Endothelial Glycocalyx in Vascular Biology and Immune Response: A Survey

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Abstract

The endothelial glycocalyx (eGCX) is a crucial component of the vascular system, acting as a protective barrier that maintains vascular health and homeostasis. This survey paper provides a comprehensive analysis of the eGCX's multifaceted roles in vascular biology and immune response. It highlights the glycocalyx's importance in regulating vascular permeability, mechanotransduction, and interactions with immune cells, which are vital for maintaining vascular integrity and modulating inflammatory responses. The paper explores the molecular mechanisms underlying endothelial dysfunction, focusing on the contributions of oxidative stress, reactive oxygen species (ROS), and matrix metalloproteinases (MMPs) to glycocalyx degradation. The role of macrophages in vascular biology and inflammation is examined, emphasizing their functional plasticity and interactions with the glycocalyx. The survey discusses the impact of inflammatory mediators on glycocalyx degradation and endothelial dysfunction, highlighting the complex interplay between immune cells and the vascular endothelium. In the context of cardiovascular diseases, the degradation of the glycocalyx exacerbates endothelial dysfunction, contributing to the pathogenesis of conditions such as atherosclerosis and diabetic retinopathy. The review concludes by emphasizing the therapeutic implications of preserving glycocalyx integrity and suggests future research directions to develop targeted interventions that mitigate vascular pathologies. Understanding the role of the eGCX in vascular biology and immune response is crucial for developing effective therapeutic strategies to preserve vascular health and prevent disease progression.

1 Introduction

1.1 Significance of the Endothelial Glycocalyx

The endothelial glycocalyx (eGCX) is a vital component of the vascular system, acting as a protective barrier essential for vascular health and homeostasis [1]. This carbohydrate-rich layer, which lines endothelial cells, regulates vascular permeability and microvascular tone, thereby contributing to the vascular network's overall functionality [2]. The integrity of the glycocalyx is crucial for endothelial function; its degradation is linked to endothelial dysfunction, a precursor to atherosclerosis and other cardiovascular diseases [2].

The glycocalyx mediates complex biochemical interactions critical for vascular biology, particularly in immune-mediated cardiovascular disorders [1]. It is involved in the formation of gaps in the endothelium, influencing immune cell extravasation and immune system functionality during infections, chronic inflammation, and tumor metastasis [3]. Moreover, the glycocalyx serves as a potential biomarker for early endothelial damage, highlighting its significance in diagnosis and intervention strategies [1].

In systemic diseases, glycocalyx degradation has profound implications. For example, in diabetic retinopathy, its protective role against endothelial dysfunction is critical, with degradation linked to severe vascular complications in conditions like sepsis [2]. Furthermore, the glycocalyx modulates

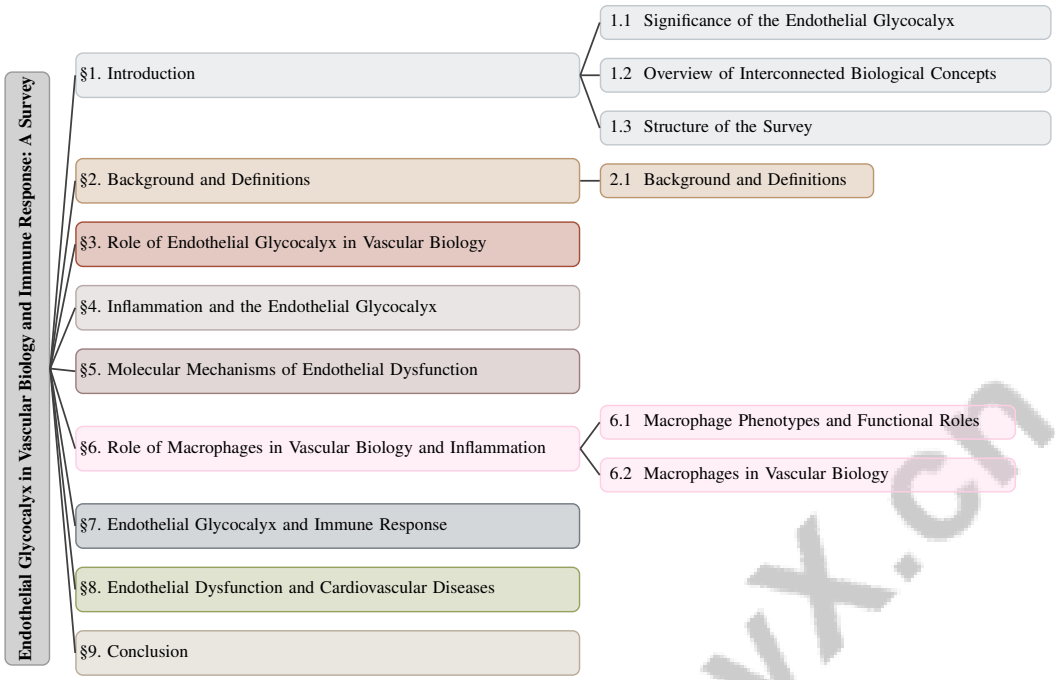

Figure 1: chapter structure

inflammatory responses, significantly impacting metabolic diseases such as diabetes, where chronic inflammation disrupts immune and metabolic balance [4]. Its degradation is associated with severe vascular complications, emphasizing its protective role in maintaining vascular integrity under pathological conditions [1].

