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Review Article

Glycosaminoglycans as Novel Targets for *in vivo* Contrast-Enhanced Magnetic Resonance Imaging of Atherosclerosis

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Abstract

Atherosclerosis is an important promoter of cardiovascular disease potentiating myocardial infarction or stroke. Current demand in biomedical imaging necessitates noninvasive characterization of arterial changes responsible for transition of stable plaque into rupture-prone vulnerable plaque. In vivo contrast enhanced magnetic resonance (MR) imaging (MRI) allows quantitative and functional monitoring of pathomorphological changes through signal differences induced by the contrast agent uptake in the diseased vessel wall, therefore it is the ideal modality toward this goal. However, studies have so far focused on the cellular targets of persisting inflammation, leaving extracellular matrix (ECM) far behind. In this review, we portray ECM remodeling during atherosclerotic plaque progression by summarizing the state of the-art in MRI and current imaging targets. Finally, we aim to discuss glycosaminoglycans (GAGs) and their functional interactions, which might offer potential toward development of novel imaging probes for in vivo contrast-enhanced MRI of atherosclerosis.

More Information

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Introduction

Atherosclerosis is a systemic inflammatory disorder which affects majorly large and medium-sized arteries [1]. It is a promoter of cardiovascular disease *(*CVD) potentiating myocardial infarction or stroke [2]. Molecular imaging studies utilizing different modalities have resulted in better understanding of the disease mechanisms, however the gravity of the health and economic burden of CVD calls for improvements in the diagnosis [3-5]. Current demand in biomedical imaging entails in vivo detection of atherosclerotic plaques with quantitative or predictive value through identifying vessel wall alterations leading to rupture-prone vulnerable plaque [6].

Contrast-enhanced magnetic resonance (MR) imaging (MRI) is the ideal modality towards this goal [7]. It allows non-invasive discrimination of major pathomorphological changes in atherosclerotic plaque progression: lipid core, fibrous cap, calcifications, intraplaque hemorrhage and acute thrombosis [8]. The use of gadolinium (Gd)-based contrast agents (CAs) on the clinical level and iron oxide nanoparticles (IONPs) in experimental studies have placed plaque biology ahead of luminal stenosis [8-12]. Coexisting with the lipid accumulation and retention, inflammatory mediators are currently extensively investigated by MRI, in which cellular components are the most attractive targets [13-17].

Although generally ignored in the field of molecular imaging, considerable attention has recently been raised toward molecular imaging of the extracellular matrix (ECM) in the context of atherosclerosis [18]. Apart from being the major component of the atherosclerotic plaque ultrastructure, coordinate synthesis and turnover of the ECM is a characteristic feature of plaque instability [19]. ECM alterations during arterial remodeling in atherosclerotic plaque progression involve highly abundant molecular interactions, which exhibit importance toward unraveling new targets, thus developing novel imaging probes.

Among ECM components, glycosaminoglycans (GAGs) are well known for their antigenic characteristics in drug development or tissue engineering [20,21]. Following reports on tissue deposition of Gd in nephrogenic systemic fibrosis

(NSF), a fatal disease observed in patients with end stage renal disease who had received Gd-based MR CAs, studies have demonstrated colocalization of elements including phosphorus or calcium [22,23]. Insoluble complex formation through transchelation of Gd by physiological anions such as glycosaminoglycans has been postulated as a plausible underlying mechanism [24,25].

In this review, we aim to explore potentials of GAGs for in vivo contrast-enhanced MR imaging of atherosclerosis with a deeper look into their features as information-loaded sensing molecules of the ECM. We will try to elucidate ECM remodeling during atherosclerotic plaque progression by examining distributions and dynamic alterations of GAGs. Finally, we will discuss functional characteristics of GAGs in molecular interactions, which could guide investigations aiming at developing novel targets to identify vessel wall alterations leading to rupture-prone vulnerable plaque.

