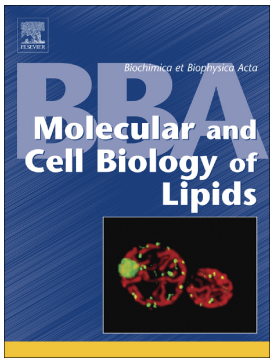

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Biglycan and atherosclerosis: lessons from high cardiovascular risk conditions

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Running title: BGN in atherosclerosis: from the evidence to mechanisms

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Abstract

Atherosclerosis (ATH) is a chronic, dynamic, evolutive process involving morphological and structural subversion of artery walls, leading to the formation of atherosclerotic plaques. ATH generally initiates during the childhood, occurring as a result of a number of changes in the intima tunica and in the media of arteries. A key event occurring during the pathobiology of ATH is the accumulation of lipoproteins in the sub-intimal spaces mediated by extracellular matrix (ECM) molecules, especially by the chondroitin sulfate/dermatan sulfate (CS/DS) –containing proteoglycans (CS/DSPGs). Among them, the proteoglycan biglycan (BGN) is critically involved in the onset and progression of ATH and evidences show that BGN represents the missing link between the pro-atherogenic status induced by both traditional and non-traditional cardiovascular risk factors and the development and progression of vascular damage. In the light of these findings, the role of BGN in dyslipidemia, hypertension, cigarette smoking, diabetes, chronic kidney disease and inflammatory status is briefly analyzed and discussed in order to shed new light on the underlying mechanisms governing the association between BGN and ATH.

Key words: Atherosclerosis; extracellular matrix; proteoglycans; biglycan; cardiovascular risk factors; inflammation.

Introduction

Atherosclerosis (ATH) is a progressive morphostructural alteration of arterial vessels, related to vascular aging phenomena, and/or chronic endothelial damage characterized by enhanced permeability, inflammation and oxidized lipid deposition in the sub-intimal space; this intricate process leads to endothelium dysfunction, loss of arterial wall elastic properties, intima-media thickening and plaques formation in the arterial tree [1-3]. ATH and ATH-related diseases (including myocardial infarction, chronic coronary artery disease, cerebral vascular disease, peripheral artery disease, chronic kidney disease) represent the leading cause of disability and mortality in the Western world [4, 5]. The pathobiology of ATH consists of a dynamic process generally starting during the childhood as a primary/early lesion, progressively leading to atherosclerotic plaque formation thus responsible of the majority of acute ischemic cardiovascular events (atherothrombosis) [2, 6, 7]. The primary lesion of progressive ATH is classified as *pathological intima thickening* (PIT) [8], characterized by thickening of vascular tunica intima due to extracellular deposition of lipids, proteoglycans (PGs) and hyaluronic acid [8]. The progression of PIT to fibroatheroma is characterized by increased inflammation and macrophage infiltration [8, 9]., However, the underlying mechanism is poorly understood so far. Endothelial dysfunction has a major contribution, both in the early stages and the progression of atherosclerotic disease. Endothelium may undergo functional and morphological modifications in response to endogenous (i.e., dyslipidemia, altered shear stress, hyperglycemia, uremia [10, 11], [12, 13]) and exogenous (i.e., drugs, toxics, diagnostic agents [14-16]) stimuli. These insults trigger homeostatic responses, such as the release of nitric oxide (NO), along with pro-inflammatory responses, such as the release of cytokines, chemokines and autacoids, which impair endothelial function. In these conditions, the endothelium can show increased permeability and favor the infiltration of both lipoproteins and proinflammatory cells in the sub-endothelial space. Here, according to the "*response-to-retention hypothesis*" [17], the interaction with the extracellular matrix and PGs can increase oxidative and retentive phenomena, favoring the development and progression of vascular damage. In this brief

review, we have sought to examine the current knowledge on the role played by PGs, particularly by BGN, in different clinical settings characterized by increased cardiovascular risk.

Role of proteoglycans in the vascular homeostasis

PGs are complex macromolecules characterized by a central core protein decorated with covalently linked glycosamminoglycans (GAGs) chains including chondroitin sulfate (CS), dermatan sulfate (DS), keratan sulphate (KS), heparin (HP), and heparan sulfate (HS). GAGs are polysaccharides made up of repeating disaccharides usually composed of acetylated esosamine (N-N-acetylgalactosamine or N-acetylglucosamine) and an uronic acid (D-glucuronic acid or L-iduronic acid). KS is the only GAG composed of N-acetylgucosamine and galactose [18].

PGs are also known to be essential molecules in maintaining vascular homeostasis, and their altered regulation is a key factor in inducing and progressing ATH [1, 4] [19]. Over the last years, a number of studies underlined the pivotal role of the PGs/lipoproteins interaction in the onset and the progression of ATH, supporting the so called *"response-to-retention hypothesis",* a theory initially proposed by Williams and Tabas [17, 20-28]. Then, the PGs emerge as key mechanistic mediators in this setting. Briefly, in the presence of a *noxa*, smooth muscle cells (SMCs) increase the local production of PGs with elevated affinity for plasma lipoproteins. The interaction between PGs and atherogenic lipoproteins occurs through ionic interactions between basic amino acids (i.e., positively charged residues) on the surface of apolipoprotein (apo) B100 and the sulphate groups of GAGs (i.e., negatively charged residues) attached to protein core of PGs. Such interaction built-up of PGs-lipoproteins aggregates in the *tunica intima* triggering a local inflammatory response and representing the first step in the pathobiology of ATH [7, 29, 30]. The triggering *"noxa"* may be identified as a series of risk factors (including hypertension, dyslipidemia, diabetes, obesity, chronic kidney disease and chronic inflammatory diseases), often coexisting in the same patient [31, 32]. Therefore, PGs may be the missing link underlying the association between these risk factors and the development of ATH from a mechanistic point of view.

The role of BGN

The most representative vascular PGs are the chondroitin sulphate PGs (CSPGs) and the dermatan sulphate PGs (DSPGs) [19, 33]. Among them, versican, decorin and BGN are the main PGs identified in the extracellular matrix (ECM) of the vascular intima. Furthermore, consistent evidence suggests that they are directly involved in the mechanisms of vascular damage [34, 35]. Particularly, studies conducted on histological sections of atherosclerotic lesions from animal models and also in humans show that plasma lipoproteins mainly co-localize with BGN because of their high affinity with its GAGs [26, 36, 37]. BGN belongs to the family of small leucine-rich PGs (SLRPGs) and consists of a core protein and chondroitin/dermatan sulphate GAG(s) chains [7, 38].