Aging also affects the endothelial glycocalyx, with its degradation correlating with impaired endothelial function and angiogenesis, underscoring its importance in sustaining vascular health across the lifespan [2]. Understanding the multifaceted roles of the glycocalyx is essential for developing therapeutic strategies aimed at preserving its integrity and enhancing vascular health, particularly in complex diseases where personalized treatment plans are critical [1].

The endothelial glycocalyx plays a crucial role in vascular biology, with its protective functions against inflammation, thrombosis, and endothelial dysfunction underscoring its importance in maintaining vascular health [1]. Its degradation exacerbates conditions such as atherosclerosis and neuroprogressive disorders, where systemic inflammation and oxidative stress are prevalent [2].

1.2 Overview of Interconnected Biological Concepts

The endothelial glycocalyx (eGCX) serves as a critical interface between the bloodstream and endothelial cells, consisting of proteoglycans, glycoproteins, and glycolipids that collectively maintain endothelial integrity and vascular homeostasis [5]. It plays essential roles in mechanosensation, inflammation, and vascular permeability, processes often disrupted in pathological conditions [6]. The glycocalyx is linked to cardiovascular health, with its degradation increasing susceptibility to disorders such as atherosclerosis and ischemia/reperfusion injury, as well as being associated with systemic inflammation and oxidative stress, which contribute to endothelial dysfunction and neuroprogressive disorders [7, 8].

Clinical scenarios like sepsis and hemorrhagic shock further compromise glycocalyx integrity, with albumin interactions affecting its structure and function [5]. In neonates, infants, and children, the physiological properties and pathological implications of the eGCX differ, necessitating consideration of age-related variations in its function [9]. Glycans within the glycocalyx are proposed to encode critical information through their diverse structures and interactions, emphasizing the glycocalyx's role in cellular communication and immune response regulation [10].

The dual roles of macrophages in homeostasis and inflammation illustrate their functional heterogeneity across organ systems, highlighting the interconnectedness of the glycocalyx with immune and vascular biology [11]. Endotoxin tolerance and macrophage priming exemplify the complex adaptations of innate immune cells, linking macrophage activity with glycocalyx function [12]. In chronic kidney disease, glycocalyx damage is evident, correlating with microalbuminuria and endothelial dysfunction [13].

Hyperglycemia's impact on endothelial cells contributes to cardiac dysfunction in diabetic patients, underscoring the glycocalyx's role in vascular biology and disease [14]. Recent research on COVID-19 has focused on glycocalyx damage mechanisms and their implications for vascular health, with therapeutic strategies being explored to mitigate this damage [15]. Computational patient models integrate various physiological frameworks to provide insights into the interconnected biological concepts related to eGCX function, essential for understanding complex interactions within the vascular system and developing targeted therapeutic approaches [16].

1.3 Structure of the Survey

This survey paper is structured to provide a comprehensive analysis of the endothelial glycocalyx (eGCX) and its multifaceted roles in vascular biology and immune response. The paper begins with an **Introduction** that highlights the significance of the eGCX in maintaining vascular health and its involvement in immune response, inflammation, macrophage activity, and endothelial dysfunction. Following this, the **Background and Definitions** section introduces core concepts such as the endothelial glycocalyx, inflammation, macrophages, and the molecular mechanisms underlying endothelial dysfunction.

The survey then explores the **Role of Endothelial Glycocalyx in Vascular Biology**, detailing the complex structure and multifaceted functions of the eGCX. This review emphasizes its critical role in maintaining vascular homeostasis, regulating vascular permeability, and facilitating mechanotransduction in response to blood flow, which collectively contribute to the integrity of the endothelial barrier. Additionally, it addresses how eGCX dysfunction can lead to various pathophysiological conditions, including inflammation, cardiovascular diseases, and other vascular complications, underscoring the importance of preserving eGCX integrity as a therapeutic target in these contexts [17, 6, 18, 19, 20]. This is followed by an exploration of **Inflammation and the Endothelial Glycocalyx**, which examines how the eGCX influences inflammation and macrophage activity.

The subsequent section, **Molecular Mechanisms of Endothelial Dysfunction**, provides an in-depth analysis of the molecular pathways involved in endothelial dysfunction, including the impact of reactive oxygen species and matrix metalloproteinases on glycocalyx degradation. The role of macrophages is further explored in **Role of Macrophages in Vascular Biology and Inflammation**, highlighting their phenotypes and functional roles.

The survey continues with **Endothelial Glycocalyx and Immune Response**, examining the interactions between the glycocalyx and immune cells. The paper comprehensively reviews **Endothelial Dysfunction and Cardiovascular Diseases**, emphasizing the critical role of endothelial dysfunction in the pathogenesis of cardiovascular diseases, particularly its association with inflammation, oxidative stress, and impaired angiogenesis. It explores how these factors contribute to atherosclerosis progression and identifies potential biomarkers and therapeutic strategies aimed at preventing endothelial damage and reducing the risk of coronary artery disease (CAD) and its complications. The discussion includes both pharmacological and non-pharmacological approaches to restore endothelial health, underscoring the importance of maintaining endothelial function for overall cardiovascular health [21, 8, 22, 23].

