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Syndecans, Signaling, and Cell Adhesion

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Abstract Syndecans are transmembrane proteoglycans which can participate in diverse cell surface interactions, involving extracellular matrix macromolecules, growth factors, protease inhibitors, and even viral entry. Currently, all extracellular interactions are believed to be mediated by distinct structures within the heparan sulfate chains, leaving the roles of chondroitin sulfate chains and extracellular portion of the core proteins to be elucidated. Evidence that syndecans are a class of receptor involved in cell adhesion is mounting, and their small cytoplasmic domains may link with the microfilament cytoskeleton, thereby mediating signaling events. The molecular details are unknown, but the conservation of regions of syndecan cytoplasmic domains, and a strong tendency for homotypic association, support the idea that the ligand-induced clustering may be a discrete source of specific transmembrane signaling from matrix to cytoskeleton, as proposed for other classes of adhesion receptors.

Key words: heparan sulfate, extracellular matrix, cytoskeleton, fibronectin, proteoglycans

The science of cell adhesion has gained considerable momentum over the past few years. We are now at the stage where specific individual adhesion molecules are being investigated in the context of discrete cell-cell and cell-extracellular matrix interactions, together with the intracellular consequences of these receptor-ligand interactions. Second messenger signaling cascades have clearly been identified in many cell adhesion processes, most notably with the integrins, which has set a trend that is likely to continue in the foreseeable future. Four major classes of adhesion molecules are known to be involved in cell-cell and cell-extracellular matrix interactions, including those of the immunoglobulin superfamily such as N-CAM and ICAM-1, the calcium sensitive cadherins, the integrins which are involved in cell-cell and cell-matrix interactions, as well as the selectins involved in heterotypic cellular interactions.

It is now appropriate to consider the cell surface proteoglycans as a fifth class of cell adhesion molecule, especially the class known as the syndecans for which there is increasing evidence in augmentation of adhesion. The syndecans contain four members in mammals [reviewed in Bernfield et al., 1992; Couchman and Woods, 1993; David, 1993] but only one in Drosophila [Spring et al., 1994], and are typical type I membrane glycoproteins with a single transmembrane spanning sequence and short cytoplasmic domain. The larger extracellular domains are substituted with a variable number of glycosaminoglycans, usually at least three. The family are known as a group of heparan sulfate proteoglycans, although it is clear that syndecan 1, for example, can additionally bear chondroitin sulfate chains, as can other members including syndecan 4 [Bernfield et al., 1992; David, 1993; Shworak et al., 1994b].

The four mammalian members of the syndecan family have different tissue distributions, and expression of their core proteins can be developmentally regulated [Bernfield et al., 1992; Couchman and Woods, 1993; David, 1993; David et al., 1993; Kim et al., 1994]. Syndecan 1, the first member to be cloned, is widely present on epithelia, both simple and stratified, but is less abundant on mesenchymal cells, except during morphogenesis, for example in developing hair follicles and teeth [Bernfield et al., 1992; Thesleff et al., 1988]. Syndecan 2, also known as fibroglycan, is often the most abundant syndecan of mesenchymal cell types such as fibroblasts, and also liver [Bernfield et al., 1992; David et al., 1993; Pierce et al., 1992]. Syndecan 3 has the largest core protein of the family, including a threonine-proline rich extracellular domain. It

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is also known as *N*-syndecan by virtue of its abundance in neural tissue, but it is also present in some muscle tissues [Bernfield et al., 1992; Kim et al., 1994]. Syndecan 4, also known as amphiglycan and ryudocan, has the smallest core protein of approximately 20kD, and is the most widespread of the four syndecans, being present on epithelia and endothelia, as well as fibroblasts, muscle cells, neural tissue and even chondrocytes [Baciu et al., 1994; Kim et al., 1994; Kojima et al., 1992].

This review will concentrate on the syndecans, but other cell surface proteoglycans, including the transmembrane, part-time proteoglycan CD44, may also have important roles in cell-extracellular matrix adhesion [reviewed in Couchman and Woods, 1993; David, 1993]. Any role in adhesion for those proteoglycans which are linked to the membrane through glycosyl phosphatidylinositol anchors, including glypican, cerebroglycan, and OCI-5, is as yet unclear.