Atherogenesis and imaging targets

Atherogenesis is the interplay of smooth muscle cells (SMCs), immune cells, fibroblasts and the ECM (Figure 1) [26]. The native endothelium maintains vascular homeostasis by the support of laminar shear stress within the arteries [27]. Altered flow conditions where turbulent flow dominates over laminar sheer stress transform the endothelium into permeable and leaky form resulting in its activation [28]. This accounts for early atherogenesis, which is characterized by the formation of neointima through low density lipoprotein

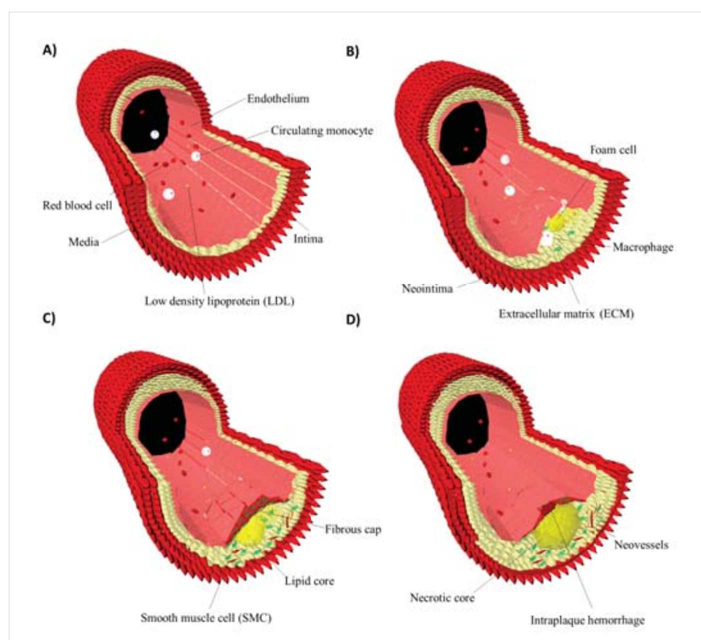

Figure 1: Atherosclerotic plaque progression. The native endothelium maintains vascular homeostasis (A). Early atherogenesis is characterized by the formation of the neointima through lipid influx, monocyte transmigration and foam cells (B). Persisting inflammation during atherosclerotic plaque progression leads to formation of lipid cores. Arterial remodeling results in increased vasa vasorum activity forming neovessels. In parallel, medial smooth muscle cells undergo phenotypic changes and migrate into the neointima. Here, they proliferate and produce new extracellular matrix molecules forming the fibrous cap. Tissue breakdown and thinning of the fibrous cap provoke erosion and renders the plaque vulnerable by inducing tears, intraplaque hemorrhage and thrombosis (C,D) [19,38].

(LDL) influx and subsequent oxidative modification [29]. Endothelial cell adhesion molecules (CAMs), transmigration of monocytes or lymphocytes through interactions with selectins or integrins and angiogenesis offer a range of imaging targets [30-32]. Among these, vascular cell adhesion molecule-1 (VCAM-1) and αvβ3-integrin have been extensively investigated [33,34]. Additionally, proinflammatory cytokines or chemokines including interleukin-1 (IL-1), monocyte chemotactic protein-1 (MCP-1) and tumor necrosis factor-α (TNF-α) are attractive imaging targets of early atherogenesis [35,36].

Arterial remodeling and increased vasa vasorum activity during plaque progression substantiate expression of early markers and expose diversity in target molecules [1-,37]. LDL influx escalates transmigration of monocytes into the neointima, where they differentiate into mature macrophages. Macrophages are the major inflammatory elements of both early and late atherosclerotic lesions, thereby their phagocytic activity has so far been the most attractive target for contrast-enhanced MRI [38,39]. Phagocytosis offers a unique strategy as it results in concentration of CAs. Macrophage uptake of IONPs in atherosclerotic plaques was reported for the first time in a rabbit model, which was followed by a multicenter phase III clinical trial documenting accumulation of IONPs around the inflamed regions of atherosclerotic plaques [40,41]. Shortly after, in an *in vivo* study on human ruptured and rupture-prone lesions, Kooi, et. al. reported substantial signal decrease 24 h after intravenous administration [42].

