Clinical Rheumatology (2023) 42:2541–2555
https://doi.org/10.1007/s10067-023-06738-x

REVIEW ARTICLE

The genesis of cardiovascular risk in inflammatory arthritis: insights into glycocalyx shedding, endothelial dysfunction, and atherosclerosis initiation

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Received: 18 July 2023 / Revised: 5 August 2023 / Accepted: 7 August 2023 / Published online: 15 August 2023

Abstract

This narrative review provides a comprehensive examination of the complex interplay between inflammatory arthritis (IA) and cardiovascular pathology. It particularly illuminates the roles of atherosclerosis initiation, endothelial dysfunction, and glycocalyx shedding. IA not only provokes tissue-specific inflammatory responses, but also engenders a considerable degree of non-specific systemic inflammation. This review underscores the accelerating influence of the chronic inflammatory milieu of IA on cardiovascular disease (CVD) progression. A focal point of our exploration is the critical function of the endothelial glycocalyx (EG) in this acceleration process, which possibly characterizes the earliest phases of atherosclerosis. We delve into the influence of inflammatory mediators on microtubule dynamics, EG modulation, immune cell migration and activation, and lipid dysregulation. We also illuminate the impact of microparticles and microRNA on endothelial function. Further, we elucidate the role of systemic inflammation and sheddases in EG degradation, the repercussions of complement activation, and the essential role of syndecans in preserving EG integrity. Our review provides insight into the complex and dynamic interface between systemic circulation and the endothelium.

Keywords Arthritis · Atherosclerosis · Biomarkers · Glycocalyx · Heart disease risk factors

Introduction

Chronic inflammation is a critical factor in the pathogenesis of cardiovascular disease (CVD), influencing each aspect from atherosclerosis to arrhythmias and heart failure [1–3]. It is well established that inflammatory arthritis (IA) such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA), among other conditions on the spondyloarthritis (SpA) spectrum, are systemic diseases associated with an augmented cardiovascular risk [4–9]. This suggests a shared pathway for the instigation and progression of endothelial dysfunction, culminating in CVD.

IA not only causes significant joint damage and disability but also leads to systemic inflammation, which has been linked to an increased risk of cardiovascular disease CVD. CVD, a leading cause of mortality globally, presents a significant health burden, with its impact further amplified in individuals with IA. Despite the well-established association between IA and CVD, the underlying mechanisms driving this relationship remain poorly understood. A key area of uncertainty lies in the complex interplay between IA and the initiation of atherosclerosis, endothelial dysfunction, and

This article is part of the Topical Collection on *Cardiovascular Issues in Rheumatic Diseases*

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glycocalyx shedding. This gap in understanding presents a significant problem. Without a clear grasp of these mechanisms, clinicians are limited in their ability to accurately predict which IA patients are at the highest risk of developing CVD. Furthermore, opportunities for targeted therapeutic interventions to mitigate this risk may be missed. Our review addresses this problem by providing a comprehensive examination of the molecular processes underpinning the relationship between IA and CVD. Risk algorithms adjusted for conventional CVD risk factors indicate that inflammation, rather than the specific nosological entity, could be the primary culprit for the heightened CVD burden [5, 7]. IA incites tissue-specific inflammatory responses but also considerable non-specific systemic inflammation. The presence of distinct underlying mechanisms and fluctuating inflammatory load in specific IA can manifest in diverse pathognomic presentations and variable CVD occurrence. This diversity makes it challenging to identify a single causative factor.

The milieu of chronic inflammation lays the foundation for CVD development and progression. This systemic inflammatory environment contributes to a variety of pathophysiological alterations that drive atherosclerosis, including endothelial dysfunction, oxidative stress, and the formation of pro-thrombotic states [10, 11]. The interplay of these factors is complex and dynamic, reflecting the multifactorial nature of CVD and the significant role of inflammation as a common denominator. The significant overlap of pathophysiological processes and the high incidence of CVD morbidity in patients with IA reinforces the emerging paradigm that views atherosclerosis as an autoimmune disease [12, 13].

The induction of atherogenesis is instigated by a chronic inflammatory state, perpetuated by immunocompetent cells, humoral factors, and a myriad of molecular mediators [13, 14]. Such inflammation can have a systemic impact as well as site-specific ramifications, causing alterations in vessel wall functionality, thereby leading to endothelial dysfunction — a critical precursor in the progression towards atherosclerosis. The compromised endothelium, as a result of the aforementioned inflammatory assault, transforms into a site conducive for lipid accumulation and retention, marking the onset of the atherosclerotic process [10, 15]. Such vascular wall disruption can be precipitated by an array of potential triggers, encompassing chemical, physical, and infectious agents; immune responses; ischemia; genetic aberrations; or nutritional insufficiencies. Each of these variables presents a different piece of the complex puzzle of atherosclerosis pathogenesis, highlighting the need for comprehensive and multifaceted strategies in its prevention and management [16–18].

The vascular endothelial layer, particularly its pericellular matrix — the glycocalyx, seems to be the primary site for the initial molecular reactions that contribute to cardiovascular damage [19]. The endothelial glycocalyx (EG) is composed of complex proteoglycan polymers, which can be rapidly shed under the influence of factors present in chronic inflammatory conditions (Fig. 1). This shedding may be the initiating event, with upregulated repair processes potentially playing a key role in lipoprotein deposition and immune cell recruitment. By-products of EG turnover are detectable in the serum of patients with IA and may serve as markers for disease activity [20, 21]. Accelerated EG degradation and