The role of BGN under increased cardiovascular risk conditions

Dyslipidemia

Elevated levels of plasma low-density lipoprotein cholesterol (LDL-C) are well-known causal factors of atherosclerosis [39]. However, mechanistic aspects underlying this connection are not fully understood so far. Co-localization studies have shown that PGs, including BGN, may contribute to the pathogenesis of atherosclerosis by trapping lipoproteins in the artery wall. Among vascular PGs, BGN is pointed out as the most involved in this path, due to its peculiar ability to bind and retain LDL in the vascular intima through the interaction with apoB, and also with apoE-containing high-density lipoproteins (HDL) [29, 36, 37]. This association has been proved to have functional relevance in experimental models. Thompson et al. created a murine model by crossing human BGN transgenic mice with atheroprone LDL receptor deficient (LDLR-/-) mice fed with a Western diet for 4-12 weeks. Authors found that LDLR-/- mice overexpressing BGN had increased atherosclerosis compared to controls because of increased vascular BGN content. Therefore, these data further support the importance of vascular BGN in the onset and progression of ATH [40].

Lipoprotein lipase (LPL) is a key enzyme in lipid metabolism and its role is closely related with BGN interaction [41]. The role of LPL in ATH is still controversial. Most prominent evidence

suggests this enzyme can be considered atheroprotective, because it catalyzes the hydrolysis of triglyceride-rich lipoproteins and patients who are deficient in LPL or have mutation on LPL gene develop ATH prematurely [42-44]. Moreover, systemic overexpression of LPL in LDL receptor or apoE knockout mice showed an atheroprotective role [45, 46]. Then, a major issue is to state whether the antiatherogenic properties of LPL are due to its increased activity or to its lipid-lowering effects.

Ichikawa et al. performed a study using transgenic rabbits overexpressing human LPL (hLPL) and control rabbits, all fed with a high cholesterol diet adjusted for achieving in both, transgenic and control rabbits, the same levels of total cholesterol (TC) for 16 weeks [47]. The authors found that, under equal condition of hypercholesterolemia, transgenic rabbits had a lipid profile characterized by reduced beta-very low-density lipoproteins (β-VLDL) and increased LDL particles as compared to controls. Furthermore, transgenic rabbits had greater aortic lesion areas than controls. In order to verify if the proatherogenic effects of LPL in transgenic rabbits were due to the alteration of lipoprotein profile, the authors studied the atherogenic properties of apoB-containing lipoproteins, measuring the susceptibility to copper-induced oxidization *in vitro*. They found that the small sized LDLs of transgenic rabbits were more susceptible to oxidation and had higher affinity for BGN than large remnant lipoproteins.

The authors concluded that in hyperlipidemic rabbits LPL exerts an antiatherogenic function by reducing the accumulation of remnant lipoproteins, but at the same time a high activity of this enzyme produce large amounts of small sized LDLs, thus exerting a proatherogenic effect [47]. These data underline the importance of small-dense LDLs as risk factors of CVD. Further research [47, 48] confirmed found LPL activity linked to an increased generation of small-sized LDL, which were more susceptible to oxidation and exhibited a higher affinity for BGN, compared to those of control individuals. These data confirmed the previous observation of Beisiegel and colleagues that in absence of LDL receptors, the LPL lipid-lowering effects may occur by an alternative pathway

mediated by LPL itself, the LDL receptor-related protein (LRP) pathway [49]. However, LPL activity under condition of hyperlipemia generates smaller and more atherogenic LDL particles [48].

A proof-of-concept study in the association between BGN expression and atherosclerosis was published by Oberkersch and coworkers; they studied the effects of hypercholesterolemia on aorta PGs in rats [28], by feeding a group of animals with a standard diet and another group with a high-cholesterol diet (H-Chol) for 30 days. The authors documented increased hypercholesterolemia in H-Chol fed rats, due to LDL, intermediate-density lipoproteins (IDL) and VLDL but not HDL. The histological analysis of the aorta sections showed that H-Chol animals did not present fully-fledged atherosclerotic lesions but, instead, hyperplasia of endothelial and smooth muscle cells of the intima, increased density of collagen fibrils and local inflammation characterized by high levels of tumor necrosis factor-alpha (TNF-α). The characterization of the different PGs from aortic cells through Western blot analysis revealed a reduced expression of decorin and BGN and an increased expression of versican in H-Chol animals respect to controls. The authors concluded that in the light of their findings the attenuation of decorin and BGN could be a promising strategy to inhibit the onset of ATH [28]. Importantly, a three-way association among atherosclerosis, PGs and inflammation (TNF-α) was suggested in this study, hence adding another layer of complexity to this study and shedding new light into the potential role of non-traditional CV risk factors.

Finally, there are some lines of evidence supporting the modulation of BGN levels as a potential therapeutic approach. Since cerivastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, was shown to inhibit human arterial smooth muscle cells (haSMC) growth [50], and ECM components play a key role in the intima plaque, Siegel-Axel et al. investigated the effects of cerivastatin treatment on ECM production [51]. By using haSMC, the authors developed an *in vitro* model of diabetes and hypercholesterolemia and treated these cells with different doses of cerivastatin in presence of glucose and LDL for 3 days. The cerivastatin treatment significantly

reduced the synthesis of BGN and other ECM components in haSMC, whereas such effects were not influenced by the increase of LDL and glucose. Then, the authors concluded that cerivastatin treatment may exert a protective effect against the formation of atherosclerotic lesion through its direct cellular effects [51]. Also, Sánchez-Quesada and collaborators suggested that the electronegative fraction of LDL may exert a phospholipase C (PLC)-like activity, stimulating lipoprotein aggregation and increasing the binding of LDL to proteoglycans, thus promoting subendothelial retention of these lipoproteins [52], better explaining the mechanisms underlying the subintimal PG/lipoproteins accumulation. Moreover, Lipoprotein(a) has been reported to co-localize with apoB and PGs, especially the chondroitin sulfate-rich proteoglycans [53], including BGN. All together, these lines of evidence remark the prominent role of PGs, and particularly BGN, in atherosclerotic CVD and point to its modulation as an attractive therapeutic target in this setting.

Hypertension

It is well established that blood pressure values have a close relationship with the incidence of CVD [54]. Furthermore, experimental evidence showed that Angiotensin II (angII) is able to promote the pathobiology of ATH stimulating the vascular SMCs to synthesize PGs with high affinity for plasma LDL [37, 55]. Based on the angII function, several authors focused on the relationship between arterial hypertension, inflammatory response and pro-atherogenic PGs synthesis. In 2002 Figueroa et al. showed that angII was able to promote atherogenesis by modulating PGs metabolism in SMCs isolated from human aorta [55]. In these series of experiments, the authors observed that PGs and particularly BGN significantly increased in such cells treated with angII, and that BGN showed increased affinity for LDL as compared to PGs produced by untreated SMCs used as control. Moreover, pretreating cells with losartan, an angII receptor type 1 (AT1) antagonist, prevented the effects of angII administration on PGs metabolism [55].

