


Glycans and Glycan-Binding Proteins in Atherosclerosis

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Abstract

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Complex glycans are readily accessible on the endothelium and on cell and plasma components. They interact with glycan-binding proteins which translate their structure into function. Advanced analytical tools are available to investigate their structure and functional interactions. Modifications to glycan structures which alter their capacity to bind proteins are particularly relevant in atherosclerosis. We summarize the regulatory role of glycans and their binding partners in the development of the disease. Given their complexity, accessibility, and important functional role, glycans and glycan-binding proteins represent promising diagnostic tools and therapeutic targets.

Introduction

Glycans are carbohydrate structures that contain more than one monosaccharide unit. The human glycome, the pool of all mainly extracellular glycans, is a complex, universal, and dynamic system which confers biological information.^{1,2} Glycans represent a profile of the condition and environment of cells which is read and translated into function by glycan-binding proteins (GBPs). Advanced biochemical tools are at hand to investigate the pathophysiological role of glycans which rely in part on their interaction with GBPs. Vascular glycans regulate the interaction between circulating cells, plasma components, and endothelial cells, and contain numerous GBPs. Therefore, alterations in the vascular glycome are associated with vascular disease and particularly the pathogenesis of atherosclerosis which is characterized by endothelial dysregulation, platelet adhesion, leukocyte recruitment, and accumulation and phagocytosis of lipoproteins. Moreover, specific glycan structures and GBPs are suitable therapeutic targets and agents. This article sum-


marizes their pathophysiological relevance and diagnostic and therapeutic potential.

The Discovery of Glycans and GBPs

The role of glycans and GBPs in vascular biology has been known for over a century. Landsteiner described the first glycan determinants, the blood groups, at the turn of the century.³ Watkins and Morgan later revealed that glycan structures create the blood group phenotypes. They were among the first to describe the presence of glycans on the cell surface.^{4,5} The discovery of the ABO system revolutionized transfusion medicine. Recently, genome-wide association studies showed that subjects with specific single-nucleotide polymorphisms (SNPs) in the ABO gene locus are at higher risk for coronary artery disease and myocardial infarction.^{6,7} In some cases, these SNPs can be linked to a non-O phenotype.⁸ Although the reasons for this correlation remain unclear, blood group glycans are also expressed on platelets and glycoproteins (GPs), and the ABO locus is associated with platelet function and plasma levels of von Willebrand factor (VWF) and low-density lipoprotein (LDL).^{6–9}

Stillmark isolated the first GBP, ricin, the hemagglutinating component of plant seed extracts.¹⁰ When the blood group specificity of hemagglutinins was discovered, they

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were termed “lectins” (from Latin *legere* = to read, collect, select).^{11,12} In the 1920s, Howell discovered heparin, the most prominent glycosaminoglycan (GAG) in clinical use. The resolution of its structure and its first application in the prophylaxis of venous thrombosis followed in the 1930s. Its anticoagulant mechanism, that is, the inactivation of factor Xa and thrombin by interaction with antithrombin, was described 40 years later.^{13–15}

The aforementioned discoveries suggest a strong link between the pathophysiological relevance of glycans and their capacity to bind GBPs.

GBPs Translate Glycan Structures into Function

The human glycome is built from 10 different monosaccharides: xylose (Xyl), glucose (Glc), galactose (Gal), N-acetylglucosamine and -galactosamine (GlcNAc/GalNAc), mannose (Man), fucose (Fuc), glucuronic acid (GlcA), enzymatically transformed to iduronic acid (IdoA), and sialic acid (Neu5Ac). These monosaccharides are linked via O-glycosidic linkages in α - or β -anomer conformation by glycosylating enzymes termed glycosyltransferases. The abundance, activity, and specificity of these enzymes and of their substrates (activated monosaccharides) determine the complexity of polysaccharides. Glycans are carbohydrate structures which contain more than one monosaccharide. They may be linear or branched. They may exist in free form but are mostly conjugated to lipids as glycosphingolipids or to proteins as GPs or proteoglycans. The glycan chains are linked to asparagine (N-glycans) or to serine or threonine (generally termed Ser/Thr-linked which comprise O-glycans and GAG conjugates, see below). The glycome is divided into GAGs and other glycan determinants. GAGs are linear glycans which consist of repetitive disaccharide units. They can occur in free form as nonsulfated hyaluronan (HA) or linked to proteins as sulfated proteoglycans. The most abundant proteoglycan is the heparan sulfate (HS) proteoglycan (→Fig. 1). All cell surface-bound glycoconjugates constitute the glycocalyx which surrounds every cell in the organism.^{1,2,16} HA is considered to be part of the glycocalyx by some authors.¹⁷

