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Matricellular proteins in atherosclerosis development

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Abstract

The extracellular matrix (ECM) is an intricate network composed of various multi-domain macromolecules like collagen, proteoglycans, and fibronectin, etc., that form a structurally stable composite, contributing to the mechanical properties of tissue. However, matricellular proteins are non-structural, secretory extracellular matrix proteins, which modulate various cellular functions via interacting with cell surface receptors, proteases, hormones, and cell-matrix. They play essential roles in maintaining tissue homeostasis by regulating cell differentiation, proliferation, adhesion, migration, and several signal transduction pathways. Matricellular proteins display a broad functionality regulated by their multiple structural domains and their ability to interact with different extracellular substrates and/or cell surface receptors. The expression of these proteins is low in adults, however, gets upregulated following injuries, inflammation, and during tumor growth. The marked elevation in the expression of these proteins during atherosclerosis suggests a positive association between their expression and atherosclerotic lesion formation. The role of matricellular proteins in atherosclerosis development has remained an area of research interest in the last two decades and studies revealed these proteins as important players in governing vascular function, remodelling, and plaque formation. Despite extensive research, many aspects of the matrix protein biology in atherosclerosis are still unknown and future studies are required to investigate whether targeting pathways stimulated by these proteins represent viable therapeutic approaches for patients with atherosclerotic vascular diseases. This review summarizes the characteristics of distinct matricellular proteins, discusses the available literature on the involvement of matrix proteins in the pathogenesis of atherosclerosis and suggests new avenues for future research.

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Author's contribution:NP, IK, and BS contributed to manuscript writing, editing, and proofreading. RVA contributed to manuscript writing. Hence, all authors have made a substantial contribution to the work and approved it for publication.

Declaration of Competing Interest

All authors declare that they have no competing interests.

Keywords

Atherosclerosis; matricellular proteins; inflammation; vascular smooth muscle cells; macrophages

1. Introduction

Although great progress has been made in the field of medicine, cardiovascular disease (CVD) remains the leading cause of morbidity and mortality globally [1]. Approximately, 19 million deaths worldwide were associated with CVD in the year 2020, which indicates an almost 18.7% rise in CVD-related mortalities in comparison to the year 2010 [2]. In the year 2020, between the age of 30–79 years, approximately 28% people (over a billion) had abnormal carotid intima-media thickness of 1 mm or above, and 21% people (approximately 816 million) and 1.5% individuals (approximately 58 million) were detected with carotid plaques and carotid stenosis, respectively. The incidence of these pathologies increases with age, and men are more susceptible to developing these diseases than women [3]. The World Health Organization in 2019 predicted that by 2030, almost 23.6 million people will die annually due to CVD.

The underlying cause of the majority of CVD is atherosclerosis, in which lipid accumulation takes place in the middle- and large-sized arteries. This lipid accumulation causes inflammation that ultimately may lead to clinical complications, myocardial infarction (MI), and stroke. Structurally, blood vessels are made up of three layers namely tunica intima, tunica media, and tunica adventitia. Tunica intima, the innermost layer, is constituted by a single layer of endothelial cells that facilitate the frictionless flow of blood, while tunica media is made up of elastic and vascular smooth muscle cells (VSMCs) that regulate the diameter of blood vessels [4]. Adventitial fibroblasts, immune cells, blood capillaries, and lymphatic vessels intricated together with ECM form tunica adventitia [5]. Atherosclerosis is characterized by intimal thickening and the formation of plaques, particularly at sites with endothelial cell injury and disturbed laminar flow [6]. It is mainly affected by the nature of the blood flow, as the regions that are subjected to laminar shear stress are protected from atherosclerosis and endothelial cells present at those sites have higher expression of atheroprotective genes [7]. Various inflammatory factors interact with vascular cells like endothelial cells, smooth muscle cells (SMCs), adventitial fibroblasts, resident macrophages, etc., and drive the progression of this devastating disease [8]. The abnormalities in the ECM structure and cellular behaviour lead to different vascular modalities. Matricellular proteins, a family of non-structural proteins that regulate the function of various ECM proteins, have emerged as important players in regulating vascular structure and function [9]. Over the past years, the involvement of various matricellular proteins in atherosclerosis development has been investigated. In this review, we will discuss the types of various matricellular proteins and summarize their role in the pathogenesis of atherosclerosis.

2. Development of atherosclerosis

The formation of fatty streaks is the first step in the development of atherosclerosis. It begins in the early ages usually in childhood and adolescence. In the subendothelial space and

underlying smooth muscles, smaller cholesterol crystals start to deposit which leads to the initiation of plaque formation. Damage to the endothelial layer of arteries due to high blood pressure, smoking, elevated levels of circulating lipoproteins and diabetes makes the intimal layer leaky, which promotes the transport of plasma low-density lipoprotein (LDL) and TG-rich lipoproteins to the subendothelial space either by trans-endothelial transport or diffusion at cell-cell junctions [10, 11] and these lipids undergo oxidation. This leads to the secretion of various proinflammatory molecules and increased expression of adhesion molecules on endothelial cells, which attract immune cells including T cells, neutrophils, monocytes, and mast cells, etc. [12, 13]. Monocytes bind to activated endothelial cells, transmigrate across the intima, and get differentiated into macrophages. These macrophages phagocytose lipids and become cholesterol-lengorged macrophages or foam cells. Further, in response to proinflammatory molecules and chemokines, VSMCs in the media transform from a contractile to a proliferative state and migrate into the intima, and subendothelial space, which leads to the formation of bulge resulting in the reduction of blood flow [14]. The continuous accumulation and coalescence of lipids lead to cell apoptosis and necrosis, which distorts and later disrupts the normal structure of intima. Failure to remove apoptotic cells results in the formation of lipid-rich necrotic cores, which is covered by fibrous cap [15]. In advanced atheroma, unchecked activity of proteolytic enzymes causes the weakening of the fibrous cap at certain places. This increases the chances of plaque rupture, thrombus formation, and blockage of blood supply to the heart or brain [15, 16]. Laboratory studies and clinical observations have greatly advanced our knowledge regarding the mechanisms involved in the pathogenesis of atherosclerosis. The pathogenesis of atherosclerosis has been reviewed earlier [17–20].

3. Matricellular proteins

The historic concept of “matricellular” was first given by Bornstein et al. while working on two novel proteins namely thrombospondin 1 (THBS1) and SPARC, which later became prototype members of this family known as matricellular proteins [21]. The term “matricellular” was coined in the year 1995 and consists of proteins that are a part of the ECM. ECM acts as a critical niche that regulates various cellular processes including survival, proliferation and migration, and thus contributes to the fundamental physiologic processes such as development, tissue homeostasis, and tissue remodeling [22]. This dynamic nature of ECM is regulated by secretory non-structural matricellular proteins in contrast to the classical ECM proteins such as collagens, fibronectin and laminin, etc., that play structural roles [23, 24]. Matricellular proteins modulate various cellular functions via interacting with cell surface receptors, proteases, hormones, and cell-matrix [25]. These proteins contain domains, which can enzymatically alter matrix components, modulate or sequester the activities of various growth factors. They are known to serve by bridging the functional gap between growth factors, proteases, cytokines, and macromolecules, and eventually function as modulators and adaptors of cell-matrix interactions [26–28]. The members of this family include thrombospondins, CCN proteins, SPARC, periostin, osteopontin, tenascins, etc. [29–32].

4. Matricellular proteins in atherosclerosis

Most of the matricellular proteins have higher expression during embryogenesis, which diminishes abruptly after birth and becomes low to absent during normal adult life. Their expression again upregulates during tumor growth, vascular pathologies and after tissue injury [31], suggesting their essential role in the migration and proliferation of malignant cells, wound healing, and ECM remodeling. In this section, we will describe the scientific evidence for the presence and function of various matricellular proteins involved in the pathogenesis of atherosclerosis (Table 1 and Fig. 1).