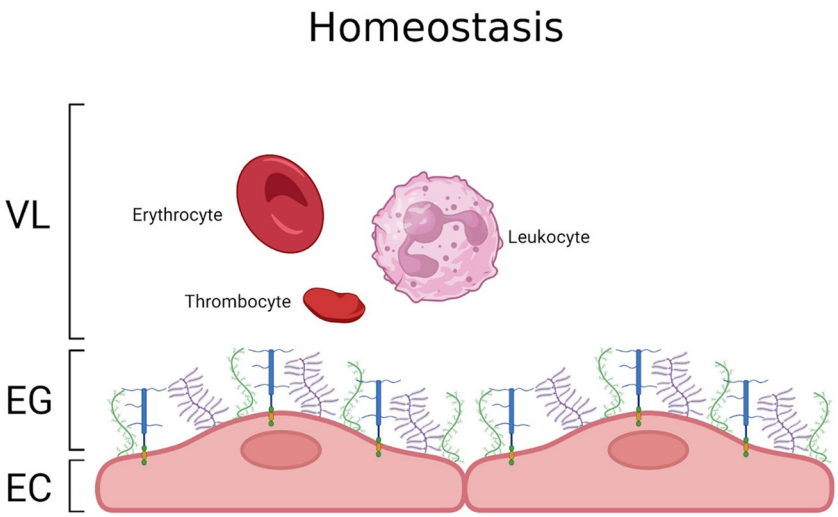

Fig. 1 Depiction of endothelial cells under normal homeostatic conditions with intact glycocalyx. The glycocalyx, represented by the dense, brush-like layer on the surface of the endothelial cells, plays a crucial role in vascular health by providing a protective barrier against harmful substances, regulating vascular permeability, and mediating cell–cell interactions. In this state, the cellular interactions with the endothelium are restricted, preventing unnecessary activation of inflammatory pathways and maintaining vascular integrity. VL, vessel lumen; EG, endothelial glycocalyx; EC, endothelial cells

subsequent endothelial dysfunction create a pathological feedback loop through impaired nitric oxide (NO) synthesis, mechanotransduction, and activation of sheddases, further facilitating vascular damage [22]. Aberrant EG degradation in critical illness like sepsis, polytrauma, and chronic kidney disease is associated with altered metabolic profile, increased inflammation, coagulation, and mortality [23].

This narrative review aims to summarize the current knowledge on chronic systemic inflammation's role in vascular damage, particularly in relation to the EG, a dynamic interface between systemic blood flow and the endothelium. We focus on its degradation and subsequent dysfunction, leading to early-stage atherosclerosis and promoting CVD progression. While our primary focus is on chronic inflammatory conditions such as IA, the pathways and processes discussed are relevant to similar inflammatory disorders. By examining the inflammatory milieu in IA, we aim to elucidate the damage to the EG, explore atherosclerosis initiation and progression, and understand how these processes accelerate CVD development. Our central interest lies in investigating the potentially deleterious effects of chronic inflammatory immune responses on vascular structures, with emphasis on the endothelial glycocalyx.

Search methodology

To understand the full scope of cardiovascular damage by the chronic inflammatory milieu, we performed a comprehensive literature review as of June 2023. We utilized the strategy from the previously published recommendations for writing a narrative review [24]. MEDLINE database via Pubmed and Scopus were queried for studies reporting potential mechanisms and biomarkers for subclinical atherosclerosis, endothelial dysfunction, and glycocalyx shedding in inflammatory arthritis. The search encompassed articles in English language from inception up to June 30, 2023, for MEDLINE, and July 1, 2023, for Scopus.

The initial query was set to include terms such as "endothelial dysfunction," "glycocalyx," "microparticles," "cholesterol," "atherosclerosis," "microtubules," "cell," "adhesion molecule," "sheddase," and "chemotaxis." To incorporate the context of inflammatory arthritis, the terms "inflammatory joint disease," "inflammatory arthritis," "rheumatoid arthritis," "spondyloarthritis," "ankylosing spondylitis," "psoriatic arthritis," and "reactive arthritis" were connected using the "OR" operator. These terms were then combined with the cardiovascular terms using the "AND" operator to narrow down the search results and identify articles that discussed both cardiovascular health and inflammatory arthritis. References of retrieved studies and relevant reviews were hand-searched for a further supplement. The final selection of studies for the present narrative review was based on authors' professional expertise, experience, existing theories, and models, creating an integrated data interpretation [24].

Cardiovascular disease burden

Patients with IA have increased vascular calcium deposition and atherosclerotic burden [25, 26]. RA with its high levels of chronic inflammation has been extensively studied to elucidate the potential mechanisms of accelerated CVD [27]. Impaired endothelial function and subclinical atherosclerosis correlated with increased epicardial adipose tissue thickness, intima-media thickness (IMT), and impaired flow-mediated dilation in SpA patients [28]. Prevalence of atherosclerotic burden and IMT is observed even in RA patients with inactive disease [29], although disease severity, rheumatoid factor isotypes, and anti-citrullinated protein antibodies are associated with increased incidence of CVD [30].

To elucidate the preceding events of the classical stages of atherosclerosis, it is essential to understand the initiator of lipid deposition and subsequent retention, which remains elusive. Retained lipoprotein modification incites the recruitment of immune cells, the release of chemoattractants, and the upregulation of adhesion molecules [31] Utilization of advanced imaging like positron emission tomography–computed tomography (PET-CT), coronary CT angiography (CCTA), and serum-based assays have been used identify subclinical coronary disease in PsA. Several potential contributors have been identified such as elevated IL-6 and increased uptake of fluorodeoxyglucose (FDG) in the liver, spleen, bone marrow, and fat. The findings reveal that PsA is characterized by metabolic dysregulation, systemic inflammation, and subclinical coronary artery disease compared to age-sex-matched volunteers. The severity of these conditions is found to be worse in subjects with moderate-severe skin disease, suggesting that the combination of severe skin inflammation and joint disease may be particularly atherogenic [32].

Individuals with arthritis are found to have a heightened risk of CVD, independently of obesity status, whereas antirheumatic drugs have a positive impact on reducing the risk [33]. This suggests that the onset of arthritis symptoms could serve as a critical point for healthcare providers to screen for latent CVD risk factors. By concurrently managing both arthritis and CVD risk factors, there is a potential to enhance the prognosis for both conditions.

