



Molecules in focus

Glycosaminoglycans: Sorting determinants in intracellular protein traffic



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ABSTRACT

Intracellular transport of proteins to their appropriate destinations is crucial for the maintenance of cellular integrity and function. Sorting information is contained either directly in the amino acid sequence or in a protein's post-translational modifications. Glycosaminoglycans (GAGs) are characteristic modifications of proteoglycans. GAGs are long unbranched polysaccharide chains with unique structural and functional properties also contributing to protein sorting in various ways. By deletion or insertion of GAG attachment sites it has been shown that GAGs affect polarized sorting in epithelial cells, targeting to and storage in secretory granules, and endocytosis. Most recently, the role of GAGs as signals for rapid trans-Golgi-to-cell surface transport, dominant over the cytosolic sorting motifs in the core protein, was demonstrated. Here, we provide an overview on existing data on the roles of GAGs on protein and proteoglycan trafficking.

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1. Introduction

Many physiological functions depend on the proper localization of proteins to specific cellular compartments. The sorting information is contained directly within the amino acid sequence or alternatively in the protein's posttranslational modifications (Bonifacino and Traub, 2003; Seaman, 2008). Even glycosylation, i.e. modifications in the lumen of the endoplasmic reticulum (ER) or the Golgi compartments and thus without direct access to cytoplasmic machineries, has been shown to act as sorting determinants. Best understood is late endosomal/lysosomal transport of proteins carrying the mannose-6-phosphate modification of *N*-linked glycans by interaction with the mannose-6-phosphate receptors (Ghosh et al., 2003). In addition, *N*- and *O*-linked glycans have been found to mediate apical sorting in polarized cells by incompletely understood mechanisms most-probably involving lectins as cargo receptors (Potter et al., 2006; Vagin et al., 2009). Since *N*- and *O*-glycosylation are also found on basolateral proteins, only a subset of carbohydrate chains seems to be responsible for polarized sorting (Kitagawa et al., 1994). Finally, glycosaminoglycans (GAGs), the defining modification of proteoglycans, are emerging as sorting determinants for various transport steps.

2. Structure

Unlike *N*- and *O*-linked glycans, GAGs are long unbranched polysaccharide chains made of two alternating monosaccharides (Fig. 1A), an uronic acid or galactose, and an amino sugar (Mikami and Kitagawa, 2013; Sarrazin et al., 2011). Structurally, GAGs are extended semi-rigid polymers adopting helical conformation with an axial rise of about 1 nm per disaccharide unit (Almond and Sheehan, 2000; Rodriguez-Carvajal et al., 2003). The length of GAG chains is variable, typically from 20 to 60 kDa (40–120 disaccharides) in proteoglycans and 6 to 34 kDa for xyloside-primed protein-free chains (Victor et al., 2009).

3. Synthesis and degradation

GAG chains synthesis is initiated in the early secretory pathway by formation of a tetra-saccharide linker on serine residues (Fig. 1B), except for keratan sulfate chains which are initiated on *N*- or *O*-linked glycans. Chain extension, deacetylation and epimerization continue during the transport through the Golgi complex. In the trans-Golgi and the trans-Golgi network (TGN), GAGs are sulfated at specific positions (Mikami and Kitagawa, 2013; Sarrazin et al., 2011). Degradation of GAG chains takes place in the lysosomes by the help of endo-type hydrolases, exolytic glycosidases and sulfatases to liberate monosaccharide moieties.

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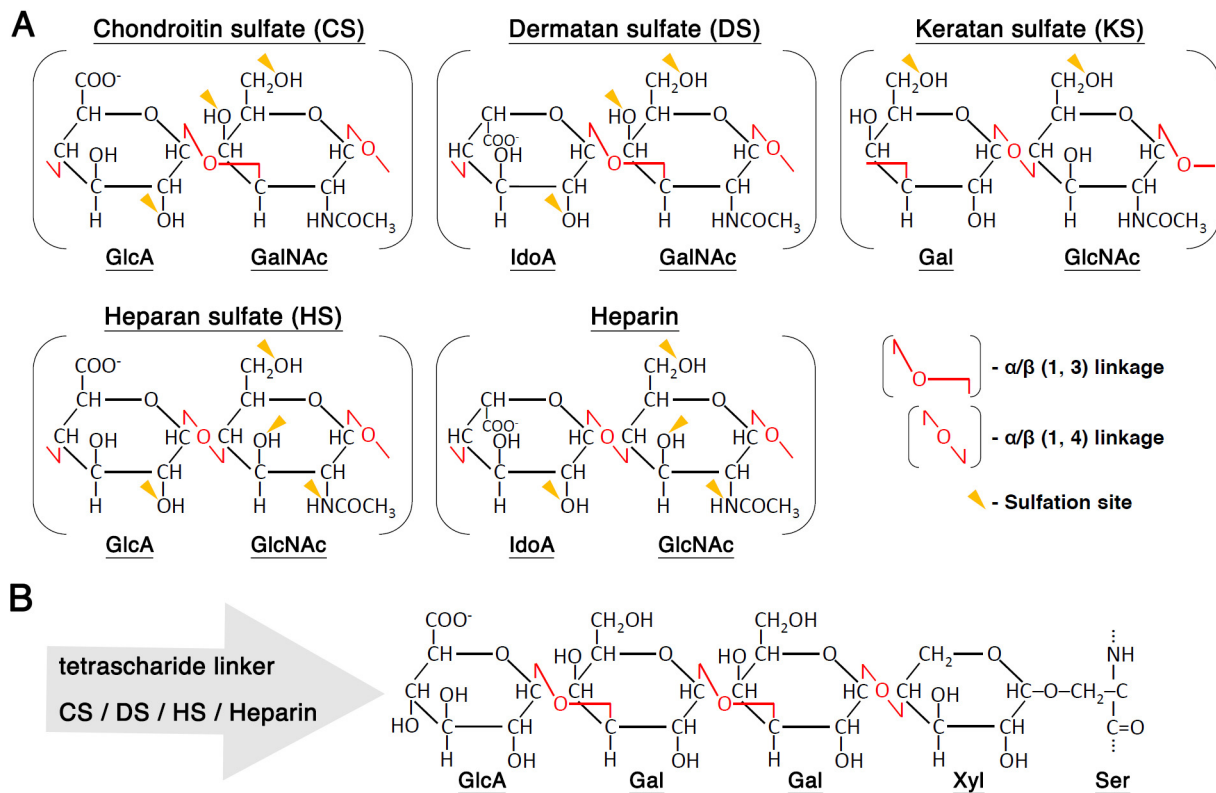


