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REVIEW ARTICLE

SYNDECAN IN HEALTH AND DISEASE – A SYSTEMATIC REVIEW

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ABSTRACT:
Syndecans are heparin sulfate protoglycans that are associated with cell surface and extra cellular matrix. Invertebrates have one syndecan core protein but in mammals there are four syndecan proteins. Each protein has three major domains; ectodomain, transmembrane domain and cytoplasmic domain. Cytoplasmic domain are the most conserved and serve to regulate the signalling of growth factors. They have also been shown to be involved in cell signalling through interaction with integrins and tyrosine kinase receptors. These cell surface proteins are thought to play an important role in cell matrix and cell - cell adhesion, migration and proliferation. So, this review summarized the structure, properties and functions of various syndecan molecules in both health and disease.
Key words: Heparin sulphate, proteoglycan, ectodomain, cell signalling, integrins

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INTRODUCTION

Cell surface heparin sulphate proteoglycans are membrane anchored glycoproteins consisting of a protein core and one or more specialised polysaccharide chains, termed as 'glycosaminoglycans'.[1] These glycosaminoglycans are covalently linked to the proteoglycans present in extracellular matrix. The glycosaminoglycans can be classified into several types such as heparin sulphate, chondroitin sulphate, dermatan sulphate, keratin sulphate and hyaluronan.[1] Two major groups of cell surface proteoglycans have been recognised and termed as 'syndecans' and 'glypicans'.[2] This paper shall review the syndecan family in terms of their structure, role in normal development and diseases. The term 'Syndecan' is derived from the Greek word "syndein" which means 'to bind together'.[3] Human syndecan gene has been mapped to chromosome 2 p 23.[4] The syndecans links the cytoskeleton to the interstitial matrix. Syndecans are type 1 transmembrane proteins that are mainly composed of heparin sulphate molecule. The syndecan family is divided into four classes: Syndecan 1, 2, 3 and 4. Each syndecan family has a distinct temporal and spatial pattern of expression. [5] Syndecan 1 expression is seen in epithelium and plasma cells. Syndecan 2 is expressed by fibroblasts, endothelial cells, neurons and smooth muscle cells. Syndecan 3 by neural cells and proliferating chondrocytes and Syndecan 4 is expressed by all cells.[5]

BASIC STRUCTURE

The syndecan core protein consists of three domains; an extracellular domain ' ecto domain', a trans membrane domain and a cytoplasmic domain (Figure 1).

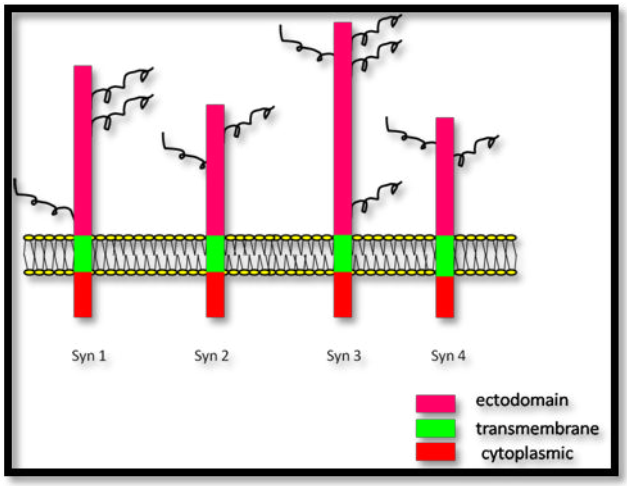

Figure 1: Basic structure of Syndecan

The glycoaminoglycans attached to the extracellular domain of the core protein are responsible for the differential binding capabilities of the syndecans.[5] The ectodomain portion is equipped with sites for glycoaminoglycan attachment that can bind to several extracellular matrix molecules. It has a conserved site near the cell membrane where the syndecans are shed by proteolytic cleavage. This shedding process has a very important role in several pathophysiological events and is stimulated by different physiological mediators. The transmembrane domain is highly homologous and contains 24 to 25 amino acids. It contains regions for interaction with other membrane proteins and for localization to distinct membrane compartments.[6] The cytoplasmic domain or the intracellular domain plays an important role in initiating the intracellular signalling cascade and also in recruitment of the intracellular proteins to the cell membrane. It has two similar regions across the membranes of syndecan family that are separated by a central variable region that is specific for each family member.[7] The syndecans have distinct functions assigned to their core proteins and heparin sulfate chains. Therefore, syndecan function varies from extracellular cell adhesion domain organization and regulation of cellular proliferation and differentiation.[8] The heparin sulfate chain binds to various ligands that regulate cell behaviour during development. (Table 1)