The **Conclusion** synthesizes the essential findings of the study, emphasizing the intricate interplay among the eGCX, inflammatory processes, macrophage activity, and the underlying molecular mechanisms that collectively influence vascular biology and immune responses. This interconnectedness highlights the dual role of macrophages as both protectors and potential disruptors of tissue integrity, particularly in the context of inflammation, and underscores the importance of eGCX integrity in maintaining microvascular homeostasis and mitigating pathological inflammation [20, 24]. The survey concludes with a discussion on **Therapeutic Implications and Future Directions**, suggesting avenues for future research and therapeutic strategies.The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Background and Definitions

The endothelial glycocalyx (eGCX), a carbohydrate-rich layer on endothelial cells, is pivotal for maintaining vascular integrity and homeostasis [6]. This structure functions as a barrier against inflammatory agents, modulates vascular permeability, and participates in mechanotransduction [25]. Its degradation is associated with adverse clinical outcomes, contributing to inflammatory vasculopathy and microvascular injury, as seen in conditions like sepsis and COVID-19 [26, 15].

Inflammation, a fundamental biological response to harmful stimuli, is crucial in immune responses but can lead to metabolic dysfunction and endothelial damage when chronic [22]. Understanding the cardiovascular and immune systems' interplay is essential for elucidating the mechanisms of inflammation and endothelial dysfunction, especially under stress conditions that exacerbate tissue damage [12].

Macrophages, key players in innate immunity and tissue homeostasis, exhibit functional plasticity, enabling adaptation to various microenvironments [12]. They are vital for resolving inflammation and tissue repair; however, dysregulation can result in chronic inflammation and fibrosis [22]. In vascular biology, macrophages interact with the eGCX, influencing its structure and function, thus contributing to atherosclerosis progression [6]. Their role in plaque development and inflammation is well-documented [27].

Endothelial dysfunction, marked by impaired vasodilation, increased permeability, and a pro-inflammatory state, precedes atherosclerosis and contributes to coronary artery disease (CAD) [22, 28]. This dysfunction arises from oxidative stress, inflammation, and glycocalyx degradation, with ongoing research into biomarkers and therapeutic strategies to mitigate CAD risk [8].

The immune response, integrating innate and adaptive immunity, is closely linked to vascular health. Pathogen-induced systemic endothelial dysfunction, such as that caused by SARS-CoV-2, exemplifies the severe clinical manifestations resulting from immune-mediated endothelial damage [16]. Understanding these molecular mechanisms is crucial for developing interventions to preserve endothelial function and prevent disease progression [29].

This review explores the interconnectedness of the eGCX, inflammation, macrophages, immune response, and endothelial dysfunction, providing insights into vascular biology's complex interactions and potential therapeutic approaches. Additionally, it underscores the role of eicosanoids in health and disease, as identified by mass spectrometry, highlighting the biochemical complexity involved [30]. Diabetic cardiomyopathy, characterized by ventricular dysfunction independent of hypertension or CAD, further illustrates the multifaceted nature of vascular health [14].

In recent years, the role of the endothelial glycocalyx in vascular biology has garnered increasing attention due to its critical functions in maintaining vascular integrity and modulating inflammatory responses. As depicted in Figure 2, the hierarchical structure of the endothelial glycocalyx is illustrated, emphasizing its multifaceted roles. This figure highlights the glycocalyx's function as a protective barrier, its involvement in mechanotransduction and vascular permeability, as well as the implications of its degradation. Understanding these aspects is essential for exploring potential therapeutic interventions aimed at preserving the glycocalyx's integrity and function in vascular health.

3 Role of Endothelial Glycocalyx in Vascular Biology

3.1 Role of Endothelial Glycocalyx as a Protective Barrier

The endothelial glycocalyx (eGCX) serves as a crucial protective barrier in vascular biology, maintaining vascular homeostasis and integrity. This glycan-rich layer, lining the endothelial cells' luminal surface, regulates vascular permeability and mediates substance exchange between the bloodstream and tissues [31]. Composed of proteoglycans, glycoproteins, and glycolipids, the glycocalyx acts as a dynamic interface, modulating interactions with circulating cells and molecules [12].

As illustrated in Figure 3, the figure highlights the key roles of the endothelial glycocalyx, emphasizing its function as a protective barrier. It categorizes the glycocalyx's contributions into maintaining