4.1. Thrombospondins (THBSs)

In the year 1978, Lawler et al. characterized, decoded the microscopic appearance and the subcellular locations of THBS proteins [33]. The THBS family consists of the 5 subtypes viz THBS1 to 5 based on their molecular architecture and oligomerization status, which are encoded by five distinct genes namely *THBS1* to *5* [34]. THBS1 is the most studied among all THBS proteins and plays significant roles in inflammatory responses, platelet aggregation, regulation of angiogenesis during tumor growth and wound healing. Most of these properties are also shared by THBS2 [35, 36]. The last member, THBS5 also called as cartilage oligomeric matrix protein (COMP) is involved in chondrocyte differentiation, attachment and in assembling cartilage ECM complex [37]. THBS1 and THBS2 function by binding to various receptors including syndecans [38, 39], LRP-1 [39], CD36 [40], CD47 [41], calreticulin [42] and integrins (α9β1, α6β1, αvβ3 and αIIββ3) [43–47]. On the other hand, THBS4 binds to CD44 [48] and THBS5 modulates cellular processes via binding to integrins (α7β1, αvβ3, α5β1, α5β3) [49, 50] and CD47 [51].

4.1.1. Thrombospondin 1 (THBS1): THBS1 levels are low in healthy blood vessels; however, elevated THBS1 expression has been associated with CVD including injury-induced neointima formation and atherosclerosis [52–54]. After vascular injury, the expression of Thbs1 was found to be elevated in diabetic rats [55]. Consistently, the blockade of Thbs1-mediated signaling increased re-endothelialization and decreased neointima formation in the carotid arteries of rats following balloon-induced injury [56]. These studies have pointed out that inhibition of Thbs1-mediated signaling may be therapeutically beneficial in vascular injury-induced neointima formation. On the other hand, *Apoe*$^{-/-}$/*Thbs1*$^{-/-}$ double knockout mice were observed to have increased atherosclerotic plaque maturation compared with control mice; however, this increase was observed only in the advanced stage of atherosclerosis [57]. In the initial stage, loss of *Thbs1* reduced atherosclerotic lesion formation, while in the advanced stage, *Thbs1* deletion was associated with elevated inflammation, defective phagocytosis and enhanced ECM remodeling that caused accelerated plaque maturation and necrosis [57].

Ganguly et al. reported reduced atherosclerotic plaque area and decreased collagen accumulation in aortic roots of *Apoe*$^{-/-}$/*Thbs1*$^{-/-}$ double knockout mice compared with *Apoe*$^{-/-}$ mice after leptin stimulation [58]. Further, the deletion of *Thbs1* in mice significantly decreased disturbed flow-stimulated carotid artery stiffness in comparison to wild-type controls, indicating that disturbed flow promotes arterial stiffening through

Thbs1-mediated signal transduction [59]. Moreover, hypoxia as found in atherosclerotic arteries has been shown to upregulate THBS1 expression in coronary artery SMCs, which in turn promotes their migration. This migration-stimulating effect of hypoxia was inhibited with THBS1-neutralizing antibody treatment, suggesting the involvement of THBS1 in the pathogenesis of atherosclerosis [60, 61]. Roth et al. demonstrated that THBS1-neutralizing antibody blocks PDGF- and cholesterol-stimulated aortic SMC proliferation, hinting the role of THBS1 in PDGF- and cholesterol-stimulated aortic SMC proliferation [62]. THBS has also been shown to bind with very-low-density lipoprotein (VLDL), which may facilitate THBS and VLDL incorporation into nascent atherosclerotic plaques [63].

THBS1 induces its downstream effects via binding to its cognate receptor CD47 (also known as the integrin-associated receptor) [41] and governs leukocyte function, vascular resistance, and intracellular signal transduction in endothelial cells and VSMCs [64]. It inhibits endothelial nitric oxide (NO) production, regulates vascular tone, and maintains systemic blood and cardiac dynamics under stress [65–68]. In addition, THBS1-CD47 signaling regulates thrombosis/hemostasis, immune responses, and mitochondrial function [69]. In VSMCs, THBS1-mediated CD47 activation stimulates Nox1-derived reactive oxygen species production, which inhibits VSMC-dependent vasorelaxation and induces vascular dysfunction [70]. It also enhances fluid-phase phagocytosis of LDL by macrophages and causes foam cell formation, a key characteristic of atherogenesis (Fig. 2a). In macrophages, THBS1-induced Nox1 activation stimulates dephosphorylation of actin-binding protein cofilin leading to cytoskeletal rearrangements and increased LDL uptake [71]. LIM-kinases and testicular protein kinases are known to cause cofilin inactivation by phosphorylating it at Ser-3 residue. On the other hand, slingshot protein phosphatases (SSH) dephosphorylate cofilin to induce its activation and regulate actin polymerization [72]. Contrary to the effects of THBS1 on cofilin activation in macrophages, VSMC-specific deletion of *Thbs1* in mice reduced cofilin phosphorylation via upregulating SSH1 protein expression, improved mechanotransduction, restored elastic lamina smooth muscle cell connections and decreased thoracic aortic aneurysm formation, suggesting the detrimental role of Thbs1 in the pathogenesis of thoracic aortic aneurysm [73]. In another study, Yamashiro et al. reported upregulated Thbs1 expression in VSMCs following mechanical stress and demonstrated that Thbs1 via binding to cell surface integrin $\alpha v\beta 1$ aids in the maturation of the focal adhesion-actin complex, reduces small GTPase Rap2 activity, promotes nuclear shutting of Yes-associated protein and stimulates downstream signaling [74]. Deletion of *Thbs1* in mice inhibited this signaling cascade, led to impaired aortic remodeling in response to transverse aortic constriction-induced pressure overload and inhibited neointima formation upon complete left carotid artery (LCA) ligation [74]. These studies indicate the important role of Thbs1 in the pathogenesis of vascular pathologies via dysregulating actin cytoskeleton remodeling. It has been shown that exposure of disturbed flow to endothelial cells causes endothelial-to-mesenchymal transition (EndoMT), which promotes atherosclerosis development [75, 76]. Elevated Thbs1 levels are also linked with EndoMT following complete LCA ligation suggesting the potential role of Thbs1 in EndoMT-mediated atherogenesis [77]. A recent study by Singla et al. reported that THBS1 inhibits lymphangiogenesis by CD47-mediated mechanisms and lymphatic endothelial cell-specific *Cd47* deletion promotes arterial lymphatic vessel formation and attenuates

atherosclerosis [78]. These data suggest the role of Thbs1-Cd47 axis in reducing removal of cholesterol from the arterial wall via adventitial lymphatics and promoting atherogenesis.

In addition to serving as a receptor for THBS1, CD47 binds with signal regulatory protein α (SIRPα) present on phagocytic cells including macrophages and dendritic cells [79]. CD47 is ubiquitously expressed on viable cells and interacts with phagocyte SIRPα to prevent the efferocytic removal of live cells [80]. However, the surface expression of CD47 downregulates on apoptotic cells allowing efferocytosis of those cells by phagocytes and inhibits necrosis-induced inflammation. This CD47-SIRPα signaling is an important immune checkpoint that helps to maintain tissue integrity and homeostasis [81]. Recently, Singla et al. demonstrated the differential effects of myeloid cell-specific *Sirpa* and *Cd47* deficiencies on atherosclerosis development [82]. Loss of myeloid cell Sirpa signaling stimulated efferocytosis, enhanced lipid efflux, decreased cholesterol accumulation, and attenuated oxidized LDL-induced inflammation in macrophages. Further, it inhibited atherosclerotic lesion formation and necrotic core formation in hypercholesterolemic mice. Conversely, deletion of *Cd47* in myeloid cells impaired efferocytosis and cholesterol efflux, augmented cellular inflammation, and promoted plaque formation [82] (Fig. 2b). Thus, interaction triangle of Thbs1-Cd47-Sirpα has several pathogenic consequences that promote atherogenesis and severity of disease. Thbs1 also mediates its effects by interaction with cell surface receptor Cd36 [83]. Thbs1 through Cd36-mediated signaling enhances proliferation of VSMCs via upregulating the expression of cell cycle promoter cyclin A. Ablation of *Cd36* in VSMCs significantly decreases cell proliferation and neointimal hyperplasia in injured carotid arteries of $Apoe^{-/-}/Cd36^{-/-}$ mice compared with $Apoe^{-/-}$ mice [84].