Glycans can bind GBPs. GBPs comprise sulfated GAG-binding proteins and lectins. Sulfated GAG-binding proteins mainly interact with negatively charged sulfate groups along GAGs via clusters of positively charged amino acids. All lectins possess a carbohydrate recognition domain (CRD) with a binding pocket exhibiting variable specificity for typically terminal glycan determinants.¹⁸ Proteins which bind to the nonsulfated GAG HA are classified as lectins because they share conserved binding modules similar to the lectin CRD (the role of HA and the binding protein cluster of differentiation [CD] 44 [→Fig. 1] in atherosclerosis will be discussed in the section “The Glycocalyx: GAGs and GAG-Binding Proteins”).

Apart from their contribution to structural scaffolding in the extracellular matrix, only those 7,000 to 8,000 of a trillion possible combinations of glycans that interact with GBPs are thought to be physiologically relevant. Therefore, GBPs provide a link between glycan structure and function.¹⁹

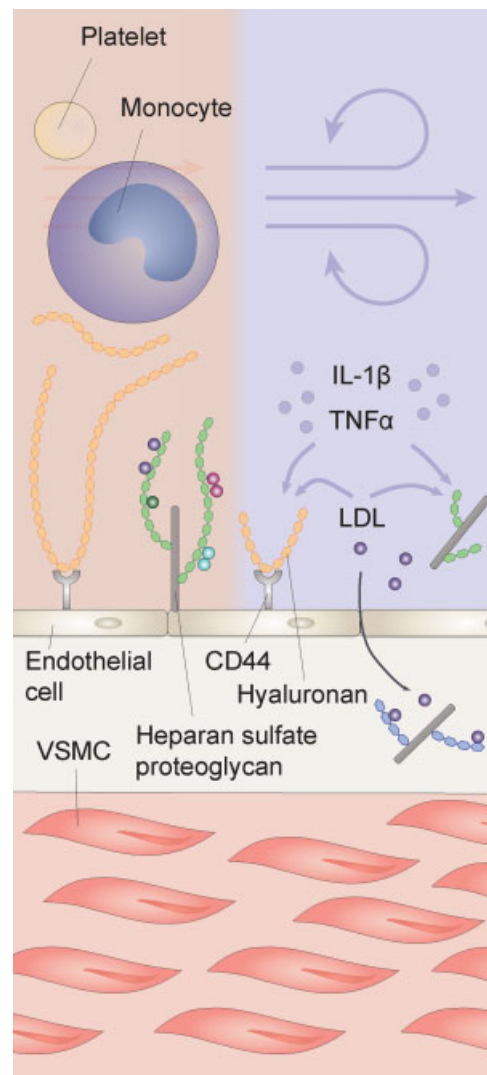


Fig. 1 The role of the endothelial glycocalyx in maintaining vascular health and its disturbance under proatherogenic conditions. The endothelial glycocalyx constitutes a sensor of blood shear stress, a barrier which prevents cells and plasma components from interacting with the endothelium and a reservoir for glycosaminoglycan (GAG)-binding proteins. Its constitution is altered by disturbed blood flow, inflammatory mediators such as IL-1 β and TNF α , and hyperlipidemia. The depiction of pathophysiological processes is simplified. CD44, cluster of differentiation 44; IL-1 β , interleukin 1 β ; oxLDL, oxidized low-density lipoprotein; TNF α , tumor necrosis factor α .