Table 1: Heparin sulphate binding proteins

Binding Proteins	Ligands
Polypeptide growth factors	Fibroblast growth factor 1 (FGF 1)
Heparin binding growth factor family (HGF)	Fibroblast growth factor 2 (FGF 2)
	Fibroblast growth factor 4 (FGF 4)
Epidermal growth factor (EGF) related growth factors	HB-EGF
	GGF
	ARIA
Hepatocyte growth factors	HGF
	Neurokinin 1 (NK 1)
	Neurokinin 2 (NK 2)
Pleiotrophin related	HB- GAM
	Midkine
Miscellaneous	Vascular endothelial growth factor (VEGF)
	Platelet derived growth factor (PDGF)
	Wnt 1
Enzymes	Lipoprotein lipase
	Acetylcholinesterase
Extracellular matrix proteins	Fibronectin
	Laminin
	Collagens
	Thrombospondin
	Tenascin
Cell cell adhesion molecules	L-Selectin
	N- CAM
	PECAM
Lipid binding proteins	LDL
	Lipoprotein lipase
Others	Influenza virus
	Diphtheria toxin
	Prion proteins

Syndecan 1

It is also called 'CD 138'. It consists of 311 amino acid long core proteins attached to heparin sulphate alone or together with chondrotin sulphate. Syndecan 1 is expressed almost exclusively by epithelial cells wherein the strongest expression has been observed by the squamous and transitional epithelial cell to cell contacts.[9,10]

In keratinocytes, syndecan 1 is localized at the cell membrane especially, the suprabasal layers.[11] It has also been shown to bind various extracellular matrix proteins such as collagen, fibronectin and tenascin.[12] By binding to extracellular matrix molecules and growth factors. Syndecan 1 plays an important role in cell extra cellular matrix interactions and also in modulation of growth factor response.[13] It has been reported to mediate cell morphology regulation and maintenance of epithelial phenotype by affecting the organization of actin cytoskeleton. It also mediates cell proliferation and hence is activated during normal cell growth while on the other hand it is suppressed in abnormal cell proliferation.[14] There is a close association between fibroblast growth factor and syndecan - 1 expression. Syndecan 1 expression is present during early embryonic development and has been localized on several developing epithelia for example epidermis, odontogenic and mammary epithelium.[15] It is considered as the earliest syndecan to be expressed during development. In a study by Sutherland et al in 1991, it has been shown that it initially appears at the four cell stage and later on, in all cells of the embryoblast in the blastocyst in mice.[10] After gastrulation, high expression is found in ectodermal and endodermal germ layers. It is also expressed in the mesenchyme during developmental stages especially, during the epithelial-mesenchymal interaction. During tooth odontogenesis, its expression is transiently present in the enamel epithelium and dental mesenchyme at bud stage and in stratium intermedium and stellate reticulum in bell stage.[16,17] It provides stability to the extracellular matrix and help control chemical mediators in wound healing process[18]. It is increased in proliferating keratinocytes and in endothelial cells of developing capillaries within the granulation tissue.[6] Syndecan-1 acts as a matrix receptor due to its binding to different extracellular matrix molecules through its heparan sulfate chains extracellularly and contacting the cytoskeleton via its cytoplasmic domain intracellulary. Syndecan-1 expression is down regulated in tumorigenesis therefore, tumor cells with decreased syndecan-1 expression lose cell surface molecules that bind them to each another and to the extracellular matrix.[19] It has been suggested that syndecan-1 is removed from the cell surface by a mechanism called "the ectodomain shedding".[20] Through this process, syndecan-1 gets converted from a membrane bound cell surface molecule to a diffusible and soluble mediator, allowing this molecule to participate in various autocrine and paracrine signaling actions. The soluble syndecan-1 molecule retains its ability to bind different ligands such as FGF.[21] Enzymatic degradation of syndecan-1 converts the soluble syndecan-1 ectodomain from an inhibitor to a potent activator of FGF. In addition to the core protein shedding, the heparin sulfate chains of syndecan-1 can also be degraded by the enzymatic activity of heparanase .[22]