The ability of angII to prime ATH by increasing vascular PGs synthesis and LDL retention in the artery wall was confirmed in 2008 by Huang and colleagues [37]. In this study, the authors infused

LDLR-/- mice with angII for 4 weeks via osmotic minipumps, feeding animals with a normal laboratory chow. At the end of this period, they measured the LDL retention rate and PGs content in carotid arteries perfused *ex vivo*. The authors found a higher content of BGN and perlecan as well as a two-fold increase in the degree of LDL retention in mice infused with angII compared with controls, receiving saline or norepinephrine by infusion. In order to elucidate if the increase of perlecan and BGN predisposed to development of ATH, authors infused LDLR-/- mice with angII, saline, or norepinephrine for 4 weeks, after this period the infusion was stopped and mice were fed with an atherogenic Western diet for another 6 weeks. Mice infused with angII showed a three-fold increased atherogenesis compared to mice receiving saline or norepinephrine. Importantly, within the lesions, apoB co-localized mainly with BGN and perlecan. These data suggest that angII promote atherosclerosis also by increasing the vascular content of BGN and thus the arterial retention of LDL. Furthermore, in SMC cultures, angII administration was observed to stimulate the synthesis of BGN, which was inhibited in cells treated either with a specific transforming growth factor-beta (TGF-β) neutralizing antibody or with the AT1 blocker losartan. In mice lacking both the LDLR and the angiotensin receptor 1 subtype a (AT1a), angII infusion did not affect BGN content, confirming that angII induces BGN expression through the interaction with AT1a receptor, which in turn mediates the release of TGF-β.

Far from being a local, vascular player, the role of BGN seems to be beyond the endothelial niche. In a series of experiments, Sardo et al. investigated the BGN expression in peripheral monocytes from a population of untreated hypertensive patients without additional risk factors for ATH and signs of CVD [56]. These authors found increased levels of BGN mRNA and protein in hypertensive subjects, irrespective from the presence of carotid intima media thickening. Interleukin-6 (IL-6), TNF-α and high-sensitive C-reactive protein (hs-CRP) were also increased, particularly in hypertensive subjects with increased IMT (IMT>1 mm). These findings support the hypothesis that BGN-mediated vascular damage may be enhanced by angII and that a number of cell compartments could be involved. Authors concluded that the angII-induced BGN expression in

monocytes from hypertensive subjects may be at least in part modulated by blocking the AT1 receptor [57]. As a further confirmation, it has been observed that BGN-enhanced expression in monocytes from hypertensive patients may be counteracted by losartan [57], thus strengthening the notion that BGN levels can be targetable. Interestingly, decreased levels of inflammatory mediators were found to correlate with BGN reduction, in line with the previous findings about non-traditional risk factors summarized above.

Cigarette smoking

Cigarette smoking (CS) contributes significantly to CVD morbidity because of its involvement in all phases of the pathogenesis of ATH, from endothelial dysfunction to acute clinical events [58]. It was shown that CS exposure promote oxidative stress inducing oxygen reactive species (ROS) release [58]. Moreover, CS impairs vascular homeostasis, including ECM organization, by reducing nitric oxide (NO) production, and promotes the inflammatory response that could be observed also in atherosclerotic lesion [59, 60].

It is important to emphasize that hypertension, typically observed in heavy smokers, promotes BGN expression [37, 61]. Furthermore, BGN expression could be stimulated by TGF-β, which is in turn increased in the small airway epithelium of smokers [62].

In 2014, Mandraffino et al. performed a study investigating the BGN expression in peripheral blood monocytes isolated from a cohort of young smokers with no additional cardiovascular risk factors (CVRFs). They found that BGN mRNA expression was higher in young smokers than in control subjects. In addition, the increased BGN expression in young smokers was associated with an altered proatherogenic profile characterized by increased fibrinogen, CRP, and IL-6, lower HDL-C, abnormal carotid arterial stiffness (AS) and intima media thickness (cIMT). Of note, these values were particularly higher in young smokers characterized by high smoke exposure index (SEIx). They concluded that BGN could be a link between the pro-atherogenic status induced by smoke

habit and the onset and progression of vascular damage [63]. Importantly, an effect beyond the vascular compartment was observed in this study.

A further study assessed the effect of long-term abstinence (12 months after smoke cessation) from smoking on monocyte BGN expression. BGN mRNA as well as BGN protein levels were significantly reduced in people who decided to quit smoking for one year. Vascular indices (i.e. carotid-femoral pulse waive velocity), HDL-C and inflammatory markers were also significantly improved. This study demonstrated for the first time that removing a well-known CVRF, such as cigarette smoking, leads to a significant reduction of BGN expression [64]. Moreover, in addition to reinforce the positive impact of BGN reduction for CVD, this study revealed for the first time the possibility of modulating BGN figures by changes in lifestyle factors, a major platform for CV risk reduction in the clinical setting.

Smoking is critically involved in initiation and acceleration of atherosclerosis and CVD mortality [65]. Although the underlying mechanisms and pathways still need to be studied in detail, BGN enhanced expression in active smokers could be mediated by increased levels of TGF-β [62], increased oxidative stress and increased arterial hypertension, all conditions commonly found related to smoke habit [37, 61].

Diabetes

Hyperglycemia significantly increases the risk to develop ATH and clinical cardiovascular events [66]. Several authors have focused on how diabetes and hyperglycemia affect ECM components during the atherosclerotic process, observing abnormalities in the PGs associated with atherosclerotic plaque during hyperglycemia. McDonalds and colleagues studied if diabetes affects the coronary arterial expression of ECM in a porcine model of hyperlipidemia and diabetes [66]. They investigated the expression of hyaluronan, BGN, versican, elastin and apoB in coronary artery sections obtained from non-diabetic normolipidemic, diabetic normolipidemic, non-diabetic hyperlipidemic and diabetic hyperlipidemic animals. In the hyperlipidemic group they found that

diabetes was associated with a significant increase of BGN, hyaluronan and versican while elastin was significantly lower. In this study, changes in ECM expression occurring in diabetes were associated with the onset of a proatherogenic profile [66]. Similarly, Mangat et al. performed a study to investigate the metabolism of apoB48-containing remnant lipoproteins in a cohort of subjects with type 1 diabetes and to investigate the effects of the accumulation of remnant lipoprotein cholesterol with BGN in the arterial wall of streptozotocin-induced diabetic Sprague Dawley male rats [67]. The authors observed that after fasting, plasma apoB48 remnants were significantly higher in subjects affected by type 1 diabetes compared with controls. Furthermore, they found that the retention of remnant cholesterol was sevenfold higher in diabetic rats with the respect to controls and the retained lipoproteins colocalized with a glycated form of arterial BGN. The authors concluded that in type 1 diabetes the retention of remnant lipoprotein-derived cholesterol is facilitated by the glycation in the arterial three and in part facilitates the atherosclerotic process [67]. However, the causes underlying the increased PG expression remained unknown.