Challenges and Opportunities in Analyzing Glycan Structure and Function

The complexity of glycan structures makes their identification and structural and functional analysis difficult, both in vitro and in vivo. Since glycans are not primary gene products, they cannot be genetically labeled or biochemically amplified. Redundancy in the biosynthesis of a specific glycan or embryonic lethality of genetic knockouts renders mutagenesis studies difficult. Mass spectrometry (MS)-based approaches allow the identification of glycan sequences in a crude sample of glycans or glycoconjugates. However, they provide only limited information on stereoisomeric conformation and linkages. Nuclear magnetic

resonance (NMR) spectroscopy yields a complete three-dimensional structure of a determinant but requires a substantial amount of material.^{20–22}

Techniques based on the interaction between glycans and GBPs, especially lectins, may complement MS and NMR. Provided that lectins with appropriate selectivity are available, the interaction of GBPs with low amounts of particular glycans may allow conclusions on many of their structural features. For example, microarray analyses are performed by immobilizing lectins on a surface and incubating them with labeled GPs. Variations of the technique allow comprehensive glycan profiling of glycoconjugates, live cells, or tissue extracts.²³

Overall, these developments show that advanced biochemical tools are at hand to investigate the pathophysiological role of glycans which rely in part on their interaction with GBPs.

Pathophysiological Relevance of Glycans in Atherosclerosis

The vasculature senses and integrates distant and local changes in the condition of the organism and reflects these changes in part through modifications of endothelial surface glycans and free glycans shed by the endothelium into the plasma. Each of the 60 trillion endothelial cells on a surface area between 4,000 and 7,000 square meters exhibits a unique and dynamic cellular glycome.^{24–26} Endothelial proteoglycans protrude into the vessel lumen and cover smaller cell-bound GBPs and glycolipids. Together these components

form the endothelial glycocalyx. It constitutes a sensor of blood shear stress, a barrier which prevents cells and plasma components from interacting with the endothelium and a reservoir for GAG-binding proteins (►Fig. 1).^{16,17,27,28} Therefore, it regulates the key mechanisms of atheroprogession: the endothelial dysregulation by disturbed blood flow and pressure, platelet adhesion to the endothelium preceding leukocyte recruitment and activation, and the accumulation and phagocytosis of lipoproteins (►Fig. 2).^{27,29–32} Accordingly, an intact glycocalyx protects from atherosclerosis.^{16,17,24,33} Cardiovascular risk factors such as inflammatory cytokines, hyperlipidemia, and hyperglycemia particularly at sites of disturbed blood flow perturb its composition (►Fig. 1).^{34–37} However, specific components of the glycocalyx may also promote atheroprogession.

The Glycocalyx: GAGs and GAG-Binding Proteins

HS and the structurally related heparin alone bind to around 450 proteins which are implicated in hemostasis (e.g., antithrombin and VWF), inflammation (chemokines and P/L-selectin), and lipid metabolism (apolipoproteins, LDL-receptor [LDLR], and lipoprotein lipase).³⁸ The specificity of their interactions with heparin and HS ranges from non-specific mostly charge-based to very specific and may vary with the pattern of sulfation.^{39,40} Sulfation of endothelial HS may regulate rolling and arrest of leukocytes on the