Fig. 1. Structure and synthesis of glycosaminoglycan chains. GAGs are long unbranched polysaccharide chains made of the following monosaccharides: xylose (Xyl), galactose (Gal), glucuronic acid (GlcA), iduronic acid (IdoA), N-acetyl-glucosamine (GlcNAc), N-acetyl-galactosamine (GalNAc). (A) The GAG chains consist of long repeats of disaccharide units, whose composition is specific for the different GAG types: CS (–4GlcA β 1–3GalNAc β 1–), DS (–4IdoA α 1–3GalNAc β 1–), KS (–3Gal β 1–4GlcNAc β 1–), HS (–4GlcA β 1–4GlcNAc β 1–) and heparin (–4IdoA α 1–4GlcNAc β 1–). GAGs can be sulfated at different sites (orange arrowheads) and the sulfation pattern further increases the complexity of their structures. (B) The synthesis of GAGs is initiated by the generation of a tetra-saccharide linked to a serine residue: GlcA β 1–3Gal β 1–3Gal β 1–4Xyl β 1–O–Ser. This linker is common for CS/DS/HS/heparin proteoglycans with the exception of keratan sulfate, which can be generated on both N- and O-linked glycans. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Biological function: GAGs as sorting determinants

Due to their many carboxylate groups and extensive sulfation, GAG chains attract water and cations forming hydrated matrices. Distinct saccharide and sulfation patterns allow specific interactions with various ligands, thus regulating cell signaling, migration, and differentiation (Mikami and Kitagawa, 2013; Sarrazin et al., 2011). Proteoglycans are prominent components at the cell surface and of the extracellular matrix (ECM), but are also found intracellularly in secretory granules and in the endosomal–lysosomal system. Initially, the protein core was believed to be solely responsible for the correct proteoglycan localization. However, several studies have demonstrated that GAGs contribute to protein traffic in a variety of ways (Fig. 2).

4.1. Polarized surface expression

In polarized epithelial cells, proteoglycans are found to be differentially distributed to the apical and basolateral sides of the cell monolayer, reflecting their specific roles on either surface. Heparan sulfate (HS) modification was proposed to mediate basolateral transport, since glypican, a glycosylphosphatidylinositol-anchored and predominantly basolateral proteoglycan in CaCo-2 and MDCK cells, was transported strictly to the apical surface, when its HS attachment sites were mutated (Mertens et al., 1996). On the contrary, chondroitin sulfate (CS) proteoglycans and free xylose-attached CS were mainly found to be secreted apically (Kolset et al., 1999). Rat growth hormone, normally secreted in a non-polarized manner from MDCK cells, was found predominantly in the apical

medium upon modification with a sequence containing multiple CS attachment sites (Hafte et al., 2011). In the contrary, however, fusion of a single CS attachment site to the asialoglycoprotein receptor H1 (ASGPR-H1), which is targeted to the basolateral surface by a cytoplasmic tyrosine motif interacting with the clathrin adaptor AP-1B (Sugimoto et al., 2002), did not alter its polarity (Kobialka et al., 2009). Similarly, natural splice variants of amyloid precursor-like protein 2 (APLP2) with and without a single CS chain were equally targeted to the basolateral surface, both as membrane-bound and secretory forms (Lo et al., 1995). The basolateral sorting information in the cytoplasmic portions of these proteins thus is dominant over the apical signal of the CS chain. Alternatively, the affinity to the apical transport machinery might depend on the number of GAG chains.

4.2. Biosynthetic export

To analyze the mechanism of proteoglycan export from the Golgi to the cell surface, HS proteoglycan-containing post-Golgi vesicles were isolated from [35 S]sulfate-labeled rat hepatocytes (Barthel et al., 1995; Nickel et al., 1994). Surprisingly, other secretory proteins, such as serum albumin, apolipoprotein E and fibrinogen, were not detected in this vesicle fraction, indicating that HS-proteoglycans are sorted into distinct types of constitutive secretory carriers at the TGN.

Additional evidence for GAG-mediated sorting in biosynthetic export was obtained by comparison of the transport kinetics of proteins with and without GAG modification (Kobialka et al., 2009). The ASGPR-H1 and α_1 -protease inhibitor (A1Pi) were used as

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