4.1.2 Thrombospondin 5 /cartilage oligomeric matrix protein (COMP):

Hedbom et al. reported the presence of COMP in bovine and rodent cartilaginous tissue [85]. Later, its expression was detected in cultured human VSMCs and also found localized in SMCs present in the medial layer of non-atherosclerotic arteries as well as in intimal SMCs of human atherosclerotic and restenotic arteries [86]. It aids in the maintenance of VSMC contractile phenotype and mediates protective effects against injury-induced VSMC dedifferentiation and neointima formation in Sprague-Dawley rats through interaction with α7β1 integrin [49]. Comp expression was also found in both inflammatory and/or fibrous atherosclerotic plaques in mice [87]. Additionally, Riessen et al. reported that VSMCs adhere strongly to COMP-coated surfaces, and it aids in the migration of VSMCs [86]. These observations suggest the possible role of COMP in vasculogenesis and vascular diseases like atherosclerosis via regulating SMC migration and adhesion. Hultman et al. in their recent study showed significantly increased COMP expression in atherosclerotic plaques from symptomatic patients compared with lesions from asymptomatic patients [88]. Further, COMP levels were positively associated with plaque lipid- and CD68-positive areas, but negatively with collagen, elastin, and SMC contents. A study has demonstrated elevated circulating levels of COMP in patients with coronary heart disease compared with control patients and observed a positive correlation between COMP levels and coronary artery calcium score, suggesting serum COMP levels can serve as a screening biomarker for coronary calcification [89]. Sandstedt et al. reported the presence of COMP neoepitope, a highly conserved sequence across several species, in carotid arteries of atherosclerotic

patients. COMP neoepitope levels in plasma and endarterectomy samples were found significantly increased in comparison to control subjects. They also detected its presence in SMCs, endothelial cells, and foam cells in carotid stenosis and suggested that degradation of COMP and generation of a specific COMP fragment COMP neoepitope may be associated with atherosclerosis progression [90]. These findings indicate an association of arterial COMP expression with plaque vulnerability in humans.

Contrarily, Fu et al. reported that Comp deficiency in mice leads to increased plaque size accompanied by increased calcification. *Apoe*$^{-/-}$/*Comp*$^{-/-}$ mice fed with a chow diet for 12 months had enhanced atherosclerotic calcification in the innominate arteries than *Apoe* null control mice. Furthermore, microarray profiling of wild-type and *Comp* knockout macrophages revealed that *Comp*-deficient macrophages have atherogenic and osteogenic characteristics. The authors concluded that Comp deficiency aggravates atherosclerotic calcification by switching macrophage phenotype toward the atherogenic and osteogenic type via integrin β3 activation [91]. Additional analysis demonstrated significantly decreased COMP expression in aortic samples of aortic aneurysm patients compared with controls [92]. COMP along with blood flow fine-tunes endothelial homeostasis, as it inhibits disturbed flow-induced endothelial activation by interacting with integrin α5. Under normal as well as pathological conditions including partially ligated carotid arteries mouse models, increased endothelial cell activation was observed in the aortic arch of *Comp*$^{-/-}$ mice compared with control mice. Moreover, Comp-derived peptidomimetics (CCPep24) mimicking a specific Comp-integrin α5 interaction, protected against endothelial cell activation and atherogenesis *in vivo* [93]. Further, Du et al. also reported Comp as a novel endogenous inhibitor of vascular calcification employing two different rat models of vascular calcification. They revealed that its inhibitory effect is exerted partially through the direct binding of its C-terminal domain to bone morphogenetic protein-2 (Bmp-2), which prevents Bmp-2 binding to its receptor and consequently inhibits Bmp-2-induced osteogenic signaling [94]. COMP also plays a catalytic function in collagen-microfibril assembly as it brings collagen molecules together, and aids in the formation of mature fibrils [95]. It has been observed that the size of inflammatory lesions significantly decreases with defective collagen assembly [96]. Having a role in the assembly of collagen fibers, COMP reduced expression accordingly affects the structure and growth of atherosclerotic lesions and its elevated levels with respect to collagen lead to the impairment of fibrillogenesis [97]. Consistently, Bond et al. showed larger plaques with higher collagen content in brachiocephalic arteries of *Comp*-deficient *Apoe*$^{-/-}$ mice [87]. The changes in morphology in brachiocephalic artery plaques in mice lacking *Comp* could be a consequence of altered collagen metabolism [87]. Consequently, the risk of rupturing the atherosclerotic plaque increases with the degradation of collagen fibers in the vessel wall. Thus, COMP stands to be a capable molecule in collagen fibrillogenesis and shows a significant anti-atherogenic effect.

4.2. CCN Family

This family of matricellular proteins got its acronym of CCN from the first three discovered members of the family known as Connective Tissue Growth factor, Cysteine-Rich Protein and Nephroblastoma Overexpressed Gene. It consists of 6 multifunctional proteins

named CCN1 to CCN6 [98]. CCN proteins regulate various cellular processes including cell adhesion, migration, chemotaxis, cell survival [99], skeletal formation and further development [99, 100], and cell proliferation [101]. These proteins drive angiogenesis by manipulating cell communication network, which integrate most of growth factors and proteins toward new vessel formation [102]. CCN1 induces its cellular effects by binding to cell surface receptors including syndecan 4 [103], αMβ2 and α6β1 [104], CCN2 binds to heparan sulfate proteoglycan [105], tropomyosin-related kinase A [106], LRP-1 [107]; CCN3 acts by binding to notch [108] and integrins (α6β1 and αvβ5). One of the important functions of CCNs appears to be as an adaptor molecule, binding growth factors, such as vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β) and shuttling them near cell surface via second binding partners, namely integrins or heparin sulfate proteoglycans. CCNs may directly bind to cell surface and initiate intracellular signaling cascades, which are critical for cellular growth and mobility during vascular development and aid in the progression of vascular diseases such as atherosclerosis and restenosis [109].

Earlier studies have shown upregulated CCN1 expression during inflammation, tissue repair, and wound healing [110]. CCN1 is considered to be an important player in inflammatory diseases including rheumatoid arthritis, bacterial and viral infections, vascular injury, and colon inflammation [111]. A case-control study was done to evaluate serum levels of CCN1 in rheumatoid arthritis patients, and then examined correlation among serum CCN1 levels, carotid intima-media thickness, and predisposition to subclinical carotid atherosclerosis. Serum CCN1 levels were found significantly elevated in rheumatoid arthritis patients compared with healthy controls and observed positively correlated with carotid intima-media thickness [112]. Similarly, a significant positive correlation between CCN1 expression and myocardial infarct size was found among ST-elevation MI patients [113]. Additionally, CCN1 levels were determined in type 2 diabetic patients and related to the occurrence of peripheral artery disease. The results demonstrated that patients with more advanced peripheral artery disease had significantly higher CCN1 levels and these levels were positively associated with disease severity [114]. Further, it has been shown associated with fibroblast migration and monocyte adhesion [110, 115], myocardial angiogenesis and remodeling of the vascular bed following myocardial injury [116].

CCN1 expression in normal endothelial cells, VSMCs and fibroblasts is very low [117], however, in atherosclerotic plaques particularly in neovascularized regions, its expression is highly elevated [118]. Additional studies reported increased CCN1 levels in human arteriosclerotic carotid and coronary arteries as well as arteriosclerotic aortas of *Apoe*-deficient mice [115, 119]. In a rat carotid artery injury model, rapid elevation in the expression of this protein was observed in the media and neointima regions, and *Ccn1* knockdown suppressed balloon injury-induced neointima formation [120]. These observations are further supported by the findings that CCN1 immunoreactivity is present in the heart tissues of patients who died of sudden cardiac death and revealed that CCN1 expression significantly associates with myocardial ischemia, interstitial edema and atheromatosis of coronary arteries [121]. Further, immunological studies identified elevated CCN1 expression in neointimal lesions and suggested a possible role of CCN1 in lysophosphatidic acid-induced vascular neointima formation [122]. Zhoa et al showed

predominant expression of Ccn1 in *Apoe*$^{-/-}$ mice aortic foamy macrophages and reported worsened hyperlipidemia, enhanced systemic inflammation, and augmented atherosclerosis in Ccn1-treated *Apoe*$^{-/-}$ mice compared with control mice. Additionally, Ccn1 treatment impaired macrophage reverse cholesterol transport capacity as well as reduced the expression of proteins associated with cholesterol clearance including ABCG5, ABCG8, liver X receptor α, cholesterol 7α-hydrolase and LDL receptor in mouse liver and exacerbated hepatic lipid accumulation [123].

