Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Extracellular Matrix: Surface Proteoglycans☆

Pyong Woo Park, Department of Medicine, Boston Children's Hospital, Boston, MA, United States; Department of Pediatrics, Harvard Medical School, Boston, MA, United States

Introduction

Nearly all mammalian cells express proteoglycans on their cell surface. The type of glycosaminoglycans (GAGs) attached to core proteins defines proteoglycans as heparan sulfate proteoglycans (HSPGs), chondroitin sulfate proteoglycans (CSPGs), dermatan sulfate proteoglycans (DSPGs), or keratan sulfate proteoglycans (KSPGs) (Park et al., 2016). Some proteoglycans are hybrid proteoglycans carrying both heparan sulfate (HS) and chondroitin sulfate (CS) chains. Surface proteoglycans include the syndecan and glypican families with four and six members in mammals, respectively, CD44, betaglycan, NG2 (AN2 in mice, CSPG4 in humans), phosphacan, thrombomodulin, neuropilin-1, invariant chain, and α5β1 integrin (Park et al., 2016). Studies on GAGs and proteoglycans date back to 1916 when heparin, a highly sulfated version of HS, was unexpectedly identified as a potent anticoagulant in liver extracts (thus, the name heparin) by a medical student who was trying to isolate a pro-coagulant molecule (Howell and Holt, 1918). HS was first considered as a contaminant in the heparin preparation, but was later distinguished from heparin in 1948 by the difference in the extent of sulfation and greater structural variability (Jorpes and Gardell, 1948; Lindahl and Kjellen, 1991). For a long time, biological functions of proteoglycans were largely speculative and, in fact, most proteoglycans were thought to be specific to cartilage, functioning as cushions in joints for variable, compressive loads. Studies in the last several decades have revealed that surface proteoglycans are important modulators of many molecular interactions, including many relevant to lung biology.

Structure

A proteoglycan consists of a core protein and one or several covalently attached GAG chains. GAGs are linear polysaccharides comprised of repeating disaccharide units that are defined by the composition and chemical linkage of the amino sugar and uronic acid monosaccharides in the disaccharide unit (Kjellen and Lindahl, 2018; Gama et al., 2006). The signature disaccharide repeat of an HS/heparin polysaccharide is GlcUAβ1-4GlcNAcα1-4, chondroitin sulfate (CS) is GlcUAβ1-3GalNAcβ1-4, dermatan sulfate (DS) is IdoUAβ1-3GalNAcβ1-4, keratan sulfate (KS) is Galβ1-4GalNAcβ1-3, and hyaluronan (HA) is GlcUAβ1-3GlcNAcβ1-4 (Kjellen and Lindahl, 2018; Esko and Selleck, 2002; Funderburgh, 2000; Trowbridge and Gallo, 2002). Except for HA, all GAGs are attached to core proteins and exist as proteoglycans in vivo. GAGs are attached to and polymerized on certain Ser residues of a Ser-Gly dipeptide sequence often repeated two or more times. The unmodified polymerized GAGs are modified in the Golgi by several sulfation and epimerization reactions that are catalyzed by distinct enzymes. Because the polymerization and modification reactions do not go to completion, the biosynthetic process generates an exceptionally diverse array of GAG structure, both in length and extent of modification. For example, HS, the most structurally heterogeneous GAG, varies in length from 20 to 150 disaccharides (~20–150 nm) with cell type and core protein (Sarrazin et al., 2011). However, a mere HS decasaccharide can potentially assume over 10^6 distinct sequences, which is already in vast excess of the estimated gene products that the whole human genome can generate. This enormous structural diversity largely explains why and how HS binds to so many proteins.

Surface proteoglycans harbor HS, CS, DS, or a combination of HS and CS. Core proteins of syndecans (Bernfield et al., 1999; Park et al., 2000b), NG2 (Tamburini et al., 2019), CD44 (Hardingham and Fosang, 1992), betaglycan (Jenkins et al., 2018), phosphacan (Maurel et al., 1994), and thrombomodulin (Parkinson et al., 1992) are type I transmembrane proteins (Couchman, 2010), whereas core proteins of glypicans are attached to the surface through a glycosylphosphatidylinositol (GPI) anchor (Filmus et al., 2008; Filmus and Selleck, 2001; Bernfield et al., 1999; Park et al., 2000b). As shown in Fig. 1, these core proteins have distinct structural designs and GAG attachment sites. For example, syndecan core proteins contain an extracellular domain extended in conformation due to a high Pro content, whereas glypican extracellular domains are globular because they contain 14 Cys residues, conserved across all six glypicans, that form intramolecular disulfide bonds. HS chains are attached distal to the plasma membrane on all syndecans and CS chains are also attached proximal to the cell surface on some syndecans (e.g., syndecan-1). GAG attachment

☆*Change History*: April 2020. PW Park updated the text. Figure titles have been added for figures 1 and 2.