Glycocalyx shedding: causes and consequences

Under pathological conditions such as the systemic chronic milieu in IA, the EG can undergo degradation, a process known as shedding. This leads to a loss of homeostatic protective functions and contributes to vascular dysfunction (Fig. 2).

Sheddases: key enzymes in EG shedding

EG shedding in IA is a complex process involving various enzymes known as "sheddases" [34]. Sheddases, a group of enzymes that facilitate the shedding of cell surface proteins, play a crucial role in the regulation of the endothelial EG. These enzymes, which include matrix metalloproteinases (MMPs), A disintegrin and metalloproteinase (ADAM) family, heparanase, and hyaluronidase, are responsible for the cleavage of core proteins and the degradation of the EG [35, 36]. The activity of sheddases is often upregulated in inflammatory conditions, leading to increased EG shedding. For instance, heparanase and hyaluronidase, key sheddases, are known to be upregulated in IA and contribute to EG degradation [37].

ADAMs and MMPs are proteolytic enzymes capable of cleaving and degrading the macromolecules comprising the glycocalyx. ADAMs, particularly ADAM17, have been implicated in EG shedding through their ability to cleave EG components such as syndecans and hyaluronan synthase 2 (HAS2), leading to the disruption of the EG structure. ADAM17, also known as tumor necrosis factor-alpha converting enzyme (TACE), is a key member of the ADAM family involved in the shedding of cell surface proteins and glycoproteins [38]. Its activation and subsequent proteolytic activity contribute to the shedding of EG components, compromising the integrity and function of the EG. MMPs, such as MMP-2 and MMP-9, have been shown to degrade EG components and contribute to glycocalyx shedding in various pathological conditions. The increased activity of MMPs in response to inflammation and oxidative stress can lead to the breakdown of the EG and impairment of endothelial function. The dysregulation of ADAMs and MMPs in glycocalyx shedding has been associated with endothelial dysfunction, increased vascular permeability, and inflammation [39]. This process results in the exposure of adhesion molecules and the release of chemokines, promoting leukocyte adhesion and extravasation, key steps in the initiation of atherosclerosis [40].

Heparanase and hyaluronidase, key sheddases, are known to be upregulated in IA and contribute to EG degradation [37, 41]. This process results in the exposure of adhesion molecules and the release of chemokines, promoting leukocyte adhesion and extravasation, key steps in the initiation of atherosclerosis [39]. Adhesion molecules, such as selectins and integrins, are also implicated in the process of EG shedding. These molecules mediate the adhesion and transmigration of leukocytes across the endothelium, a process that can lead to EG degradation. The exposure of adhesion molecules following EG shedding can promote further leukocyte adhesion, creating a vicious cycle of inflammation and EG degradation [36, 41].

Interplay between complement system and EG shedding

C3a and C5a are important components of the complement system, a part of the immune system involved in inflammation and immune responses. In the context of IA, C3a and C5a play significant roles in the pathophysiology and

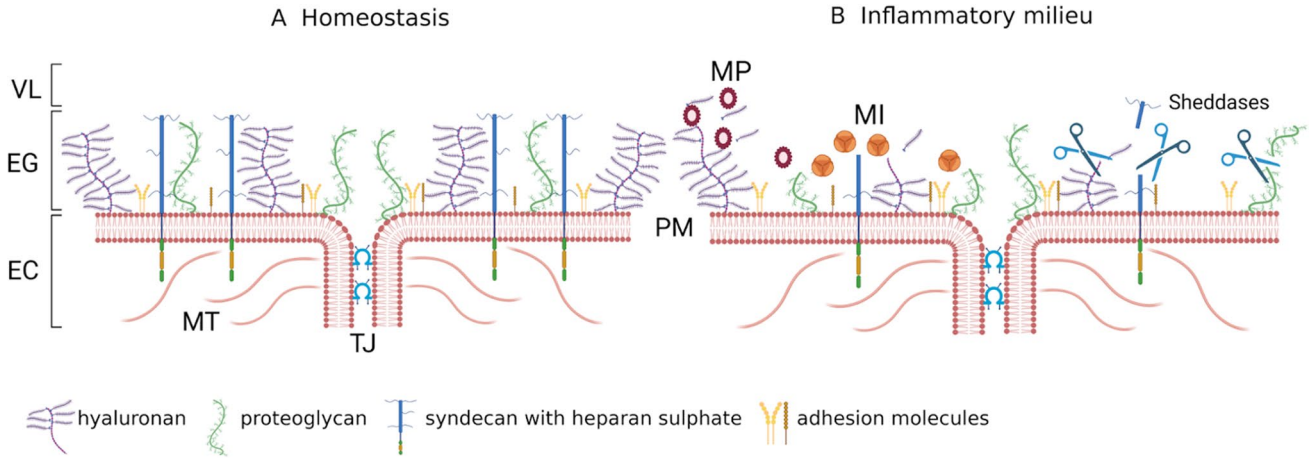

Fig. 2 Detailed depiction of the endothelial cell membrane with an attached glycocalyx under different conditions. Panel A: Homeostatic condition. The endothelial cell membrane is shown with an intact glycocalyx. The expression of adhesion molecules such as PECAM-1, ICAM-1, and VCAM-1 is minimal, reflecting the low level of cellular interactions in this state. Panel B: milieu present in inflammatory arthritis. The endothelial glycocalyx is shown under the influence of inflammatory mediators such as C-reactive protein and tumor necrosis factor, matrix metalloproteinases, and sheddases. These factors contribute to the degradation of the glycocalyx, leading to an increase in the expression of adhesion molecules. The damaged glycocalyx is represented as a sparse layer, indicating the loss of its protective function and the increased vulnerability of the endothelium. VL, vessel lumen; EG, endothelial glycocalyx; EC, endothelial cells; MT, microtubules; TJ, tight junction; PM, phospholipid endothelial cell membrane; MP, microparticles; MI, mediators of inflammation

progression of the disease, contributing to the inflammatory processes and immune dysregulation. They can stimulate the production of matrix MMPs and other proteolytic enzymes, which contribute to the degradation of cartilage [42]. Activation of this particular component of complement system has been shown to induce EG shedding and bind to their respective receptors on endothelial cells, triggering intracellular signaling pathways that lead to the activation of enzymes responsible for EG degradation, such as heparanase and hyaluronidase.