Disturbed blood flow-induced CCN1 expression in endothelial cells has been shown to regulate endothelial cell functional phenotypes. CCN1-α6β1 mediates shear stress-induced NF-κβ activation and expression of atheroprone genes in endothelial cells. Activation of NF-κβ by CCN1/α6β1 works through a positive-feedback loop and enhances the production of CCN1 and α6β1 [124]. Besides, a mutation in *Ccn1* gene that prevents binding of Ccn1 with its receptor integrin α6β1 attenuates partial left carotid artery ligation-stimulated atherosclerosis in *Apoe*$^{-/-}$ mice. During atherosclerosis development, Ccn1 also regulates tumor necrosis factor-α (TNF-α)-induced vascular endothelial cell apoptosis via p53 and NF-κβ activation [125]. Thus, CCN1 is a critical pathophysiological regulator mediating the endothelial dysfunction induced by disturbed blood flow and can be targeted for therapeutic restoration of endothelial function to prevent atherosclerosis [126].

4.3. Secreted phosphoprotein 1 (SPP1)

Secreted Phosphoprotein 1 is also called as Osteopontin. It exists both as a component of the ECM and a soluble cytokine. It regulates bone formation and ECM mineralization. It is considered as a strong predictor of calcification, biomineralization, vascular diseases like atherosclerosis and is also a prognostic indicator for inflammatory heart diseases [127, 128]. SPP1 interacts with cell surface integrins [αv (β1, β3, β5, β6)] and modulates a variety of biological processes such as migration, cell adhesion and survival, ECM remodeling and regulates vascular calcification [129, 130]. It is also highly expressed in cancer models and has shown a possibility of enhancing cancer cell survival [131].

Previous studies have investigated the role of SPP1 in atherosclerosis and examined the effects of its overexpression/deficiency on atherosclerotic lesion formation [132, 133]. Elevated SPP1 levels were observed in patients with coronary artery disease (CAD) [134]. In a pilot study, plasma SPP1 concentrations were found significantly higher in patients with confirmed presence of rupture plaque in comparison to healthy individuals [135]. A significant association was also detected between plasma SPP1 levels and increased risks of adverse outcomes after ischemic stroke [136]. SPP1 expression is localized in atherosclerotic lesions, especially in macrophages- and foam cell-positive areas, suggesting its role in the development and progression of atherosclerosis and vascular remodeling [133, 137, 138]. Under normal physiological circumstances, the circulating/tissue SPP1 levels are low but enough to maintain normal arterial physiology [139, 140].

It is now well known that SPP1 acts as a physiological inhibitor of vascular calcification. Vascular cell types comprising endothelial cells, VSMCs, and macrophages are the major source of SPP1 in the arterial wall [141]. Upregulation of Spp1 was observed in response to ischemic injury in the murine model of hindlimb ischemia [142], that in turn promotes

cell adhesion, proliferation, migration, and survival assisting in the healing process [143, 144]. Matsui et al. using *Spp1* knockout mice on *Apoe* null background showed reduced atherosclerotic lesion areas in female heterozygous ($Spp1^{+/-}$) and homozygous ($Spp1^{-/-}$) mice compared with wild-type ($Spp1^{+/+}$) mice. However, no differences in atherosclerosis were observed in male mice demonstrating the sex-specific role of Spp1 in atherosclerotic lesion formation. Additionally, significantly increased vascular calcification was observed with *Spp1* deletion in male 60-week-old mice indicating an inhibitory effect of Spp1 on vascular calcification [145]. Altogether, these findings suggest that SPP1 plays a promoting effect on atherosclerosis development and an inhibitory effect in vascular calcification. Chiba et al. examined the effects of Spp1 overexpression in hematopoietic cells on atherosclerotic lesion formation and reported that Spp1 overexpression in lymphoid tissues associates with an increase in aortic lesion size in atherogenic diet-fed mice. Further, they showed significantly higher expression of Spp1 in lesional foamy macrophages of *Spp1* transgenic mice compared with such macrophages in control mice [133]. Additional experiments revealed that higher Spp1 levels in atherosclerotic lesions were not due to the deposition of serum Spp1, but mainly due to production of Spp1 by infiltrating macrophages. Consistently, Isoda et al. showed that global overexpression of Spp1 in atherogenic diet-fed mice results in larger atherosclerotic lesions compared with control non-transgenic mice [138].

In diabetic vascular disease, Spp1 secretion was also observed to increase with high glucose concentrations in the rat aortic SMCs *in vitro* [146]. SPP1 also regulates the recruitment of inflammatory cells and adhesion or migration of foam cells by binding to its receptors such as integrins (avb3, avb1, avb5, and a4b1) or the splice variant of CD44 v3-v6, AT1, or AT2 [147, 148]. A recent study by Yu et al. has reported that Nox4-induced Spp1 expression in VSMCs is partially responsible for AngII-stimulated aortic aneurysm and atherosclerosis [149]. Collectively, SPP1 seems to exert an important role in the formation of atherosclerotic plaque, enhances vascular inflammation, and participates in vasculopathy by increasing proliferation of endothelial and VSMCs [150].

4.4. Roof plate-specific spondins (RSPOs)

RSPOs get their name due to the discovery of RSPO1 in mouse roof plate of neural tube during development. In vertebrates, four types of RSPOs namely RSPO1–4 are identified [151]. RSPOs serve as ligands for various receptors including leucine-rich repeat containing G-protein coupled receptors 4–6 [151, 152], ZNRF3/RNF43 [153] and heparan sulfate proteoglycan. RSPOs play various physiological and pathophysiological roles. RSPOs potently bind with leucine-rich repeat-containing G protein-coupled receptors (LGRs) and prevent the degradation of Wnt receptors, thereby stimulate Wnt-stimulated signaling [154]. Wnt signaling is pivotal for developmental processes, including cell proliferation, differentiation and tissue patterning. The cardiovascular system in healthy adults has little Wnt activity, however, this signaling pathway reactivates during heart or blood vessel pathological conditions [155]. Wnt signaling has gained interest as a potential therapeutic target because of its higher expression in various pathologies [155]. Various studies reported a protective role for Wnt signaling in cholesterol trafficking and its accumulation in tissues, even the arterial wall [156–158].

The role of RSPO2 in atherosclerosis development has been recently reported by Singla et al. [159]. Elevated RSPO2 expression was observed in various cell types present in the different layers of human and mouse atherosclerotic arteries including medial SMCs, intraplaque macrophages and adventitial fibroblasts. Using *in vitro* and *in vivo* experiments, the authors revealed the inhibitory role of RSPO2 on VEGFC/VEGFR3-mediated lymphangiogenesis. Further, RSPO2 limited the activation of AKT-eNOS signaling via LGR4-mediated mechanisms. NO signaling has been shown critical for lymphangiogenesis and maintenance of lymphatic function [160], therefore RSPO2 via suppressing NO signaling in lymphatic endothelial cells prevented arterial lymphangiogenesis and impaired arterial cholesterol removal that in turn led to increased atherosclerotic lesion formation [159] (Fig. 3). Interestingly, perivascular application of LGR4-extracellular domain peptide suppressed atherosclerotic lesion formation and increased arterial lymphatic vessel density in hypercholesterolemic mice following partial left carotid artery ligation. Moreover, the authors demonstrated that RSPO2 inhibited Wnt-β-catenin signaling in lymphatic endothelial cells via diminishing NO-mediated nuclear translocation of β-catenin [159] (Fig. 3). On contrary, Carmon et al. reported the induction of Wnt signaling following RSPO2 exposure in other cell types like MDCK, HEK293T and HeLa cells, suggesting the cell-specific effects of RSPO2 treatment on Wnt-β-catenin pathway [161]. Future studies are needed to better understand the roles of RSPOs in regulating atherosclerotic lesion formation, underlying mechanisms, and RSPOs' cell-specific effects during atherogenesis.

4.5. Vitronectin (VTN)

VTN is synthesized in the liver and secreted into the plasma. It serves as a ligand for integrins αvβ1, αvβ5, αvβ3 and αIIbβ3 [162]. Like other matricellular proteins, it has a crucial role in various biological processes such as adhesion, angiogenesis and cell migration [163]. It also regulates processes including coagulation, blood fibrinolysis, complement-depended immune responses, pericellular proteolysis, etc. [164–167]. It is found to be accumulated in atherosclerotic plaque [164–167] and mediates platelet aggregation and adhesion at the vascular injury sites [168]. In contrast, reduced levels of VTN in airways of asthmatic and chronic pulmonary disease patients, contributes to the airways remodeling as seen in obstructive airway disorder [169].