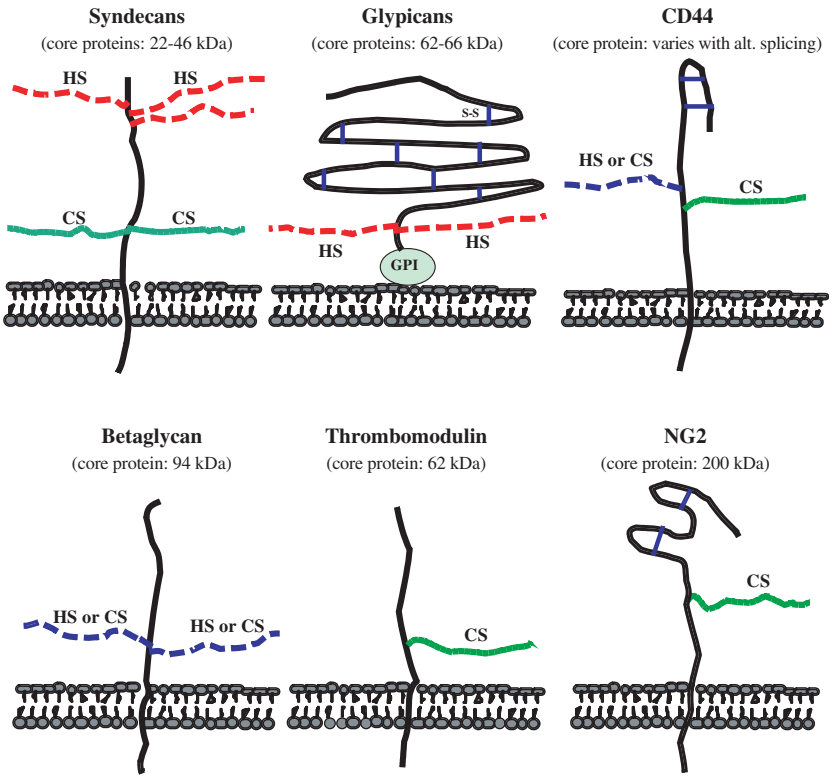

Fig. 1 Schematic depiction of cell surface HSPGs.

sites in NG2 (CS) and CD44 (HS/CS) are located in the middle portion of the core protein, whereas those of glypicans (HS), thrombomodulin (CS), and betaglycan (HS/CS) are proximal to the cell surface. The short cytoplasmic domain of syndecans contains several signaling and scaffolding motifs, such as three highly conserved Tyr, one highly conserved Ser, and a C-terminal PDZ binding domain (Bernfield et al., 1999). The NG2 cytoplasmic domain also contains a PDZ binding domain and several Thr residues that may be phosphorylated (Tamburini et al., 2019). Similarly, cytoplasmic domain of betaglycan contains a PDZ binding motif that interacts with β-arrestin (Bilandzic and Stenvers, 2011), in addition to Ser- and Thr-rich regions that may be modified by members of the protein kinase C (PKC) family (Lopez-Casillas et al., 1991). The CD44 cytoplasmic domain contains an ezrin, radixin, moesin (ERM) motif that may link surface CD44 to the actin cytoskeleton. The cytoplasmic domain of thrombomodulin also contains an ezrin binding site which, through interactions with ezrin and actin, is thought to regulate cell morphology and migration (Hsu et al., 2012).

Regulation of Production and Activity

The temporal and spatial expression patterns of surface proteoglycans are highly regulated. For example, syndecan-1 is first detected at the 4-cell stage in mouse embryos, suggesting that its expression is zygotically activated (Bernfield et al., 1992). In adult lung, syndecan-1 is the predominant HSPG expressed on the basolateral surface of airway and alveolar epithelia (Li et al., 2002). Lung epithelia also express syndecan-4, although its expression is much lower than that of syndecan-1. Several inflammatory mediators (e.g., TGFβ, antimicrobial peptides) and pathological conditions (e.g., cancer, myocardial infarction) regulate the expression of surface proteoglycans at the transcriptional and post-transcriptional level (Bernfield et al., 1992, 1999; Teng et al., 2012; Couchman, 2010). Furthermore, surface expression of syndecans and CD44 can be regulated by a proteolytic cleavage mechanism called ectodomain shedding (Hayashida et al., 2010; Lichtenthaler et al., 2018; Arribas and Borroto, 2002). Ectodomain shedding is of paramount importance to proteoglycan biology because it both rapidly changes the surface phenotype of affected cells by reducing the amount of surface GAGs and generates soluble proteoglycan ectodomains replete with all their GAGs that can function as autocrine or paracrine effectors. Glypicans are also released from the cell surface by cleavage of their GPI anchor by phopholipases in vitro (Filmus et al., 2008; Filmus and Selleck, 2001; Bernfield et al., 1999), suggesting that glypicans also function as soluble molecules in vivo. Most of the other surface proteoglycans are also found in soluble form, but how they are released from the cell surface is not known. The activity of proteoglycans is largely mediated by the sulfate motifs elaborated in the attached GAG chains (Gama et al., 2006). Thus, mechanisms that regulate the sulfation patterns have a direct effect on proteoglycan functions. For

example, the HS sulfatases, SULF1 and SULF2, remove 6-*O*-sulfates from HS (Dhoot et al., 2001) and inhibit cellular responses to FGF and FGF-induced angiogenesis (Wang et al., 2004).

Biological Functions

Surface proteoglycans, especially those elaborating the highly structurally diverse HS chains, bind and regulate a wide variety of biological molecules through their HS chains. The list includes ECM components, growth factors, chemokines, proteinases, antimicrobial peptides, and many more (Bernfield et al., 1999; Park et al., 2000b; Perrimon and Bernfield, 2000; Couchman, 2010). Surface proteoglycans can serve as primary receptors for some ligands (e.g., lipoproteins), but in most cases, surface proteoglycans function as coreceptors that capture ligands and catalyze the encounter between ligands and their respective signaling receptors in a multi-receptor complex. Surface proteoglycans can also regulate receptor-ligand interactions by affecting the stability, conformation, oligomerization state, and spatial distribution of either ligand or signaling receptor (Sarrazin et al., 2011). Furthermore, binding of chemokines and some morphogens to surface proteoglycans generates a directional gradient that guides cell migration (Handel et al., 2005; Yan and Lin, 2009). In addition, ectodomain shedding generates soluble forms of the surface proteoglycans that show functions similar to or distinct from their immobilized counterparts.