Syndecan-1 is normally absent in the stromal cells though an increased expression in the stromal (fibroblasts and myofibroblasts) component of the neoplastic tissues has been reported. This stromal expression has been associated with poor prognosis in gastric, ovarian, breast, and head and neck cancers.[23-25] Various studies have indicated that syndecan-1 may enhance tumor growth by facilitating angiogenesis.[26]

Syndecan-1 expression is reduced or lost in carcinoma cells, as compared with their normal counterparts that enables the cells to detach and invade. This loss of expression may be an early event that contributes to neoplastic progression.[23] In potentially premalignant disorders, such as oral epithelial dysplasia, its expression decreases as compared with normal oral stratified squamous epithelium. Therefore, syndecan-1 has been suggested as a marker for dysplastic changes.[27,28]

Ro et al (2006) reported that reduction of syndecan-1 expression correlated with increased tumor size and invasion in squamous cell carcinomas of the tongue.[29] Muramatsu et al (2008) examined the expression of syndecan-1 in oral cancer cell lines and found that reduction of syndecan-1 led to higher cell proliferation.[30]

Syndecan-1 expression has been found to be reduced in odontogenic cysts and tumors when compared to normal cells of tooth buds. Bologna-Molina et al. (2008) reported decreased expression of syndecan-1 in solid ameloblastoma compared to the unicystic ameloblastoma.[31] In another study, syndecan-1 expression when compared among peripheral, desmoplastic ameloblastomas and ameloblastic carcinoma, syndecan-1 expression was found to be decreased in ameloblastic carcinoma compared to other ameloblastomas.[32] Similarly, loss of syndecan-1 expression appears to correlate with poor prognosis in stomach, breast, and head and neck neoplasms.[25,29,33,34]

Syndecan 2

It is termed as 'fibroglycan' as it is mainly produced by mesenchymal cells. It is predominantly expressed during embryonenesis.[35] Although its role in adult tissues has not been fully established, recent studies suggest its involvement in regulation of TGFβ signalling. TGFβ binds to the β glycan, which is transferred to the type II receptors that undergo autophosphorylation.[36] The phosphorylated type I and type II receptor complexes then engage in downstream cellular signalling. Betaglycan binds to the synectin that helps in retaining them on the cell surface, thus, preventing degradation. Synectin also binds to syndecan 2. Increase in the syndecan protein increases the type I and type II TGFβ receptor expression and decreases β glycan. This decrease in β glycan expression leads to deregulated activity of type I/ II TGFβ receptor complex.[37]

Syndecan 3

It is the largest syndecan in mammals which comprises of both heparin sulfate and chondroitin sulfate chains. It is also called 'neural syndecan' although its expression is seen in some stratified epithelia and differentiating cartilage.[38] It plays an important role in regulation of the skeleton muscle development. Its level has been shown to be increased during developing limb bud and totally absent in adult skeleton muscle. The skeleton muscle myoblasts are held in undifferentiated state until they receive signals for further differentiation.[39] These signals are mediated by specific growth factors such as FGF2, HGF, TGFβ.

It also appears to be involved in regulation of Hh signalling activity that plays an important role in embryogenesis and differentiation. One of the mammalian family of Hh member is 'Indian Hh' which is produced by prehypertrophic chondrocytes and regulates chondrocyte differentiation.[40]