Previous data suggest that the liver is a major site of VTN biosynthesis [170]. Normal plasma concentration of VTN ranges from 200 to 400 μg/mL and it constitutes 0.2–0.5% of total plasma protein [171, 172]. Expression of VTN is considered to be related to the development of atherosclerosis. Guettier et al. reported the presence and accumulation of VTN in atherosclerotic plaques [166]. It was speculated that VTN accumulation in atherosclerotic plaques resulted from its diffusion from plasma, where it is released either by activated platelets through damaged endothelium or synthesized by cells involved in atherosclerotic plaque formation [173]. VTN triggers adhesion and aggregation of platelets at the sites of injury in blood vessels, hence considered as a contributor of atherosclerosis and thrombosis [174]. It is prominent player in the development of aortic inflammation and its expression is a useful indicator in the determination of plaque burden and stability [175]. Its role was further verified by quantifying the plasma levels of VTN in patients suffering from CAD, and increased VTN levels were detected in these patients. The plasma level of

VTN showed a positive correlation with the severity of the disease [176, 177]. Based on the experimental and clinical evidence, it is now established that VTN plays a very essential role in establishing the initial response to tissue injury and is thus considered as a significant biomarker of atherosclerosis [178].

VTN has been shown to be involved in adhesion and migration of SMCs, neural crest cells, and keratinocytes [179, 180]. Migration of SMCs is a contributor to the intimal thickening during atherogenesis. Interestingly, chemotactic and haptotactic activity of VTN are mediated by its receptor αVβ3 in cultured SMCs [179]. Further, Dufourcq et al. reported that treatment with neutralizing anti-Vtn antibody inhibits VSMC migration and suppresses neointima formation after vascular injury [181]. Although, in rabbits VTN was reported to be localized in atherosclerotic arteries and its role was highlighted in regard to the abnormalities in platelets like platelet activation & aggregation in CAD [182, 183]. Recent findings by Chakravarty et al. have shown a reciprocal relationship of VTN with cholesterol load and unveiled its multi-functional role beyond adhesion function. They reported that the inflammation and plaque progression is associated with systemic deficiency of *Vtn* in *Apoe*$^{-/-}$ mice. Imbalance in its levels facilitates the trafficking of the inflammatory cells to the plaque microenvironment, and decreased Vtn expression due to high cholesterol load and aortic inflammation leads to the formation of advanced necrotic atheroma [175].

4.6. Tenascins (TN)

This family of matricellular proteins comprises of four large glycoproteins namely tenascin W (TNW), tenascin C (TNC), tenascin R (TNR) and tenascin X (TNX) [184]. TNC expression is stimulated by various growth factors, mechanical stress and cytokines. Even having significant structural homology, these four members exhibit distinct expression patterns. TNW is mostly restricted to the skeletal system during remodeling or development phases; TNC is expressed in multiple cells and tissues depending on types of stimuli; TNR is restricted to the central nervous system (CNS) and whereas TNX is expressed in connective tissues [185]. These proteins function via interacting with receptors integrin α8β1 [186], IgCAM/contactin [187], myelin associated glycoprotein [188] and heparan sulphate proteoglycan [189].

Among all the four members, TNC is the most studied protein and reported to have a role in various CVD including the promotion of cardiac fibrosis, myocardial hypertrophy [190], cardiac dysfunction [191], and vascular diseases by showing atherogenic effects via induction of TLR4-dependent foam cell formation [192]. Significantly elevated levels of TNC were found in serum samples of CAD patients in comparison to non-CAD patients, and a positive correlation between TNC levels and severity of atherosclerosis was observed [193, 194]. Recently, Gholipour et al. reported increased TNC levels in exosomes isolated from CAD patients than non-CAD patients [195]. In a prospective observational study, higher plasma TNC levels predicted overall and cardiovascular mortality, and were associated with higher occurrence of cardiovascular events in chronic kidney disease patients [196]. Tnc expression was found increased with progression of atherosclerosis in atheroprone *Apoe*$^{-/-}$ mice [197]. Balloon catheter-induced vascular injury has also been shown to upregulate Tnc expression specifically in neointimal lesions [198]. Moreover,

lipopolysaccharide (LPS) treatment induces *Tnc* expression in THP-1 macrophages *in vitro* in a dose- and time-dependent manner and it augments LPS-induced foam cell formation [199]. Besides, TNC produced by oxidized LDL-stimulated macrophages increases foam cell formation through TLR4 and scavenger receptor CD36 [192].

TNC expression was specifically detected in the macrophage-rich areas of atherosclerotic plaques [200]. TNC can act as damage-associated molecular patterns to activate macrophages and fibroblasts and induce inflammatory cytokine expression through TLR-4 receptor [201, 202]. Wang et al. demonstrated a higher expression of Tnc and annexin II in atherosclerotic plaque and their interaction facilitated macrophage migration and VEGF expression via Akt, NF-κB and ERK1/2 pathway [203]. In diabetic-acute MI patients, increased TNC expression in coronary artery atherosclerotic lesions was found to be associated with increased TGF-β, macrophage accumulation and TUNEL-positive apoptotic cells [204]. Wallner et al. reported minimal and random TNC expression in fibrotic but lipid-poor atherosclerotic plaques. In contrast, all advanced stage plaques with an organized lipid core or ruptured intimal surface has elevated expression of TNC, which was preferentially concentrated around the lipid core, shoulder regions, and ruptured area of the plaques but not in the fibrous cap. Further, TNC expression was found to be associated with the degree of inflammation present, but not with plaque size [200]. Contrary to this, Wang et al. reported the atheroprotective role of Tnc utilizing atheroprone *Apoe*$^{-/-}$ mice, in which they showed that *Tnc* gene deletion leads to upregulation of eotaxin, a chemokine that promotes migration and activation of eosinophils and plasma eotaxin elevation correlates with atherosclerosis development [205]. They unveiled a protective role for Tnc in atherosclerosis and suggested its potential to reduce atherosclerosis, in part by modulating Vcam-1 expression.

4.7. Galectins

Galectins is a family of β-galactoside-binding lectins that have emerged as crucial modulators of inflammatory processes [206]. They are involved in intercellular signaling, cell-cell and cell-to-matrix adhesion, apoptosis, angiogenesis, and innate and adaptive immunity [207]. Galectins are coded by the genes named *Lgals*. Till date, fifteen different types of galectins have been identified, out of which only two have been included in matricellular family namely galectin 1 (Gal1) and Gal3. Both Gal1 and Gal3 play important roles in regulating immune responses by serving as damage-associated molecular patterns [208, 209]. These proteins have been linked to various diseases such as cornea proliferative vitreoretinopathy [210, 211], Fuch's endothelial corneal dystrophy [212], age-related macular degeneration [213], diabetic retinopathy [214–216].

Gal1 plays an essential role in cardiovascular pathophysiology by moderating acute and chronic inflammatory responses [217]. For instance, patients suffering from MI, heart failure, or Chagas cardiomyopathy have increased GAL1 expression in cardiomyocytes [218]. *Lgals1*-deficient mice after acute MI exhibited enhanced cardiac inflammation and worsened ventricular remodeling [219]. Additionally, circulating GAL1 levels associate with the severity of CAD and subsequent occurrence of major adverse cardiovascular events in patients with CAD [220]. Moreover, upregulated GAL1 expression has been reported to

associate with stroke outcome in large artery atherosclerotic stroke [221]. Gal1 and Gal3 are the predominant galectins observed in atherosclerotic plaques and have specific spatial and temporal intraplaque expression patterns during atherosclerosis progression [222]. GAL1 serves as an adapter between cells and ECM and modulates adhesion, migration and proliferation of SMCs. Moiseeva et al. demonstrated increased GAL1 expression in proliferating SMCs [223]. Moreover, GAL1 fusion protein stimulated serum-induced DNA synthesis in human SMCs grown on plastic or endogenous ECM, and increased SMC adhesion to ECM. It affected SMC adhesion by interacting with β1 integrin present on cell surface and inducing outside-in signaling [223]. VSMCs-deficient in *Lgals1* exhibited greater motility but adhered slower on fibronectin than wild-type control cells. Likewise, their migration was inhibited by a redox-insensitive but activity-preserved Gal1 (CSLgal1) in a glycan-dependent manner [224]. The authors concluded that Gal1 restricts VSMC migration by modulating cell-matrix interaction and focal adhesion turnover, which limits neointimal formation post vascular injury.

Interestingly, Roldán-Montero et al. reported a protective role of Gal1 in pathological vascular disorders through modulation of lipid uptake by macrophages, alterations in mitochondrial function and phenotypic switch of VSMCs. The authors observed reduced expression of Gal1 in advanced human atherosclerosis and abdominal aortic aneurysm. They showed that treatment with recombinant Gal1 prevent both atherosclerosis and abdominal aortic aneurysm in mice, which indicate it as a novel therapeutic target for attenuating the severity of chronic vascular pathologies [225].