Furthermore, the membrane attack complex (MAC), the end product of complement activation, can cause direct damage to the endothelium and contribute to EG shedding. Therefore, complement activation and EG shedding represent interconnected processes in the pathogenesis of IA and other inflammatory conditions [43].

Implications of EG shedding in inflammatory processes

Syndecans, a family of transmembrane proteoglycans, are a major component of the endothelial EG. They play a crucial role in maintaining the structural integrity of the EG and mediating its various functions. Syndecans consist of a core protein with covalently attached heparan sulfate chains, which contribute to the negative charge and hydration of the EG, thereby influencing its barrier function and interaction with circulating cells and molecules. The shedding of syndecans from the EG is a key event that contributes to glycocalyx degradation and the subsequent onset of inflammation and vascular diseases. This shedding process is primarily mediated by sheddases, such as heparanase and MMPs, which cleave the syndecan core protein and release the ectodomains into the circulation [20, 44].

Interestingly, these shed syndecan ectodomains are not merely by-products of EG degradation, but can act as effector molecules themselves. They have been found to modulate various biological processes, including inflammation, coagulation, and vascular permeability. For instance, shed syndecan-1 ectodomains can bind to inflammatory cytokines and chemokines, thereby modulating their bioavailability and activity. They can also interact with growth factors and coagulation factors, influencing cell proliferation, tissue repair, and blood clotting [45].

Cathepsin, a lysosomal cysteine protease, has been implicated in the pathogenesis of IA. It is known to be involved in the degradation of extracellular matrix proteins and is overexpressed in synovial fibroblasts, the cells that line the joints. This overexpression is thought to contribute to the joint damage seen in these conditions by promoting the degradation of cartilage and bone [46]. In addition to its role in joint tissue degradation, studies have suggested that cathepsin may also be involved in the shedding of the EG, a protective layer on the surface of endothelial cells. While the exact mechanisms are still being elucidated, it is thought that cathepsin may contribute to glycocalyx shedding by degrading its protein components, leading to a loss of integrity and function [47].

Advancements in non-invasive imaging tools, such as GlycoCheck, have made it possible to directly measure EG shedding. By assessing the perfused boundary region, an indicator of EG health, these tools can provide valuable insights into the extent of EG shedding in IA patients [48, 49]. Further research into the mechanisms of endothelial EG shedding and its implications in IA and CVD could lead to novel therapeutic strategies and improved patient outcomes. Understanding the regulation and involvement of sheddases in EG degradation may provide valuable therapeutic targets for the treatment of IA and associated CVD, enhancing disease monitoring and evaluating the effectiveness of interventions.

Mediators of inflammation and microtubule dynamics

Microtubules, as integral components of the cellular cytoskeleton, are implicated in a myriad of cellular functions, encompassing cell division, intracellular transport, and the maintenance of cell structure and motility. Their significance becomes particularly pronounced in the context of IA, where they play a pivotal role in the migration and activation of immune cells.

Microtubules: role in cellular functions and disease processes

The chemotaxis of leukocytes, the primary mediators of the immune response, is heavily reliant on microtubules. The polarization of these cells and their subsequent movement towards inflammation sites is contingent upon the reorientation of the microtubule-organizing center. This reorientation facilitates the directed secretion of inflammatory mediators, thereby modulating the immune response. Moreover, microtubule dynamics are instrumental in regulating the stiffness of endothelial cells. These cells undergo extensive morphological changes during angiogenesis, a process integral to both the progression of atherosclerosis and healing. Atherosclerotic regions are often characterized by aberrant angiogenesis, a process governed by the intricate balance between microtubule polymerization and depolymerization. Disruption of microtubule dynamics in endothelial cells has been linked to the induction of a pro-inflammatory state and increased leukocyte adhesiveness, a critical step in the initiation of atherosclerosis. Thus, the role of microtubules extends beyond structural support, influencing key cellular processes and disease progression [50, 51].

EG-microtubule crosstalk: signaling and cellular processes

The EG serves as a crucial interface for maintaining vascular homeostasis. It is increasingly recognized that the EG can signal to the cell interior and influence the organization and dynamics of microtubules, which are key components of the cytoskeleton. The EG can modulate microtubule behavior through various signaling pathways. For instance, shear stress forces detected by the EG can activate integrins, which in turn can stimulate Rho GTPases such as RhoA and Rac1. These molecules are known to regulate microtubule stability and dynamics, thus influencing cell shape, polarity, and motility. Additionally, the EG can influence the activity of microtubule-associated proteins (MAPs), which can stabilize or destabilize microtubules. Moreover, the EG can also influence the activity of endothelial nitric oxide synthase (eNOS), which produces nitric oxide (NO), a molecule known to influence microtubule dynamics. NO can nitrosylate tubulin, the building block of microtubules, leading to changes in microtubule stability. Therefore, through these and potentially other mechanisms, the EG can signal to microtubules and influence their organization and dynamics, thereby affecting various cellular processes such as cell shape changes, migration, and response to mechanical forces. However, the precise mechanisms of EG-microtubule crosstalk are still not fully understood and are an active area of research [52, 53].

Mechanotransduction, by the EG, is the process of converting mechanical stimuli into biochemical signals. This mechanotransduction is particularly important in the context of shear stress, a force exerted by blood flow on the endothelial cells lining the blood vessels. The EG, particularly its component heparan sulfate (HS), acts as a mechanotransducer, transmitting the shear stress signals to the endothelial cells. This mechanotransduction process regulates various cellular functions, including the expression of angiopoietin-2 (Ang-2), a key mediator of vascular disease. Cleavage of HS from the EG impairs shear stress-related AMPK/FoxO1 signaling, leading to increased expression of Ang-2. This finding suggests that the disruption of the EG, specifically the cleavage of HS, can alter the mechanotransduction process, leading to dysregulated cellular responses such as increased Ang-2 expression. This process could potentially contribute to the pathogenesis of sepsis and other vascular diseases. Furthermore, the study found that the plasma levels of HS, a marker of EG degradation, peaked before the plasma levels of Ang-2 in both children and mice with sepsis. This observation suggests a temporal association between EG damage and the subsequent upregulation of Ang-2, further highlighting the potential mechanistic link between EG injury and vascular disease progression [54, 55].