Syndecan - 4

It is the smallest syndecan and most extensively studied member of the syndecan family. It is also called 'amphiglycan' as it is expressed both by the epithelial and fibroblastic cells.[41] It has a number of activities including cell adhesion, migration, proliferation endocytosis and mechanotransduction. It interacts with numerous heparin binding growth factors like fibroblast growth factors, vascular endothelial growth factors and platelet derived growth factors. Through the binding of these factors, syndecan-4 is able to organise their distribution in the extracellular space. Extracellular signalling of syndecan-4 is mediated by cleavage and shedding of its extracellular domain. In extracellular matrix, its binding with tenascin C, leads to matrix contraction thus playing an important part in wound healing. Syndecan-4 along with integrins, act as mediators of focal adhesion formation. It activates ADP ribosylation factor-6 which is involved in membrane trafficking, actin cytoskeletal remodelling and cell motility. It has also been suggested to function as sensors of extracellular stress that are capable of transmitting mechanical force into signalling events. Another function of syndecan 4 is activation of PKCα in absence of Ca^{+} ions. Colocalization of these proteins in focal adhesion suggests a role in cell adhesion and stress fibre formation.[42]

Syndecan-4 up regulation has been noted in hepatocellular carcinomas and malignant mesotheliomas and such over-expression may be correlated with increased tumor cell proliferation. Additionally, syndecan-4 has been shown to enhance β1 integrin function and can trigger signalling cascades required for cell spreading either by exposing a cryptic binding site for β1 integrins or by modulating the activity of β1 integrins. The molecular mechanism required for syndecan-β1 integrin receptor cross-talk involves syndecan-4 dependent activation of PKCα.[43] This activation process is required for cell spreading. Additional effectors required for cell spreading which are activated downstream of the syndecan-integrin signalling complex and include Rac1 and the lipid kinase, phosphoinositide-3-kinase. Activation of RhoA is required for stress-fiber formation, but not for cell spreading. A disintegrin and metalloproteinase-12 (ADAM-12) has been implicated in the differentiation and fusion of skeletal myoblasts and its expression is dramatically upregulated in a number of carcinomas. It interacts directly with the actin cytoskeleton via α-actinin and contains several Src homology 3 (SH3) binding motifs which have been shown to interact with and stimulate the activity of Src tyrosine kinase and PI-3K. Thus indicating that ADAM-12-syndecan signalling complexes may regulate cell adhesion and migration during the processes of development and metastasis.[44]

CONCLUSION

Syndecans by virtue of their Heparin sulfate chains functionally sense extracellular environments. As co-receptors for cell adhesion, cell proliferation and fate determination molecules and other extracellular signals, they collaborate with 'primary' receptors to control signalling (Figure 2). Thus, Syndecan plays an important role in the development of embryogenesis, inflammatory diseases, cancers and infection.

