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Roles of galactose 3′-*O*- sulfation in signaling

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Abstract Galactose-3′-*O*- sulfation is specific and exists in many important molecules from various human tissues, and the sulfation modification results in alteration of host molecule recognition and interaction with partner molecules which lead to signaling. The modification is thus associated with the regulation of cellular adhesion and interaction, and involved in cell recognition and even in tumor metastasis process since the binding affinity to their extracellular ligands has changed. Sulfated glycoproteins or glycolipids may also trigger signaling in the cells, which is important in regulating cell-cell and cell-extracellular matrix interaction, and in adhesion molecule transcription activation.

Keywords Sulfated galactose · Interaction · Signal transduction · Integrin

Introduction

Carbohydrate chains on cell surface are very complex, but important in cell behaviors, especially in cell adhesion, recognition, migration processes, and cell-cell communication. Glycans are structural components of some important receptors that transmit information between the microenvironment and cells to control fundamental aspects of cell behaviors. The cell surface and secreted glycans include structural diverse glycoproteins and glycolipids. The structural variability of glycans and the expression profiles of a set of these glycans represent the glycoforms that are specific to the tissues and associate with the corresponding physiological and pathological functions of the cells. Sulfation modification of galactose makes glycan moiety more diverse in structure. In N-as well as in O-glycans, galactose constitutes an important residues. In human milk oligosaccharides, galactose residues often attach to the innermost glucose as well as to the peripheral residues. In N-linked sugar chain, galactose is generally located outside the common core structure and may become rich in the complex type sugar chain. However, galactose usually constitutes the main residues in the core structure of O-linked sugar chain apart from peripheral sugar chain. Sugar chains may be branched from the galactose residue and form diverse structures. The nonreducing terminal galactose can be further modified by sulfate groups to make up so called acidic glycans. On the nonreducing terminal β-galactoside of an oligosaccharide, a sulfation reaction can happen to either 3’ or 6’ hydroxyl group of the galactose residues on the oligosaccharide chains. Modification with the sulfation makes the oligosaccharide negative in charge in physiological circumstance. The interaction of the sulfated molecules with others changes subsequently, and the recognition or the affinity to their ligands is hence altered [1], leading to the regulation of cellular signal cascades if the modified oligosaccharide is attached to a membrane molecule. This terminal modification with a sulfate group especially at the 3′ hydroxyl group of the galactose exists broadly in many important cell adhesion molecules, but most of the biological and pathological roles still remain great elusive. This review is going to summarize the advances in the field of galactose 3′-*O*-sulfation (Gal3S) and illustrate its regulation of integrin and cell adhesion.

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Control of galactose 3′-*O*- sulfation

Addition of sulfate group to the 3′ hydroxyl group of galactose is catalyzed by the enzyme Gal3STs, which recognize 3′-phospho-adenosine-5′-phosphosulfate (PAPS) as the donor

of active sulfate group, and transfers it to the 3′ hydroxyl group of the terminal galactose in either O-linked or N-linked glycans. So far, there are four galactose-3-*O*-sulfotransferases that have been cloned, and they are cerebroside 3′-*O*-sulfotransferase (*CST*, Gal3ST-1), Gal:3-*O*-sulfotransferase-2 (Gal3ST-2), Gal:3-*O*-sulfotransferase-3 (Gal3ST-3), and Gal:3-*O*-sulfotransferase-4 (Gal3ST-4). All these enzymes rest in *Golgi apparatus*. *CST* is the first member identified in Gal3ST family, also called Gal3ST-1. *CST* recognizes glycolipid substrates including cerebroside, lactosylceramide and GalEAG (galactosylalkylacylglycerol) [2]. Gal3ST-2 is also called GP3ST, transferring a sulfate group to 3′ hydroxyl group of the nonreducing β-galactoside in oligosaccharides without lipid. Gal3ST-2 is widely expressed and most strongly in epithelial cells of colon, where a considerable amount of generated and secreted mucin. Gal3ST-3 is predominantly expressed in the brain, kidney and thyroid, and it adds a sulfate group exclusively to the 3′-hydroxyl group of galactose in N-acetyllacyosamine in both N- and O-glycans. Gal3ST-4 recognizes Galβ1→3GalNAc structure as good substrates and Galβ1→3/4GlcNAc.