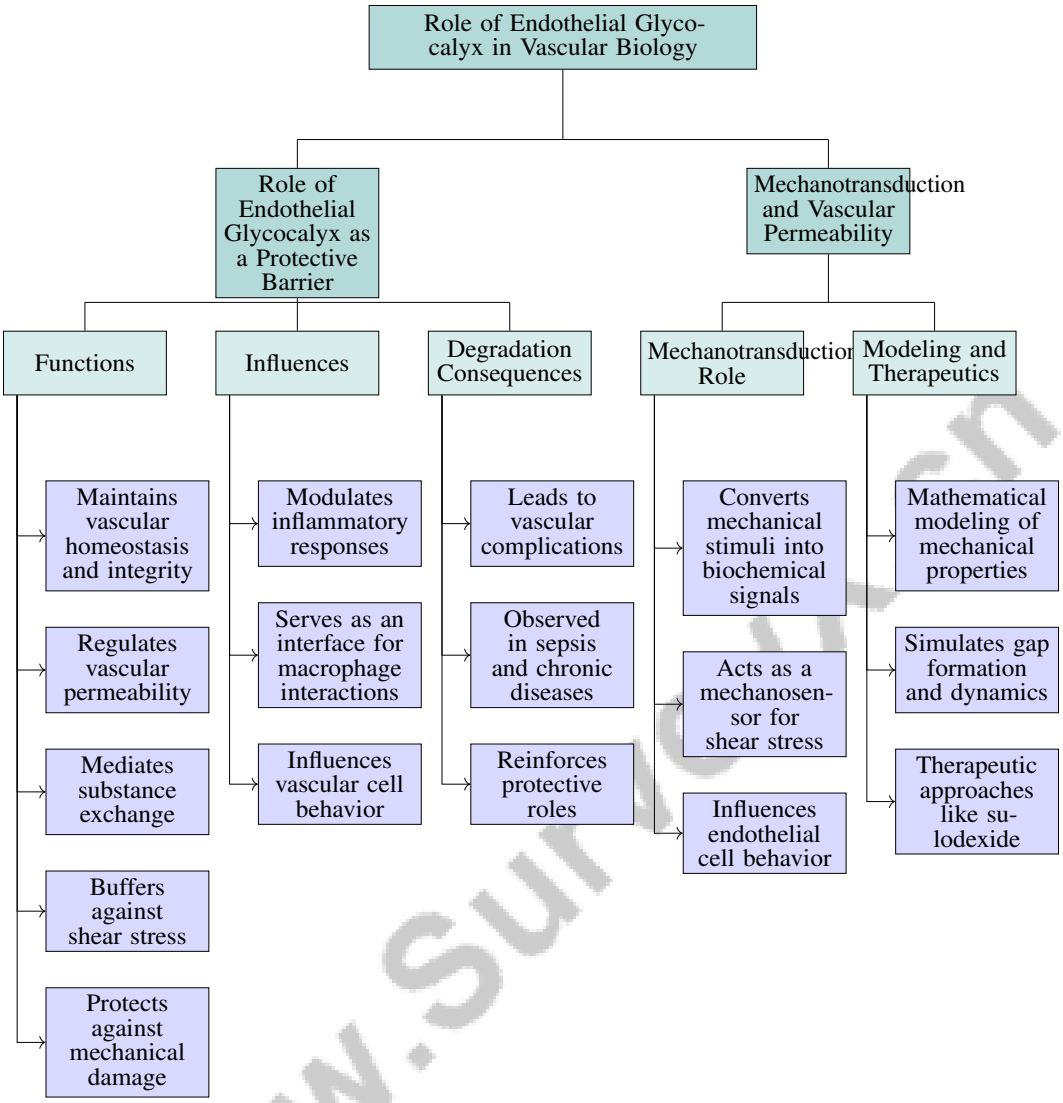

Figure 2: This figure illustrates the hierarchical structure of the role of endothelial glycocalyx in vascular biology, highlighting its function as a protective barrier, its involvement in mechanotransduction and vascular permeability, and the implications of its degradation. The diagram emphasizes the glycocalyx's multifaceted roles in maintaining vascular integrity, modulating inflammatory responses, and potential therapeutic interventions.

vascular homeostasis and integrity, modulating inflammatory responses, and addressing the impact of its degradation. The components and mechanical properties of the glycocalyx are depicted, alongside its critical role in inflammation and disease conditions such as sepsis.

Beyond regulating permeability, the glycocalyx significantly contributes to the endothelium's mechanical properties. It functions as a compliant spring system, buffering against shear stress from blood flow and protecting endothelial cells from mechanical damage, thus maintaining vascular integrity under varying hemodynamic conditions [32]. This mechanical resilience is essential for preventing endothelial damage and dysfunction, precursors to various cardiovascular diseases [2].

Furthermore, the glycocalyx influences inflammatory responses by modulating vascular cell behavior. It serves as a critical interface for macrophage interactions, vital for resolving inflammation and maintaining tissue homeostasis [11]. Computational models simulating glycocalyx interactions provide insights into its protective functions under physiological and pathological conditions [4].

These models elucidate the complex dynamics of vascular inflammation and the glycocalyx's role in mitigating inflammatory damage [27].

Glycocalyx degradation, observed in conditions like sepsis and chronic diseases, leads to significant vascular complications, highlighting the importance of preserving its integrity for cardiovascular health [2]. Advanced imaging techniques have visualized its three-dimensional ultrastructure, revealing disruption under endotoxemic conditions and reinforcing its protective role [31].

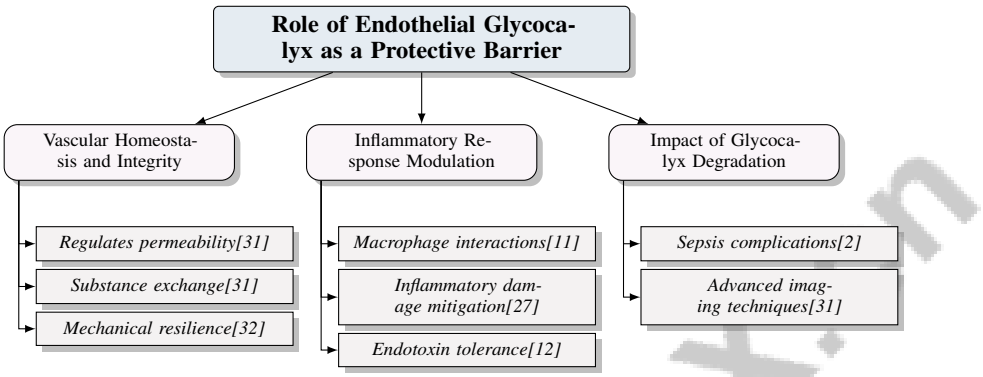

Figure 3: This figure illustrates the key roles of the endothelial glycocalyx in vascular biology, focusing on its function as a protective barrier. The primary categories include its role in maintaining vascular homeostasis and integrity, modulating inflammatory responses, and the impact of its degradation. The figure highlights the glycocalyx's components, mechanical properties, and its role in inflammation and disease conditions like sepsis.