The syndecans represent, at first sight, a simpler situation than the integrins, whose numerous alpha and beta subunits can form a large number of heterodimers [Cheresh and Mecham, 1994]. The four mammalian syndecan core proteins form homopolymers but not, apparently, heteropolymers. Furthermore, no alternate splicing of syndecans at the mRNA level has yet been recorded. However, although syndecans may appear to be a straightforward class of adhesion molecule, understanding the control and significance of the posttranslational modifications of the core protein will present a considerable challenge. All syndecans are substituted with glycosaminoglycan chains whose chain length can vary, and it is clear that there is also considerable complexity in terms of the fine structure of the heparan sulfate chains [Kato et al., 1994; Shworak et al., 1994a; Turnbull et al., 1992]. These appear to mediate all syndecan interactions on the extracellular face of the cell membrane, although a subject for much future study will be whether the core proteins themselves are also involved.

The unifying feature of syndecan core proteins is the structure of their transmembrane and cytoplasmic domains. These are highly homologous and each core protein is highly conserved between different species [Bernfield et al., 1992; Couchman and Woods, 1993; David, 1993]. The single transmembrane sequence is strictly conserved across species for each syndecan, and may be partly responsible for the homotypic association of the core protein [Carey et al., 1994]. In addition, there are four highly conserved tyrosine residues present in the cytoplasmic domains of all syndecans from *Drosophila* to man [Spring et al., 1994]. As depicted in Figure 1, the cytoplasmic domains of the syndecans are very similar, but there is a central more variable region (V), surrounded by more highly conserved regions (C1 and C2). The subject of debate and experimentation at the current time is whether the cytoplasmic domains of the syndecans interact with the cytoskeleton or other cytoplasmic molecules, and this is discussed further below. Certainly the conservation of tyrosine residues would imply that there are important intermolecular interactions between the cytoplasmic domains and other cytoplasmic components, but these have remained elusive.

An understanding of transcriptional and post-transcriptional controls which underlie syndecan expression is only in its infancy at the current time. While growth factors such as TGF-β and FGF-2 may regulate syndecan expression [reviewed in Couchman and Woods, 1993], a recent study from Gallo et al. [1994] shows that syndecan 1, and particularly syndecan 4 core

	C1	V	C2
SYN D	YRMRKKDEGSYAL	DEPKRSPANNSYAK-	NANNREFYA
SYN 1	YRMKKKDEGSYSL	EEPKQA-NGGAYQK-	PTKQEEFYA
SYN 3	YRMKKKDEGSYTL	EEPKQA--S*VTYQK-	PDKQEEFYA
SYN 2	YRMRKKDEGSYDL	GERK--PS SAAYQKA	PTK--EFYA
SYN 4	YRMKKKDEGSYDL	G-KK--P---IYKKA	PTN--EFYA

Fig. 1. Cytoplasmic domain sequences of Drosophila and rat syndecans. The two constant regions (*C1* and *C2*) and the variable region (*V*) are indicated. For syndecan 1, the rat, human, mouse, and hamster sequences are identical as are rat and human syndecan 2 sequences. Rat and chicken syndecan 3 sequences are identical except as denoted by the asterisk [S → N]. For syndecan 4, rat, human and chicken sequences are identical. The conserved tyrosine residues are indicated in bold. Abbreviations are: SYN, syndecan; D, *Drosophila*.

protein gene expression can be markedly regulated by the wound fluid peptide PR-39. The molecular basis behind this evidently precise control is unknown. There are, at least in some cells, posttranscriptional regulation mechanisms as shown by Yeaman and Rapraeger [1993], where treatment of mouse peritoneal macrophages with cAMP promotes the appearance of syndecan 1 on the cell surface.

Syndecans as Co-Receptors

The ligands for syndecan glycosaminoglycan chains can be broadly grouped into growth factors and cytokines such as members of the fibroblast growth factor (FGF) family, extracellular matrix molecules, enzymes and protease inhibitors [David, 1993]. Syndecan 1, for example, can interact with FGF2 as well as fibronectin, types I, III, and V collagens, tenascin, thrombospondin, and antithrombin III. Bernfield et al. [1992] coined the term co-receptor, based largely on information from the growth factor field. FGF2 appears to require interaction with heparin, or heparan sulfate, in order to be favorably presented to the high affinity receptors, FGFRs, which then induce transmembrane signaling and downstream events. Further, discrete heparan sulfate fine sequences have been described for which FGF2 has high affinity [Guimond et al., 1993; Turnbull et al., 1992]. Mutant cells lacking cell surface heparan sulfate proteoglycans cannot respond to FGF2 in the absence of heparin [Yayon et al., 1991] and other recent data show that FGF2 internalized on heparan sulfate proteoglycans enters a different cytoplasmic compartment than FGF2 presented in the context of heparan sulfate to high affinity receptors [Reiland and Rapraeger 1993]. The binding and presentation of growth factors is a complex phenomenon, and it is not yet clear whether the ability of syndecans to act as growth factor co-receptors is a widespread phenomenon. Purified syndecans 1 and 2, and the GPI-anchored glypican, do not appear, in some circumstances, to present FGF2 to high affinity receptors. Indeed the basement membrane heparan sulfate proteoglycan perlecan, quite unrelated to the cell surface proteoglycans, may be a key player in this process [Aviezer et al. 1994].