The biological significance and relevance of surface proteoglycan functions is perhaps best exemplified by phenotypes of mice made null for the various biosynthetic enzyme and core protein genes. For example, mice lacking *N*-deacetylase/*N*-sulfotransferase-1 (*Ndst1*) (Ringvall et al., 2000; Fan et al., 2000) or C5 epimerase (Li et al., 2003), enzymes required for the synthesis of sulfated HS, die shortly after birth due to various developmental abnormalities, including lung defects. The *Ndst1* null mice, in particular, show an incomplete maturation of type II pneumocytes. CD44 null mice show defects in the tissue distribution of myeloid progenitors (Schmits et al., 1997). Glypican-3 null mice show phenotypes resembling Simpson Golabi Behmel Syndrome, a human overgrowth disorder, and these mice also show abnormal lung development (Cano-Gauci et al., 1999; Capurro et al., 2009). Glypican-6 mice display embryonic lethality due to various development defects that are apparently caused by deficient Hedgehog signaling which glypicans negatively regulate (Capurro et al., 2017). Mutations in glypican-4 cause Keipert syndrome in humans, and while some features of this genetic disease are recapitulated in glypican-4 null mice, the phenotypes are substantially milder than in the human disease (Amor et al., 2019). Similarly, syndecan-2 null mice are viable with no gross abnormalities, although close examination revealed developmental abnormalities in retinal blood vessels (Corti et al., 2019). No apparent major developmental abnormalities have so far been found in mice that lack syndecan-1 (Alexander et al., 2000; Park et al., 2001), -3 (Kaksonen et al., 2002) or -4 (Echtermeyer et al., 2001). However, syndecan-1 and -4 null mice show abnormal phenotypes when subjected to experimental models of tissue injury and infection as described below.

Surface Proteoglycans in Respiratory Diseases

Several lines of evidence indicate that surface proteoglycans are central players in the pathogenesis of respiratory diseases (Fig. 2). In general, low expression of surface proteoglycans is associated with a poor prognosis in lung and other cancers. For example, syndecan-1 is expressed by most types of lung cancer cells (Kind et al., 2019), but expression is generally reduced in lung cancers (Nackaerts et al., 1997), and higher expression of syndecan-1 is associated with a better prognosis in non-small cell lung carcinomas, including adenocarcinoma and squamous cell carcinoma (Shah et al., 2004; Anttonen et al., 2001). Similarly, glypican-3 expression is decreased in lung adenocarcinoma (Kim et al., 2003), suggesting that both syndecan-1 and glypican-3 are potential lung tumor suppressors. The biological basis for the association between surface proteoglycan expression and lung cancer has yet to be clearly defined, but it is speculated that normal expression of surface proteoglycans is required to suppress cellular activities central to cancer progression, such as abnormal cell migration, proliferation, and differentiation. By contrast, syndecan-2 is overexpressed in lung adenocarcinoma and is thought to potentiate the invasiveness of lung adenocarcinoma cells (Tsoyi et al., 2019). Because most HSPGs are thought to function through their HS chains, the opposite functions of surface HSPGs may suggest that the fine structure of HS is different among these proteoglycans. Alternately, their pro- or anti-tumor functions may be mediated by their core proteins or they may harbor other GAG chains under tumorigenic conditions. The tetrasaccharide link domain that is *O*-linked to Ser residues of proteoglycan core proteins primes synthesis of all GAGs except for HA. Thus, in principle, GAG attachment may be regulated by the transformation state of the cell and the microenvironment in which the transformed cell resides. In fact, CS/DS levels are decreased in lung cancer tissues (Li et al., 2017), which may suggest a shift in the expression of GAGs or downregulation of CSPG and DSPG core proteins. Furthermore, high levels of soluble syndecan-1 ectodomains are associated with a poor outcome in lung carcinomas (Joensuu et al., 2002), suggesting that aberrant activation of syndecan-1 shedding may promote lung cancer progression.

Lung inflammation is exacerbated in CD44 null mice instilled intratracheally with bleomycin (Teder et al., 2002) and in syndecan-1 null mice instilled intranasally with allergens (Xu et al., 2005), suggesting that these surface proteoglycans mitigate inflammatory responses. In the mouse model of interstitial pneumonia, CD44 is required to clear apoptotic neutrophils and accumulated HA fragments at sites of tissue injury, and to assure the correct activation of TGFβ1. In the mouse model of allergic lung inflammation, syndecan-1 attenuates inflammation by inhibiting the recruitment of Th2 cells to the lung, a central process in asthma pathogenesis. Here, syndecan-1 shedding by airway epithelial cells is activated by allergen challenge and shed ectodomains