Regulation by sulfation

Alteration after sulfation

The molecules that are modified by Gal3ST become negative in charge since sulfate (SO_3^{2-}) group is added at the 3′ hydroxyl group in galactose. This negative charge of the molecules also leads to the change of interaction among molecules and cells or between cells and microenvironment where the cells reside. The altered microenvironment due to the sulfation may thus affect the cell behaviors. The attached sulfate group resides on either glycolipids or glycoproteins, and forms a part of determinants for the molecular interactions and thus affects the binding ability with their ligands. For example, sulfatide, the product of cerebroside sulfation, becomes the strong antigen stimulating and activating type II natural killer T lymphocytes and regulates immune or autoimmune responses [3].

Regulation in lipids

Several proteins have been found to recognize the sulfated cerebroside (sulfatide) and the recognition between them via interaction is important for their functions. P-selectin, a sulfatide binding partner interacts and recognizes sulfated cerebroside, which is concentrated in lipid rafts, contributing to cell-cell interactions and facilitating adhesion. Meanwhile, metabolic inhibition of sulfation almost completely abrogated P-selectin binding [4]. L-selectin also recognizes sulfatide as an endogenous ligand, which is dependent on the position of the sulfate, but not cerebroside that lacks sulfate group. Sulfatide has also been recognized as the endogenous ligand of nucleotide oligomerization domain 2 (NOD2) after cerebroside getting a sulfate group and becomes pivotal for regulating autophagy in hypoxic cells [5]. Laminin anchors sulfated cerebroside, but not cerebroside, on cell surfaces to initiate basement membrane reassembly [6]. Without the sulfate group, laminin fails to anchor and initiate basement membrane reassembly. The laminin-sulfatide interactions are important in the formation of functional membrane microdomains essential for myelination [7]. Also, disruption of laminin-2-sulfatide interactions impedes oligodendrocyte differentiation and myelin-like membrane formation. These proteins that recognize sulfatide as ligands generally exhibit a hydrophobic cavity that is responsible for the interaction with the sulfatide acyl chain, whereas the hydrophilic, negatively charged moiety can be found either buried in the hydrophobic cavity of the protein or exposed for additional intermolecular associations. Therefore, the sulfation of cerebroside changes its interaction with ligand proteins, leading to regulation of molecular recognition and cell-matrix interaction [1].

Regulation in proteins

3-sulfo Lewis^x is a preferred ligand for L-selectin compared to conventional Lewis^x, by which the interaction is important in the process of cell adhesion and migration. Sulfated Lewis (a) tetra- and pentasaccharides of ovarian cystadenocarcinoma glycoprotein emerge as the most potent E-selectin ligands compared to those of the sialyl-Lewis^a and sialyl-Lewis^x analogues. Circulating 3-sulfo Lewis^a is thus considered as an important biomarker reflecting cell mobility and tumor cell metastasis potentials [8]. In high endothelial venules, L-selectin binds its glycoprotein ligands such as GlyCAM-1, CD34 and podocalyxin-like protein more potently when sulfation is on these ligands both *in vitro* and *in vivo*; while, treatment of lymph node organ culture with chlorate (an inhibitor of sulfation) or deficiency of the sulfotransferase in mutant mice abrogated or substantially diminished interaction between L-selection and its ligands [9]. Glycoprotein and sulfation are both required for binding with selectins, but it is the sulfation that augments the binding ability between selectins and their ligands. Integrins are important adhesion receptors, consisting of α and β subunits. After activation integrins on the surface become clustered. This process may involve the sulfation of integrins since integrins are essentially glycoproteins, containing galactose, on which Gal3ST can act directly and produce the 3′-sulfated integrins [10].