3.2 Mechanotransduction and Vascular Permeability

Mechanotransduction, a key function of the endothelial glycocalyx (eGCX), plays a crucial role in regulating vascular permeability. This process converts mechanical stimuli from blood flow into biochemical signals, essential for maintaining endothelial integrity and function [6]. Acting as a mechanosensor, the glycocalyx transmits shear stress information to endothelial cells, influencing their behavior and modulating vascular permeability.

Mathematical modeling of the glycocalyx's mechanical properties and endothelial cell interactions has simulated gap formation and dynamics, providing insights into the mechanisms underlying changes in vascular permeability [3]. These models highlight the glycocalyx's role in balancing mechanical forces and cellular responses, crucial for preventing pathological conditions such as edema and inflammation.

Moreover, chemokines like MCP-1 influence monocyte migration in a 3D vascular tissue model replicating the subendothelial extracellular matrix (ECM). This model facilitates the study of local concentration gradients and their effects on vascular permeability, emphasizing the interplay between chemical signals and mechanical forces in regulating endothelial function [33].

Therapeutic approaches targeting the glycocalyx, such as sulodexide (SDX), show promise in restoring glycocalyx integrity by inhibiting enzymes that degrade its components. This restoration enhances vascular integrity and reduces permeability, underscoring the potential of glycocalyx-targeted therapies in treating vascular disorders [34].

4 Inflammation and the Endothelial Glycocalyx

4.1 Interaction with Immune Cells and Inflammatory Mediators

The endothelial glycocalyx (eGCX) functions as a crucial interface between the vascular endothelium and immune cells, orchestrating immune responses and modulating inflammatory mediators. Composed of glycoproteins and proteoglycans, it acts as both a selective barrier and a signaling platform, regulating immune cell adhesion and transmigration [26]. This regulation is vital for vascular homeostasis and preventing excessive inflammation that could lead to vascular pathophysiology.

Advances in computational and experimental methodologies have highlighted the glycocalyx's role in immune cell adhesion, emphasizing its structural integrity's influence on promoting or inhibiting adhesion and transmigration based on its condition [26]. Inflammatory mediators, including cytokines and chemokines, alter the glycocalyx's structure, leading to its degradation and endothelial dysfunction, key events in inflammatory disease pathogenesis [26]. This degradation enhances vascular permeability, facilitating immune cell infiltration and exacerbating inflammation.

Macrophages, essential to the innate immune system, interact closely with the glycocalyx, with their function influenced by the local microenvironment and inflammatory mediators [35]. The inflamed tissue environment can induce macrophage phenotypic changes, contributing to inflammatory disease progression. Understanding macrophage priming and tolerance balance is crucial for developing therapies to modulate immune responses and mitigate inflammation [35].

The importance of the eGCX in vascular health and its potential for therapeutic restoration to mitigate inflammatory damage is emphasized in ongoing research [26]. As illustrated in Figure 4, the hierarchical structure of endothelial glycocalyx interaction with immune cells and inflammatory mediators highlights its roles in immune modulation and barrier function, macrophage interactions, and the effects of cytokines and chemokines. Further studies are needed to clarify glycocalyx interactions with blood components and their impact on vascular pathophysiology. Understanding the eGCX's role in modulating immune cell interactions and inflammatory mediators is crucial for maintaining vascular homeostasis. Disruptions in this balance can lead to endothelial dysfunction, a precursor to cardiovascular diseases, highlighting the need to understand these mechanisms to prevent vascular complications [2, 36].

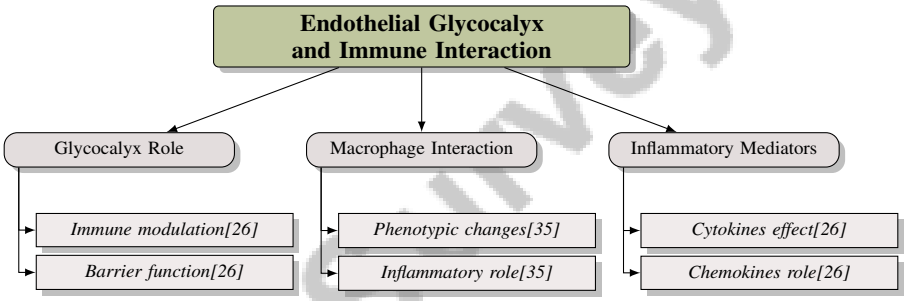

Figure 4: This figure illustrates the hierarchical structure of endothelial glycocalyx interaction with immune cells and inflammatory mediators, highlighting its roles in immune modulation and barrier function, macrophage interactions, and the effects of cytokines and chemokines.

4.2 Inflammatory Mediators and Endothelial Dysfunction

Inflammatory mediators are pivotal in endothelial dysfunction pathogenesis, a precursor to cardiovascular diseases. Activated immune cells, such as macrophages, release cytokines and chemokines that drive inflammation. The eGCX is particularly susceptible to degradation by these mediators, initiating a cascade culminating in endothelial dysfunction [6].