Wilson et al. investigated the involvement of metabolic factors associated with diabetes in the alteration of PGs structure and composition [68]. For this purpose, authors evaluated the effects of glucose, insulin, free fatty acid, TGF-β1 and platelet-derived growth factor (PDGF) on PGs metabolism in SMCs, endothelial cells and macrophages. Interestingly, while PGs metabolism was not influenced by glucose concentration, insulin and free fatty acid, they found that TGF-β enhanced the synthesis of BGN and versican, and their metabolism. As a consequence, the authors concluded that the altered PGs synthesis observed in diabetes is due to the elevated levels of TGF-β and not directly to the metabolic factors associated with this pathological condition [37, 68, 69].

Chronic Kidney Disease

CVD is the main cause of morbidity and mortality in chronic kidney (CKD) patients. The process of CV damage starts very early during CKD progression, hence underlining the need of early biomarkers to assist in patient stratification. The connections between CKD and CVD are very complex, involving both inflammation and endothelial dysfunction. Moreover, the associations of CKD with dyslipidemia and diabetes are well-known. Taken together, these lines of evidence point to a potential role for PGs in the development of CVD in CKD.

PGs expression has been observed in kidneys in several studies [70]. BGN is expressed in the interstitium in normal kidneys, mainly in the peritubular and perivascular space as well as in endothelial cells in the glomerulus. Interestingly, other PGs such as decorin exhibit a different expression pattern, hence suggesting different pathophysiological roles for the different PGs [71]. In fact, a number of studies support a crucial role for PGs in CKD pathogenesis. Lee et al. had formerly suggested that glomerular lipid deposition is a common finding in routine kidney biopsies [72], and lipid accumulation has been described to accelerate and exacerbate renal injury [73]. In line with the "response-to-retention" hypothesis, several evidences point to PGs as key players of this phenomenon, as in the case of dyslipidemia. Renal PGs exhibit a high affinity binding to LDL [74]. Thomson et al. recently reported that lipid accumulation could be attributed to glomerular expression of BGN in diabetic nephropathy [75]. Again, a link between BGN and TGF-β was observed. Indeed, BGN overexpression could be regarded as a protective response to neutralize TGF-β activity and thus, kidney fibrosis. However, it could lead to lipid accumulation instead, especially in a high lipid context (such as CKD, dyslipidemia, etc…), hence reinforcing its pathogenic role.

Additionally, a growing body of evidence supports a role for BGN in renal inflammation [70]. On the one hand, BGN is involved in the initiation of inflammation by acting as a cluster of differentiation (CD) 14 ligand and promoting macrophage infiltration [76]. On the other hand, soluble BGN (sBGN) acts as an endogenous ligand of innate immunity Toll-like receptors (TLR)-2

and -4 [77, 78]. As such, sBGN can elicit the production of several inflammatory mediators such as chemokine «C-X-C motif» ligand 13 (CXCL13), regulated on activation, normal T cell expressed and secreted (RANTES), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1-alpha (MIP1-α) and TNF-α via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway activation [78]. Furthermore, it may also lead to IL-1β production and nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome activation, in this case via P2X4/P2X7 purinergic receptors [79, 80]. Taken together, these lines of evidence can account for the association between BGN expression as well as TLR-2/4 activation and renal injury in non-infection models of kidney disease [81], underlining the role of BGN as a danger signal that can trigger sterile inflammation in kidney pathology. Importantly, BGN has been also observed to activate B cells in lupus nephritis [82]. Moreover, in a series of elegant experiments encompassing in vitro techniques and patient samples, Nastase et al. have recently elucidated the mechanisms by which BGN can recruit T helper (T_h) 1 and T_h17 cells into the kidney and contribute to the production of CXCL10 and chemokine «C-C motif» ligand 20 (CCL20) [83], suggesting a broad range of mechanisms in CKD pathology, including adaptive response, associated to BGN.

There are several similarities between atherosclerosis and CKD, hence suggesting shared mechanisms or triggers in the pathogenesis of both disorders, like excess and remodeling of extracellular matrix, lipid and lipoprotein accumulation and macrophage involvement. Then, it is tempting to speculate a role for PGs in CVD in the setting of CKD. Although there is no clear evidence for BGN, consisting evidence underlines a role for endocan in this scenario. Yilmaz et al. have reported that endocan serum levels were positively correlated with CKD stage and were independent predictors of subclinical vascular abnormalities (flow mediated dilatation and carotid intima-media thickness). Moreover, endocan was a significant predictor of all-cause and CVD mortality in these patients and it provided an improved the re-classification capacity of non-traditional CV risk factors [84]. These findings not only support a role for endocan in CVD

development but also pave the ground for its implementation as an early biomarker [85]. A number of effects, such as increasing resistin levels, enhancing inflammation, re-arranging endothelial cytoskeleton or up-regulating soluble intercellular and vascular cell adhesion molecules, namely sICAM-1 and sVCAM-1, have been postulated to explain the effects of endocan on CVD [86]. Additionally, Su et al. have recently reported that in TNF-activated endothelial cells endocan expression increased over-time in parallel with a decrease of IL-10 and a limited TGF-β response, which can reflect an inflammatory and reparative response aimed at removing the damaged endothelium, clearing inflammation and thus repairing the injured tissue [87].

Inflammation

Several studies support the hypothesis of inflammation as a causative process of ATH and therefore the possibility to manipulate the immune response to prevent CV events [88-90]. Importantly, the immune system had a key role in modulating BGN levels in a number of scenarios, as previously discussed.

Some PGs could be also found in a soluble form originated by partial proteolysis of ECM or by *de novo* synthesis by activated cells. Several studies have shown that in such form these molecules can activate the immune system mediating the sterile inflammation, an endogenous response occurring also in chronic disease such as ATH [91, 92]. In physiological conditions, BGN is incorporated in the ECM of various organs. However, following tissue stress or injury, PGs undergo proteolytic cleavage and release from the ECM, acting as a danger signal for the immune system. BGN in its soluble form (sBGN), the intact molecule of such PG, acts as an endogenous ligand for TLR-2 and TLR-4, mediating *ex novo* or amplifying the inflammatory process by mimicking the response to gram-positive (via TLR-2) and gram-negative (via TLR-4) pathogens. Several enzymes have been described to cleave the protein domain of BGN, i.e. matrix metalloproteinase (MMP)-2, MMP-3 and MMP-13 [93-95].

