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Mini reviews

Heparan sulfate in the nucleus and its control of cellular functions ☆

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ABSTRACT

Heparan sulfate proteoglycans (HSPG) are present on the cell surface, within the extracellular matrix, and as soluble molecules in tissues and blood. HSPGs are known to regulate a wide range of cellular functions predominantly by serving as co-receptors for growth factors, chemokines, and other regulatory proteins that control inflammation, wound healing and tumorigenesis. Several studies have demonstrated the presence of heparan sulfate (HS) or HSPGs in the cell nucleus, but little attention has been focused on their role there. However, evidence is mounting that nuclear HS and HSPGs have important regulatory functions that impact the cell cycle, proliferation, transcription and transport of cargo to the nucleus. The discovery of proteoglycans in the nucleus extends the list of "non-traditional nuclear proteins" that includes, for example, cytoskeletal proteins such as actin and tubulin, and growth factors and their receptors. In this review we discuss the discovery and fascinating roles of HS and HSPGs in the nucleus and propose a number of key questions that remain to be addressed.

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1. Discovery of heparan sulfates in the nucleus

The first reports demonstrating localization of HS within the nucleus of cells date back to the mid-1970s (Bhavanandan and Davidson, 1975; Margolis et al., 1976). It was proposed that HS played a regulatory role by interacting with cationic molecules within the nucleus, or by transporting molecules to the nucleus. Later, HS was found in the nucleus of hepatocytes where its presence or absence correlated with changes in cellular growth rates (Ishihara et al., 1986). These early studies measured radiolabeled HS in different subcellular fractions and because they were based solely on biochemical assays, were somewhat controversial due to the potential for contamination of cell fractions during the lysis

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procedure. This concern was founded on the fact that HS with its strong anionic charge would readily bind to cationic molecules resident within the nucleus (e.g., histones). However, it was argued that if the fractions were contaminated there would be a similar heterogeneous population of HS in the different cellular fractions, but instead, results demonstrated that the HS in the nucleus was structurally distinct from that present in the other cellular fractions (Ishihara et al., 1986). With the advent of improved molecular techniques including the use of high resolution imaging and high affinity antibodies, the presence of HS and HSPGs in the nucleus has been confirmed, and in fact, nuclear HS and HSPGs are likely more prevalent than first thought (Table 1). It is noteworthy that not all cells have HS or HSPGs in their nucleus, while some may have dermatan sulfate and/or chondroitin sulfate localized to the nucleus (Stein et al., 1975; Hiscock et al., 1994).

2. Regulation of HS/HSPG trafficking to the nucleus

2.1. Regulation by heparan sulfate

Although it is unclear exactly how HS is transported to the nucleus, early work demonstrated that nuclear HS in hepatocytes was enriched in sulfated glucuronic acid residues (Fedarko and Conrad, 1986; Ishihara et al., 1986). This indicated that a particular fraction of HS may be marked for trafficking to the nucleus. The authors speculated that ligands bound to certain fractions of HS protected the HS from degradation or helped shuttle them to the nucleus. Later, studies examining fibroblast growth factor-2 (FGF-2) and HS catabolism revealed that FGF-2, presumably via its binding to HS, protects regions of HS from lysosomal degradation and may also enhance HS translocation to the nucleus (Tumova et al., 1999). In addition, work utilizing lung epithelial cells demonstrated that once internalized, HS undergoes processing and that a specific fraction of HS, that is anti-proliferative, is transported to the nucleus (Fedarko and Conrad, 1986; Cheng et al., 2001).

Several studies indicate that modification or degradation of HS can reduce the presence of HS or HSPGs in the nucleus. Work from our lab has demonstrated that when heparanase expression is elevated in myeloma cells, the size of the syndecan-1 proteoglycan and the amount of proteoglycan present in the nucleus are significantly reduced (Chen and Sanderson, 2009). This is also the case in esophageal keratinocytes where heparanase in the nucleus greatly reduces the amount of HS present (Kobayashi et al., 2006). This may be due to a preference for shuttling high molecular weight species of HS to the nucleus as seen in some cells (Richardson et al., 2001).