Sulfation triggers cellular signaling

Sulfation can bring a negative charge group to the acceptor molecules. Which can act as a chemical signal to stimulate

cells to respond and adapt to the microenvironmental change. If the sulfation happens in extracellular matrix proteins, which results in alteration of the microenvironment, and then may affect the interaction of microenvironment with cells, subsequently cellular signaling. If the sulfation occurs in membrane molecules, the sulfated membrane proteins or lipids may produce a signal in the cells. Both of the situations are of great significance for the signaling pathways by involving in Src tyrosine kinase activation.

Activation of Src

The membrane microdomains formed by glycosphingolipids interaction are usually associated with Src family tyrosine kinases. Meanwhile, interaction between sulfated cerebroside and its ligand laminin molecules enables basement membrane assembly which is characterized by coalescence of sulfatide, dystroglycan, and c-Src into a laminin-associated complex; and initiates activation of Src related signal transduction pathways by Src activation and by integrin-dependent focal adhesion kinase phosphorylation (Fig. 1). However, when cells were treated with arylsulfatase, an enzyme that hydrolyzes sulfates from sulfatides, but not from glycosaminoglycans, the treatment prevented laminin accumulation and c-Src activation, suggesting sulfation is important for the activation of c-Src [6].

Sulfatide can induce chemokine receptor CXCR4 upregulation in human and mouse leukocyte subsets through interaction with L-selectin, and tyrosine kinase activation, including other members of the Src family, which is essential for L-selectin regulating CXCR4 signaling. While, compared to sulfatide, the control galactosylcerebroside showed very low level of tyrosine kinase activation of Src [11]. In addition, sulfatide triggers Src-related signaling not only by interaction with ligands, but also by direct binding with Src family members. These signal molecules identified in the immunocomplex precipitated by an anti-sulfatide antibody in oligodendrocytes include Src family tyrosine kinases Fyn, Lyn, and alpha subunit of the heterotrimeric G protein [12], suggesting physical association of sulfatide with Src and G proteins.

Activation of integrin-linked kinase

After Src is activated by sulfatide, phoshporylation of transcription factors such as Sp1 can be observed. We found that sulfatide could enhance Sp1 transcription activity by increasing its phosphorylation level via Src and Erk1/2 pathway [13], followed by the increased expression of integrin αV subunit. Phosphorylated Sp1 subsequently strengthened the promoter activation of integrin αV subunit gene. After Erk1/2 phosphorylation is inhibited by MEK1/2 inhibitor, Sp1 phosphorylation is also suppressed. Therefore, sulfatide regulates integrin expression via Src/Erk/Sp1 phosphorylation signaling pathway. On the other hand, ILK (integrin-linked kinase) as a cytoplasmic effector of integrin receptors, binds to the cytoplasmic domains of integrin β1 and β3 subunits, and bridge them with the actin cytoskeleton. Treatment with Lewis^x trisaccharide 3'-sulfate sodium directly upregulated the phosphorylation of AKT (Protein Kinase B) and ERK by ILK, and resulted in increasing expression of an anti-apoptotic protein, Bcl-2 [10], which suggests that sulfation can produce signaling through the related signal molecules including ILK, AKT, ERK besides Src and play a crucial role in regulating the expression of cell adhesion molecules including integrins. ILK, as an important signal molecule, can activate PKB/AKT [14–16] or glycogen synthase kinase 3 (GSK-3) [15, 17] signaling by phosphorylating them on serine-473 and serine-9 respectively (Fig. 2), which constitute an important pathway that regulates the signaling of multiple essential biological processes including cell migration, survival, and cell adhesion.