Whether syndecans act as co-receptors in cell adhesion processes is not fully understood. Certainly, syndecan 4 can be readily demonstrated in cell-matrix adhesion plaques known as focal adhesions, together with integrins. Whether this is a case of ligand presentation by the syndecan to the integrins is unclear, and perhaps unlikely in view of a variety of evidence concerning integrin-ligand interactions. It is however, clear that heparin interactions with the glycoprotein fibronectin induces conformational changes [Hynes, 1990] which may affect the availability of the integrin-binding sites. A third situation where syndecans may act as co-receptors, involves the heparan sulfate-sensitive mechanisms by which some viruses obtain entry into cells. It is not known whether cell surface proteoglycans act in concert with partner receptors in this process.

The Carbohydrate Connection

Syndecans appear to function in adhesion through their glycosaminoglycan chains. Heparan sulfate glycosaminoglycan chains are subject to considerable fine structural specificity emphasizing that the extent and position of sulfation and epimerization of glucuronic acid to iduronic acid is not random. This is entirely commensurate with the idea that growth factors and extracellular matrix ligands for heparan sulfate require specific patterns of heparan sulfate structure. The most well known example, and first to be characterized, was the structural requirements for binding of heparin to antithrombin III [Kjellén and Lindahl, 1991]. Three principles have emerged with respect to syndecan glycanation. First, a single species of syndecan core protein may bear heparan sulfate chains with cell type-specific fine structure. Elegant analysis by Kato et al. [1994] has shown that syndecan 1 heparan sulfate isolated from three different cell lines is distinct. While the overall block structure of low sulfated regions and high sulfated regions remained constant, the extent of 6-O-sulfation was variable. This apparently

TABLE I. Distributions of the Syndecans

SYN D. Haemopoietic organs, nervous system, basal surfaces of gut epithelia.
SYN 1. Epithelial cells, embryonic mesenchyme, pre B lymphocytes and plasma cells, vascular smooth muscle, endothelial and neural cells.
SYN 2. Mesenchymal cells, particularly in presumptive precursors of hard and connective tissues, liver, muscle, brain.
SYN 3. Neural tissues, precartilaginous condensations, cardiac and smooth muscle.
SYN 4. Widespread, including epithelial, endothelial, muscle, neural, lymphoid, and mesenchymal tissues.

had no impact on interactions with FGF2, but altered the ability of the heparan sulfate to interact with type I collagen. This, clearly, has implications for cell-matrix adhesion events mediated by syndecans. Moreover, the affinity of intact syndecan for collagen was markedly higher than that of its individual glycosaminoglycan chains, suggesting a role for cooperative binding of syndecans to matrix molecules.

The second principle to emerge from studies of syndecan heparan sulfates, is that the same fine structure may be present on more than one syndecan core protein in a single cell type. Kojima et al. [1992], for example, have shown that both syndecan 1 and 4 heparan sulfate chains may bear the appropriate structure for interaction with antithrombin III. Syndecans 1 and 3 have been shown to bind FGF2, whereas syndecans 1, 2, and 4 interact with glycoproteins such as fibronectin. There may be two ways of looking at this apparently confusing phenomenon. In the first place, when syndecans act as co-receptors, core protein specificity may not have an over-riding influence on subsequent events. In contrast, where syndecans may act as direct receptors, with consequent signaling events, the biological response may be governed by the abundance of syndecan core proteins, together with specificity of cytoplasmic interactions.