5. Conclusions

Atherosclerotic vascular diseases are responsible for one fourth of deaths worldwide. The investigations into its pathogenesis, therapeutics and role of various endogenous factors regulating distinct aspects of atherosclerotic lesion formation are of great medical importance. Discoveries made during the last two decades have significantly advanced our understanding of the roles of various matricellular proteins in atherosclerosis. The elevated levels of these proteins significantly correlate with atherosclerosis development and are thus considered as potential biomarkers with considerable diagnostic value. However, some studies have even reported atheroprotective roles of these matricellular proteins. Experimental loss-of-function and overexpression studies have demonstrated that vascular injury via dysregulating the expression of matrix proteins contribute to atherosclerotic lesion formation. However, atherosclerosis being a complex inflammatory disease, the mechanisms stimulated/inhibited by these proteins in plaque formation needs future investigations. Further and extensive research is needed to understand the exact mechanisms by which various matricellular proteins promote endothelial cell activation, neointima formation and atherosclerotic plaque development. Performing studies using cell-specific knockout mice, gene overexpression and rescue experiments may reveal cell type-specific mechanisms involved in the disease development. This information will aid in discovering new treatment modalities for patients with atherosclerotic disease. Since THBS1 is a highly studied matricellular protein for its role in the pathogenesis of vascular pathologies, targeted therapies to block signaling stimulated by THBS1 may be tested as a potential therapeutic approach for atherosclerosis. For instance, TAX2, a CD47-derived

cyclic peptide that targets THBS1 and selectively blocks THBS1:CD47 interaction can be evaluated for anti-atherogenic effects [226]. However, the shorter half-life of TAX2 in circulation remained an issue for its therapeutic use. Utilization of function-blocking anti-THBS1 monoclonal antibodies has also been considered as therapeutic strategy. C6.7 anti-Thbs1 antibody has been demonstrated to facilitate reendothelialization and decrease neointimal lesion formation in balloon-injured rat arteries [56]. Blocking THBS1:CD47 interaction using CD47 soluble receptor or CD47-blocking antibodies can also be viable therapeutic approach for the treatment of atherosclerosis. Recombinant human CD47 peptide that specifically binds and prevents THBS1's effects, has been shown to improve vasorelaxation [227]. Further pharmacological studies are warranted to evaluate its effects in resistance vessels. Besides, integrins serve as receptors for various matricellular proteins and inhibitors blocking the integrins' receptor function can also be evaluated for their efficacy in attenuating atherosclerotic lesion formation. Additional studies identifying the functional domains of matricellular proteins and cell surface binding partners will help in designing therapeutic peptidic inhibitors and blocking antibodies with longer half-life. Clearly, future investigations are required to better understand the role of matricellular proteins in the pathogenesis of atherosclerosis and whether inhibition of matricellular proteins-stimulated pathways in arterial wall truly represents a therapeutic target in patients with atherosclerotic vascular disease.

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Abbreviations

ECM	extracellular matrix
CVD	cardiovascular disease
MI	myocardial infarction
VSMCs	vascular smooth muscle cells
SMCs	smooth muscle cells
LDL	low-density lipoprotein
VLDL	very-low-density lipoprotein
THBS	thrombospondin
SPARC	secreted protein, acidic and rich in cysteine
COMP	cartilage oligomeric matrix protein
LRP	low density lipoprotein-related receptor
CD	cluster of differentiation

PDGF	platelet-derived growth factor
SIRPα	signal regulatory protein α
BMP-2	bone morphogenetic protein-2
VEGF	vascular endothelial growth factor
TGF-β	transforming growth factor-β
TNF-α	tumor necrosis factor α
SPP1	secreted phosphoprotein 1
CAD	coronary artery disease
RSPOs	roof plate-specific spondins
LGRs	leucine-rich repeat-containing G protein-coupled receptors
YAP	yes-associated protein
EndoMT	endothelial-to-mesenchymal transition
NO	nitric oxide
VTN	vitronectin
TN	tenascin
LPS	lipopolysaccharide
VCAM-1	vascular cell adhesion molecule-1
Gal	Galectin.

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Highlights

- Matricellular proteins are secreted non-structural proteins that play important roles in the maintenance of tissue homeostasis.
- The elevated levels of matricellular proteins correlate with atherosclerosis development.
- Matricellular proteins stimulate multiple steps of atherogenesis ranging from endothelial cell activation to plaque vulnerability.
- Integrins serve as receptors for various matricellular proteins. Inhibiting integrins' receptor function may be a viable therapeutic strategy to suppress atherogenesis.
- THBS1 is a highly studied matricellular protein for its role in the pathogenesis of vascular pathologies and targeted therapies to prevent THBS1-induced signaling may serve as a potential therapeutic approach for atherosclerosis.

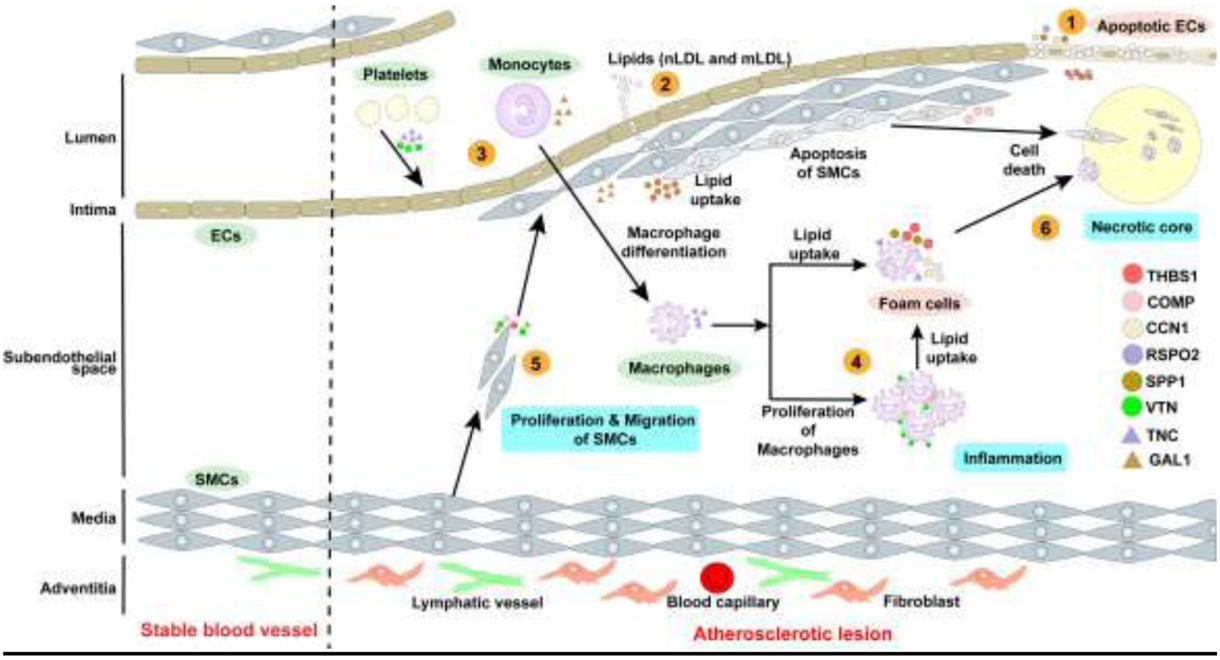

Figure 1: Role of matricellular proteins in the development of atherosclerosis.

Matricellular proteins play roles in various stages of atherosclerosis development, which include: 1. Endothelial damage - Damage to endothelial cells induces endothelial cell inflammation and promotes adhesion and transmigration of monocytes across intima. 2. Lipoprotein entry into subendothelial space - Leaky intima promotes the transport of plasma LDL to the subendothelial space, where LDL particles undergo oxidative and acetylated modifications. 3. Leukocyte recruitment- Endothelial cells with increased expression of adhesion molecules release chemo-attractants which attract monocytes and T lymphocytes. 4. Foam cell formation- Monocytes differentiate into macrophages and engulf native and modified LDL and become foam cells. 5. Plaque progression-Contractile VSMCs in the media dedifferentiate into a synthetic state and migrate into the intima and subendothelial space to form a fibrous cap. 6. Necrotic core formation-Accumulation and coalescence of lipids lead to cell apoptosis and necrosis. Failure to remove apoptotic cells results in the formation of lipid-rich necrotic core.