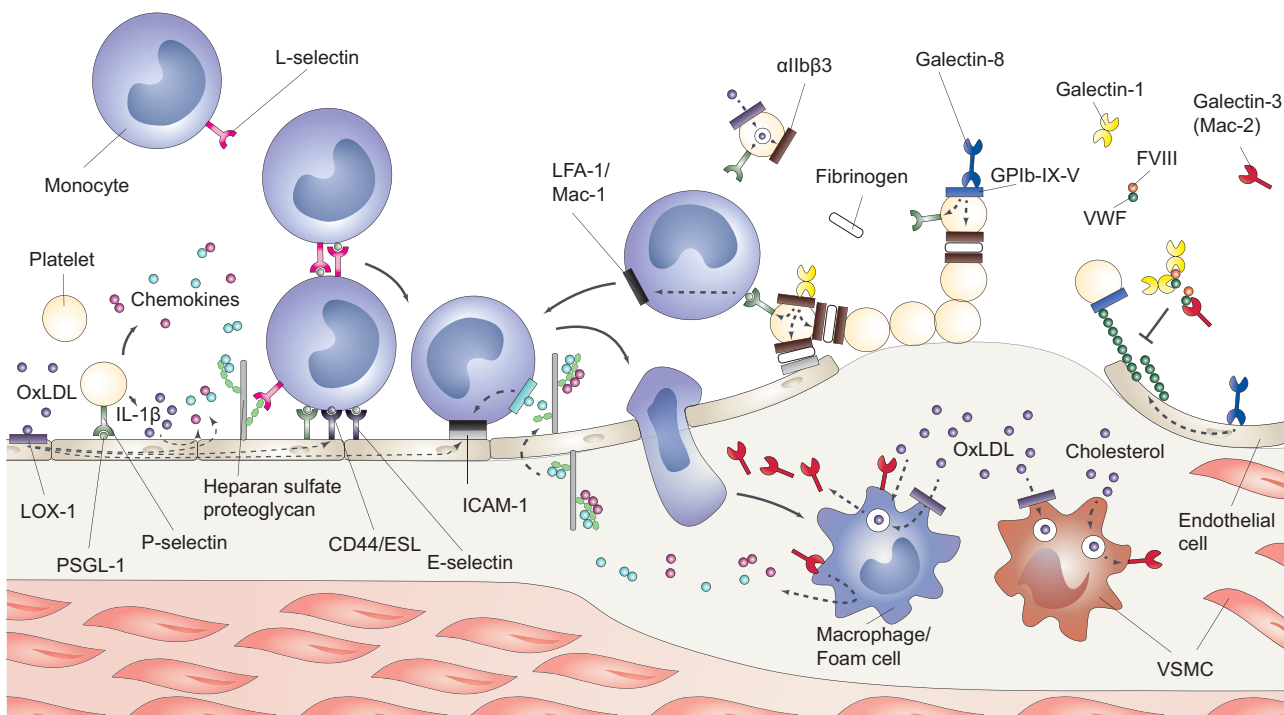


Fig. 2 Glycans and glycan-binding proteins (GBPs) in atheroprogession. The pathogenesis of atherosclerosis is characterized by endothelial dysregulation, platelet and leukocyte recruitment, the accumulation and phagocytosis of lipoproteins by macrophages and vascular smooth muscle cells (VSMCs), and thrombosis after plaque rupture. The depiction of pathophysiological processes is simplified. CD44/ESL-1, cluster of differentiation 44 and E-selectin ligand 1; FVIII, factor VIII; ICAM-1, intercellular adhesion molecule 1; IL-1 β , interleukin 1 β ; LFA-1/Mac-1, lymphocyte function-associated antigen 1 and macrophage-1 antigen; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; Mac-2, macrophage-2 antigen; oxLDL, oxidized low-density lipoprotein; PSGL-1, P-selectin glycoprotein ligand 1; VWF, von Willebrand factor.

endothelium at sites of inflammation by modulating L-selectin binding, and transcytosis and presentation of chemokines to their receptors on leukocytes (►Fig. 2, for a more detailed discussion on the role of selectins see the “C-type lectins” section).^{41–46} Heparin and its derivatives may exert an anti-inflammatory effect by blocking P- and L-selectin without affecting hemostasis.⁴⁷ The expression, sulfation, and degradation of HS is regulated. For example, inflammatory cytokines such as interleukin 1 β (IL-1 β) differentially regulate expression and sulfation of HS in human endothelial cells in vitro and increase shedding in vivo (►Fig. 1).^{34,35} Interindividual differences in glycocalyx thickness, basal turnover, speed and severity of deterioration after insult, and renal excretion of HS have been suggested.⁴⁸ These regulations may affect the capacity of HS to interact with selectins and chemokines (►Figs. 1 and 2).

HA expressed by endothelial cells in response to proinflammatory IL-1 β and tumor necrosis factor α (TNF α) has been shown to mediate the adhesion of monocytes to the endothelium via simultaneous interaction with leukocytic and endothelial CD44.⁴⁹ However, it is unclear whether intraluminal leukocyte–HA interactions are involved in atheroprotection.