The third principle, is that glycanation of syndecan core proteins can be subject to variation. Analysis of syndecan 1 has shown that the three most distal glycosaminoglycans substitution sites are predominantly heparan sulfate, but with some chondroitin sulfate. In contrast, the two glycosaminoglycan substitution sites closer to the cell membrane are usually occupied by chondroitin sulfate chains [Kokenyesi and Bernfield, 1994]. On the other hand, the three glycosaminoglycan substitution sites in syndecan 4 may bear any or all combinations of heparan and chondroitin sulfates [Shworak et al., 1994b]. While no distinct function has yet been ascribed to chondroitin sulfate chains on syndecan core proteins, this is an area for future research, since regulation of glycanation may profoundly impact the ability of syndecans to interact with many of its ligands. Indeed, detailed studies with endothelial syndecans also indicate that transfection, with subsequent overexpression of syndecan core proteins, can saturate the heparan sulfate synthesis machinery, with a consequent down regulation of heparan sulfate chains which bear anti-thrombin III binding activity [Shworak et al., 1994a]. This raises a concern that experiments designed to examine syndecan-ligand interactions need to be performed carefully, with consideration of the ligand-binding properties of the over-expressed syndecan. It seems likely that the phenomenon observed with antithrombin III binding may also be true of growth factor and matrix interactions.

Syndecan 1 and Cell Adhesion

Syndecan 1 has been shown to interact with several extracellular matrix molecules, through its heparan sulfate chains, and many studies implicate syndecan 1 with a role in cell-matrix adhesion. Leppä et al. [1991] have investigated the role of syndecan 1 in adhesion of the androgen-responsive carcinoma cell line S115. These cells, when plated in the absence of hormone, retain an epithelial morphology, with well developed microfilament bundles terminating at focal adhesions, but on exposure to androgens, they assume a more fibroblastic morphology with a disassembly of the microfilament system and focal adhesions. This change in morphology is accompanied by down regulation of syndecan 1 expression on the cell surface, and could be prevented by overexpressing syndecan 1, indicating that proteoglycan expression correlates with the acquisition and retention of an epithelial morphology. Other experiments with Schwann cells, have shown a profound influence of syndecan 1 on cell spreading and adhesion. Carey et al. [1994] have shown that overexpressing syndecan 1 in these cells causes them to flatten, and develop microfilament bundles which terminate in focal adhesions. However, syndecan 1 itself does not become incorporated into these adhesions even though during cell spreading, syndecan 1 codistributes with the underlying cytoskeleton. Further, when syndecan 1 is crosslinked by antibodies, the clusters are colinear with the microfilament bundles, and, perhaps more importantly as an indicator of their association with the underlying cytoskeleton, become resistant to extraction by nonionic detergents [Carey et al., 1994]. In contrast, clustering of overexpressed truncated syndecan 1 lacking most of the cytoplasmic domain, does not induce detergent resistance. This interesting series of experiments points to an important role for the cytoplasmic domain, namely an interaction with the underlying cytoskeleton. This had been suggested some years ago [reviewed in Bernfield et

al., 1992], but is an area still not fully resolved. Other data indicates that the cytoplasmic domain of syndecan 1 does not become cytoskeleton-associated [Miettinen and Jalkanen, 1994], but in this case similar crosslinking experiments were not performed. One hypothesis is that syndecans, which may naturally occur on the cell surface as dimers, or even oligomers, may need to be associated into higher order structures before signaling to, and becoming associated with, the cytoskeleton. The nature of syndecan self-association is intriguing and unresolved, but apparently resides in the transmembrane and/or cytoplasmic domains of these molecules. Indeed, dimerization and oligomerization must be a stable phenomenon since the intact syndecan core proteins form SDS-resistent dimers when resolved by polyacrylamide gel electrophoresis [Carey et al., 1994; Miettinen et al., 1994].

A third series of experiments with mammary epithelial cells shows that syndecan expression on the cell surface may be coordinated with the expression of other cell adhesion molecules. Kato et al., [1995] have shown very recently that down regulating the expression of syndecan 1 on the cell surface, using antisense constructs, leads in turn, to a down regulation of E-cadherin, but not other adhesion receptors, such as integrins. The mechanism behind this is clearly important to understand, but currently unknown. Again, this raises an issue regarding transfection experiments, since one can apparently not assume that depressing or augmenting syndecan expression on the cell surface is without effect on other adhesion systems.