REFERENCES

1. Couchman JR. Syndecans: proteoglycan regulators of cell surface microdomains Nat Rev Mol Cell Biol 2003; 4: 926-937.
2. Filmus J, Capurro M, Rast J. Glypicans. Genome Biol 2008; 9:224.
3. Saunders S, Jalkanen M, O'Farrell S, Bernfield M. Molecular cloning of syndecan, an integral membrane proteoglycan. J Cell Biol 1989;108(4):1547-1556.
4. Ala-Kapee M, Nevanlinna H, Mali M, Jalkanen M, Schroder J. Localization of gene for human syndecan, an integral membrane proteoglycan and a matrix receptor to chromosome 2. Somat Cell Mol Genet 1990;16(5):501-505.
5. Kim CW, Goldberger OA, Gallo RL, Bernfield M. Members of the syndecan family of heparin sulfate proteoglycans are expressed in distinct cell-, tissue-, and development-specific patterns. Mol Biol Cell 1994;5(7):797-805.
6. Elenius K, Jalkanen M. Function of the syndecans--a family of cell surface proteoglycans. J Cell Sci 1994;**107**(11):2975-2982
7. Rapraeger AC, Ott VL. Molecular interactions of the syndecan core proteins. Curr Opin Cell Biol 1998;10(5):620-628.
8. Bernfield M, Gotte M, Park PW, Reizes O, Fitzgerald ML, Lincecum J, Zako M. Functions of cell surface heparan sulfate proteoglycans. Annu Rev Biochem 1999;68:729-777.
9. Hayashi K, Hayashi M, Jalkanen M, Firestone J, Trelstad R, Bernfield M. Immunocytochemistry of cell surface heparan sulfate proteoglycan in mouse tissues. A light and electron microscopic study. J. Histochem. Cytochem. 1987;35(10):1079-1088.
10. Sutherland AE, Sanderson RD, Mayes M, Seibert M, Calarco PG, Bernfield M, Damsky CH. Expression of syndecan, a putative low affinity fibroblast growth factor receptor, in the early mouse embryo. Development 1991;113(1):339-351.
11. Sanderson RD, Hinkes MT, Bernfield M. Syndecan-1, a cell surface proteoglycan, changes in size and abundance when keratinocytes stratify. J Invest Dermatol 1992;99:390-396.
12. Elenius K, Salmivirta M, Inki P, Mali M, Jalkanen M. Binding of human syndecan to extracellular matrix proteins. J. Biol. Chem. 1990;265(29):17837-17843.
13. Bernfield M, Kokenyesi R, Kato M, Hinkes MT, Spring J, Gallo RL, Lose EJ. Biology of the syndecans: a family of transmembrane heparan sulfate proteoglycans. Annu Rev Cell Biol 1992;8:365-393.
14. Leppa S, Mali M, Miettinen HM, Jalkanen M. Syndecan expression regulates cell morphology and growth of mouse mammary epithelial tumor cells. Proc Natl Acad Sci U S A 1992;89(3):932-936.
15. Trautman MS, Kimelman J, Bernfield M. Developmental expression of syndecan, an integral membrane proteoglycan, correlates with cell differentiation. Development 1991;111(1):213-220.
16. Thesleff I, Jalkanen M, Vainio S, Bernfield M. Cell surface proteoglycan expression correlates with epithelial-mesenchymal interaction during tooth morphogenesis. Developmental Biology 1988;129(2):565-572.
17. Vainio S, Jalkanen M, Vaahtokari A, Sahlberg C, Mali M, Bernfield M, Thesleff I. Expression of syndecan gene is induced early, is transient, and correlates with changes in mesenchymal cell proliferation during tooth organogenesis. Developmental Biology 1991;147(2):322-333.
18. Elenius K, Vainio S, Laato M, Salmivirta M, Thesleff I, Jalkanen M. Induced expression of syndecan in healing wounds. J. Cell Biol. 1991;114(3):585-595.
19. Stetler-Stevenson WG, Aznavoorian S, Liotta LA. Tumor cell interactions with the extracellular matrix during invasion and metastasis. Annu Rev Cell Biol 1993;9:541-573.
20. Kim CW, Goldberger OA, Gallo RL, Bernfield M. Members of the syndecan family of heparin sulfate proteoglycans are expressed in distinct cell, tissue, and development-specific patterns. Mol Biol Cell 1994;5(7):797-805.
21. Klagsbrun M. The affinity of fibroblast growth factors (FGFs) for heparin; FGF-heparan sulphate interactions in cells and extracellular matrix. Curr Opin Cell Biol 1990;2(5):857-863.
22. Bame KJ. Heparanases: endoglycosidases that degrade heparan sulfate proteoglycans. Glycobiology 2001;11(6):91R-98R
23. Wiksten J-P, Lundin J, Nordling S, Lundin M, Kokkola A, Boguslawski Kv, Caj Haglund. Epithelial and stromal syndecan-1 expression as predictor of outcome in patients with gastric cancer. International Journal of Cancer 2001;95(1):1-6.
24. Leivonen M, Lundin J, Nordling S, von Boguslawski K, Haglund C. Prognostic value of syndecan-1 expression in breast cancer. Oncology 2004;67(1):11-18.
25. Miklo´s Ms, Suba Z, Németh Z, Ttrai P, Füle T, Borgulya G, Barabs Jz, Kovalszky I. Stromal syndecan-1 expression is an adverse prognostic factor in oral carcinomas. Oral Oncol 2006;42(5):493-500.
26. Stanley MJ, Stanley MW, Sanderson RD, Zera R. Syndecan-1 expression is induced in thestroma of infiltrating breast carcinoma. Am J Clin Pathol 1999;112(3):377-383.
27. Kurokawa H, Matsumoto S, Murata T, Yamashita Y, Tomoyose T, Zhang M, Fukuyama H, Takahashi T. Immunohistochemical study of syndecan-1 down regulation and the expression of p53 protein or Ki-67 antigen in oral leukoplakia with or without epithelial dysplasia. J Oral Pathol Med 2003;32(9):513-521
28. Soukka T, Pohjola J, Inki P, Happonen R-P. Reduction of syndecan-1 expression is associated