TNF-α and CRP: impact on microtubule dynamics and EG integrity

Upregulation and overexpression of tumor necrosis factor alpha (TNF-α) is present in IA by various distinct cell types such as macrophages, myeloid cells, and T and B lymphocytes among others that modulate disease development through diverse mechanisms [56]. TNF-α is a crucial participant in the initiation of multiple molecular cascades and maintenance of systemic chronic inflammation. Of particular interest is the exertion of direct effects on cell microtubule and EG dynamics. It exerts direct effects on cell microtubule and extracellular matrix dynamics, including EG degradation, induction of cytoskeleton destabilization, and the formation of intercellular gaps [57, 58]. Elevated levels of osteoprotegerin (OPG), a member of the TNF receptor superfamily, are detected in sera from patients with IA [59, 60]. In the past OPG has been portrayed as an anti-resorptive cytokine but now its function is acknowledged in the pathophysiology of vascular, tumor, and immune diseases. EG and other extracellular and vascular components like syndecan-1, von Willebrand factor/factor VIII complex, heparin, RANKL, glycosaminoglycans, and proteoglycans can act as ligands for OPG and promote cell adhesion and migration. It takes part in bone metabolism regulation and atherosclerosis initiation and progression. Increased circulation of OPG is independently positively associated with higher artery calcium and subclinical atherosclerosis [61–63].

C-reactive protein (CRP) is a prototypical marker of inflammation and has been implicated in direct mediation of lipid uptake, complement activation, expression of adhesion molecules, monocyte infiltration, NO inhibition, endothelial dysfunction, and atherogenesis [64]. CRP has widespread clinical use in rheumatology for monitoring disease activity and therapeutic outcomes [65]. It has been observed that CRP in a dose-dependent matter impairs EG structural and functional integrity inducing endothelial dysfunction [66]. Elevated constituents of the EG, suggestive of shedding like hyaluronan, syndecan, and heparan sulfate, have been detected and correlated with IL-6 and CRP in sepsis. Although there is a bacterial etiology, the activation of similar inflammatory pathways can be extrapolated [67]. CRP can also bind to low-density lipoprotein (LDL), and may play a role in the development of atherosclerosis by promoting the uptake of LDL by macrophages in the arterial wall, leading to the formation of foam cells, a hallmark of atherosclerotic plaques [68]. The NLRP3 inflammasome is a multi-protein complex component of the innate immune system and is implicated in the pathogenesis IA. Activation of the NLRP3 inflammasome leads to the release of pro-inflammatory cytokines like IL-1β and IL-18, contributing to chronic inflammation in these conditions. Increased NLRP3 expression

and inflammasome activation have been observed in the synovium and skin lesions [69, 70]. In the context of atherosclerosis, activation of the NLRP3 inflammasome in macrophages and endothelial cells can contribute to plaque formation and progression. NLRP3 inflammasome activation leads to increased production of pro-inflammatory cytokines and chemokines, promoting leukocyte adhesion and extravasation, and disrupting contractility and intercellular connections. This can lead to endothelial dysfunction. In addition, NLRP3 inflammasome activation can lead to pyroptosis, a form of inflammatory cell death, further contributing to plaque instability and the risk of plaque rupture [71].

Cellular interactions

IA is characterized by a complex interplay of cellular and molecular events that contribute to the pathophysiology of the disease. Among these, the role of various immune cells, including macrophages, thrombocytes, and neutrophils, is of particular interest. These cells not only contribute to the inflammatory milieu characteristic of IA but also play a crucial role in the process of EG shedding.

Thrombocytes, traditionally known for their role in hemostasis, have been implicated in chronic inflammatory processes as well. In a hypercoagulable state, often promoted by chronic inflammation, there is an excessive activation of the coagulation cascade, coupled with a chronic inhibition of the anti-coagulation and fibrinolytic pathways. In this state they can contribute to inflammation through the release of pro-inflammatory mediators, creating a feed-forward loop that further exacerbates the inflammatory response. The interaction of platelets with the endothelium, facilitated by selectins and other adhesion molecules, is also critical for immune cell recruitment and activation. This process, known as margination, plays an essential role in inflammation. These cellular interactions can upregulate immune responses, further promoting the chronic inflammation typically seen in IA and cardiovascular disease [72, 73]. Macrophages, as key immune cells, play a significant role in the pathogenesis of IA and contribute to the process of endothelial EG shedding and endothelial dysfunction. In IA, macrophages infiltrate the synovium and become activated, releasing pro-inflammatory cytokines such TNF-α and IL-1β. These cytokines promote the degradation of the EG. The loss of the EG exposes the underlying endothelial cells and their adhesion molecules, facilitating the adhesion and transmigration of leukocytes, including macrophages, into the inflamed joints. Furthermore, macrophages themselves can directly contribute to EG shedding through the release of MMPs, including MMP-2 and MMP-9, which degrade the EG components. This disruption of the EG integrity and subsequent endothelial dysfunction further exacerbate the inflammatory process and contribute to the pathophysiology of CVD [39, 74–76].