Syndecan 4 and Cell Adhesion

Syndecan 4 is the most widespread of all the syndecans in mammalian and avian tissues, and our recent work has shown that this proteoglycan becomes incorporated into focal adhesions [Woods and Couchman, 1994], as may syndecan 1 in a few cases [Yamagata et al., 1993]. Focal adhesions represent points of strong cell-matrix interaction, and in vivo homologs may be involved with wound healing by myofibroblasts, and resistance to shear stress by conducting vessel endothelia [Burridge et al., 1988; Woods and Couchman, 1988]. Other potential parallels are the dense bodies of smooth muscles, and myotendinous junctions. Interest in focal adhesions has increased dramatically over the past few years, with the recognition that integrins are essential for their formation, and that they arise as a result of a complex series of transmembrane signaling events. A schematic structure of focal adhesions is shown in Figure 2. Using either recombinant segments of fibronectin or fragments derived by proteolysis and subsequent purification, we have shown that two distinct signals are induced by the glycoprotein fibronectin when it is used as a substrate for cell adhesion [reviewed in Couchman and Woods, 1993]. Cells inhibited from endogenous matrix synthesis, when plated on the central cell-binding domain, that interacts with integrins, can attach and spread well, but do not form focal adhesions. This is in contrast to whole, intact fibronectin or large fragments encompassing both integrin-binding and heparin-binding domains of the molecule. The high affinity Hep II domain of fibronectin, in combination with the integrin-binding domain of fibronectin, does, however, lead to focal adhesion formation in primary fibroblasts and other cell types. Other studies, using mutant cells lacking cell surface heparan sulfate, together with experiments where cells are pretreated with heparitinase enzyme [Woods et al., 1993], indicate that the Hep II domain of fibronectin interacts with a cell surface heparan sulfate proteoglycan, and that this interaction is essential for focal adhesion formation. Syndecan 4 incorporation into focal adhesions is independent of the integrin ligated, which can be $\beta 1$ or $\beta 3$ in nature. Whether syndecan 4 acts as a co-receptor with integrins in the formation of focal adhesions is not entirely clear, but may be unlikely. The Hep II domain can work independently, at very low concentrations, and will trigger focal adhesion formation in cells already spread on the integrin-binding domain of fibronectin. Thus, two fibronectin domains need not be covalently bound to each other for activity, and may also function with different kinetics. Second, the requirement for cell surface proteoglycan can be bypassed by triggering focal adhesion formation in spread cells through phorbol ester activation of protein kinase C [Woods and Couchman, 1992]. This might imply that syndecan 4 can directly signal to the cytoskeleton of cells using distinct pathways from integrins, which are now known to trigger a cascade of tyrosine kinase phosphorylation events. As with the experiments involving the crosslinking of syndecan 1, it is clear that syndecan 4 become clustered and linked to the cytoskeleton in the focal adhesion. Third, the cytoplasmic domain of syndecan 4, but not the other

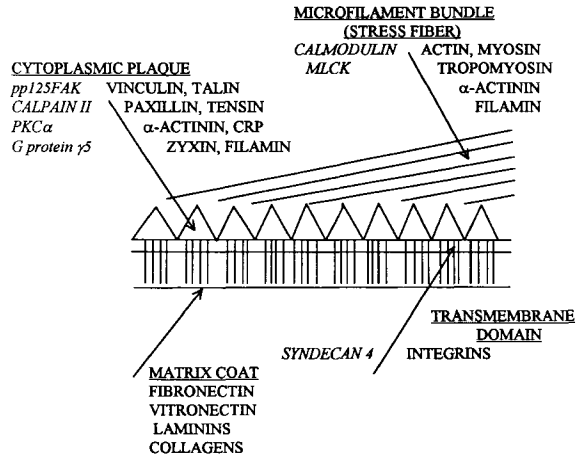

Fig. 2. Focal adhesion components. There are four domains (underlined) with specific components. Potential regulatory components are shown in italics. Abbreviations are: FAK, focal adhesion kinase; PKC, protein kinase C; CRP, cysteine-rich protein; MLCK, myosin light chain kinase.

syndecans, contains some homology to integrin $\beta 1_A$, including the NPXY sequence postulated to be involved in focal adhesion localization of the integrin [see Woods and Couchman, 1994]. Thus, it may be independently drawn into association with microfilament associated proteins. Much remains to be established, including the mechanisms by which syndecan 4 (presumably its cytoplasmic domain) may trigger protein kinase C activity, the downstream events mediated by protein kinase C signaling, as well as the extracellular requirements in term of interactions with the heparin binding domains of fibronectin and other extracellular matrix molecules.* In any event, the fact that focal adhesions are a clearly discernible end point in the adhesion of many different cell types in vitro, and probably in vivo, lends itself to investigation. For all the reasons stated above though, it is clear that outwardly simple experiments such as overexpressing dominant negative forms of syndecan 4 may not be straightforward, since unlike integrin-ligand interactions, the primary site of interaction of syndecan is through their heparan sulfate chains. These are subject to tremendous variability in their fine structure and present a challenge for the future.

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*NOTE ADDED IN PROOF

Baciu and Goetinck [Mol. Biol. Cell 6:1503–1513, 1995] have also reported that protein kinase C activation correlates with syndecan 4 recruitment to focal adhesions.

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