Activation of Focal Adhesion Kinase

Src seems to bind constitutively and directly to β3 integrins, and clustering of β3 integrins induces autophosphorylation and activation of Src [18]. And Src can also be associated with FAK (Focal Adhesion Kinase), which has been shown to bind directly to the intracellular domain of the β1-integrin subunit [19]. The autophosphorylation of FAK at Tyr397, which serves as a binding site for Src-family protein kinases (Fig. 2) [19, 20], is followed by further activation, phosphorylating a variety of substrates such as paxillin and other phosphorylation sites of FAK including Tyr407, Tyr861, Tyr925 (Fig. 1), and activates a number of protein kinase cascades [20]. The phosphorylation of FAK at Tyr-925 site by Src provides the binding site for adaptor GRB/SOS, which links integrins to MAP Kinase pathway, orderly activating the Ras/Raf/MEK/MAPK signaling pathway (Fig. 2) [19, 20]. Therefore, the signaling that involves sulfatide regulations may include the Src/FAK/Ras/Raf/MEK/MAPK signaling although some synthetic sulfatides inhibited the activation of FAK, Akt, and extracellular signal-regulated kinase signaling in melanoma cells where sulfatide is not naturally synthesized. The signal pathways of sulfatide regulating cell adhesion are summarized in the Fig. 2.

Superoxide anion

Lactosyl ceramide (LacCer) sulfation can affect the signaling pathway independent of integrins. After the human aortic smooth muscle cells were treated with sulfatide superoxide anion production increased, which reminds us that in this modification, reactive oxygen species (ROS) may serve as a signaling molecule to activate protein kinases and

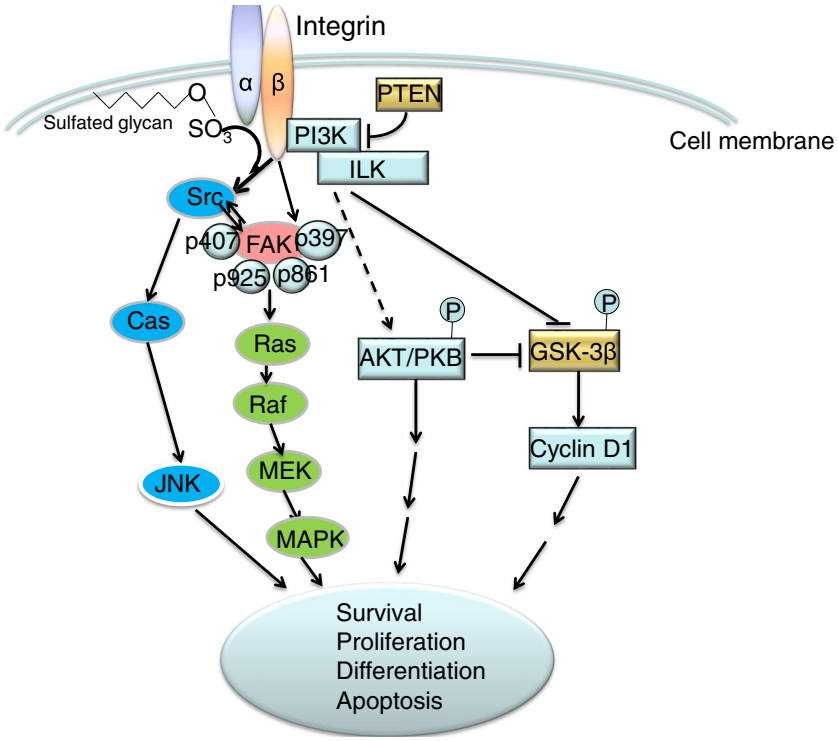

Fig. 1 Sulfation signaling involves integrin-related pathway.ILK and FAK are two important kinases in the integrin related signaling pathway. After their activation, they subsequently send signals to Ras/Raf/MEK/MAPK, Src/Ras/JNK and AKT/PKB, and promote cell migration or survival. Whereas, the GSK-3β activation inhibits cell survival. However, activation of either FAK or Src kinase can be regulated by galactose sulfation. *ILK* integrin-linked kinase; *FAK* Focal Adhesion Kinase; *GSK*-3β Glycogen synthase kinase-3β; *HDAC* histone deacetylase; *JNK* c-jun N-terminal kinase; *PTEN* phosphatase and tensin homolog deleted on chromosome ten, *PI3K* Phosphatidylinositol-4,5-bisphosphate 3-kinase