Besides phagocytosis, proteolysis as a cohort of SMCs, macrophages, mast cells and T-lymphocytes allows monitoring of ECM degradation and thinning of the collagen-rich fibrous cap [43,44]. Matrix metalloproteinases (MMPs), cathepsin or serine proteases, chymase, tryptase or stromelysin-1 are targeted to assess the susceptibility to rupture or thrombosis [45-47]. Finally, screening for upregulated vasa vasarum activity, late stage immune cell antigens, activated platelets, fibrin and apoptosis markers such as annexin-V are among major targets of imaging vulnerable plaques [48-50].

MR imaging of the extracellular matrix

ECM is a highly organized three-dimensional network of fiber forming and non-fiber forming molecules cross-linked into a biomechanically viscoelastic composition (Figure 2) [51]. ECM components consist of collagen, elastin and fibrin, proteoglycans (PGs), glycosaminoglycans (GAGs) and glycoproteins such as fibronectin, vitronectin, laminin and tenascin [20,52]. Deposition and remodeling of the ECM are among the hallmarks of atherosclerosis [53]. Early atherosclerotic lesions are characterized by the deposition of molecules that create a loose matrix, also known as 'provisional matrix' [54]. The major molecular composition of this proliferative phase consists of fibronectin, tenascin and thrombospondin [55]. ECM of fatty streaks in human atheroma

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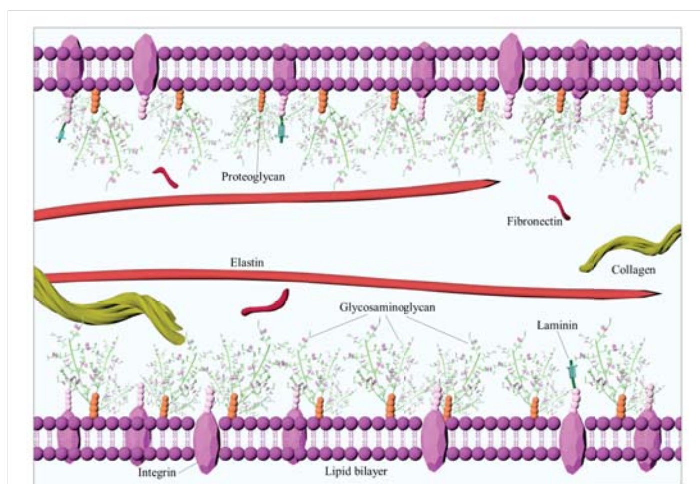

Figure 2: Extracellular matrix structure. Extracellular matrix is a highly organized three dimensional network of fiber forming and non-fiber forming molecules cross-linked into a biomechanically viscoelastic composition [51]. It's major components are collagen, elastin, fibrin, proteoglycans, glycosaminoglycans, glycoproteins such as fibronectin, vitronectin, laminin and tenascin.

was shown to contain substantial level of fibronectin, which attracts fibrillogenesis and fibronectin isoforms for MR imaging of early angiogenesis [56,57].

Transformation of the provisional matrix to fibrous matrix happens upon upregulation of the fibrous ECM components [55]. Collagen is the principal constituent of this state with varying types and tissue distributions [58]. It's relative abundance, major role in maintaining the structural integrity and participation in the key inflammatory reactions make it a valuable target [59-61]. Collagenous thickening of the fibrous cap, retention of oxidized LDL (ox-LDL) by binding to collagen type I, III, IV and V as well as its turnover by the MMP activity result in a large pool of imaging targets [62-66].