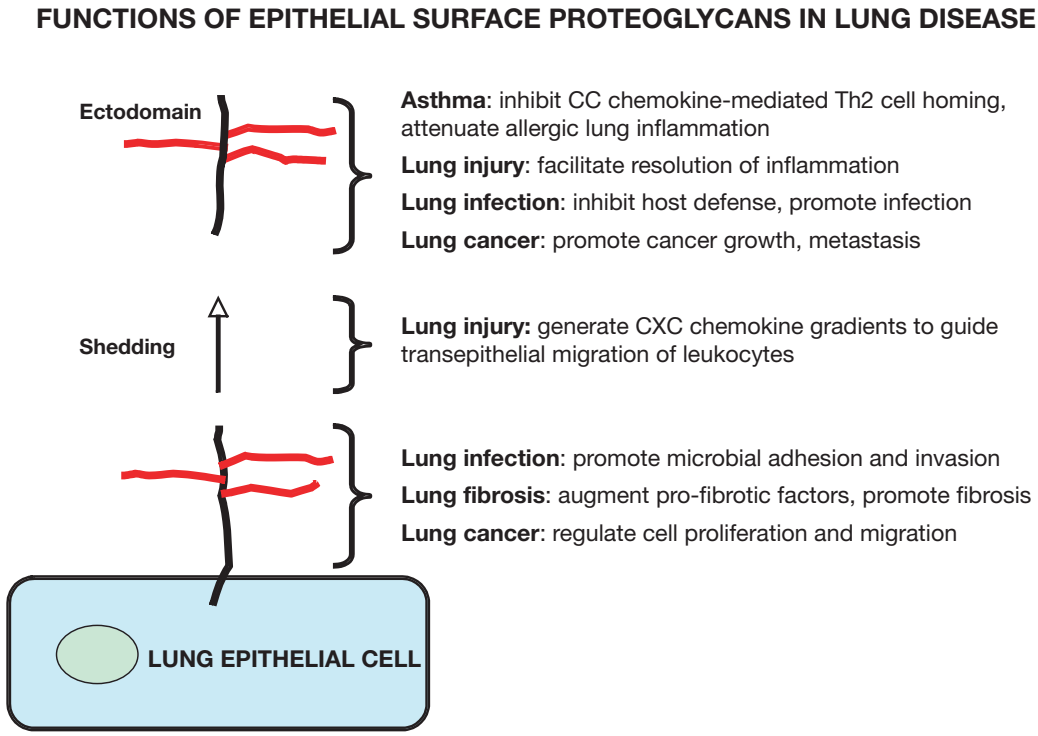

Fig. 2 Major functions of epithelial cell surface HSPGs in lung disease.

attenuate lung inflammation by binding and inhibiting the CC chemokines CCL7, CCL11, CCL17 through their HS chains. Syndecan-1 shedding has also been found to modulate lung inflammation in bleomycin-induced acute lung injury (Li et al., 2002). Upon injury, newly synthesized KC (CXCL1, functional homologue of human IL-8) binds to syndecan-1 HS on alveolar epithelial cells and the syndecan-1/KC complex is shed by MMP-7. This process generates a KC gradient that guides the transepithelial migration of neutrophils into the alveolar compartment. On the other hand, when the inflammatory stimulus is administered systemically, syndecan-1 shedding removes chemokines tethered to endothelial cells, dissipates chemokine gradients, and facilitates the resolution of neutrophilic inflammation. Consistent with this mechanism, syndecan-1 null mice are hypersusceptible to endotoxemia-induced acute lung injury when LPS is injected intravenously (Hayashida et al., 2009). Syndecan-1 also attenuates lung injury in influenza infection by stimulating pro-survival signaling and suppressing epithelial apoptosis (Brauer et al., 2016), but it is not known if the cell surface or shed form of syndecan-1 mediates the observed protection.

Similar to the different functions in lung cancer, syndecans apparently have opposing functions in lung fibrosis. Syndecan-2 inhibits fibroblast activation via its interaction with CD148 and attenuates radiation-induced lung fibrosis (Tsoyi et al., 2018). Similarly, syndecan-4 binding to CXCL10 inhibits chemokine-mediated fibroblast recruitment and mitigates lung fibrosis. Consistent with these mechanisms, syndecan-4 null mice are hypersusceptible to bleomycin-induced lung fibrosis (Jiang et al., 2010). In contrast, syndecan-1 promotes lung fibrosis by augmenting TGFβ and Wnt signaling (Parimon et al., 2019). The reason for these different phenotypes are not understood, but because syndecan-1 is expressed by lung epithelial cells, whereas syndecan-2 and syndecan-4 are expressed primarily by lung endothelial cells and fibroblasts, respectively, the cell-specific expression pattern and level of expression are thought to underlie how syndecans function distinctly and specifically in pulmonary fibrosis. Similar to the role of syndecan-1, inhibition or ablation of CD44 inhibits fibroblast invasion and myofibroblast activation, and attenuates bleomycin-induced lung fibrosis, indicating that CD44 promotes the progression of disease (Li et al., 2011). However, it is not know if the proteoglycan isoform of CD44 mediates these effects. Similarly, while NG2 is a biomarker for pericytes (Stallcup, 2018), which are mesenchymal cells that promote lung fibrosis when activated (Barron et al., 2016; Hung et al., 2019), the role of NG2 in the pro-fibrotic activities of pericytes is not known.

In lung infection, many bacterial and viral pathogens exploit surface proteoglycans as attachment and invasion receptors. Respiratory pathogens, such as *Mycobacterium* spp., *Bordetella pertussis*, *Haemophilus influenzae*, SARS-CoV, metapneumovirus, parainfluenza virus and respiratory syncytial virus, bind to the HS moiety of surface HSPGs for their attachment and invasion (Bartlett and Park, 2010; Aquino and Park, 2016). For example, syndecan-1 and -4 have been shown to directly mediate *M. tuberculosis* entry in human and mouse lung epithelial cells (Zimmermann et al., 2016), consistent with the finding that *M. tuberculosis* uses a heparin-binding hemagglutinin to enter alveolar epithelial cells (Menozzi et al., 1998; Pethe et al., 2001). HSPGs can also serve as coreceptors for respiratory pathogens. SARS-CoV uses ACE2 as its entry receptor (Dimitrov, 2003), but at least in cell-based assays, ACE2 expression alone is not sufficient for cellular infection. Instead, SARS-CoV initially binds to surface

HSPGs and this interaction is thought to increase virus density at the cell surface to facilitate the interaction of SARS-CoV with ACE2 for viral entry (Milewska et al., 2014).