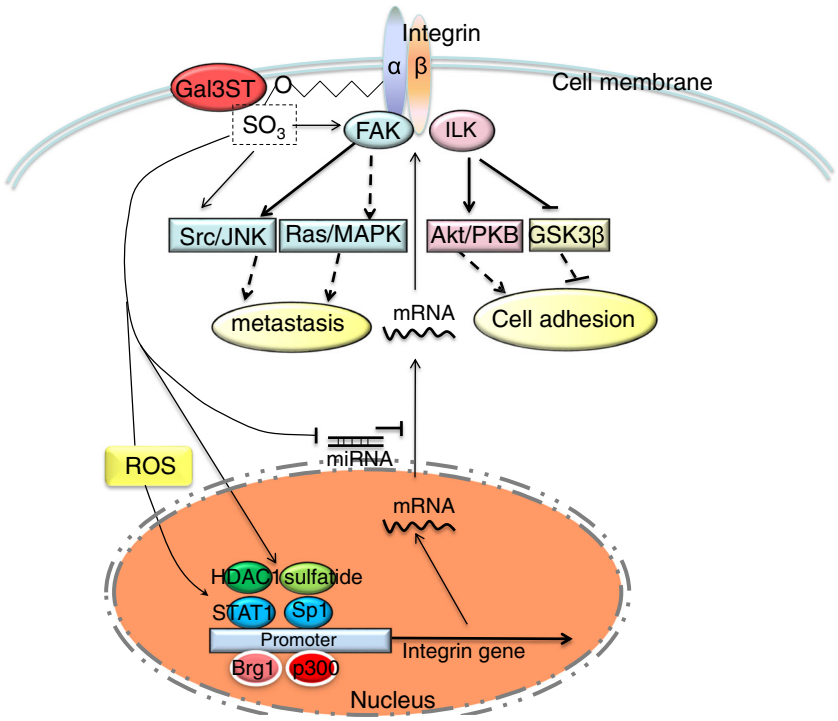

Fig. 2 Putative signaling pathways by galactose 3′-*O*-sulfation. 3′ sulfated glycans influences cellular behaviors through signal pathway, transcriptional factor microRNA(miRNA) and gene expression regulations. Gal3ST sulfonylizes its substrate molecules, which trigger signaling and subsequently affects transcription factors that regulate the transcription expression of genes (e.g. integrin) or cellular adhesion. The signaling pathways can be further activated or inactivated. The sulfation-modified molecules by Gal3ST induce reactive oxygen species ROS in cells that can activate or inactive protein kinases and transcription factors, resulting in alteration of specific gene expression (adhesion molecules such as ICAM-1 and VCAM-1) and the signaling pathway. 3′ sulfated glycans, such as sulfatide, can directly associate with Src and activate Src kinase. The active Src then stimulates the downstream signal pathways including ERK/MAPK and AKT/PKB signaling. These regulation pathways can interact with each other. In the figure pathways about FAK regulating Ras/MAPK[19] and Src/JNK[27], ILK regulating AKT/PKB [14, 16] and GSK3β [15, 17] may directly or indirectly be regulated.Bold line: integrin-dependent signaling; Fine line: integrin-independent signaling. Dashed line: indirect regulation. Brg1: Brahma-related gene1

transcription factors, resulting in alteration of specific gene expression and the signaling pathway, and then cellular function. On contrary, enhancement of oxidative stress is associated with the reduction of sulfation [21] in the liver, which seems to be a feedback regulation.