In fact, complete inhibition of HA synthesis increased atherosclerosis in apolipoprotein E (ApoE)^{-/-} mice on a Western diet and thrombosis likely by increased interaction of monocytes and platelets with the vascular wall due to reduced steric hindrance by the glycocalyx.³³ HA shedding possibly induced by hyperglycemia or TNF α was observed in 100 patients with type I diabetes compared with healthy controls.³⁶

By contrast, partial inhibition of HA synthesis in vascular smooth muscle cells (VSMCs) induced by IL-1 β after monocyte migration into atherosclerotic plaque decreased atherosclerosis.⁵⁰ Interstitial HA expressed by VSMCs fosters

VSMCs migration and VSMCs switching from a contractile to a synthetic and proliferative phenotype and increases retention and activation of macrophages in the plaque.⁵¹

Furthermore, GAGs may control lipid metabolism. A reduction of HS and HA surface expression located at lesion-prone sites in the vasculature and induced by hyperlipidemia was associated with increased LDL leakage into the subendothelium (►Fig. 1).³⁷ By contrast, subendothelial retention of LDL by direct proteoglycan-binding was critical for the progression of atherosclerosis (►Fig. 1).⁵² HS may also be required for the binding of proprotein convertase subtilisin/kexin type 9 (PCSK9) to hepatic LDLR which induces LDLR internalization and degradation and increases LDL plasma levels (►Fig. 3). Remarkably, it has been suggested that the liver-specific effect of PCSK9 may be based on its selective binding to hepatic HS proteoglycans (►Fig. 3).⁵³

Other Glycan Determinants and Their Lectins

C-Type Lectins

Lectins are subdivided into evolutionary-related families based on structural similarities. The three major families of mammalian lectins in vascular biology are C-type, I-type, and galectins. The C-type constitutes the largest family of lectins. It comprises selectins, endocytic receptors which internalize and deliver their ligands to lysosomes, collectins, and several proteoglycans.

Selectins

Three types of selectins exist: E-selectin (expressed by the endothelium upon activation), P-selectin (stored in platelet α -granules and endothelial Weibel–Palade bodies and exposed upon activation), and L-selectin (constitutively expressed on