Elastin is the second most abundant fibrous constituent of the ECM, majorly found in the media of the healthy arterial wall [67]. Besides maintaining the structural integrity, it prevents LDL penetration by forming lamellar layers [68]. Degradation and fragmentation of elastin, thus its absence in the newly remodeled matrix lead to increased LDL retention [69]. Alterations between elastogenesis and the turnover empower it's use in monitoring lesion progression and determining the propensity into the rupture-prone plaque [70,71]. Characterization and quantification of the plaque burden by an elastin-targeting CA was reported promising for screening large human populations [72,73].

Fibrin, although less abundant then collagen and elastin, is another fibrous molecule especially overexpressed in the ECM of advanced plaques with erosions, which result in fissures reaching into the necrotic core and hemorrhage [74]. Fibrin-rich ECM aggregation leads to activation of the coagulation cascades, and recruitment of proinflammatory cells [75,76]. Domain-based modular interactions and the procoagulant activity render fibrin an important target for the detection of high-risk plaques with subacute and acute indications [77-80].

Glycosaminoglycans

GAGs are linear polysaccharides consisting of alternating disaccharide units of an amino sugar and uronic acid mostly found covalently attached to a core protein (Figure 3) [81]. They are a minor constituent of the healthy arterial wall, but their upregulation during lesion progression has been well documented [82,83]. Important types of GAGs in the vasculature are heparan sulfate (HS), heparin, chondroitin sulfate (CS), dermatan sulfate (DS) and hyaluronan (HA) [84]. GAGs differentiate from one another by their monomeric building blocks, position and configuration of the glycosidic linkages, chain length, and by the degree and position of sulfation and epimerization [85]. All GAGs except HA are sulfated or epimerized at variable degrees, which are coordinated in a specific manner [85]. The combinatorial biosynthetic process, chain elongation, and modifications give rise to an incredible structural diversity, imposing GAGs to be the most information-dense molecules in biology [86,87].

Immunohistochemical studies on atherosclerotic lesion progression have revealed distinct topography of GAGs with differences in spatial and temporal distribution [88]. Overall, CS/DS is known to increase, and HS is known to decrease [89-91]. Early lesions with stable endothelium, contractile SMC phenotype and occasional macrophage content display GAG distribution restricted to the cellular areas, whereas advanced lesions characterized by dysfunctional endothelium, synthetic SMC phenotype and macrophage content display highly complex distribution [88,92,93].

GAGs play important roles in supporting the structural organization of the ECM, regulating viscoelasticity and tissue permeability, lipid metabolism, cell signaling, migration, and differentiation [94-96]. Some of their critical functions have been decoded through genetic studies, in which manipulations

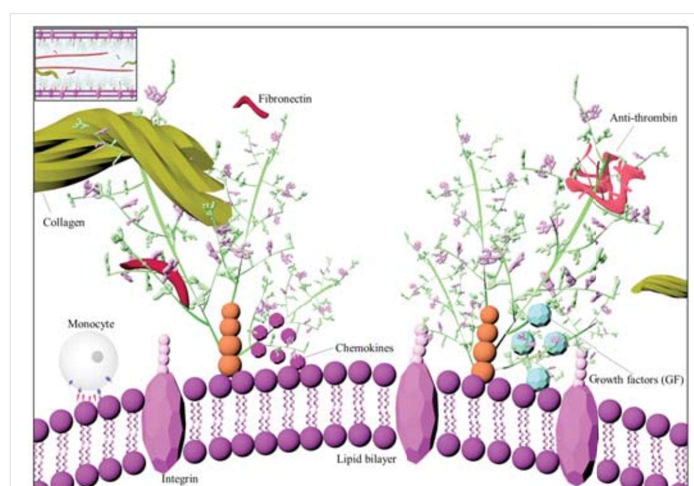

Figure 3: Illustration of glycosaminoglycan structure and interactions. Glycosaminoglycans are linear polysaccharides consisting of alternating disaccharide units of an amino sugar and uronic acid mostly found covalently attached to a core protein [81]. Glycosaminoglycan chains contribute to tertiary complex formation through establishing electrostatic bridges between nearby molecules and assist higher level interactions involving hydrophobic forces, hydrogen bonding or ionic interactions between proteins [99,100].