miRNA

Epigenetic mechanisms, specifically involving microRNAs (miRNAs), are increasingly implicated in the pathophysiological processes underlying both IA and CVD. miRNAs are emerging as not only promising biomarkers for disease onset, activity, progression, and therapeutic response but also as pivotal regulators in the intercellular communication network displaying hormone-like activities [77–79]. However, the precise transport mechanisms by which miRNAs traverse the cell membrane remain elusive. Several theories exist, including clathrin or lipid raft endocytosis, phagocytosis, direct membrane fusion, and toll-like or specific miRNA receptors [80]. In normal conditions the sialic acid-containing glycoproteins of the EG and its anionic effects impede the approach of exogenous nucleic acids [81]. It can be speculated that inflammatory driven EG shedding can escalate miRNA transport and expression. Even after adjusting for traditional risk factors, a plasma miRNA panel demonstrates a high prediction rate for coronary artery calcium prevalence in RA, indicating a direct role of miRNAs in the cardiovascular complications of RA [82]. It is now evident that miRNAs engage in intricate molecular circuits that influence disease pathology. Altered expression of miRNAs in a specific tissue due to disease state can inadvertently trigger systemic damaging effects, thereby instigating comorbidities [83]. MiRNAs regulate the production of pro-inflammatory cytokines such as TNF-α and IL-1β. This can contribute to cardiovascular pathology by promoting endothelial dysfunction, vascular inflammation, and atherogenesis (Fig. 3). In experimental models, it has been demonstrated that inhibition of TNF-α prevents specific miRNA upregulation and subsequently improves vasorelaxation, hinting at the vast therapeutic potential of targeting miRNA pathways [84]. Additionally, high-intensity interval training has been shown to induce changes in the EG and associated miRNAs, which may serve as a tool for monitoring early vasculoprotective adaptations to physical activity [85].

Dysregulated lipid metabolism

Alterations in lipid profiles, including increased levels of total cholesterol, low-density lipoprotein (LDL), and triglycerides, as well as decreased levels of high-density lipoprotein

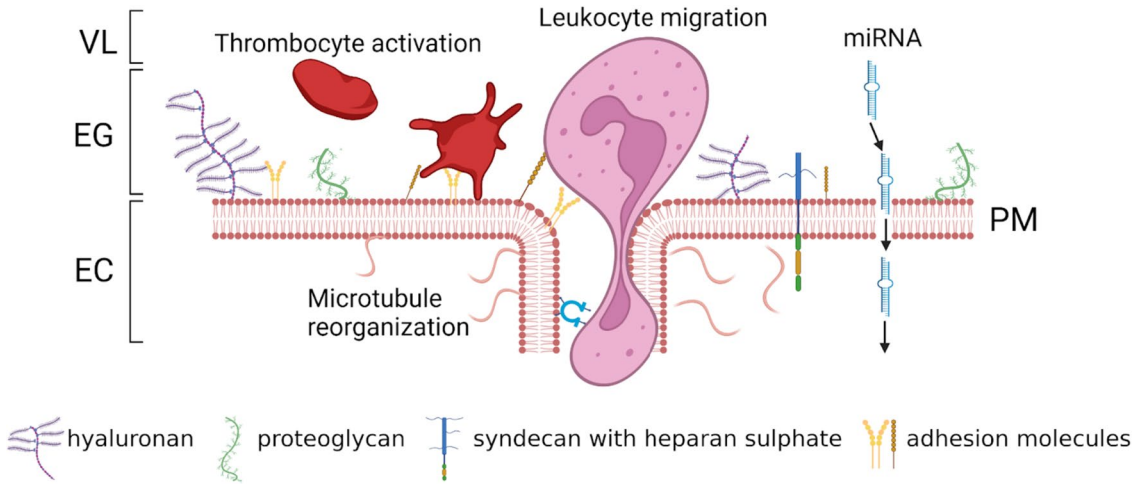

Fig. 3 Consequences of glycocalyx degradation on endothelial cell function and cellular interactions. The degradation of the glycocalyx leads to microtubule reorganization within endothelial cells, resulting in decreased junctional integrity. This facilitates increased leukocyte adhesion and migration, platelet margination and activation, and enhanced microRNA traffic. These changes in endothelial cell function and cellular interactions are key preluding factors to the development of atherosclerosis, underscoring the critical role of the endothelial glycocalyx in vascular health. VL, vessel lumen; EG, endothelial glycocalyx; EC, endothelial cells; PM, phospholipid endothelial cell membrane

(HDL), have been observed in patients with IA. These lipid abnormalities are believed to result from chronic inflammation, immune dysregulation, and systemic effects of the diseases. The dysregulation of lipid metabolism in IA can have significant implications for cardiovascular health. Elevated levels of LDL cholesterol and triglycerides, along with reduced levels of HDL cholesterol, contribute to the development of atherosclerosis, a major cardiovascular risk factor. Furthermore, the presence of chronic inflammation in IA can further exacerbate lipid abnormalities and promote endothelial dysfunction, oxidative stress, and plaque formation. The dysregulated lipid metabolism in IA is not only linked to cardiovascular risk but also influences disease activity and progression. Lipid mediators, such as pro-inflammatory cytokines and eicosanoids derived from arachidonic acid, play a role in the inflammatory processes underlying IA. Dysfunctional lipid metabolism can perpetuate the inflammatory response, leading to joint damage and disease progression [86]. Understanding the interplay between dysregulated lipid metabolism and IA can provide valuable insights into the mechanisms driving both the joint pathology and cardiovascular complications associated with these conditions. Its impact on the EG has been investigated. Disturbed flow-induced changes to the EG components have been shown to correlate with heterogeneity in the cellular uptake of oxidized LDL and can initiate pro-atherosclerotic endothelial cell behavior. The lack of EG in cells containing cytoplasmic oxidized LDL indicates a link between EG degradation and the internalization of oxidized LDL. These findings suggest that the dysregulation of lipid metabolism and disturbed flow can contribute to GCX dysfunction, promoting the initiation and progression of atherosclerosis [87, 88]. Oxidized LDLs bind to lectin-like receptor (LOX-1) in endothelial cells, triggering signaling pathways involved in the synthesis of chemokines and cell adhesion molecules. Additionally, class B scavenger receptor CD36 mediates the uptake and degradation of oxidized LDL by macrophages, transforming them into foam cells, a hallmark of atherosclerotic plaque formation [89]. TNF has been shown to upregulate LOX-1 expression in endothelial cells, enhancing the uptake of oxidized LDL [90]. Understanding the intricate interplay between lipid metabolism, EG integrity, and atherosclerosis can provide valuable insights into the mechanisms underlying CVD and IA. Further research is needed to explore the precise mechanisms by which dysregulated lipid metabolism influences EG function and the progression of atherosclerosis.