Sphingolipid signaling is critically involved in metabolic diseases including diabetes, metabolic syndrome and ATH and are implicated in the modulation of several inflammatory pathways [96, 97].

Hsieh et al. have shown that, through TLR-4/Toll/interleukin-1 receptor domain-containing adaptor protein inducing interferon-β (TRIF) signaling, sBGN promotes the expression and activity of sphingosine kinase 1 (SphK1), a crucial downstream mediator of BGN-triggered CCL2 and CCL5 expression in murine primary macrophages. SphK1 catalyzes the phosphorylation of sphingosine to produce sphingosine 1-phosphate (S1P), whose activity is a target in many pathological conditions including ATH, acute pulmonary injury, tumorigenesis and more in general in inflammation [98, 99]. Therefore, authors concluded that targeting SphK1 might represent a therapeutic approach to counteract sBGN-mediated sterile inflammation [100].

In macrophages, sBGN mediates the production of the proinflammatory cytokine TNF-α by binding TLR-2 and -4 with a consequent downstream activation of p38 mitogen-activated protein kinases, extracellular signal–regulated kinases 1/2 (ERK 1/2), and NF-κB pathways in a Myeloid differentiation primary response 88 (MyD88)-dependent manner [101]. Furthermore, through TLR-2 and -4 signaling, sBGN mediates the synthesis of various chemokines for neutrophils and macrophages, such as MIP-1α, MIP-2, MCP-1 and RANTES, mediating *ex novo* or amplifying inflammation [82, 101]. Activated cells at the site of injury or damage synthetize *ex novo* BGN, which in turn amplifies the inflammatory response via TLRs [101].

Beside the TLRs, sBGN signaling involves also a member of NOD-like receptors (NLR) family, the pyrin domain-contain 3 (NLRP3) [80]. Once activated, these receptors trigger the formation of NLRP3 inflammasome, a macromolecular complex which induces the release of IL-1β, IL-18 and an inflammatory form of cell death termed as pyroptosis [102]. Actually, Babelova et al. showed that in macrophages sBGN drives the releasing of IL-1β by clustering the TLR-2/-4 with the

purinergic receptor P2X7 [80]. This function, enhanced also by ROS production and by the release of heat shock protein 90 (HSP90), induces a massive inflammatory response [80].

Regarding the pro-inflammatory properties of sBGN, it is not surprising to hypothesize a direct involvement of such PG in the inflammatory status associated with the atherosclerotic lesion.

The interplay between lipids and immune cells is believed to be a driving force in the chronic inflammation of the arterial wall during atherogenesis, therefore several chronic inflammatory conditions are associated with a higher risk of CVD. Accordingly, conditions in which the biological interplay between sBGN/ECM degradation and TLRs has a prominent role, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and inflammatory bowel disease (IBD), have been associated with increased prevalence of CVD. In such diseases, induced and/or accelerated ATH has been proposed as a major mediator of the CVD susceptibility, fostered by altered lipid profile, high levels of circulating inflammatory mediators and activated cells [103].

Importantly, to date a number of observations associating BGN/sBGN activities with ECM remodeling have been revealed in inflammatory rheumatic diseases, but the attention appeared to be focused mainly on cartilage [104, 105], immune nephritis [82, 83, 106] and other pathways involved in disease pathogenesis [107]. Disease-specific evidences about the potential role of BGN or other proteoglycans in inducing/maintaining arterial atherosclerotic vascular damage in immune disease are still lacking.

BGN in atherosclerosis: a focus on the mechanisms

Evidence confirmed that BGN has a pivotal role in the early phases of atherosclerotic process, mainly due to its ability to bind and retain plasma apoB-containing lipoproteins in the subintimal spaces. Retained lipoproteins are more susceptible to chemical-physical modifications (i.e., oxidation). These events progressively promote foam cells formation and ECM remodeling, contributing to atherosclerotic lesion formation and therefore the subversion of artery wall (**Figure 1)**. At molecular level, the peculiar interactions between infiltrated lipoproteins, mainly native or

modified LDL, and BGN account for this phenomenon. More in depth, under high-risk conditions, such as hypercholesterolemia, hypertriglyceridemia, diabetes and severe renal disease, circulating lipoproteins begin to change their electrostatic charge, lipid composition and spatial conformation [108, 109] For example, in these conditions, an increasing proportion of electronegative LDL (LDL(-)) has been found. LDL(-) particles have higher affinity to arterial PGs than native LDLs, because of apoB-100 conformation differences affecting both the amino- and carboxyl-terminal ends. ApoB is a large protein (4536 amino acids) wrapping around the particle and is not exchangeable between other lipoproteins. Two main sites on apoB structure have been proposed to act cooperatively in the association with proteoglycans, even as for the native LDLs: site A (residues 3148–3158) and site B (residues 3359–3369), all located in the receptor-binding area [109]. It has been shown that LDL(-) bind with higher affinity to arterial PGs, mainly due to their increased ability to form aggregates. Aggregated LDL(-) expose additional binding sites, such as site B-Ib (residues 84–94), which plays a major role in the increased binding to PGs [108].

Additional features, such as alterations in the fatty-acid composition of LDL core cholesteryl esters may affect the binding to PGs and thus atherogenicity of those particles. A study performed on murine models [110] brilliantly demonstrated that the enrichment of LDL core with cholesteryl oleate increased the affinity for LDL binding to BGN and promoted atherosclerosis. The peculiarity of this study lies in the using of surface plasmon resonance technique, which allowed to measure the rate and extent of formation and dissociation of LDL-BGN complexes, in real-time and with the highest sensitivity.

Moreover, plasma lipolytic enzymes such as LPL, sphingomyelinase (SMase) and secretory group II phospholipase A_2 ($sPLA_2$) may directly modify circulating LDLs, increasing their binding affinity for PGs (**Figure 1**). Indeed, BGN activity is closely related to LPL activity. In normal conditions LPL catalyzes the hydrolysis of triglyceride-rich lipoproteins with a consequent production of non-esterified fatty acids and 2-monoacylglycerol utilized for tissues metabolic needs.

On the other hand, in high plasma lipids contexts – as well as in the presence of triggering noxae - LPL produces large amounts of small-sized LDLs reducing the accumulation of remnant lipoproteins. Small-sized LDLs could be modified and retained by BGN in the sub-intimal compartment. These events are related to hyperplasia of endothelial and smooth muscle cells of the intima, increased density of collagen fibrils and local inflammation characterized by high levels of TNF-α. A lipid lowering therapy reduces BGN expression and activity with important consequences in the pathobiology of ATH.