of genes encoding their biosynthetic enzymes resulted with severe disruptions [97]. GAGs exert their functions through localization, stabilization, activation or inactivation of proteins (Figures 3,4) [98]. GAG chains contribute to complex formation through establishing electrostatic bridges and assist higher level interactions [99,100]. For instance, GAG-LDL complexes were reported to be internalized by macrophages easier than LDL alone [101]. Lipid retention happens upon initial electrostatic binding with CS/DS chains of the PGs secreted by vascular SMCs and is followed by hydrophobic self-association of the lipoprotein [102,103]. However, positively charged amino acids on the apolipoprotein B, and their interactions with the sulfate or carboxylate groups on the GAG chains are crucial for binding [104,105].

Versatile binding ability permits different GAGs to interact with the same protein or different proteins simultaneously (Figure 4) [85,106]. Platelet factor-4 (PF4) binding is good example for cooperative activity [107]. During coagulation, PF4 is released from the α-granules of activated platelets by the coordinated transfer from the CS to more sulfated polysaccharides [108]. PF4 binds to and neutralizes heparin upon which it modulates fibroblast growth factor-2 (FGF-2) activity [109]. Similarly, the interaction between PF4 and neutrophil cell surface CS constitutes an essential mechanism for modulation of immune response by GAGs serving as physiologically relevant receptors [110].

Finally, GAGs perform the highest affinity binding by inducing conformational changes and surface complementarity on the proteins, attributed to torsional angle changes in the backbone chains of GAGs [111,112]. HS-FGF and heparin-anti thrombin-III (AT-III) are the most well-known examples for such interactions. HS enhances FGF binding and oligomerization at its receptor owing to the presence of rare sulfation and epimerization patterns on at least tetrasaccharides [113,114]. AT-III is an inhibitor in the coagulation cascade, which binds to thrombin in 1:1 molar ratio [81]. Heparin forms a tight ternary complex with the AT-III through a specific pentasaccharide consensus motif and accelerates the rate of thrombin inhibition [111,115]. A unique sequence having four anionic groups (two N- and two O-sulfates, 3-O-sulfation being critical) on the glucosamine residues has been shown to be crucial for the ionic contacts with the protein [116]. DS-heparin cofactor II interaction was also reported to take place through binding of a specific DS hexasaccharide, which constitutes only 2% of hexasaccharides in DS, rendering it an important example for rare modifications on GAGs necessary for their functional roles [117,118].