Microparticles

Microparticles: origins, composition, and functions

Another key "participant" that could play a critical role in the pathogenetic process of atherosclerosis are microparticles (MPs) [91]. MPs are vesicle-like membrane fragments of the cell membrane, 0.1 to 1.0 μm in size, released after apoptosis or cellular activation of many cell types, including leukocytes, platelets, ECs, erythrocytes, and SMCs. MPs can be found in plasma, blood, and others. They express various molecules that provide information about the origin of their parent cells and may also express other markers of cellular activation [92].

The majority of circulating MPs originate from platelets and megakaryocytes, which have multiple receptors on their surface. The most expressed surface markers are CD41, CD42b, CD41a, CD61, CD62P, and AA. They influence inflammation, thrombosis, immunoregulation, and transmission of biological information, mainly due to the content of messenger RNA (mRNA), micro RNA (miRNA), and bioactive lipids through fusion or internalization with target cells and cytoplasmic and membrane protein from platelets [93]. MPs are capable of regulating a diverse series of events that result in cell proliferation, angiogenesis, immune response, and coagulation [94, 95].

Microparticles and atherosclerosis: implications for plaque formation

MPs have the ability to regulate cytokines and intercellular adhesion molecule-1 expression, which induces the migration of leukocytes to the vascular wall, which in turn leads to the initiation of atherosclerotic plaque formation [96]. In addition, MPs mediate inflammation by reducing on NO levels [97]. MPs contribute to platelet adhesion upon exposure to the subendothelial matrix [98]. Furthermore, they activate corneal division of smooth muscle and the activation of platelets and endothelial cells through the activation of bioactive lipids, which leads to the production of cytokines and tissue factors [99]. Another important aspect for the involvement of MPs in the atherosclerotic process is their proven presence in atherosclerotic plaques [100].

MPs also express target level markers, developing the markers vascular adhesion molecule-1 (VCAM-1), intertarget adhesion molecule-1 (ICAM-1), VE-cadherin (CD144), PECAM-1 (platelet-endothelial cell adhesion molecule 1/CD31), αv integrin, endoglin (CD105), melanoma endothelial adhesion molecule (MCAM) (CD146), VEGF (vascular endothelial growth factor) receptor 2, von Willebrand factor, E-selectin, and others. Many of these markers are both true soluble molecules and by expression of these different markers of target damage on the endothelial MPs may reflect the degree of endothelial dysfunction [101, 102]. Szotowski et al. have ascertain evidence of the link between the formation of reactive oxygen species (ROS) and the production of tissue factor familiar with EMP. Inhibition of ROS production was associated with lower expression of thrombogenic EMP, highlighting the positive relationship between ROS and the formation of thrombogenic EMP [103]. High levels of ROS can disrupt the redox balance of cells, causing oxidative stress and disruption of cell membrane organization, then releasing membrane microparticles initiating complete apoptosis [104].

Microparticles in IA: endothelial dysfunction and cardiovascular risk

MPs can be significantly elevated in patients with inflammatory rheumatic diseases and they have been considered as factors playing a role in the pathogenesis of some rheumatic diseases [105]. The positive correlation between the degree of RA activity and the levels of MPs has been investigated [106]. MPs in patient sera with IA can induce activation of endothelial cells, mainly those in the macrovasculature. This response is evidenced by an increase in the expression of the adhesion molecules CD54 and CD102; the production of inflammatory mediators, such as IL-6, CCL2, and CCL5; and by the adherence of monocytes to these cells. These vesicles also promote significant changes in the structure of endothelial monolayers, which reduces cell–cell adhesion, depolymerizes actin filaments, and induces cell death. All these changes can contribute to the increase in endothelial permeability observed in the response to MPs, which leads to the beginning of the formation of the atherosclerotic process [107]. MPs may represent a link between autoimmune responses and endothelial dysfunction by expressing TNF-α, altering endothelial apoptosis and autophagy [108].

Emerging evidence underscores the pivotal role of TNF-α, expressed on the surface of microparticles, in modulating endothelial cell function in rheumatoid arthritis patients. MPs isolated from RA patients have been shown to exercise pathological effects on endothelial cells via surface-bound TNF-α. Remarkably, upon exposure to a TNF-α inhibitor, which likely binds to and blocks the action of surface-bound TNF-α, this detrimental impact on endothelial cells is significantly mitigated. This suggests the existence of a novel mechanism of endothelial injury that is mediated by MPs. The findings also reaffirm the protective benefits of anti-TNF therapy against endothelial damage in the context of RA patients. The interactions between MPs, endothelial cells, and the inflammatory milieu, particularly in conditions such as RA, constitute a critical area of investigation. Furthermore, these findings may have implications for the broader understanding of endothelial glycocalyx degradation, given the central role the glycocalyx plays in preserving endothelial integrity in the face of inflammatory assault [109].

Continuing the exploration of MPs role in IA, the study conducted by Sari et al. [110] provides further insight. The authors measured the levels of two specific types of MPs in men with AS, endothelial microparticles (EMPs) and platelet microparticles (PMPs). Elevated levels of both EMPs and PMPs were observed in the patients, indicating the potential involvement of these MPs in the pathogenesis of AS and possibly other IA. Endothelial microparticles, derived from endothelial cells, are particularly intriguing as they are

known to carry various bioactive molecules and are considered as markers of endothelial dysfunction. Their presence in increased quantities could indicate ongoing endothelial damage or activation, which is a key event in the pathogenesis of atherosclerosis. On the other hand, PMPs, as products of activated or apoptotic platelets, are known to exhibit procoagulant properties and can contribute to a hypercoagulable state, further complicating the cardiovascular risk profile of IA patients. Interestingly, the study also noted a positive correlation between the levels of EMPs and disease activity in AS, suggesting that monitoring EMP levels could potentially serve as a marker for disease activity and cardiovascular risk in these patients [110].