Several respiratory bacterial pathogens, such as *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pneumoniae*, take advantage of syndecan-1 shedding in lung epithelial cells to promote their pathogenesis. Syndecan-1 shedding is specifically activated by secreted virulence factors: LasA for *P. aeruginosa* (Park et al., 2000a), α-toxin and β-toxin for *S. aureus* (Park et al., 2004), and ZmpC for *S. pneumoniae* (Chen et al., 2007), and the shed ectodomains inhibit innate defense factors (e.g., antimicrobial peptides, collectins) through their HS chains (Park et al., 2001; Hayashida et al., 2015). ZmpC directly cleaves syndecan-1 ectodomains, whereas LasA and α-toxin stimulate the host cell's shedding mechanism, suggesting that shedding activation is receptor mediated. Syndecan-1 ablation causes a gain of function where syndecan-1 null mice are significantly less susceptible to intranasal *P. aeruginosa* lung infection, and wild type mice are protected from infection by intranasal administration of inhibitors of syndecan-1 shedding and HS (Park et al., 2001), indicating that activation of syndecan-1 shedding is an important virulence activity shared by several respiratory bacterial pathogens. Interestingly, syndecan-4 null mice are more susceptible to pneumococcal pneumonia (Nikaido et al., 2015). Because syndecan-4 ectodomains are not shed by pneumococcus, perhaps surface syndecan-4 has functions that attenuate pneumococcal colonization in the lung. Regardless, these studies highlight the functional complexity of surface proteoglycans. Furthermore, these studies underscore the importance of surface proteoglycans in the pathogenesis of several major respiratory diseases. Additional studies directed at further defining the molecular and cellular mechanisms of surface proteoglycans in lung disease should lead to a better understanding of how fundamental functions of these complex glycoproteins influence the onset, progression, and outcome of lung disorders.

References

Alexander CM, Reichsman F, Hinkes MT, Lincecum J, Becker KA, Cumberledge S, and Bernfield M (2000) Syndecan-1 is required for Wnt-1-induced mammary tumorigenesis in mice. *Nature Genetics* 25: 329–332.

Amor DJ, Stephenson SEM, Mustapha M, Mensah MA, Ockeloen CW, Lee WS, Tankard RM, Phelan DG, Shinawi M, de Brouwer APM, Pfundt R, Dowling C, Toler TL, Sutton VR, Agolini E, Rinelli M, Capolino R, Martinelli D, Zampino G, Dumic M, Reardon W, Shaw-Smith C, Leventer RJ, Delatycki MB, Kleefstra T, Mundlos S, Mortier G, Bahlo M, Allen NJ, and Lockhart PJ (2019) Pathogenic variants in GPC4 cause Keipert syndrome. *American Journal of Human Genetics* 104: 914–924.

Anttonen A, Heikkila P, Kajanti M, Jalkanen M, and Joensuu H (2001) High syndecan-1 expression is associated with favourable outcome in squamous cell lung carcinoma treated with radical surgery. *Lung Cancer* 32: 297–305.

Aquino RS and Park PW (2016) Glycosaminoglycans and infection. *Frontiers in Bioscience* 21: 1260–1277.

Arribas J and Borroto A (2002) Protein ectodomain shedding. *Chemical Reviews* 102: 4627–4638.

Barron L, Gharib SA, and Duffield JS (2016) Lung pericytes and resident fibroblasts: Busy multitaskers. *The American Journal of Pathology* 186: 2519–2531.

Bartlett AH and Park PW (2010) Proteoglycans in host-pathogen interactions: Molecular mechanisms and therapeutic implications. *Expert Reviews in Molecular Medicine* 12: e5.

Bernfield M, Kokenyesi R, Kato M, Hinkes MT, Spring J, Gallo RL, and Lose EJ (1992) Biology of the syndecans: A family of transmembrane heparan sulfate proteoglycans. *Annual Review of Cell Biology* 8: 365–393.

Bernfield M, Götte M, Park PW, Reizes O, Fitzgerald ML, Lincecum J, and Zako M (1999) Functions of cell surface heparan sulfate proteoglycans. *Annual Review of Biochemistry* 68: 729–777.

Bilandzic M and Stenvers KL (2011) Betaglycan: A multifunctional accessory. *Molecular and Cellular Endocrinology* 339: 180–189.

Brauer R, Ge L, Schlesinger SY, Birkland TP, Huang Y, Parimon T, Lee V, McKinney BL, McGuire JK, Parks WC, and Chen P (2016) Syndecan-1 attenuates lung injury during influenza infection by potentiating c-Met signaling to suppress epithelial apoptosis. *American Journal of Respiratory and Critical Care Medicine* 194: 333–344.

Cano-Gauci DF, Song HH, Yang H, McKerlie C, Choo B, Shi W, Pullano R, Piscione TD, Grisaru S, Soon S, Sedlackova L, Tanswell AK, Mak TW, Yeger H, Lockwood GA, Rosenblum ND, and Filmus J (1999) Glypican-3-deficient mice exhibit developmental overgrowth and some of the abnormalities typical of Simpson-Golabi-Behmel syndrome. *The Journal of Cell Biology* 146: 255–264.

Capurro MI, Li F, and Filmus J (2009) Overgrowth of a mouse model of Simpson-Golabi-Behmel syndrome is partly mediated by Indian hedgehog. *EMBO Reports* 10: 901–907.