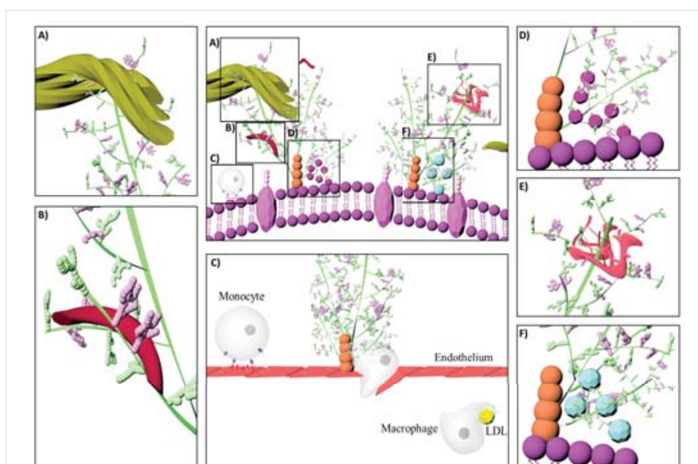

Figure 4: Schematic illustration of different glycosaminoglycan interactions. Glycosaminoglycans localize, stabilize, activate or inactivate proteins [98]. Decorin is a proteoglycan form of dermatan sulfate, which binds to collagen (A). Heparin interacts with fibronectin (B) [133]. Monocyte transmigration happen through interactions with the cell surface heparan sulfates on the endothelium and glycosaminoglycan low density lipoprotein complexes are more easily internalized by macrophages than lipoproteins alone (C) [101,127]. Glycosaminoglycans serve as storage reservoir for chemokines (D) and growth factors (F) [128]. They perform the highest affinity binding by inducing conformational changes and surface complementarity on the proteins [111,112]. Heparan sulfate-fibroblast growth factor and heparin anti thrombin III are the most well-known examples for such interactions (E).

GAGs as novel targets in contrast-enhanced MRI

Toward the goal of detecting atherosclerotic plaques at early stages, it is imperative to enhance the diagnostic value of existing approaches in characterizing the transition of stable plaque into vulnerable plaque [16]. In that regard, high spatial resolution-based investigations determining microdistribution of CAs in atherosclerotic plaques and their interactions with the ECM components would be beneficial [119]. Additionally, immunohistochemical investigations supporting existing MRI approaches should be reinforced by GAG immunostaining methods and complemented by elemental microscopy [120-122]. GAGs are a minor constituent of the healthy arterial wall but their rapid upregulation during lesion formation and progression along with their functional roles in major inflammatory processes highlight their potency in developing novel CAs that might offer advantages over existing MRI methods [82,83].

In summary, the contrast function of the agents administered arise from catalytically shortening the relaxation times of bulk water protons [123]. The polyelectrolyte nature of GAGs exposes them as the major charge hotspots in the ECM, making it suitable for exploring their properties in binding to and clustering CAs [124]. Also, lesion formation induces high expression of antigenic structures. These are almost always in the form of GAGs or glycoprotein conjugates [20]. Immune cells are often activated by these molecules and guided to the site of action through interactions of chemokines or cytokines with GAGs [125,126]. This applies to concentration of growth factors (GFs), enzymes or enzyme inhibitors as well [127,128]. Identifying types or compositions of GAG molecules in such interactions allow the mimicry of these by GAG-CA conjugates. Similarly, major pathomorphological changes during lesion progression involve GAGs, which can be tailored to purpose of imaging. Among those, interactions of CS/DS chains secreted by vascular SMCs with LDL molecules and hydrophobic self-association might serve well for the development of novel liposome-based CAs [69]. Moreover, decorin is a PG-form of DS

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that binds to collagen, thereby might be engineered to monitor processes including thinning of the fibrous cap, erosions or calcifications [93,129]. Notably, elastin assembly, elastin binding of fibronectin or coagulation cascades, which display versatile affinity binding ability of GAGs offer useful strategies for targeting approaches not only through traditional protein components, but also through GAGs [85,106,130].

Finally, sulfation holds the key for elucidating unfamiliar features of GAGs during atherosclerotic plaque progression [131]. Variations in type, position or degree of sulfation, which result in distinct domain formations with particular or even rare-type of modifications are the core factors underlying their functional interactions [132]. Thus, it is highly conceivable that better understanding of these features is promising toward unraveling new targets, and development of more sophisticated MR contrast agents.

Conclusion

In this review, we aimed to explore potentials of GAGs for vivo contrast-enhanced MR imaging of the ECM in the context of atherosclerosis. D*iseases* present qualitative and quantitative changes in the ECM, in which GAGs take on diverse functional roles. ECM has been receiving attention as a potential area of research in molecular imaging. In parallel, technological advances in glycobiology have been increasing, among which chemical synthesis of oligosaccharides with desired modifications holds great potential for future investigations. Differential spatial or temporal distribution of GAGs in the vasculature, their rapid upregulation upon atherosclerotic plaque formation and functional roles in molecular interactions arising from versatile binding characteristics praise them as potent candidates toward development of novel imaging probes for in vivo contrast-enhanced MRI of atherosclerosis.

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