In addition to LPL, $sPLA_2$ is known to modify native LDLs, particularly reducing their phospholipid and free-cholesterol content, and making them more susceptible to further lipolysis by SMase [111]. This event tend to reduce polar components at the surface of LDL particles, favouring their aggregation, increase in binding affinity for extracellular proteoglycans, such as BGN, and their irreversible entrapment into subendothelial space.

$sPLA_2$- and SMase-mediated lipolysis has been also linked to LDL(-) production, which are particular prone to aggregation [108], as stated above.

However, BGN proatherogenic effects extend far beyond the lipoprotein binding and retention. BGN interacts and modulates several pathways; indeed, classic and non-classic CV risk factors affect BGN actions, also through the multiple targeting on angII/AT1, TGFβ/TGFR and MAPK - mediated pathways.

Experimental models confirmed that BGN expression and activity could be enhanced by angII, and negatively modulated by AT1 receptors blocking. This can explain at least one of different ways through which high blood pressure promotes atherosclerosis (**Figure 2**).

As reported, BGN expression increases in heavy smokers and correlates to an altered inflammatory/proatherogenic profile, characterized by increased pro-inflammatory cytokines.

BGN could be affected by NO unbalanced synthesis and altered ROS production, typically observed in essential hypertension and also in heavy smokers. TGF-β also affects the expression and activity of BGN. Again, hypertension per se as well as the alterations observed in heavy smokers induce TGF-β protein and mRNA hyperexpression in endothelial cells and in peripheral blood monocytes. A pathway involving BGN enhanced expression via TGF-β activity has been proposed [112]. Indeed, TGF-β enhances BGN expression via TGFRI and TGFRII-Smad signaling. Furthermore, angII enhances TGF-β expression via AT1R-jak-stat and AT2R-MAPKs signaling. In light of this evidence, the existence of a vicious circle can be hypothesized: in essential hypertension, reduced NO associated with increased angII activity stimulates TGF-β production, which in turn promotes BGN synthesis and activity, beyond further reducing NO production. Since angII is able to enhance BGN synthesis and activity, it could be proposed that both TGF-β and angII signaling in high plasma lipid contexts (such as CKD, dyslipidemia, diabetes mellitus, etc.) exert a synergic effect on BGN with pro-atherogenic potential.

A role for BGN and TGF-β pathways was reported in experimental models of diabetes and CKD. In diabetes, BGN-mediated retention of remnant lipoproteins is enhanced by increased glycation of arterial three and by an increased production of TGF-β [67], and this arrangement could be involved in the atherosclerotic process observed in T2DM [68]. Indeed, in a model of diabetic LDLR-/- mice Thompson and colleagues suggested a role of TGF-beta as the univocal proatherogenic mediator of BGN [113].

Concerning CKD, the overexpression of BGN could be regarded as a protective response to neutralize TGF-β activity and thus, kidney fibrosis; however, under hyperlipidemic conditions BGN also promotes lipid deposition and therefore atherogenesis. BGN, once excised or released from activated cells, acts as a danger signal promoting sterile inflammation by binding TLRs 2 and 4 thus reinforcing its pathogenetic role (Figure 3).

The question of whether soluble BGN has a key pro-atherogenic role remains unsolved; however, an increased expression of TGF-β promoting endothelial ECM remodeling and enhancing the activity of matrix proteases such as MMPs, could promote BGN cleavage which in turn participates to systemic and/or local inflammation promoting thus endothelial activation.

Importantly, activation of innate immunity via TLRs, NFkB, NODs pathways and NRLP3 signaling has been consistently linked to ATH progression and plaque destabilization [114]. Taken together, these lines of evidence point to BGN as a potential mechanistic missing link between risk factor-related inflammation pathways and atherosclerosis development and progression.

Conclusions

ATH is a chronic and evolutive disease which leads to a morpho-functional subversion of artery wall layers. In the last twenty years, new important acquisitions contributed to improve the knowledge on the pathogenesis and the evolution of atherosclerotic damage. Among them, the alteration of ECM and in particular of PGs has been recognized as a determining factor in the pathobiology of atherosclerotic process. Here we reported a collection of data referred to the BGN expression and its relative role in the onset of atherosclerosis in presence of cardiovascular risk conditions. As described, BGN is expressed in the early phases of pre-atherosclerotic lesion and exerts a crucial role for the initial deposition of lipids in the sub-intimal space. This literature revision highlights how the expression of this proteoglycan increases and participates both directly and indirectly to the atherosclerotic process (as confirmed by *in vivo* and *in vitro* studies), particularly in the presence of a triggering "noxa", such as dyslipidemia, hypertension, cigarette smoking, diabetes, chronic kidney disease and inflammatory status, able to ingenerate a systemic relapse. Moreover, several of the reviewed models seem to suggest a close interrelationship between BGN and apoB-containing lipoprotein-cholesterol. Furthermore, the studies reported here show how the effects of BGN and other PGs involved in the atherosclerotic process are sometimes

reversible, albeit little is known on the possibility to slow down the process once started, and/or to modulate the inflammatory response related to this process, involving both innate and adaptive mechanisms and with a special focus on TNF-α and TGF-β responses. As general concept, a research agenda pertaining the association between BGN and atherosclerosis (Table) can be outlined to achieve a better understanding of BGN changes and falls in the modulated pathways may significantly contribute to improve the current knowledge of atherogenesis, thus providing the rationale for new therapeutic approaches, including pharmacological and non-pharmacological strategies.

Figure/Illustrations legends

Figure 1. Pro-atherosclerotic processes supported by biglycan. Atherogenic lipoproteins infiltrate the sub-endothelial space and bind biglycan with high affinity, mainly through ionic interactions. Small dense LDL, generated by the lipolytic/hydrolytic activity of plasma LPL, $sPLA_2$ and SMase on native LDL, easily reach the subendothelial space (bold dotted line) and show the highest binding affinity for BGN. The formation of such complexes promotes lipoprotein retention, aggregation and chemical-physical modifications (i.e., oxidation). Tissue-resident or blood monocyte-derived macrophages mediate the removal of modified lipoproteins (browned particles), progressively transforming into foam cells, releasing proinflammatory cytokines and chemokines, and contributing to the atherosclerotic lesion development. Similar to native and small size LDL, Lp(a) may undergo to internalization and modification, since it has been found to colocalize with BGN in atherosclerotic lesions. Abbreviations - Lp(a), lipoprotein(a); LDL, low density lipoprotein; LPL, lipoprotein lipase; $sPLA_2$, secretory phospholipase A_2; SMase, sphingomyelinase; VSMC: vascular smooth muscle cells.