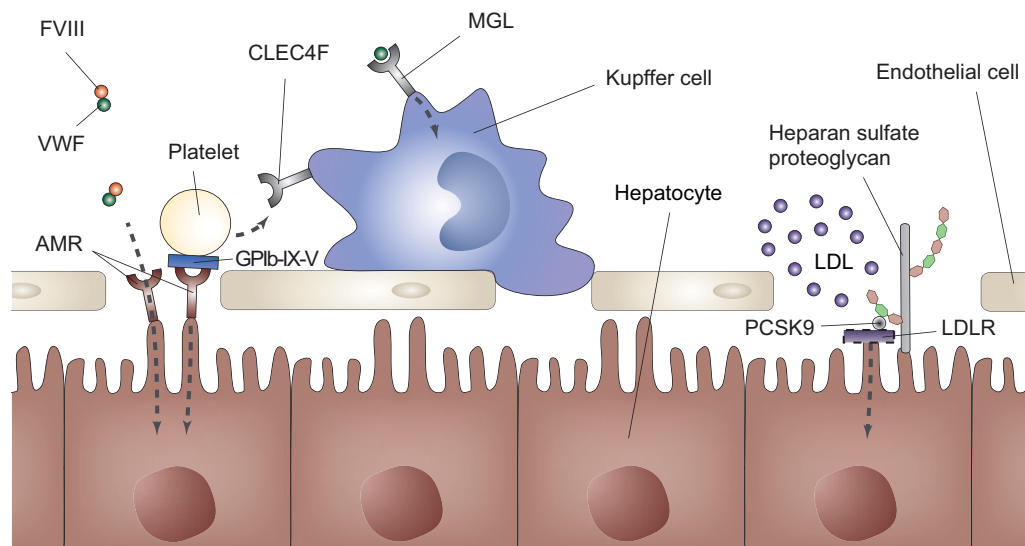


Fig. 3 Glycans and glycan-binding proteins (GBPs) in the hepatic clearance of coagulation factors and platelets and lipid metabolism. Heparan sulfate (HS) mediates the binding of PCSK9 to the hepatic LDLR which induces LDLR internalization and degradation. The AMR binds VWF, FVIII, and glycoprotein (GP) Ib-IX-V on platelets and mediates their phagocytosis. CLEC4F and MGL on Kupffer cells are involved in the hepatic clearance of platelets and VWF, respectively. The depiction of pathophysiological processes is simplified. AMR, Ashwell–Morell receptor; CLEC4F, C-type lectin domain family 4 member F; FVIII, factor VIII; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; MGL, macrophage galactose-type lectin; PCSK9, proprotein convertase subtilisin/kexin type 9; VWF, von Willebrand factor.

leukocytes). Selectins promote capture, rolling, and adhesion of platelets (P-selectin) and capture and rolling of leukocytes (E-, P-, and L-selectin) on the endothelium, secondary capture between freely flowing and rolling leukocytes (L-selectin), and between leukocytes and platelets (P-selectin) in a shear stress-dependent manner (►Fig. 2).^{43,54–63} All selectins bind the sialyl Le^x-tetrasaccharide, but differ in their specificity for variants of the tetrasaccharide at different sites in the vasculature as well as for the GP to which the variants are conjugated.⁶⁰ While P- and L-selectin only bind sialyl Le^x conjugated to P-selectin glycoprotein ligand 1, E-selectin also binds to CD44, E-selectin ligand 1, and, depending on cell type and pathophysiological context, CD43 and glycolipid conjugates (►Fig. 2).^{58,62} Because of their role in platelet rolling and adhesion and leukocyte recruitment to the vascular wall, the impact of P-, E-, and L-selectin on atheroprotection has been studied extensively.^{63,64}

The Ashwell–Morell Receptor

Furthermore, the hepatic Ashwell–Morell receptor (AMR), an endocytic C-type lectin, is expressed on hepatocytes and specifically recognizes terminal Gal and GalNAc residues. The AMR binds VWF (defect or deficiency leads to von Willebrand disease, the most common inherited bleeding disorder), factor VIII (FVIII, defect or deficiency leads to hemophilia A), and the GPIb-IX-V on platelets via N-glycans which expose Gal residues due to deficiency in terminal Neu5Ac and mediates their phagocytosis (►Fig. 3).^{65–68} In line with these findings, platelets from mice deficient in the Neu5Ac-adding sialyltransferase ST3Gal-IV are removed from the circulation.^{66–68} A role for two other endocytic C-type lectins, the C-type lectin domain family 4 member F and macrophage galactose-type lectin, expressed on Kupffer cells, liver-resident macrophages, in the hepatic clearance of platelets, and VWF expressing desialylated O-glycans, respectively, has recently been suggested (►Fig. 3).^{69,70}

Interestingly, a loss of function mutation in the main component of the AMR was associated with lowering of LDL plasma levels and a reduced risk for coronary artery disease in an Icelandic case–control study with 269,344 participants. The authors suggest that the AMR may interact with a desialylated form of the LDLR and mediate its LDL-independent internalization producing an increase in LDL plasma levels.⁷¹ Moreover, it has been shown that hypersialylated LDLRs internalize LDL more effectively and mice with a deficiency in Neu5Ac-removing sialidase exhibit lower LDL plasma levels.⁷² Sialylation of LDL affected its uptake by macrophages.⁷³ Notably, a SNP in the ST3Gal-IV gene was associated with increased LDL plasma levels in 95,454 patients.⁷ Recently, small interfering ribonucleic acid which downregulates PCSK9 in patients with elevated LDL cholesterol, was conjugated to GalNAc to specifically bind the hepatic AMR to reduce doses and side effects.^{74,75}

Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 and Mannose-Binding Lectin

Several other endocytic C-type lectins are implicated in atherosclerosis. Although the role of glycans in their actions has not

been investigated or they exert their function in a glycan-independent manner, lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) and mannose-binding lectin (MBL) will be briefly discussed. LOX-1 serves as a scavenger receptor for oxidized LDL (oxLDL) on endothelial cells (►Fig. 2). The uptake of oxLDL is atherogenic as it leads to upregulation of adhesion receptors and chemokines (►Fig. 2). LOX-1 also mediates the uptake of oxLDL by platelets, macrophages, and VSMCs (►Fig. 2).^{76,77} The uptake of oxLDL by platelets has recently been shown to induce the expression of P-selectin and the activation of α IIb β 3 integrin on platelets (►Fig. 2) and chemokine release.⁷⁸ Plasma levels of shedded LOX-1 had a higher sensitivity in the diagnosis of an acute coronary syndrome than troponin T or high-sensitivity C-reactive protein and may potentially even predict it.⁷⁹

MBL, a member of the collectin subfamily of C-type lectins, is expressed in human atherosclerotic plaque but not in healthy vascular tissue and may exert an atheroprotective effect, potentially by supporting the clearance of apoptotic cells by macrophages.⁸⁰ In a case–control study with 1,309 participants, MBL plasma levels were found to correlate with the risk of myocardial infarction in patients with diabetes or hypercholesterolemia. The authors discovered that MBL binds oxLDL and suggested that it may mediate its noninflammatory clearance.⁸¹

I-Type Lectins

I-type lectins belong to the immunoglobulin superfamily. Among I-type lectins, siglecs which bind sialic acid are the best characterized subgroup. Other I-type lectins, such as the intercellular adhesion molecule 1 (ICAM-1), exhibit varying sugar-binding specificities and are less well characterized.⁸² The glycan-dependency of the function of I-type lectins is unclear.

ICAM-1 mediates the adhesion of platelets and the arrest of leukocytes on the endothelium by interacting with platelet α IIb β 3 via fibrinogen as bridging molecule or lymphocyte function associated antigen 1 (LFA-1) and macrophage-1 antigen (Mac-1) integrins (►Fig. 2).^{25,41,55,83}

Siglec-1 is expressed in atherosclerotic plaques from ApoE^{-/-} mice on a Western diet.⁸⁴ Siglec-1 knockdown reduced atherosclerotic plaque formation, macrophage accumulation in plaque, and cytokine expression by atherosclerotic plaque, and by endothelial cells. Furthermore, oxLDL uptake and subsequent cytokine secretion by macrophages in vitro was mediated by Siglec-1.^{84,85} Siglec-1 expression in blood monocytes was significantly higher in patients with coronary artery disease compared with healthy controls.⁸⁶ A higher expression of Siglec-3 in classical monocytes correlated with a higher uptake of acetylated LDL particles.⁸⁷

Galectins

Galectins share sequence homology in their CRDs and binding affinity for β -galactose-containing glycoconjugates. Three different types exist in humans: the prototype which consists of a single CRD, the chimera-type galectin-3 (Gal-3) that contains a CRD and an N-terminal tail, and the tandem-repeat type which comprises two CRDs connected by a linker.

Galectins may form noncovalently bound homo- or hetero-oligomers.^{88,89} Galectins play a prominent role in atherosclerosis by regulating coagulation factors, activating platelets, affecting leukocyte adhesion and migration, and the phagocytosis of LDL. They differ in their affinity for specific glycans.⁹⁰

On the one hand, galectin-1 (Gal-1) and Gal-3 exhibit anticoagulant effects by interacting with N-glycans on VWF and preventing the formation of VWF bundles on the endothelium which interact with platelets via GPIb-IX-V to promote thrombosis (► Fig. 2).^{55,91} As a result, Gal-1^{-/-}/Gal-3^{-/-} mice show more arterial thrombi.⁹¹ Gal-1 binds to N-glycans on FVIII associated with VWF and reduces its activity (► Fig. 2). The authors speculate that Gal-1 may modulate FVIII plasma levels by mediating its endocytosis in the liver.⁹² On the other hand, Gal-1 induces P-selectin expression and aggregation of platelets by binding to the integrin α IIb β 3 in a glycan-dependent manner (► Fig. 2).^{93,94} The aggregation of platelets and interaction of platelets with the endothelium is induced by the upregulation of α IIb β 3. Integrin α IIb β 3 interacts with other platelet α IIb β 3 and endothelial ICAM-1 via fibrinogen (► Fig. 2). Fibrinogen also mediates the interaction of platelet α IIb β 3 with the endothelial integrin α V β 3 (not shown).^{55,95} Furthermore, it has been demonstrated that platelet α IIb β 3 interacts with endothelial GPIb-IX-V and α V β 3 via VWF and with endothelial α V β 3 via fibronectin (not shown). Fibrinogen, VWF, and fibronectin are expressed by platelets and released upon activation.^{55,95} Platelet adhesion to the endothelium and platelet aggregation induce platelet activation and endothelial activation by platelet IL-1 β and upregulation of adhesion receptors and release of chemokines in both cell types (► Fig. 2).^{32,54}