2.2. Presence of nuclear localization sequence

Some HSPGs contain a putative nuclear localization sequence (NLS) in their core protein which might explain how they translocate to the nucleus. Glypican was discovered in the nucleus of neurons and glioma cells (Liang et al., 1997), and the deletion or mutation of the NLS KRRRAK in glypican greatly reduced its presence in the nucleus. The sequence motif MKKK was recently shown to be required for the internalization of syndecan-1 after clustering at the cell surface (Chen and Williams, 2013), while the RMKKK motif was shown to be necessary and sufficient for syndecan-1 translocation to the nucleus of mesenchymal tumor cells (Zong et al., 2009). Additionally, factors that bind to HS may chaperone HS to the nucleus, particularly if the factors contain their own NLS. For example, the nuclear oncoprotein DEK which is typically found in the nucleus can be secreted from cells. The secreted DEK can then bind to HSPGs at the cell surface and translocate to the nucleus (Saha et al., 2013). It is possible that the interaction between DEK and HSPG is maintained and that they are translocated to the nucleus together.

2.3. Regulation by the extracellular matrix

Interactions between cells and the extracellular matrix (ECM) can alter the localization of HSPGs to the nucleus. Corneal fibroblasts cultured on fibronectin had 60% more HSPG localized in the nucleus as compared to corneal fibroblasts grown on collagen (Richardson et al., 2001). It was proposed that the interaction between the heparin-binding region of fibronectin and the HSPGs on the cell surface induces intracellular signaling events or alters the association of HSPGs with other cell surface proteins which lead to an increase of HSPG trafficking to the nucleus. If a general inhibitor of protein kinase C is added to the corneal fibroblasts growing on fibronectin, there is a dramatic increase in nuclear HSPGs (Richardson et al., 2001). Conversely, the constitutive activation of protein kinase C severely hindered the translocation of HSPGs to the nucleus of corneal fibroblasts grown on fibronectin. Thus, phosphorylation state of the cytoplasmic domain of HSPGs may determine whether it is marked for cell surface retention or for trafficking to the nucleus.

Table 1
HS and HSPG in the nucleus.

Cell type	Proteoglycan or glycosaminoglycan	Publication
Astrocytes	HS*, PLC, GPC-1 SDC-2, SDC-3	Leadbeater et al. (2006)
Bladder carcinoma	HS	Nilsson et al. (2010)
Breast carcinoma	SDC-1	Brockstedt et al. (2002)
Chinese hamster ovary cells	HS, HSPG	Buczek-Thomas et al. (2008), Hsia et al. (2003), Sandgren et al. (2002)
Chondrosarcoma	SDC-2	Schrage et al. (2009)
Corneal fibroblasts and endothelial cells	HS, HSPG	Buczek-Thomas et al. (2008), Hsia et al. (2003), Richardson et al. (2001), Schubert et al. (2004)
Esophageal keratinocytes	HS	Kobayashi et al. (2006)
Glioma	HS, GPC-1	Liang et al. (1997); Schubert et al. (2004)
Hepatocytes, hepatocellular carcinoma	HS	Dudas et al. (2000), Fedarko and Conrad (1986), Fedarko et al. (1989), Ishihara et al. (1986, 1987)
Lung carcinoma, adenocarcinoma, fibroblasts	HS, SDC-1	Brockstedt et al. (2002), Cheng et al. (2001)
Melanoma	HS	Bhavanandan and Davidson (1975)
Mesothelioma	SDC-1	Brockstedt et al. (2002), Zong et al. (2009)
Monocytic leukemia	HS	Kovalszky et al. (1998)
Myeloma	SDC-1	Chen and Sanderson (2009), Purushothaman et al. (2011)
Neuroblastoma	SDC-1	Brockstedt et al. (2002)
Neurons	HS, PLC, GPC-1 SDC-2, SDC-3	Leadbeater et al. (2006), Liang et al. (1997)
Rat brain nuclei	HS	Margolis et al. (1976)

*Some data only specified the presence of HS or HSPG in the nucleus, where as other data specified specific proteoglycans (e.g., SDC-1).
Abbreviations: HS, heparan sulfate; HSPG, heparan sulfate proteoglycan; GPC-1, glypican-1; PLC, perlecan; SDC-1, syndecan-1; SDC-2, syndecan-2; SDC-3, syndecan-3.

