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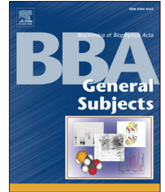

Review

Nuclear translocation of heparan sulfate proteoglycans and their functional significance☆

Ilona Kovalszky [a], Anders Hjerpe [b], Katalin Dobra [b,*]

[a] First Department of Pathology & Experimental Cancer Research Semmelweis University, Üllői street 26, Budapest 1085, Hungary
[b] Department of Laboratory Medicine, Karolinska Institutet, Karolinska University Hospital F46, SE-141 86 Stockholm Sweden

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ABSTRACT

Background: Heparan sulfate proteoglycans (HSPGs) are important constituents of the cell membrane and they act as co-receptors for cellular signaling. Syndecan-1, glypican and perlecan also translocate to the nucleus in a regulated manner. Similar nuclear transport of growth factors and heparanase indicate a possible co-regulation and functional significance.

Scope of review: In this review we dissect the structural requirement for the nuclear translocation of HSPGs and their functional implications.

Major conclusions: The functions of the nuclear HSPGs are still incompletely understood. Evidence point to possible functions in hampering cell proliferation, inhibition of DNA topoisomerase I activity and inhibition of gene transcription.

General significance: HSPGs influence the behavior of malignant tumors in many different ways. Modulating their functions may offer powerful tools to control fundamental biological processes and provide the basis for subsequent targeted therapies in cancer. This article is part of a Special Issue entitled Matrix-mediated cell behavior and properties.

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1. Short history of proteoglycan discovery

Polymeric acid carbohydrate moieties were recognized in the late 19th century as major components of connective tissue matrices. It was then demonstrated that these structures are linked to proteins, a finding that was not elaborated on for many years. Biochemical analysis of these so-called "mucopolysaccharides", later called "glycosaminoglycans" (GAGs) identified their structure as polymeric disaccharides. These repeating units consist of an amino sugar and an uronic acid or neutral sugar. The structure may also include one or more O-linked, and less frequently N-linked sulfate groups, which together with the uronic acid give the polysaccharide a strongly polyanionic character. Based on the structural features, the different GAGs were categorized as heparan sulfate (HS), dermatan sulfate (DS), chondroitin sulfate (CS), keratan sulfate and hyaluronic acid (HA). HA, now called hyaluronan, lacks sulfate groups and it differs from the others in molecular size and biosynthetic pathway.

The most abundant and therefore first studied GAG is CS that is present in connective tissues, whereas other GAGs including HS could be isolated from a large number of cellular tissues such as the liver. In fact, these molecules have been isolated from the cell surface glycocalyx [1]. A modification of HS, heparin was shown to interact with blood coagulation, and has gained widespread clinical use [2]. The biological functions of GAGs were generally less characterized. Because of their large molecular size and strongly polyanionic nature, they were considered spacers, regulating the transport of ions through tissues and mineral precipitation.

The proteoglycan (PG) nature of these mucopolysaccharides was thus not established until the sixties. It was only in the eighties when the revolution of molecular biology provided tools to reveal the structure of the various protein cores. Since then the PGs are classified according to their protein core. The combination of molecular biology and immunology made it possible to gain understanding of their localization and much of their function. The role of PGs in living organisms is, however, far from completely clarified. One reason for this is the enormous structural heterogeneity in their carbohydrate chains. The diversity rests in the length of the GAG chain, its sulfation at different positions, and the presence of various uronic acid epimers. This variety in negative charges results in a tremendous variability in polarity and tertiary structures of the chains, thereby influencing their ability to interact with surrounding molecules.

Later PGs have been identified as active participants of physiological and pathological events. They form concentration gradients during embryonic development, which, in turn, determine the structural assembly of tissues and organs. Depending on their structure and localization, PGs

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* Corresponding author.
E-mail address: katalin.dobra@ki.se (K. Dobra).

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are not only space filling structural tissue components, but also interfere with signal transduction, influence hemostasis, inflammation and regeneration. Thus, they are important factors during tumor formation and progression [3,4]. Notably, various stimuli, such as inflammation or cell injury, initiate characteristic shedding of transmembrane proteoglycans. The released fragments retain the regulatory functions of the polysaccharide chains and they exert PG actions at distance from the cell surface, in the surrounding extracellular matrix or in the systemic circulation [5].

It is still unclear what determines which GAG chain will be synthesized on the core protein. In general, the majority of CS-DS PGs reside in the extracellular matrix, whereas most cellular PGs carry HS chains. As HS and DS contain iduronic acid (conferring additional sulfation and altered tertiary structure to these molecules) PGs-glycanated with these two types of GAG are more prone to molecular interactions.

In the late eighties significant efforts were devoted to study the fine structure of HS chains and specific sequences that interact with particular protein structures. A number of interactions have been revealed, often involving a HS stretch of 5–6 monosaccharides. HS binds a large number of ligands including ECM components and cell-surface adhesion molecules [6,7], chemokines [8], growth factors and growth factor receptors [9–11]. The best studied ligation reactions are those involving the activation of antithrombin III and the binding of FGF-2 to its cell surface receptor [12]. It is well documented that HS interacts with both FGF2 and FGF receptor-1 (FGFR1) thereby forming a ternary complex that exerts efficient cell growth signaling properties [9].

