycosaminoglycans. *Trends Immunol*. 2019;40(6):472–481. doi:10.1016/j.it.2019.03.009
95. Skaria T, Bachli E, Schoedon G. Gene ontology analysis for drug targets of the whole genome transcriptome of human vascular endothelial cells in response to proinflammatory IL-1. *Front Pharmacol*. 2019;10:414. doi:10.3389/fphar.2019.00414
96. Puhlmann M, Weinreich DM, Farma JM, Carroll NM, Turner EM, Alexander HR Jr. Interleukin-1beta induced vascular permeability is dependent on induction of endothelial tissue factor (TF) activity. *J Transl Med*. 2005;3:37. doi:10.1186/1479-5876-3-37
97. Ferrero E, Villa A, Ferrero ME, et al. Tumor necrosis factor alpha-induced vascular leakage involves PECAM1 phosphorylation. *Cancer Res*. 1996;56(14):3211–3215.
98. Park KY, Kim SJ, Oh E, Heo TH. Induction of vascular leak syndrome by tumor necrosis factor-alpha alone. *Biomed Pharmacother*. 2015;70:213–216. doi:10.1016/j.biopha.2015.01.021
99. Fahey E, Doyle SL. IL-1 family cytokine regulation of vascular permeability and angiogenesis. *Front Immunol*. 2019;10:1426. doi:10.3389/fimmu.2019.01426