3. Functions of HS/HSPG in the nucleus

3.1. Control of cell cycle and proliferation

The tightly controlled regulation of HS/HSPG trafficking to the nucleus or, in some cell types, the complete lack of HS/HSPGs in the nucleus, argues that they have specific and synchronized regulatory functions. The composition of HS in the nucleus may dictate whether cell division is stimulated or blocked. For example, early work demonstrated that as cells reach confluency, HSPG production is ramped up, nuclear HS levels increase 3-fold, and the structure motifs of HS in the nucleus change (Fedarko and Conrad, 1986). The nuclear fraction of HS contains high amounts of 2-O sulfated glucuronic acid, and as the cells transition from logarithmic growth to confluency, there is a higher degree of sulfation within the nucleus. Therefore, increased levels of sulfation may decrease cell proliferation. Addition of exogenous HS to hepatoma cells causes cell division arrest in the G1 phase (Fedarko et al., 1989). As nuclear levels of HS decrease, the cell cycle progresses through S, G2 and M phases. Therefore, cells undergoing mitosis lose nuclear HS, but after mitosis the HS reappears in the nucleus. In mesothelioma, the nuclear translocation of syndecan-1 was linked to specific points of the cell cycle through interactions with microtubule structures (Brockstedt et al., 2002). Additionally, the distribution of glypican in neurons was dynamic and changes correlated with different phases of the cell cycle (Liang et al., 1997). Moreover, drug-induced cell division arrest in the G2 phase inhibits syndecan-1 translocation to the nucleus (Zong et al., 2009). These data demonstrate a clear correlation between cell cycle stage and nuclear localization of HSPGs. However, the current data does not clarify whether the HSPGs in the nucleus regulate cell cycle progression or whether cell cycle stage regulates the localization of HSPGs in the nucleus. This is an area of research that needs further exploration.

Highly sulfated, L-iduronic acid-rich HS fractions have been shown to have anti-proliferative properties. The anti-proliferative HS was shown to inhibit proliferation of normal fibroblasts but had no effect on lung carcinoma cells demonstrating that some malignant cells may lose the ability to respond to HS (Cheng et al., 2001). It was found that the anti-proliferative HS bound poorly to the carcinoma cell surface and was not readily internalized. Thus, alteration of HS receptors on the cell surface may represent a mechanism whereby tumor cells escape the anti-proliferative effect of HS. However, it should be noted that HS is not always anti-proliferative. When HS was added to hepatoma cells growing in serum-free and insulin-deficient conditions, cell proliferation was increased (Fedarko et al., 1989). Thus, the effect of HS on tumor cells may depend on the HS structure, the type of tumor cell and/or the tumor microenvironment.

3.2. Chromatin modification

The polyanionic charge of HS makes it an ideal candidate to interact with positively charged molecules within the nucleus such as histones. Several studies have demonstrated that HS and HSPGs act as inhibitors of histone acetylation thereby regulating gene expression. HSPGs isolated from corneal and pulmonary fibroblasts were shown to inhibit histone acetyltransferase (HAT) activity, and addition of heparin to pulmonary fibroblasts decreased histone acetylation by 50% (Buczek-Thomas et al., 2008). The uptake of HS by tumor cells is a selective process and their inhibition of histone acetylation is dependent upon HS chain length and sulfation pattern (Buczek-Thomas et al., 2008; Nilsson et al., 2010). In multiple myeloma, loss of the HSPG syndecan-1 from the nucleus results in increased acetylation of histone and transcription of genes known to promote aggressive tumor behavior (Purushothaman et al., 2011). Because syndecan-1 derived from myeloma cells binds to p300, a HAT enzyme, it was speculated that syndecan-1 in the nucleus regulates gene expression by inhibiting HAT enzymatic activity (Purushothaman et al., 2011). Interestingly, HS also plays an important role in regulating chromatin during fertilization. In sperm, dense packing of the chromatin is facilitated by protamines rather than histones. Upon fertilization, HS facilitates the removal of protamines thus allowing the sperm nucleus to decondense and fusion of the male and female chromatin to proceed (Romanato et al., 2008).

3.3. Regulation of transcription machinery

In addition to altering gene expression through modification of chromatin structure, HS or HSPG can interact directly with the transcription machinery. Transcription factors are sensitive not only to electrostatic charge, but also to the structural motifs present in HS. Heparan sulfates are capable of inhibiting the interaction of transcription factors, such as AP-1, SP-1, ETS-1 and nuclear factor κB, with their consensus oligonucleotide elements (Busch et al., 1992; Dudas et al., 2000). The DNA binding domains of these transcription factors contain sequences similar to proteins that exhibit high affinity heparin binding. Interestingly, peritumoral HS decreased the binding of AP-1 and SP-1 to their consensus oligonucleotide elements, but tumor derived HS did not block their binding to DNA (Dudas et al., 2000). However, the tumor derived HS did block the ETS-1–DNA interaction (Dudas et al., 2000). This difference observed between normal and malignant cells may explain how cancerous cells express genes that favor tumorigenesis. Additionally, during the course of tumor progression, HS structure and length are altered, events that appear to impart a growth and survival advantage to the cancer cells (Nakamura and Kojima, 1981). When bound to HS, transcription factors may be protected from degradation thereby providing a reservoir of readily available, active transcription factors. Alternatively, at times when the concentration of HS exceeds a certain threshold in the nucleus, transcriptional activity may be attenuated or blocked.