The complex relationship between IA and cardiovascular pathology is significantly influenced by the release and activity of MPs, particularly PMPs and EMPs. Successful treatment with anti-TNF-α significantly reduced circulating MPs, including PMPs and EMPs, in patients with severe psoriasis [111]. Elevated PMP levels were reported in psoriasis patients without concurrent cardiovascular disease. These levels were directly proportional to the degree of inflammation and disease severity, providing a potential link between systemic inflammation seen in IA and the increased cardiovascular risk [112]. Interestingly, PMPs were also found to negatively impact the endothelial glycocalyx area and downregulate the expression of glypican-1 and occludin, crucial players in maintaining vascular homeostasis [113].

MPs, bearing bioactive molecules on their surface, play a critical role in the intercellular communication network, influencing endothelial function in the context of IA. In light of these findings, the study of MPs presents promising opportunities for unravelling the intricate pathways contributing to cardiovascular pathology, and for the potential development of novel therapeutic strategies.

Clinical implications

Risk prediction models that account for traditional CVD risk factors suggest that the systemic inflammation inherent to IA, rather than the specific type of arthritis, may be the primary driver of the increased CVD risk in these patients [5]. However, it is important to note that the manifestation of CVD can vary among different types of IA, likely due to their unique pathophysiological characteristics. PsA patients often present with metabolic syndrome, a known risk factor for CVD, which is less commonly observed in RA or AS patients [114]. Additionally, the concomitant hyperuricemia observed in PsA patients may have significant implications for cardiovascular health. In an animal model, uric acid has been found to induce endothelial-to-mesenchymal transition, a process often associated with endothelial dysfunction and cardiovascular disease. Concurrently, uric acid also prompts the shedding of the EG, mediated by MMPs. These mechanisms collectively suggest a potential pathway by which hyperuricemia could exacerbate the cardiovascular risk associated with PsA [115]. In PsA, an intriguing hypothesis known as the Koebner phenomenon has been proposed, which suggests that post-traumatic events can lead to the new onset of skin psoriasis or arthritis. This hypothesis can be extended to vascular trauma, where an initial injury could potentially exacerbate, through an immune hyper-reaction, into an atherosclerotic lesion. This process could lead to endothelial dysfunction and calciphylaxis. However, this remains speculative and further research is needed to confirm this hypothesis and to understand its potential implications for cardiovascular health in PsA patients [116–118].

Uveitis, an intraocular inflammatory condition commonly associated with SpA, has been identified as a potential predictor of atherosclerosis-related CVD. A systematic review and meta-analysis found that uveitis was linked to a 1.49-fold increase in atherosclerosis-related CVD in AS patients [119]. The relationship between AS, and large-vessel vasculitis (LVV) such as aortitis, is a topic of ongoing research. Aortitis, a form of LVV, involves inflammation of the aorta and can lead to serious complications such as aneurysm or aortic dissection. In the context of AS, this association is particularly noteworthy as it suggests a potential overlap in the pathophysiological mechanisms of these conditions. Patients with coexisting SpA and LVV were younger and had higher CRP levels at presentation, indicating a more severe inflammatory response [120]. While the association between IA and CVD is well-established, the specific pathophysiological changes underlying this association in different types of IA remain to be fully elucidated. The observed variations in cardiovascular manifestations among different types of IA suggest that unique pathophysiological mechanisms may be at play in each condition. Further research is needed to fully understand these mechanisms and to develop targeted strategies for cardiovascular risk reduction in patients with different types of IA.

The assessment of CVD risk is a crucial strategy in managing patients with IA. Conventional algorithms such as Framingham and SCORE often underestimate the risk in many RA patients, providing a suboptimal risk stratification and consequently limiting proper clinical management, especially in those categorized as having a low to intermediate risk. Several CV imaging techniques have been reported as being useful in assessing CVD involvement, both for screening, diagnosis, and follow-up. However, it is still unclear which methods should be used to evaluate the CV risk in IA patients in clinical practice, taking into account costs and availability [121].

Conclusion

This review has underlined the intricate interactions between IA and CVD, demonstrating the impact of IA-induced chronic inflammation not only on local joint pathology but also on systemic vascular health. The EG, suffering degradation under chronic inflammation, emerges as a crucial element in this scenario, contributing to endothelial dysfunction and thus paving the way for CVD development and progression. The molecular pathways at play, involving enzymatic actions of heparanase and hyaluronidase, chemotaxis, and various immune cells, present both enlightening insights into disease pathogenesis and potential therapeutic targets. Furthermore, the advent of novel tools enabling non-invasive, direct assessment of EG degradation marks a significant step forward in tracking disease progression and gauging the efficacy of treatment modalities. Hence, to further our therapeutic strategies and improve patient outcomes, it is imperative to deepen our understanding of the dynamic interactions between IA, EG degradation, and endothelial dysfunction. Future research should maintain its focus on elucidating these links, discovering novel therapeutic targets, and enhancing disease progression monitoring tools.

Acknowledgements Figures were created with BioRender.com.

Author contribution All authors have played a substantial role in shaping the study's conception and design. They have actively engaged in acquiring and analyzing the data, as well as interpreting the results. Furthermore, the authors have collectively contributed to both the initial draft and subsequent critical revisions of the manuscript, providing their invaluable insights. Each author has granted their final approval for the manuscript's submission to this journal, demonstrating their commitment to taking responsibility for all aspects of the work and being accountable for any potential concerns that may arise. Lastly, all contributing authors have meticulously reviewed and endorsed the final version of the manuscript and take full responsibility for the integrity and accuracy of all aspects of the work.

Declarations

Disclosures None.

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