This process begins with immune cell activation, leading to pro-inflammatory cytokine and chemokine secretion that interacts with endothelial cells, upregulating adhesion molecules and facilitating leukocyte transmigration [27]. Macrophage recruitment and activation within the vascular wall are critical in endothelial dysfunction and atherosclerosis pathogenesis.

Inflammatory mediators can induce reactive oxygen species (ROS) and matrix metalloproteinases (MMPs), degrading the glycocalyx and extracellular matrix [8]. This degradation weakens the endothelial barrier, increasing permeability and inflammatory cell infiltration. The inflammatory environment promotes oxidative stress and endothelial activation, contributing to cardiovascular disease progression.

Macrophages, with their phenotypic plasticity, play a crucial role, capable of resolving or exacerbating inflammation [12]. Dysregulated macrophages can lead to chronic inflammation and tissue damage. The interplay between macrophages, the glycocalyx, and inflammatory mediators is complex, with each component dynamically influencing the others. Understanding these interactions is essential

for developing targeted therapies to prevent and treat endothelial dysfunction and its associated pathologies.

5 Molecular Mechanisms of Endothelial Dysfunction

The interplay between oxidative stress and endothelial dysfunction is pivotal in vascular pathology. Oxidative stress, primarily through reactive oxygen species (ROS), significantly contributes to endothelial glycocalyx (eGCX) degradation, compromising vascular integrity and inciting inflammation. This section delves into oxidative stress and ROS's roles in endothelial dysfunction pathophysiology.

5.1 Role of Oxidative Stress and ROS

Oxidative stress and ROS are integral to endothelial dysfunction and cardiovascular disease progression. The eGCX, a crucial barrier and signaling interface, is highly susceptible to oxidative damage, leading to its degradation [13]. ROS, including superoxide anions, hydrogen peroxide, and hydroxyl radicals, are byproducts of cellular metabolism and are heightened by inflammation and metabolic disorders [28]. Excessive ROS inflicts oxidative harm on cellular components, impairing endothelial function [37], and is linked to NLRP3 inflammasome activation, a key player in inflammation and endothelial injury.

The interaction between oxidative stress and inflammatory mediators is central to endothelial dysfunction, marked by vasodilation-vasoconstriction imbalance, elevated ROS, and reduced nitric oxide (NO) bioavailability. Inflammatory cytokines and pathways, notably the NLRP3 inflammasome, exacerbate this dysfunction, especially in aging populations and those with chronic conditions. Understanding these dynamics is crucial for developing therapies to restore endothelial function and improve cardiovascular health [2, 22, 38, 23]. Cytokines such as TNF- and IL-1 promote ROS production, further activating the NLRP3 inflammasome and perpetuating a cycle of inflammation and oxidative damage, which exacerbates endothelial injury and fosters a pro-inflammatory, pro-thrombotic state.

Biomarkers like hyaluronan and syndecan-1 in the bloodstream indicate glycocalyx degradation and endothelial dysfunction, highlighting oxidative stress and ROS's impact on vascular health [13]. Glycocalyx degradation increases vascular permeability and immune cell infiltration, exacerbating inflammation and contributing to cardiovascular disease pathogenesis.

5.2 Matrix Metalloproteinases and Glycocalyx Degradation

Matrix metalloproteinases (MMPs), zinc-dependent endopeptidases, are crucial for extracellular matrix (ECM) remodeling and eGCX degradation. These enzymes participate in various physiological and pathological processes, including tissue remodeling, inflammation, and vascular integrity [34]. Under normal conditions, MMP activity is tightly regulated, but dysregulation can lead to excessive glycocalyx degradation, contributing to endothelial dysfunction and vascular pathologies.

The glycocalyx, a complex glycoprotein and proteoglycan layer, acts as a protective barrier on the endothelial surface, regulating vascular permeability and mechanotransduction. MMP-mediated degradation compromises this layer's integrity, increasing permeability and facilitating inflammatory cell infiltration [34]. This process is particularly pronounced in inflammatory conditions where MMPs are upregulated, leading to the breakdown of glycocalyx components such as heparan sulfate and syndecans, vital for endothelial function.

Pharmacological interventions targeting MMP activity show promise in preserving glycocalyx integrity. Sulodexide (SDX), for instance, accelerates glycocalyx restoration in sepsis by inhibiting heparanase and MMPs [34]. This dual inhibition is crucial for preventing excessive glycocalyx degradation, maintaining vascular homeostasis, and reducing endothelial dysfunction risk.

6 Role of Macrophages in Vascular Biology and Inflammation

6.1 Macrophage Phenotypes and Functional Roles

Macrophages exhibit significant plasticity, adapting to various microenvironments and playing essential roles in innate immunity and tissue homeostasis [11]. Their differentiation into distinct

phenotypes is driven by environmental cues, influencing their roles in inflammation and tissue repair. M1 macrophages, activated by cytokines like IFN-, produce inflammatory mediators and ROS, crucial for pathogen defense but potentially causing tissue damage if persistent [22]. Conversely, M2 macrophages facilitate tissue repair and inflammation resolution [11], enabling a dynamic shift between pro- and anti-inflammatory states to maintain homeostasis [35].