Figure 2. Cardiovascular risk factors, angII and TGFβ-mediated increased biglycan expression and secretion. Several cardiovascular risk factors, i.e. cigarette smoking, mediate the increase of BGN expression and secretion (dotted line), although the molecular mechanisms underlying these pathways have not been elucidated so far. On the other hand, through the activation of its AT1 receptor, angII may increase the expression of TGFβ. Once secreted, TGFβ may interact with its own receptor in an autocrine fashion, in turn upregulating both the expression and secretion of BGN, and its pro-fibrotic pathways. The angII-TGFβ-BGN loop is particularly relevant in some high risk conditions, such as hypertension and CKD. Finally, the upregulation of BGN contributes to the vascular damage, according to the "response-to-retention" hypothesis (box at the bottom right).

Abbreviations – CKD, chronic kidney disease; angII, angiotensin II; AT1, angiotensin II receptor type 1; TGFβ, transforming growth factor beta; MAPK, mitogen-activated protein kinase; BGN, biglycan.

Figure 3: Biglycan induces pro-inflammatory cascades in macrophages. Macrophages may respond to the biglycan (BGN) stimuli by secreting several cytokines and chemokines, thus fostering the inflammatory reaction. Following tissue stress or injury, BGN may be released from the extracellular matrix by proteolytic cleavage and, as soluble molecule (sBGN), it activates TLR-2 and TLR-4, mediating *ex novo* or amplifying inflammatory processes. Sphingolipid signaling is critically involved in metabolic and inflammatory diseases. Through the direct stimulation of TLR-dependent pathways and via NF-κB, sBGN promotes the expression and activity of sphingosine kinase 1 (SphK1), the enzyme catalyzing the phosphorylation of sphingosine to sphingosine 1-phosphate (S1P), triggering the BGN-mediated secretion of MCP-1 (CCL2) and RANTES (CCL5). Moreover, sBGN promotes the clustering of TLRs and P2X4/7, leading to increased IL-1β production and secretion, via inflammasome (NLRP3) activation.

Abbreviations – IL-1β, interleukin-1 beta; NLRP3, nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; TLRs, Toll-like receptors; CD14, cluster of differentiation 14, P2X4/7, P2X purinoceptor 4/7; TNF-α, tumor necrosis factor alpha; MCP-1, monocyte chemoattractant protein 1 (or chemokine «C-C motif» ligand 2, CCL2); MIP-1α: macrophage inflammatory protein 1-alpha (or chemokine «C-C motif» ligand 3, CCL3); CXCL13, chemokine «C-X-C motif» ligand 13; RANTES, regulated on activation, normal T cell expressed and secreted; SphK1, sphingosine kinase 1.

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Highlights

- Matrix proteoglycans mediate lipid accumulation in subendothelial space
- Cardiovascular risk factors affect lipoprotein/proteoglycans interactions
- Understanding PGs could unveil the link between CV risk factors and atherosclerotic damage.

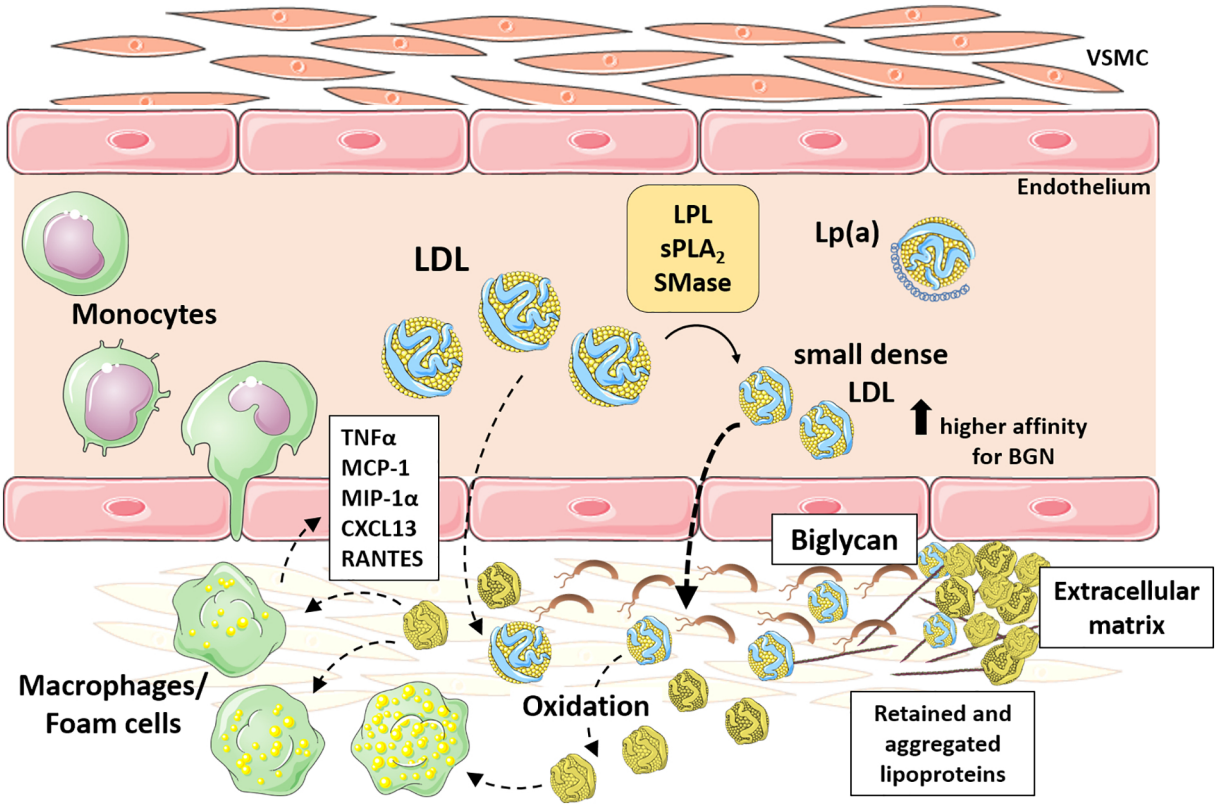
VSMC
Endothelium
LDL
LPL
sPLA2
SMase
Lp(a)
Monocytes
small dense
LDL
higher affinity
for BGN
TNFα
MCP-1
MIP-1α
CXCL13
RANTES
Biglycan
Extracellular
matrix
Macrophages/
Foam cells
Oxidation
Retained and
aggregated
lipoproteins