Heparan sulfate can also block DNA topoisomerase I activity in the cell nucleus (Kovalszky et al., 1998). DNA topoisomerases are essential in regulating the relaxation of DNA strands. This regulation is required to allow certain regions of DNA to be accessible for transcription of genes. Heparan sulfate from human liver cells prevents the relaxation of supercoiled DNA by blocking DNA topoisomerase I activity (Kovalszky et al., 1998). Interestingly, HS from neoplastic human liver did not exert a block on the relaxation of supercoiled DNA indicating that specific HS moieties are required for DNA topoisomerase blockade. Thus, cancer cell-derived HS may block the transcription of genes necessary for tumor suppression or other key regulatory functions necessary to maintain normal cellular functions.

3.4. Heparan sulfate-mediated transport of cargo to nucleus

Since the discovery of heparin-binding motifs in proteins such as chemokines, cytokines and growth factors, their interplay with HSPGs has been extensively studied. Cell surface proteoglycans play a major role in presenting these factors to their high affinity receptors and are also important for their uptake by cells. Therefore, it is not unreasonable to suspect that the HS or HSPG transported to the nucleus is able to carry these factors with them. In fact, studies have indicated that FGF-2 binds to HSPGs and translocates to the nucleus as a complex (Amalric et al., 1994; Hsia et al., 2003; Zong et al., 2009). Syndecan-1 has been shown by immunohistochemistry to colocalize with FGF-2 in the nucleus of mesothelioma cells (Zong et al., 2009). Once in the nucleus, FGF-2 is able to directly interact with nuclear machinery and promote cell growth. For example, FGF-2 interacts with and activates casein kinase-2 (CK2), an ubiquitous serine-threonine kinase involved in the control of cell proliferation at the nuclear level (Amalric et al., 1994; Bailly et al., 2000). Fibroblast growth factor-2 was shown to bind to CK2 and stimulate its activity, resulting in increased phosphorylation of nucleolin (Bailly et al., 2000). Therefore, nuclear FGF-2 may be involved in induction of ribosomal gene transcription via stimulation of CK2. Furthermore, cell surface HS chains have been implicated in the cellular uptake and nuclear translocation of heparanase and angiogenin, though these have not been extensively studied (Moroianu and Riordan, 1994;

Schubert et al., 2004). Heparanase in the nucleus can associate with euchromatin and modulate histone H3 methylation through its interaction with a transcriptional complex (He et al., 2012). Importantly, HSPG-mediated transport of heparanase, FGF-2 and other heparin binding proteins to the nucleus are dependent on the HS chains of the proteoglycan.

Cell surface HSPGs are also implicated in the nuclear targeting of viral proteins. The addition of an HIV-Tat derived peptide to cells resulted in an accumulation of HSPGs in vesicular compartments which were further transported to the nucleus (Sandgren et al., 2002). Thus, targeting of HSPG to the nucleus may play important roles in viral pathologies.

4. Concluding remarks

In conclusion, there is now solid evidence that HS and HSPGs are present in the nucleus of some cells, where they influence the regulation of gene expression to control cellular behavior. Although the initial discovery of HS in the nucleus was made over three decades ago, many important questions remain. For example, how do HS/HSPGs translocate to the nucleus? Which endocytic pathway is utilized for the transport of HS/HSPGs to the nucleus? What functional motifs within HS are required for translocation to the nucleus? What cargo do they carry with them into the nucleus, and what is the function of that cargo? Can soluble HSPGs be taken up by surrounding cells and delivered to the nucleus thereby facilitating intercellular communication? Can HS/HSPGs be utilized to deliver genes or drugs to the nucleus? Addressing these questions will lead to a broader understanding of how nuclear HS and HSPGs regulate cell behavior in both normal and diseased tissue.

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