Capurro M, Izumikawa T, Suarez P, Shi W, Cydzik M, Kaneiwa T, Gariepy J, Bonafe L, and Filmus J (2017) Glypican-6 promotes the growth of developing long bones by stimulating Hedgehog signaling. *The Journal of Cell Biology* 216: 2911–2926.

Chen Y, Hayashida A, Bennett AE, Hollingshead SK, and Park PW (2007) *Streptococcus pneumoniae* sheds syndecan-1 ectodomains through ZmpC, a metalloproteinase virulence factor. *The Journal of Biological Chemistry* 282: 159–167.

Corti F, Wang Y, Rhodes JM, Atri D, Archer-Hartmann S, Zhang J, Zhuang ZW, Chen D, Wang T, Wang Z, Azadi P, and Simons M (2019) N-terminal syndecan-2 domain selectively enhances 6-O heparan sulfate chains sulfation and promotes VEGFA165-dependent neovascularization. *Nature Communications* 10: 1562.

Couchman JR (2010) Transmembrane signaling proteoglycans. *Annual Review of Cell and Developmental Biology* 26: 89–114.

Dhoot GK, Gustafsson MK, Ai X, Sun W, Standiford DM, and Emerson CP Jr. (2001) Regulation of Wnt signaling and embryo patterning by an extracellular sulfatase. *Science* 293: 1663–1666.

Dimitrov DS (2003) The secret life of ACE2 as a receptor for the SARS virus. *Cell* 115: 652–653.

Echtermeyer F, Streit M, Wilcox-Adelman S, Saoncella S, Denhez F, Detmar M, and Goetinck P (2001) Delayed wound repair and impaired angiogenesis in mice lacking syndecan-4. *The Journal of Clinical Investigation* 107: R9–R14.

Esko JD and Selleck SB (2002) Order out of chaos: Assembly of ligand binding sites in heparan sulfate. *Annual Review of Biochemistry* 71: 435–471.

Fan G, Xiao L, Cheng L, Wang X, Sun B, and Hu G (2000) Targeted disruption of NDST-1 gene leads to pulmonary hypoplasia and neonatal respiratory distress in mice. *FEBS Letters* 467: 7–11.

Filmus J and Selleck SB (2001) Glypicans: Proteoglycans with a surprise. *The Journal of Clinical Investigation* 108: 497–501.

Filmus J, Capurro M, and Rast J (2008) Glypicans. *Genome Biology* 9: 224.

Funderburgh JL (2000) Keratan sulfate: Structure, biosynthesis, and function. *Glycobiology* 10: 951–958.

Gama CI, Tully SE, Sotogaku N, Clark PM, Rawat M, Vaidehi N, Goddard WA 3rd, Nishi A, and Hsieh-Wilson LC (2006) Sulfation patterns of glycosaminoglycans encode molecular recognition and activity. *Nature Chemical Biology* 2: 467–473.

Handel TM, Johnson Z, Crown SE, Lau EK, and Proudfoot AE (2005) Regulation of protein function by glycosaminoglycans—As exemplified by chemokines. *Annual Review of Biochemistry* 74: 385–410.

Hardingham TE and Fosang AJ (1992) Proteoglycans: Many forms and many functions. *The FASEB Journal* 6: 861–870.