Figure 1

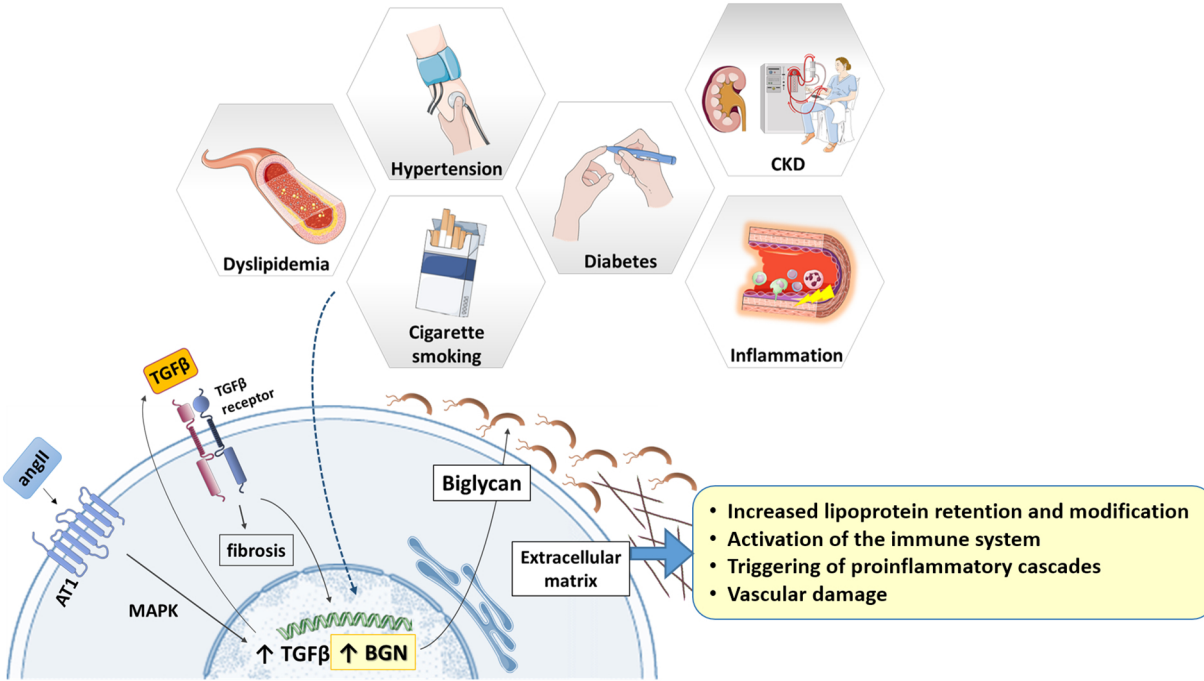
Hypertension
CKD
Dyslipidemia
Diabetes
Cigarette smoking
Inflammation
TGFβ
TGFβ receptor
angII
AT1
MAPK
fibrosis
↑ TGFβ
↑ BGN
Biglycan
Extracellular matrix
• Increased lipoprotein retention and modification
• Activation of the immune system
• Triggering of proinflammatory cascades
• Vascular damage

Figure 2

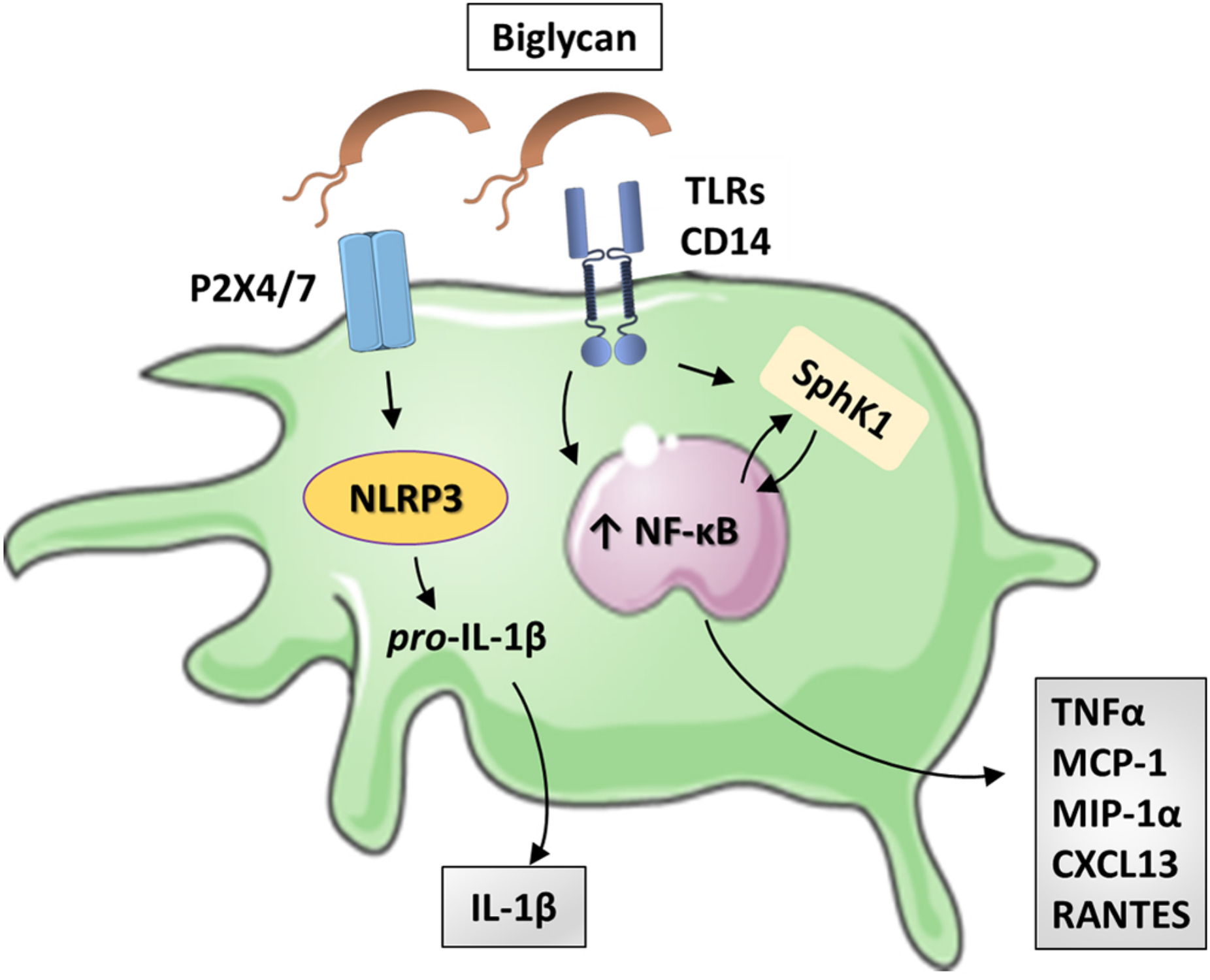
Biglycan
TLRs
CD14
P2X4/7
SphK1
NLRP3
↑ NF-κB
pro-IL-1β
IL-1β
TNFα
MCP-1
MIP-1α
CXCL13
RANTES

Figure 3