In vascular biology, macrophages are crucial for endothelial integrity, interacting with the endothelial glycocalyx and influencing atherosclerosis development [6]. They modulate inflammation and lipid accumulation in arterial walls, contributing to plaque formation [27]. Computational models reveal their complex interactions with the glycocalyx and vascular environment, highlighting their dual roles in inflammation [4].

Advanced techniques like multispecies spatial transcriptomics and topological data analysis have improved the evaluation of macrophage phenotypes and spatial distributions, enhancing understanding of their roles in tissue homeostasis and immune responses, with implications for tumor microenvironments and patient outcomes [35, 39, 4, 11]. The heterogeneity of macrophages and their adaptability to different environments are vital for their roles in vascular inflammation.

Understanding macrophage phenotypes is crucial for developing targeted therapies. The interplay between macrophages, the glycocalyx, and immune components underscores the complexity of the vascular microenvironment, necessitating comprehensive approaches to address vascular dysfunction, particularly given the glycocalyx's role in regulating inflammation and angiogenesis in cardiovascular disorders linked to hypertension, diabetes, and obesity [7, 19].

6.2 Macrophages in Vascular Biology

Macrophages are integral to vascular biology, maintaining endothelial homeostasis and modulating inflammation. Their interactions with the endothelial glycocalyx significantly influence vascular integrity and immune cell behavior, as demonstrated by differential patient responses to SARS-CoV-2 infection, underscoring macrophage dynamics in vascular contexts [40].

Mechanical cues, such as substrate stiffness, affect macrophage behavior and their interactions with the glycocalyx, altering cell responses and highlighting macrophages' mechanosensitivity within the vascular environment [41]. This sensitivity is crucial for processes like endothelial repair and inflammation resolution.

In atherosclerosis, macrophages play key roles in plaque development and stability, with their activity, including death and efferocytosis, determining plaque composition [42]. Their adaptability to oxygen tensions further emphasizes their influence in vascular biology, particularly in plaque interactions [27].

Macrophage interactions with the glycocalyx impact vascular function and pathology. They are involved in extracellular matrix remodeling and preserving endothelial integrity, essential for vascular homeostasis and preventing dysfunction. Macrophages participate in tissue development, angiogenesis, and wound healing, regulating endothelial function through environmental sensing and signaling molecule production. This regulation prevents pathological conditions like inflammation-induced endothelial to mesenchymal transition, which can lead to vascular complications [24, 35, 37, 43]. Understanding these interactions is vital for developing therapeutic strategies to modulate macrophage activity and preserve vascular health.

7 Endothelial Glycocalyx and Immune Response

7.1 Interaction with Immune Cells

The endothelial glycocalyx (eGCX) plays a crucial role in modulating interactions between endothelial cells and circulating immune cells, essential for vascular homeostasis and immune regulation. It functions as both a barrier and mediator, controlling leukocyte adhesion and transmigration across the endothelium, which is vital for effective host defense and tissue repair during inflammatory responses [25, 12]. The eGCX influences leukocyte recruitment and activation by interacting with adhesion molecules and chemokines, directing immune cells to inflammation sites [11]. Maintaining its structural integrity is essential for preserving selective barrier functions, preventing excessive leukocyte adhesion and migration, thereby mitigating unnecessary inflammation [6]. Degradation

of the glycocalyx, as seen in sepsis and diabetes, results in increased vascular permeability and inflammation [15].

Interactions between the glycocalyx and immune cells, including macrophages, neutrophils, and lymphocytes, are pivotal in modulating immune responses [11]. Macrophages, in particular, play a significant role in resolving inflammation and facilitating tissue repair, with their interactions with the glycocalyx affecting recruitment and activation within the vascular wall [12]. Balancing pro-inflammatory and anti-inflammatory responses is critical for vascular health and the prevention of chronic inflammatory diseases [22].

In pathologies such as sepsis and atherosclerosis, glycocalyx degradation exacerbates vascular permeability and leukocyte adhesion, intensifying inflammatory responses and promoting vascular diseases [25]. Thus, preserving the glycocalyx's structure and function is essential for vascular health and immune response modulation. Composed of glycoproteins and proteoglycans, the glycocalyx forms a protective gel layer on the endothelium, regulating vascular permeability and facilitating mechanotransduction in response to blood flow. It is integral to leukocyte adhesion, rolling, and extravasation, crucial for immune regulation. The glycocalyx's integrity is vital for preventing pathogen extravasation and maintaining vascular health, with its degradation linked to pathologies such as atherosclerosis and diabetes-related vascular complications. Current research focuses on elucidating mechanisms governing glycocalyx stability and developing therapeutic interventions to enhance its integrity, thereby improving vascular function and reducing disease risk [17, 6]. Understanding these interactions is essential for developing targeted therapies to preserve vascular health and prevent disease progression.

8 Endothelial Dysfunction and Cardiovascular Diseases

8.1 Endothelial Dysfunction in Specific Conditions

Endothelial dysfunction is a precursor to cardiovascular diseases like atherosclerosis, hypertension, and diabetic vasculopathy, marked by imbalanced vasodilation and vasoconstriction, elevated reactive oxygen species (ROS), and reduced nitric oxide (NO) bioavailability, impairing vascular function. Aging exacerbates this dysfunction through increased inflammation and disrupted angiogenesis, reducing tissue perfusion and raising cardiovascular risk. Understanding these mechanisms aids in identifying biomarkers and therapeutic strategies to prevent or reverse endothelial damage, thus lowering cardiovascular disease risk [21, 22, 23]. Dysfunction manifests as reduced vasodilation, increased vascular permeability, and a pro-inflammatory state, affecting disease pathophysiology.