with dysplastic oral epithelium. J Oral Pathol Med 2000;29(7):308-313.
29. Ro Y, Muramatsu T, Shima K, Yajima Y, Shibahara T, Noma H, Shimono M. Correlation between reduction of syndecan-1 expression and clinico-pathological parameters in squamous cell carcinoma of tongue. Int J Oral Maxillofac Surg 2006;35(3):252-257.
30. Muramatsu T, Saitoh M, Ro Y, Uekusa T, Iwamura E, Ohta K, Kohno Y, Abiko Y, Shimono M.Inhibition of syndecan-1 expression and function in oral cancer cells. Oncol Rep 2008;20(6):1353-1357.
31. Bologna-Molina R et al.Syndecan-1 (CD138) and Ki-67 expression in different subtypes of ameloblastomas. Oral Oncol 2008;44(8):805-811.
32. Bologna-Molina R et al. Comparative expression of syndecan-1 and Ki-67 in peripheral and desmoplastic ameloblastomas and ameloblastic carcinoma. Pathol Int 2009;59(4):229-233.
33. Mukunyadzi P, Liu K, Hanna EY, Suen JY, Fan CY. Induced expression of syndecan-1 in the stroma of head and neck squamous cell carcinoma. Mod Pathol 2003;16(8):796-801.
34. Chen CL, Ou DL. Expression of syndecan-1 (CD138) in nasopharyngeal carcinoma is correlated with advanced stage and poor prognosis. Human Pathology 2006;37(10):1279-1285.
35. Couchman JR. Syndecans: proteoglycan regulators of cell-surface microdomains. Nat Rev Mol Cell Biol. 2003;4:926 –937.
36. Chen L, Klass C, Woods A. Syndecan-2 regulates transforming growth factor-beta signaling. J Biol Chem. 2004;279:15715–15718.
37. Klass CM, Couchman JR, Woods A. Control of extracellular matrix assembly by syndecan-2 proteoglycan. J Cell Sci. 2000;113:493–506.
38. Carey, D. J., Evans, D. M., Stahl, R. C., Asundi, V. K., Conner, K. J, Carbes, P. and Cizmeci-Smith, G (1992). Molecular cloning and characterization of N-syndecan, a novel transmembrane heparan sulphate proteoglycan. J Cell Biol. 117, 191-192.
39. Brunetti A, Goldfine ID. Role of myogenin in myoblast differentiation and its regulation by fibroblast growth factor. J Biol Chem. 1990;265:5960–5963.
40. Shimo T, Gentili C, Iwamoto M, Wu C, Koyama E, Pacifici M. Indian hedgehog and syndecans-3 coregulate chondrocyte proliferation and function during chick limb skeletogenesis. Dev Dyn. 2004;229:607–617.
41. Davies EJ, Blackhall FH, Shanks JH, David G, McGown AT, Swindell R, Slade RJ, Martin-Hirsch P, Gallagher JT, Jayson GC. Distribution and clinical significance of heparin sulfate proteoglycans in ovarian cancer. Clin Cancer Res 2004;10(15):5178-5186.
42. Oh ES, Woods A, Couchman JR. Syndecan-4 proteoglycan regulates the distribution and activity of protein kinase C. J Biol Chem. 1997;272: 8133–8136.
43. Lim ST, Longley RL, Couchman JR, Woods A. Direct binding of syndecan-4 cytoplasmic domain to the catalytic domain of protein kinase C alpha (PKC alpha) increases focal adhesion localization of PKC alpha. J Biol Chem. 2003;278:13795–13802.
44. Kang Q, Cao Y, Zolkiewska A: Metalloprotease-disintegrin ADAM 12 binds to the SH3 domain of Src and activates Src tyrosine kinase in C2C12 cells. Biochem J 2000, 352:883-892.

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