Hayashida K, Parks WC, and Park PW (2009) Syndecan-1 shedding facilitates the resolution of neutrophilic inflammation by removing sequestered CXC chemokines. *Blood* 114: 3033–3043.
Hayashida K, Bartlett AH, Chen Y, and Park PW (2010) Molecular and cellular mechanisms of ectodomain shedding. *The Anatomical Record* 293: 925–937.
Hayashida A, Amano S, Gallo RL, Linhardt RJ, Liu J, and Park PW (2015) 2-*O*-sulfated domains in syndecan-1 heparan sulfate inhibit neutrophil cathelicidin and promote *Staphylococcus aureus* corneal infection. *The Journal of Biological Chemistry* 290: 16157–16167.
Howell WH and Holt E (1918) Two new factors in blood coagulation—heparin and pro-antithrombin. *The American Journal of Physiology* 47: 328–341.
Hsu YY, Shi GY, Kuo CH, Liu SL, Wu CM, Ma CY, Lin FY, Yang HY, and Wu HL (2012) Thrombomodulin is an ezrin-interacting protein that controls epithelial morphology and promotes collective cell migration. *The FASEB Journal* 26: 3440–3452.
Hung CF, Wilson CL, and Schnapp LM (2019) Pericytes in the lung. *Advances in Experimental Medicine and Biology* 1122: 41–58.
Jenkins LM, Horst B, Lancaster CL, and Mythreye K (2018) Dually modified transmembrane proteoglycans in development and disease. *Cytokine & Growth Factor Reviews* 39: 124–136.
Jiang D, Liang J, Campanella GS, Guo R, Yu S, Xie T, Liu N, Jung Y, Homer R, Meltzer EB, Li Y, Tager AM, Goetinck PF, Luster AD, and Noble PW (2010) Inhibition of pulmonary fibrosis in mice by CXCL10 requires glycosaminoglycan binding and syndecan-4. *The Journal of Clinical Investigation* 120: 2049–2057.
Joensuu H, Anttonen A, Eriksson M, Makitaro R, Alfthan H, Kinnula V, and Leppa S (2002) Soluble syndecan-1 and serum basic fibroblast growth factor are new prognostic factors in lung cancer. *Cancer Research* 62: 5210–5217.
Jorpes JE and Gardell S (1948) On heparin monosulfuric acid. *The Journal of Biological Chemistry* 176: 267–276.
Kaksonen M, Pavlov I, Voikar V, Lauri SE, Hienola A, Riekki R, Lakso M, Taira T, and Rauvala H (2002) Syndecan-3-deficient mice exhibit enhanced LTP and impaired hippocampus-dependent memory. *Molecular and Cellular Neurosciences* 21: 158–172.
Kim H, Xu GL, Borczuk AC, Busch S, Filmus J, Capurro M, Brody JS, Lange J, D'Armiento JM, Rothman PB, and Powell CA (2003) The heparan sulfate proteoglycan GPC3 is a potential lung tumor suppressor. *American Journal of Respiratory Cell and Molecular Biology* 29: 694–701.
Kind S, Merenkow C, Buscheck F, Moller K, Dum D, Chirico V, Luebke AM, Hoflmayer D, Hinsch A, Jacobsen F, Gobel C, Weidemann S, Fraune C, Moller-Koop C, Hube-Magg C, Clauditz TS, Simon R, Sauter G, Wilczak W, Bawahab AA, Izbicki JR, Perez D, and Marx A (2019) Prevalence of syndecan-1 (CD138) expression in different kinds of human tumors and normal tissues. *Disease Markers* 2019: 4928315.
Kjellen L and Lindahl U (2018) Specificity of glycosaminoglycan-protein interactions. *Current Opinion in Structural Biology* 50: 101–108.
Li Q, Park PW, Wilson CL, and Parks WC (2002) Matrilysin shedding of syndecan-1 regulates chemokine mobilization and transepithelial efflux of neutrophils in acute lung injury. *Cell* 111: 635–646.
Li J, Gong F, Hagner-McWhirter A, Forsberg E, Åbrink M, Kisilevsky R, Zhang X, and Lindahl U (2003) Targeted disruption of a murine glucuronyl C5-epimerase gene results in heparan sulfate lacking *L*-iduronic acid and in neonatal lethality. *The Journal of Biological Chemistry* 278: 28363–28366.
Li Y, Jiang D, Liang J, Meltzer EB, Gray A, Miura R, Wogensen L, Yamaguchi Y, and Noble PW (2011) Severe lung fibrosis requires an invasive fibroblast phenotype regulated by hyaluronan and CD44. *The Journal of Experimental Medicine* 208: 1459–1471.
Li G, Li L, Joo EJ, Son JW, Kim YJ, Kang JK, Lee KB, Zhang F, and Linhardt RJ (2017) Glycosaminoglycans and glycolipids as potential biomarkers in lung cancer. *Glycoconjugate Journal* 34: 661–669.
Lichtenthaler SF, Lemberg MK, and Fluhrer R (2018) Proteolytic ectodomain shedding of membrane proteins in mammals-hardware, concepts, and recent developments. *The EMBO Journal* 37: e99456.
Lindahl U and Kjellen L (1991) Heparin or heparan sulfate—What is the difference? *Thrombosis and Haemostasis* 66: 44–48.
Lopez-Casillas F, Cheifetz S, Doody J, Andres JL, Lane WS, and Massague J (1991) Structure and expression of the membrane proteoglycan betaglycan, a component of the TGF-beta receptor system. *Cell* 67: 785–795.
Maurel P, Rauch U, Flad M, Margolis RK, and Margolis RU (1994) Phosphacan, a chondroitin sulfate proteoglycan of brain that interacts with neurons and neural cell-adhesion molecules, is an extracellular variant of a receptor-type protein tyrosine phosphatase. *Proceedings of the National Academy of Sciences of the United States of America* 91: 2512–2516.
Menozzi FD, Bischoff R, Fort E, Brennan MJ, and Locht C (1998) Molecular characterization of the mycobacterial heparin-binding hemagglutinin, a mycobacterial adhesin. *Proceedings of the National Academy of Sciences of the United States of America* 95: 12625–12630.
Milewska A, Zarebski M, Nowak P, Stozek K, Potempa J, and Pyrc K (2014) Human coronavirus NL63 utilizes heparan sulfate proteoglycans for attachment to target cells. *Journal of Virology* 88: 13221–13230.
Nackaerts K, Verbeken E, Deneffe G, Vanderschueren B, Demedts M, and David G (1997) Heparan sulfate proteoglycan expression in human lung-cancer cells. *International Journal of Cancer* 74: 335–345.
Nikaido T, Tanino Y, Wang X, Sato S, Misa K, Fukuhara N, Sato Y, Fukuhara A, Uematsu M, Suzuki Y, Kojima T, Tanino M, Endo Y, Tsuchiya K, Kawamura I, Frevert CW, and Munakata M (2015) Serum syndecan-4 as a possible biomarker in patients with acute pneumonia. *The Journal of Infectious Diseases* 212: 1500–1508.
Parimon T, Yao C, Habiel DM, Ge L, Bora SA, Brauer R, Evans CM, Xie T, Alonso-Valenteen F, Medina-Kauwe LK, Jiang D, Noble PW, Hogaboam CM, Deng N, Burgy O, Antes TJ, Konigshoff M, Stripp BR, Gharib SA, and Chen P (2019) Syndecan-1 promotes lung fibrosis by regulating epithelial reprogramming through extracellular vesicles. *Journal of Clinical Investigation Insight* 5: 129359.
Park PW, Pier GB, Preston MJ, Goldberger O, Fitzgerald ML, and Bernfield M (2000a) Syndecan-1 shedding is enhanced by LasA, a secreted virulence factor of *Pseudomonas aeruginosa*. *The Journal of Biological Chemistry* 275: 3057–3064.
Park PW, Reizes O, and Bernfield M (2000b) Cell surface heparan sulfate proteoglycans: Selective regulators of ligand-receptor encounters. *The Journal of Biological Chemistry* 275: 29923–29926.
Park PW, Pier GB, Hinkes MT, and Bernfield M (2001) Exploitation of syndecan-1 shedding by *Pseudomonas aeruginosa* enhances virulence. *Nature* 411: 98–102.
Park PW, Foster TJ, Nishi E, Duncan SJ, Klagsbrun M, and Chen Y (2004) Activation of syndecan-1 ectodomain shedding by *Staphylococcus aureus* alpha-toxin and beta-toxin. *The Journal of Biological Chemistry* 279: 251–258.
Park PW, Hayashida K, Aquino RS, and Jinno A (2016) Proteoglycans. In: Bradshaw RA and Stahl PD (eds.) *Encyclopedia of Cell Biology*. Waltham, MA: Academic Press.
Parkinson JF, Koyama T, Bang NU, and Preissner KT (1992) Thrombomodulin: An anticoagulant cell surface proteoglycan with physiologically relevant glycosaminoglycan moiety. *Advances in Experimental Medicine and Biology* 313: 177–188.
Perrimon N and Bernfield M (2000) Specificities of heparan sulphate proteoglycans in developmental processes. *Nature* 404: 725–728.
Pethe K, Alonso S, Biet F, Delogu G, Brennan MJ, Locht C, and Menozzi FD (2001) The heparin-binding haemagglutinin of *M. tuberculosis* is required for extrapulmonary dissemination. *Nature* 412: 190–194.
Ringvall M, Ledin J, Holmborn K, van Kuppevelt T, Ellin F, Eriksson I, Olofsson AM, Kjellen L, and Forsberg E (2000) Defective heparan sulfate biosynthesis and neonatal lethality in mice lacking *N*-deacetylase/*N*-sulfotransferase-1. *The Journal of Biological Chemistry* 275: 25926–25930.
Sarrazin S, Lamanna WC, and Esko JD (2011) Heparan sulfate proteoglycans. *Cold Spring Harbor Perspectives in Biology* 3: a004952.
Schmits R, Filmus J, Gerwin N, Senaldi G, Kiefer F, Kundig T, Wakeham A, Shahinian A, Catzavelos C, Rak J, Furlonger C, Zakarian A, Simard JJ, Ohashi PS, Paige CJ, Gutierrez-Ramos JC, and Mak TW (1997) CD44 regulates hematopoietic progenitor distribution, granuloma formation, and tumorigenicity. *Blood* 90: 2217–2233.
Shah L, Walter KL, Borczuk AC, Kawut SM, Sonett JR, Gorenstein LA, Ginsburg ME, Steinglass KM, and Powell CA (2004) Expression of syndecan-1 and expression of epidermal growth factor receptor are associated with survival in patients with nonsmall cell lung carcinoma. *Cancer* 101: 1632–1638.
Stallcup WB (2018) The NG2 Proteoglycan in Pericyte biology. *Advances in Experimental Medicine and Biology* 1109: 5–19.