The effect of Gal-8 is more consistent. It induces the endothelial expression of VWF and promotes platelet adhesion to the endothelium (► Fig. 2).⁹⁶ It also fosters P-selectin expression and platelet aggregation by binding platelet GPIb-IX-V in a glycan-dependent manner (► Fig. 2).⁹⁷

The best characterized galectin in atherosclerosis is Gal-3 (Mac-2). Monocytes strongly upregulate Gal-3 when they differentiate into macrophages which accumulate in mouse and human atherosclerotic plaques.^{98–100} Gal-3 mediates the uptake of oxLDL, and oxLDL increases Gal-3 expression (► Fig. 2).^{101,102} It has also been shown that VSMCs upregulate Gal-3 after cholesterol uptake and transdifferentiation into a macrophage-like phenotype (► Fig. 2).¹⁰³ Moreover, Gal-3 may attract monocytes either directly or by inducing the expression of chemokines in a glycan-dependent manner (► Fig. 2).^{98,99} Gal-3^{-/-}/ApoE^{-/-} mice and ApoE^{-/-} mice treated with a glycan to block the Gal-3 CRD exhibit less atherosclerotic lesions and inflammatory plaque infiltrates.^{98,104}

Therapeutic Potential of Glycans and GBPs in Atherosclerosis

The implication of glycans and GBPs in the pathophysiology of atherosclerosis raises interesting therapeutic and diagnostic opportunities. For example, synthetic heparins and HS with specific anti-inflammatory, anticoagulant, or lipid-low-

ering capacities may be customized for the individual patient and the disease state. This approach may limit unwanted side effects or conversely exploit the manifold potential of heparins. Detection of specific variants of endogenous HS in plasma may prove useful for the assessment of the condition of the vascular system.⁴⁸

Furthermore, biological or synthetic lectins may specifically bind a particular glycan and prevent it from interacting with its receptor. Moreover, the possibility to specifically target the liver with a compound conjugated to a simple monosaccharide is intriguing.^{74,75} The approach may be applied to reach other organs. The analysis of the glycosylation profile of GPs, platelets, or LDL particles for diagnostic purposes seems promising.

Biological and synthetic lectins may lend themselves as therapeutics. Galectins for example may be used to specifically target thrombosis or serve as an intermediary between a pharmaceutical and its target. One may also block the CRD of galectins and other lectins with metabolically inert glycans to interfere with their function. Lectins may also serve as biomarkers.⁷⁹

Exploiting these targets may address so far underappreciated pathways and limit side effects of pharmaceuticals which result from their insufficient specificity to diseased tissue.

Conclusion

Glycans and GBPs constitute a complex and often highly specific system. This system is accessible to analytical techniques which rely in part on their interaction. Both glycans and their binding partners are heavily involved in key mechanisms of the pathogenesis of atherosclerosis, thrombosis, leukocyte adhesion and migration, and lipid metabolism. Activated monosaccharides or more complex glycan determinants, therapeutics conjugated to monosaccharides, or lectins may be used to specifically prevent or inhibit the development of the disease. The analysis of altered glycan structures on GPs, platelets, LDL particles, or differently expressed lectins may serve diagnostic purposes. With the exception of heparin and its derivatives, very few glycan-based compounds have reached the market. The glycome therefore represents a promising and underappreciated tool and target for future pharmaceutical developments in atherosclerosis.

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Conflict of Interest

None declared.

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