In atherosclerosis, endothelial dysfunction initiates plaque development. Impaired NO production decreases vasodilation and promotes a pro-inflammatory, pro-thrombotic environment [28]. ROS and matrix metalloproteinases (MMPs) degrade the endothelial glycocalyx (eGCX), worsening dysfunction, increasing permeability, and facilitating inflammatory cell infiltration.

Diabetic vasculopathy highlights endothelial dysfunction's critical role. Hyperglycemia-induced oxidative stress degrades the glycocalyx, impairing vasodilation and increasing cardiovascular risk in diabetics [14]. The interaction between oxidative stress and inflammatory mediators disrupts vascular homeostasis, worsening dysfunction and diabetic vascular complications.

In COVID-19, endothelial dysfunction significantly impacts severe manifestations. SARS-CoV-2 induces systemic endothelial damage, leading to inflammation and thrombosis, key features of severe COVID-19 [15]. Glycocalyx degradation correlates with increased permeability and inflammation, worsening disease severity [15].

Chronic kidney disease (CKD) also involves endothelial dysfunction, linked to microalbuminuria and cardiovascular morbidity [13]. Glycocalyx damage in CKD patients highlights the need to maintain endothelial integrity to prevent vascular complications [13].

8.2 Therapeutic Strategies for Endothelial Dysfunction

Addressing endothelial dysfunction requires a comprehensive strategy targeting underlying molecular mechanisms, integrating pharmacological and non-pharmacological interventions to restore endothelial health, target inflammatory pathways, and identify biomarkers for treating coronary artery disease and atherosclerosis. Understanding cellular and molecular alterations in endothelial dysfunction,

especially in aging populations, is crucial for developing therapies that enhance vascular function and reduce cardiovascular event risk [38, 23, 37, 8, 21].

Targeting oxidative stress and ROS production is promising, as they contribute to endothelial damage. Antioxidant therapies aim to alleviate oxidative stress, preserving endothelial glycocalyx integrity and preventing degradation.

The NLRP3 inflammasome, crucial in the inflammatory response and endothelial dysfunction, offers another therapeutic target. Inhibiting NLRP3 may reduce inflammation and preserve endothelial function, potentially leading to new cardiovascular treatments [44].

MMPs, which degrade the glycocalyx and extracellular matrix, are also targets. Inhibiting MMPs can prevent excessive glycocalyx breakdown, maintaining vascular homeostasis and reducing dysfunction risk [34]. Pharmacological agents like sulodexide (SDX) have shown efficacy in restoring glycocalyx integrity by inhibiting MMPs and other degrading enzymes, offering a therapeutic option for vascular disorders [34].

Strategies to restore glycocalyx structural integrity are under investigation, including glycocalyx-replenishing therapies like exogenous glycosaminoglycan administration to enhance eGCX protective functions and improve vascular health [34]. These approaches are relevant in conditions with glycocalyx degradation, such as sepsis and chronic inflammatory diseases, where preserving the glycocalyx can mitigate vascular complications and improve outcomes [26].

9 Conclusion

9.1 Therapeutic Implications and Future Directions

The exploration of the endothelial glycocalyx (eGCX) within the context of vascular biology and immune response underscores its therapeutic potential, particularly in addressing cardiovascular and inflammatory ailments. Prioritizing research efforts to preserve or restore glycocalyx integrity is imperative for maintaining vascular health and preventing endothelial dysfunction. The degradation of the glycocalyx, prevalent in conditions such as sepsis and chronic inflammation, highlights the need for therapeutic interventions focused on damage mitigation and recovery enhancement.

Emerging therapies, such as the administration of exogenous glycosaminoglycans, show promise in replenishing the glycocalyx and improving vascular function. Additionally, targeted therapies for critically ill patients, including those with COVID-19, are being evaluated for their potential to alleviate severe clinical symptoms and improve patient outcomes. Investigating the mechanisms by which treatments like sulodexide (SDX) bolster glycocalyx integrity can lead to improved clinical outcomes across various pathological states.

Macrophages' role in vascular biology and inflammation presents opportunities for therapeutic advancements. Understanding macrophage plasticity and their interactions with the glycocalyx is crucial for developing targeted treatments for conditions like atherosclerosis. Research should focus on elucidating the mechanisms through which macrophages affect the glycocalyx and vascular pathology while exploring interventions to modulate macrophage activity, thereby reducing inflammation and promoting vascular health.

Computational models play a pivotal role in simulating the complex interactions within the glycocalyx and the vascular milieu. Future research should aim to expand these models by incorporating additional biological factors and validating predicted mechanisms of priming and tolerance through empirical studies. Such efforts can deepen our understanding of endothelial dysfunction mechanisms and inform the development of innovative therapeutic strategies.

In chronic conditions like diabetes, it is vital to target interventions to prevent hyperglycemia-induced endothelial dysfunction. The adverse effects of hyperglycemia on endothelial cells and its contribution to cardiac dysfunction in diabetic patients emphasize the importance of the glycocalyx in vascular biology and disease. Future investigations should focus on strategies to prevent glycocalyx degradation and maintain vascular function in diabetic populations.

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