2. Presence of heparan sulfate in the cell nucleus

The identification of heparan sulfate in the cell nucleus and its potential regulatory role in cell proliferation were reported as early as 40 years ago. This unusual localization of GAG chains alone, or as part of PG molecules, however, became generally accepted only quite recently. Accumulating evidence suggests possible functions of nuclear HS in cell differentiation and proliferation although they may carry additional regulatory properties. The first experiments indicating the presence of HS in the cell nucleus date back to 1974, when Kinoshita showed that the mucopolysaccharide in the cell nucleus localizes in the template active part of the chromatin and augments of RNA synthesis [13]. The following year it was reported that mucopolysaccharides stimulate transcription by making new RNA polymerase binding sites available on the chromatin [14]. Scientists managed to isolate CS and HS from purified nuclei of brain tissue and melanoma cells [15,16]. Two papers were published in 1986 [17,18] describing the link between transport of HS to the nucleus and inhibition of cell division [19]. Following metabolic labeling with sulfate, Ishihara and Fedarko detected free HS in the nuclei of cultured hepatoma cells. This HS was more abundant in confluent cells representing slightly more than 6% of the total cell-associated HS. The structure of this nuclear HS was similar in proliferating and confluent cells, but differed from that of HS isolated from other cell compartments. Disaccharide analysis revealed that nuclear HS carries a sulfated glucuronic acid residue as a unique structural feature. Although the precise structure of this HS was unknown, it was hypothesized that this GAG might interact with histone proteins. Any functional effect of the nuclear HS was, however, not established at the time of the report.

In 1992 Busch *et al.* observed that heparin interferes with the TPA induced jun/fos AP1 mediated transcription, concluding that nuclear GAGs can exert similar effects [20]. Shortly thereafter Kovalszky *et al.* discovered that nuclear HS co-localizes with FGF-2 [21], and subsequently it was shown that an antiproliferative HS can be detected in fibroblasts [22]. This HS was rich in L-iduronic acid, and its presence in cell nuclei correlated with inhibition of cell proliferation.

3. General feature of proteoglycans detected in the nucleus

PGs are ubiquitously present in the extracellular matrix, or on the cell surface, either as transmembrane proteins, such as the syndecans, or covalently bound to the plasma membrane, like the glypicans. During the last decade it has become evident that PGs can also be present in the cell nucleus. While the scientific community slowly accepted the existence of HS in the nucleus, the presence of proteoglycans was still debated in 2001–2002. Finally two independent reports verified the presence of syndecan-1 and HSPG in the nucleus of various tumor cells and stromal fibroblasts [23,24]. These PGs, however, translocate from other cell compartments, and no PG has been constitutively found inside the cell nucleus.

3.1. Syndecans

Syndecans constitute a family of 4-transmembrane HS proteoglycans (HSPGs) that are typically present on the cell surface [10,25], although they have also been found in the cell nucleus [23] and in shed forms in blood [26–29]. Each syndecan is expressed in a highly regulated cell-, tissue- and development-specific manner [11,30]. Syndecan-1 is the major syndecan on epithelial cells [25], syndecan-2 is present on mesenchymal cells [31], syndecan-3 in neuronal tissue and cartilage [32,33] while syndecan-4 is expressed in most cell types [34,35].

Syndecan-1 has been detected in the nuclear compartment of a wide range of cancer types including malignant mesothelioma, multiple myeloma, breast carcinoma, lung adenocarcinoma and neuroblastoma [24,36–38]. Syndecan-2 has been identified in the nuclei of injured cerebral cortex neurons and astrocytes [36] and in chondrosarcoma [37].

The core proteins of syndecans consist of a C-terminal cytoplasmic domain, a transmembrane domain and an N-terminal extracellular domain [11,39]. While the single-pass transmembrane domain is highly conserved, the ectodomains vary in length and in amino acid sequence and contain conserved motifs for GAG attachment, cell interaction, proteolytic cleavage and oligomerization. The cytoplasmic region binds cytoskeletal and PDZ-domain proteins, thus influencing the dynamics of the actin cytoskeleton and membrane trafficking. These interactions control syndecan recycling through endosomal compartments, promote internalization of accompanying protein cargo, and regulate cell adhesion and various signaling systems [40–42].

The intact ectodomain of syndecan-1 is constitutively shed from the cell surface by endogenous proteolytic cleavage [30,43] as part of normal cell surface PG turnover [44]. Elevated levels of soluble syndecan-1 ectodomain have been demonstrated in sera from patients with lung cancer [28], multiple myeloma [27] and Hodgkin's lymphoma [29]. Shedding can be accelerated by a variety of physiological stimuli, including growth factors, chemokines, bacteria, and cellular stress [45]. Recent studies showed that heparanase enhances syndecan-1 shedding by stimulating the expression of the active protease, thereby stimulating tumor growth and spread [46,47]. The release of the syndecan-1 ectodomain has functional consequences. While membrane-bound syndecan-1 may stimulate proliferation and inhibit invasiveness of tumor cells, overexpression of a constitutively shed syndecan-1 decreases the proliferation and promotes the invasiveness of cancer cells [48].

It is noteworthy that heparanase and syndecan-1 interact not only on the cell surface but they also co-localize in the nucleus. It seems that the sub-cellular localization of syndecan-1 might be crucial for its function and the nuclear translocation adds further complexity that needs to be further addressed in the context of variably differentiated tumor components.

3.2. Glypicans

The glypican family consists of six members of HS proteoglycans. Although they reside on the surface of epithelial cells, they are attached to the cell surface by their C termini, which are covalently linked to glycosyl-phosphatidyl-inositol (GPI) molecules. The glypican core proteins are similar in size, three-dimensional structure and they have a conserved domain of 14 cysteine residues in identical location. Unlike

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