Sulfation signal involves expression regulation of integrin genes

The expression of integrins and activation of integrin-related signals that are important for cell adhesion or migration, seem to be regulated by sulfation signaling. Decreased expression of integrins (α5, α6, and β1) on the cell surface and their whole cellular levels were seen in murine 3LL Lewis lung carcinoma cells overexpressing sulfatide [22]. The endogenous sulfatide negatively regulates β1 integrin expression at the transcriptional level in the *CST* transfectants. Some synthetic sulfatides inhibited α5, β1, but not αv or β3 integrin expression in murine melanoma B16F10 cells [23]. However, sulfatide-expressing Hep3B cells showed elevated expression of integrin αVβ3 and higher adhesive ability to vitronectin compared to mock cells [1]. Sulfatide, the sulfated cerebroside, rather than galactocerebroside, stimulates the transcription expression of integrin αV, but not α5, β5, or β1 subunit in hepatocellular carcinoma cells by activation of Src and ERK [13]. These suggest that the expression of integrin subunits can be regulated by the signal of cerebroside sulfation. We also noted that 3′-sulfo-Lewis^x, the product of Gal3ST-2, but not Lewis^x, can also induce the transcription expression of integrin αv subunit in hepatocellular cancer cells [10, 24]. The structure of sulfo-Lewis^x is quite different from sulfatide except the moiety of galactose sulfation, suggesting that the common sulfate group is important for the regulation [13]. The sulfate group on the galactose moiety may send a regulatory signal to regulate integrin expression, or perhaps integrins themselves are glycoproteins which may serve as the substrates being modified by sulfation directly [24].

Regulation of integrins is related to transcription control

The expression of integrin proteins is generally controlled by transcriptional factors. Promoters of the integrin subunit genes have many transcription factor binding sites, including transcription factors Sp1, Sp3V1, Sp3V2, ETS, Egr1, Egr2, AP-1, AP2, Elk1, foxc2, Sp3. These transcription factors can bind to corresponding sequence of the promoters of the integrin genes and regulate the transcription of integrins by altering the binding affinity to the promoter, or by changing the expression or activation of themselves. Transcription factors Sp3, ATF-2 and Sp1 are required for the transcription expression of integrin β8. Forkhead transcription factor Foxc2 directly induces expression of the integrin β3 subunit. ETS is another transcription factor, which is involved in transcriptional activation of the α3 integrin gene. The binding ability of transcription factor Sp1 to the gene promoters of integrin αV, and the expression levels of transcription factors can be affected by the sulfation product of cerebroside, sulfatide [13]. Sulfatide also activates the transcription factor NF-κB, which plays a pivotal role in gene expression of integrin molecules.

Apart from activation or regulation of transcription factors, the signals produced by sulfation are also related to epigenetic control of gene expression. Sphingosine lipid is generally believed to be located in membranes, but recently it is considered an important component of the nucleus where it activates sphingosine kinase [25]. Sulfation of cerebroside may produce a signal for chromosome remodeling through histone acetylation since sulfated cerebroside is found in the transcription initial complex (Fig. 2) and enables modulation of histone acetylation via interaction with histone acetylase and deacetylase [26]. Occupancy on the promoter of integrin genes by sulfated cerebroside interacts with the transcription factors which are bound to the transcription initial complex, interferes the binding of the transcription factors to the promoter sequence and regulates the transcription expression.

Perspectives

In this review, we mainly discussed the galactose 3′-*O*-sulfation and its roles in signal transduction which leads to gene expression regulation by transcription factors and even microRNA [26]. Sulfated cerebroside has been shown its importance in nervous system and immune system for the reason of enrichment. Interestingly, sulfatides are also elevated in hepatic carcinoma, but its pathological roles of the elevated sulfatides is still not fully understood in hepatic carcinoma. There are still some problems and questions remain to be answered for the roles of sulfation. However, the study on sulfation modification may provide insight into the importance of sulfation in signal regulation and gene transcription regulation, which links sulfation modification to signaling.

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