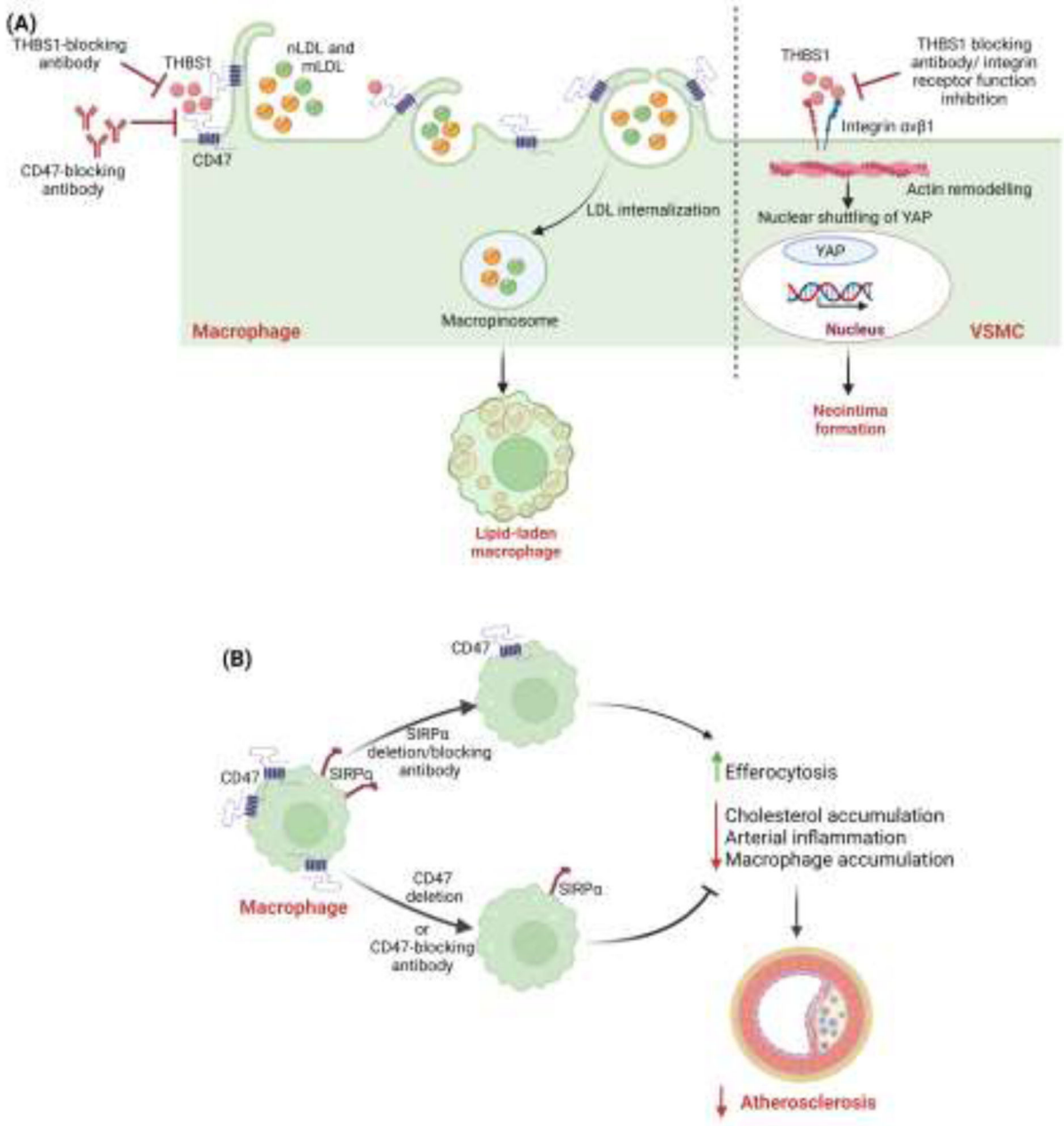

Figure 2:

(A) THBS1 via CD47 activation induces foam cell formation in macrophages. THBS1 binds with CD47 receptors in macrophages, stimulates receptor-independent macropinocytic internalization of native LDL (nLDL) and modified LDL (mLDL), and contributes to foam cell formation. Modulation of THBS1/CD47 signaling may work as therapeutic target for treating atherosclerosis. THBS1 secreted in response to mechanical stress, binds to VSMC integrin αvβ1 which helps in the maturation of the focal adhesion–actin complex, mediating activation of nuclear shuttling of YAP and ultimately leading to neointima formation. THBS1 targeted therapies using THBS1-blocking antibodies or integrin receptor function inhibitors may also serve as a potential therapeutic target for

treating atherosclerosis. **(B) Differential effects of myeloid cell-*Sirpa* and -*Cd47* deletion on macrophage efferocytosis and atherosclerosis.** Loss of Sirpa signaling in macrophages stimulates efferocytosis, reduces cholesterol accumulation, promotes lipid efflux, and suppresses atherosclerosis. Conversely, myeloid cell-*Cd47* deletion inhibits efferocytosis, impairs cholesterol efflux, augments cellular inflammation, and promotes plaque formation.

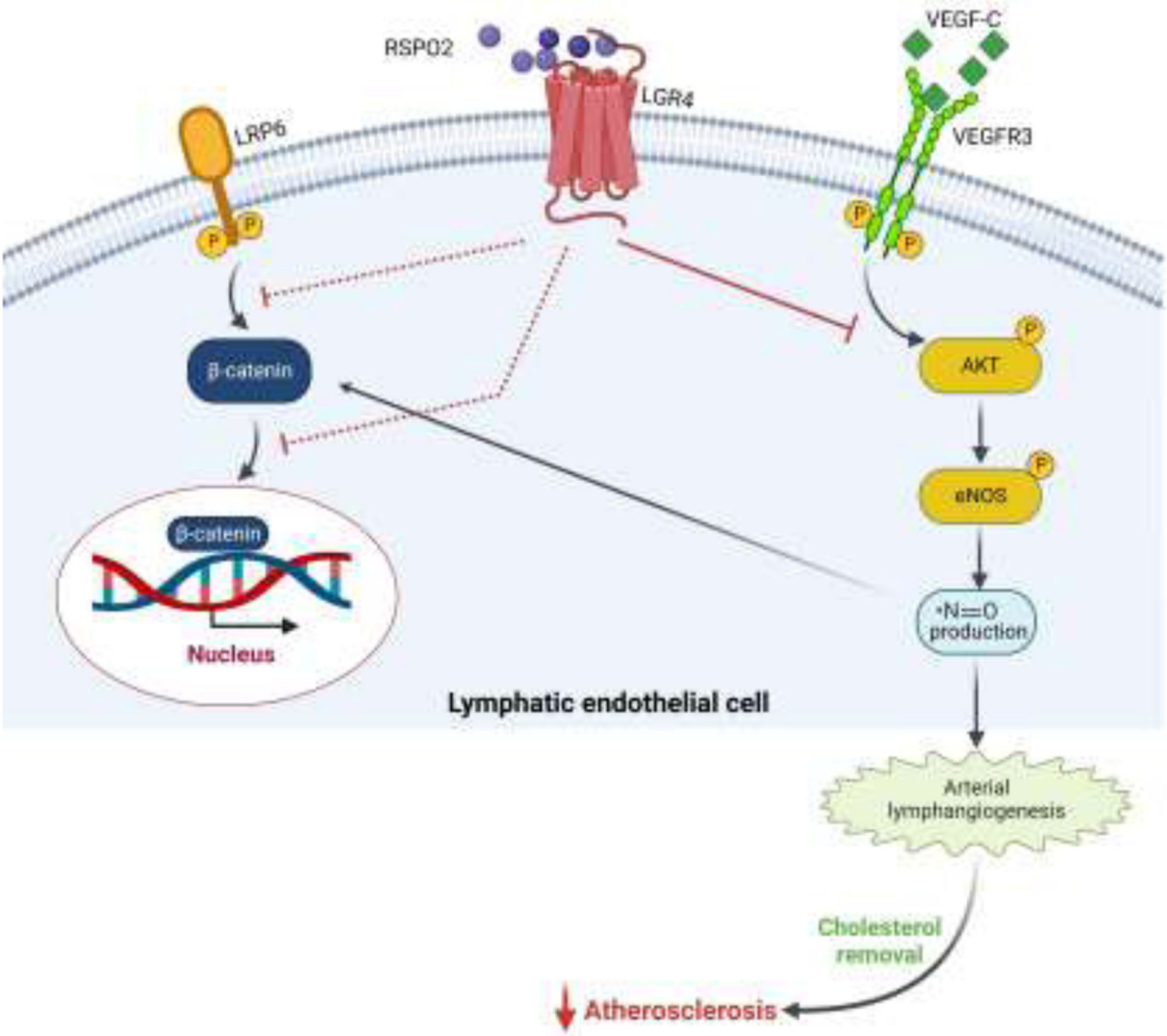

Figure 3: RSPO2 inhibits lymphangiogenesis and contributes to atherosclerosis development.