Tamburini E, Dallatomasina A, Quartararo J, Cortelazzi B, Mangieri D, Lazzaretti M, and Perris R (2019) Structural deciphering of the NG2/CSPG4 proteoglycan multifunctionality. *The FASEB Journal* 33: 3112–3128.

Teder P, Vandivier RW, Jiang D, Liang J, Cohn L, Púre E, Henson PM, and Noble PW (2002) Resolution of lung inflammation by CD44. *Science* 296: 155–158.

Teng YH, Aquino RS, and Park PW (2012) Molecular functions of syndecan-1 in disease. *Matrix Biology* 31: 3–16.

Trowbridge JM and Gallo RL (2002) Dermatan sulfate: New functions from an old glycosaminoglycan. *Glycobiology* 12: 117R–125R.

Tsoyi K, Chu SG, Patino-Jaramillo NG, Wilder J, Villalba J, Doyle-Eisele M, McDonald J, Liu X, El-Chemaly S, Perrella MA, and Rosas IO (2018) Syndecan-2 attenuates radiation-induced pulmonary fibrosis and inhibits fibroblast activation by regulating PI3K/Akt/ROCK pathway via CD148. *American Journal of Respiratory Cell and Molecular Biology* 58: 208–215.

Tsoyi K, Osorio JC, Chu SG, Fernandez IE, De Frias SP, Sholl L, Cui Y, Tellez CS, Siegfried JM, Belinsky SA, Perrella MA, El-Chemaly S, and Rosas IO (2019) Lung adenocarcinoma syndecan-2 potentiates cell invasiveness. *American Journal of Respiratory Cell and Molecular Biology* 60: 659–666.

Wang S, Ai X, Freeman SD, Pownall ME, Lu Q, Kessler DS, and Emerson CP Jr. (2004) QSulf1, a heparan sulfate 6-O-endosulfatase, inhibits fibroblast growth factor signaling in mesoderm induction and angiogenesis. *Proceedings of the National Academy of Sciences of the United States of America* 101: 4833–4838.

Xu J, Park PW, Kheradmand F, and Corry DB (2005) Endogenous attenuation of allergic lung inflammation by syndecan-1. *Journal of Immunology* 174: 5758–5765.

Yan D and Lin X (2009) Shaping morphogen gradients by proteoglycans. *Cold Spring Harbor Perspectives in Biology* 1: a002493.

Zimmermann N, Saiga H, Houthuys E, Moura-Alves P, Koehler A, Bandermann S, Dorhoi A, and Kaufmann SH (2016) Syndecans promote mycobacterial internalization by lung epithelial cells. *Cellular Microbiology* 18: 1846–1856.