RSPO2 via binding to LGR4 receptors on lymphatic endothelial cells (LEC) hinders VEGF-C-stimulated AKT and eNOS activation, leading to impaired NO production and reduces lymphatic vessel formation. It also inhibits activation of the canonical Wnt-β-catenin pathway in LEC in a NO-dependent manner, thus decreasing lymphatic vessel-mediated LDL drainage from the arterial wall and promoting atherosclerosis.

Table 1:

Studies investigating the role of matricellular proteins in atherosclerosis.

Protein	Role	Study type	Cell/animal model type	Diet// concentration	References
THBS1	• Promotes the migration and proliferation of SMCs	*In vitro*	Human aortic SMCs	5 μg/mL	[228]
		In vitro	Bovine pulmonary artery SMCs	100 nM	[229]
	• Decreases cAMP/cGMP levels by inhibiting endothelial cell NO production	*In vitro*	Bovine aortic endothelial cells	2.2 nM	[64, 67, 230, 231]
		In vitro	Human umbilical vein endothelial cells	100 pM	[231]
	• Blocks NO-stimulated VSMC adhesion	*In vitro*	Human aortic SMCs	2.2 nM	[64]
	• Induces oxidative stress • Inhibits VSMC-dependent vasorelaxation	*In vitro*	Human aortic SMCs	2.2 nM	[70, 232, 233]
			Rat aortic SMCs	2.2 nM	
	• *Thbs1* deletion prevents leptin-induced atherosclerosis • Deletion blocks leptin-induced vascular inflammation • Deletion inhibits SMC dedifferentiation	*In vivo*	*Apoe*$^{-/-}$ and *Apoe*$^{-/-}$/ *Thbs1*$^{-/-}$ mice	Normocholesterolemic chow diet Murine recombinant leptin (5 μg/g body weight, 3 weeks before sacrifice)	[58]
	• In the early stage, lack of Thbs1 reduces plaque area • In the advanced stage, *Thbs1* loss enhances plaque necrosis	*In vivo*	*Apoe*$^{-/-}$ and *Apoe*$^{-/-}$/ *Thbs1*$^{-/-}$ mice	Normocholesterolemic chow diet (6 months and 9 months)	[57]
	• *Thbs1* deletion in mice promotes maladaptive remodeling in response to pressure overload via inhibiting Thbs1/integrin β1/YAP signaling • *Thbs1* deletion inhibits neointima formation upon carotid artery ligation	*In vivo*	*Thbs1*$^{-/-}$ mice	Normal chow diet (3 weeks)	[74]
COMP	• Facilitates VSMC adhesion and migration	*In vitro*	Human arterial SMCs	20 μg/mL	[86]
	• Reduced COMP levels exacerbate VSMC calcification	*In vitro*	Bovine aortic SMCs	COMP overexpressed by using adeno associated virus and silenced by using SiRNA	[94]
	• COMP blocks BMP-2-mediated osteogenic signaling				
	• Maintains VSMC contractile phenotype	*In vitro*	Rat aortic SMCs	Comp overexpressed by using adeno associated virus and silenced by using SiRNA	[49]

Protein	Role	Study type	Cell/animal model type	Diet// concentration	References
	• Comp mediates its protective effects via integrin α7β1				
	• Lack of Comp induces aging-related vascular dysfunction, stiffness and senescence	*In vivo*	*Comp*$^{-/-}$ mice	Regular chow diet and $CaCl_2$	[234]
	• *Comp* deletion augments atherosclerosis	*In vivo*	*Apoe*$^{-/-}$ and *Comp*$^{-/-}$/*Apoe*$^{-/-}$ mice	High fat diet and periadventitial collar injury	[87]
CCN1	• Promotesneovascularization	*In vitro*	Human umbilical vein endothelial cells	1, 10 & 100 ng/ mL	[235]
	• CCN1 overexpression promotes endothelial cell apoptosis in the presence of TNF-α	*In vitro*	Human coronary arterial endothelial cells	CCN1 overexpression was done by treating cells with 0.5 μg of mouse CCN1 cDNA in the presence of Lipofectamine® (Invitrogen). CCN1 silencing was done by using SiRNA	[125]
	• Supports VSMC adhesion • Enhances proliferation and migration of VSMCs	*In vitro*	Rat aortic VSMCs	0.5–20 μg/mL	[120]
	• Reduces reverse cholesterol transport	*In vitro*	Murine macrophages	1.25, 2.5, 5, and 10 ng/mL	[123]
	• Triggers macrophage M1 phenotype	*In vitro*	Splenic macrophage cell line I-13.35	10 μg/mL	[236]
	• Upregulated levels in atherosclerotic aortas of *Apoe*$^{-/-}$ mice • Promotes atherosclerosis	*In vivo*	*Apoe*$^{-/-}$ mice	Regular chow diet and intraperitoneal injections of CCN1 (10 μg/day/kg body weight, 4 weeks)	[123]
	• Promotes neovascularization	*In vivo*	C57BL/6 wild type mice	Regular chow diet	[235]
	• Elevated Ccn1 expression in atherosclerotic arteries	*In vivo*	*Apoe*$^{-/-}$ mice	High fat diet (8 weeks and 16 weeks)	[125]
	• Overexpressed in VSMCs of atherosclerotic arteries	*In vivo*	Sprague–Dawley rats	Standard lab diet	[120]
RSPO2	• Suppresses lymphangiogenesis and inhibits Wnt-β-catenin pathway in lymphatic endothelial cells	*In vitro*	Human dermal lymphatic endothelial cells	100 ng/mL	[159]
	• Blockade of perivascular Rspo2-Lgr4 signaling promotes arterial lymphangiogenesis and reduces atherosclerosis	*In vivo*	*Apoe*$^{-/-}$ mice	Western diet and periadventitial Lgr4-ECD (Rspo2's decoy receptor)	
Osteopontin	• Expression associates with plaque burden	Clinical	Human aorta samples	-	[237]

Protein	Role	Study type	Cell/animal model type	Diet// concentration	References
	• Plasma levels are higher in CAD patients and patients with calcified arteries	Clinical	Human blood samples	-	[238]
	• Deficiency reduces atherogenesis	*In vivo*	*Apoe*$^{-/-}$/*Ldlr*$^{-/-}$/*Spp1*$^{-/-}$ triple knockout mice	High fat diet	[239]
	• Deletion reduces atherosclerosis • Deletion stimulates vascular calcification.	*In vivo*	*Apoe*$^{-/-}$/*Spp1*$^{-/-}$ mice (36-week-old)	Normal chow diet	[145]
Vitronectin	• Serum levels were elevated in CAD patients	Clinical	Human blood samples	-	[177]
	• Promotes VSMC migration	*In vitro*	Human aortic SMCs		[179]
Tenascin C	• TNC expression correlates with macrophage infiltration	Clinical	human coronary and inteinal mammary arteries	-	[200]
	• TNC polymorphisms correlate with atherosclerosis/CAD	Clinical	Hman aorta samples and CATHGEN cardiovascular study	-	[240]
	• Deletion in mice promotes mast cell migration	*In vivo*	*Apoe*$^{-/-}$/*Tnc*$^{-/-}$ mice	High fat diet	[205]
Galectin 1	• Circulating levels correlate the severity of CAD • Higher LGAL1 concentrations are found older patients with hypertension, diabetes, chronic kidney disease, and heart failure. • Predicts incidence of major adverse cardiovascular events	Clinical	Human blood samples	-	[220]
	• *Lgal1* deletion aggravates atherosclerosis	*In vivo*	pAAV/D377Y-mPCSK9 injected *Lgals1*$^{-/-}$ mice	High fat diet	[225]
	• Stimulates monocyte migration	*In vitro*	Human peripheral blood mononuclear cells	10 μg/mL	[241]