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Developmental expression of the syndecans: possible function and regulation

Merton Bernfield[1,*], Michael T. Hinkes[1] and Richard L. Gallo[2]

[1]Joint Program in Neonatology and [2]Department of Dermatology, Harvard Medical School, Boston, MA 02115, USA

*Author for correspondence

SUMMARY

Recent work has made clear that heparan sulfate at the cell surface is essential for a wide variety of interactions of cells with their microenvironment, including the action of growth factors, extracellular matrix, proteases and protease inhibitors. A major source of this cell surface heparan sulfate is a multigene family of proteoglycans, the syndecans, that are expressed developmentally in association with changes in tissue organization and morphology and induced during wound repair. In this review, we describe mechanisms underlying the differential expression of the syndecans, focusing on syndecan-1. The induction of syndecan-1 can result from soluble extracellular factor(s) acting at multiple levels of cellular regulation. At the transcriptional level, the promoter of the murine syndecan-1 gene contains potential recognition sites for several well-known regulatory genes, including *Hox* and *MyoD* family members. Because changes in syndecan expression enable cells to become more or less responsive to their microenvironment, understanding these regulatory mechanisms can lead to an improved understanding of how cellular behavior is controlled during development and wound repair.

Key words: syndecan, heparan sulfate, proteoglycans, cell adhesion

INTRODUCTION

Morphogenesis, the process of cellular organization, determines the form and function of the organs. A relatively few cellular behaviors are responsible for all of organ morphogenesis: changes in cell shape, motility, adhesion, proliferation and differentiation. These behaviors are initiated, controlled and integrated by effectors in a cell's microenvironment, especially extracellular matrix components, growth factor peptides, proteases and anti-proteases. A few years ago, we realized that a wide variety of components of the cellular microenvironment bind with appreciable affinity (K_d as low as 5 nM) to heparin, a structural analog of the highly anionic heparan sulfate that is at the surface of all adherent vertebrate cells (Bernfield et al., 1992; see Table 1). Thus, we hypothesized that (i) heparan sulfate proteoglycans could bind these molecules to the cell surface, acting as "molecular flypaper", and (ii) that changes in their amount and binding properties could regulate the action of these effector molecules, thus controlling morphogenetic cell behavior and, because similar processes and molecules are involved, the reparative response to injury. Our approach was to identify the cell surface protein(s) that display heparan sulfate chains, assess the extent and selectivity of their interactions, establish their expression patterns during development and in repair of injury, and evaluate their regulation. In this paper we will review our progress briefly, focusing on recently emerging information on how the expression of these molecules may be regulated.

THE SYNDECANS ARE A GENE FAMILY OF HEPARAN SULFATE PROTEOGLYCANS

We identified and molecularly cloned a transmembrane proteoglycan at the cell surface which we named syndecan (from the Greek *syndein*, "to bind together") (Saunders et al., 1989). This proteoglycan was the prototype of a gene family that consists of four distinct syndecan genes in mammals (see Table 2). Their chromosomal localization, exon organization and sequence relationships with a *Drosophila* syndecan indicate that the mammalian syndecan family arose by gene duplication and divergent evolution from a single ancestral gene (Bernfield et al., 1992; unpublished data). Each of the syndecans consists of a single polypeptide chain containing heparan sulfate chains on its N-terminal extracellular domain (see Fig. 1). Where studied, the syndecans show conserved heparan sulfate attachment sequences encoded by a single exon within otherwise highly variable extracellular sequences, suggesting that this domain evolved solely to bear the glycosaminoglycan chains (Hinkes et al., 1993). Their transmembrane and cytoplasmic domains, also encoded by a single exon, are highly homologous, suggesting that these regions interact with evolutionarily stable elements inside the cell. (Recent reviews include David, 1993 and Jakanen et al., 1993).

Table 1. Binding interactions of heparin/heparan sulfate with components of the cellular microenvironment*

Matrix components	Growth factors	Degradative enzymes
Fibronectin	FGF family	Acetylcholinesterase
Interstitial collagens types I, III, V	aFGF, bFGF, KGF	Elastase
Laminin	*hst*/K-fgf, *int*-2	Extracellular superoxide dismutase
Pleiotropin	Heparin-binding-EGF	Thrombin
Tenascin	Hepatocyte GF (scatter factor)	Tissue plasminogen activator
Thrombospondin	PDGF	
Vitronectin	Schwannoma-derived GF (amphiregulin)	Protease inhibitors
wnt-1	Vascular endothelia GF (vascular permeability factor)	Antithrombin III
Cell adhesion molecules		Heparin cofactor II
N-CAM		Leuserpin
PECAM	Chemokines	Plasminogen activator inhibitor-1
	MIP-1β	Protease nexin I
	Rantes	

*Incomplete listing; for references see Bernfield et al. (1992).

Syndecan-1, studied most extensively, binds a wide variety of matrix molecules and growth factors (e.g. collagens I, III, V, fibronectin, bFGF) via its heparan sulfate chains and associates, at least in epithelia, with actin-containing microfilaments via its cytoplasmic domain (Bernfield et al., 1992). Thus, syndecan-1 appears "to bind together" components of the cellular microenvironment with the cytoskeleton. Syndecan-1 on epithelia acts as a matrix anchor, binding the cells to the substratum. Indeed, syndecan-1 polarizes on these cells by being shed, but not replaced, at the apical cell surface (Jalkanen et al., 1987). Transfection-induced changes in syndecan-1 expression cause epithelial cells to alter their shape, behavior and cytoskeletal organization (Kato and Bernfield, 1990; Leppä et al., 1992).

The syndecan family members are distributed widely, but each has a tissue-specific pattern of expression (Kim et al., 1993). In mature mouse tissues, syndecan-1, the most prevalent syndecan, is expressed predominantly in epithelial tissues, where it polarizes to basolateral cell surfaces. Syndecan-2 predominates in tissues that are rich in endothelial cells, syndecan-3 is primarily in neural tissues, and syndecan-4 is expressed in most tissues, but especially in liver and kidney. This tissue-specific distribution implies that these proteoglycans have distinct activities. Indeed, in contrast to syndecan-1, syndecan-3 binds fibronectin and collagen types I and V poorly, but like syndecan-1 will bind bFGF (Chernousov and Carey, 1993).

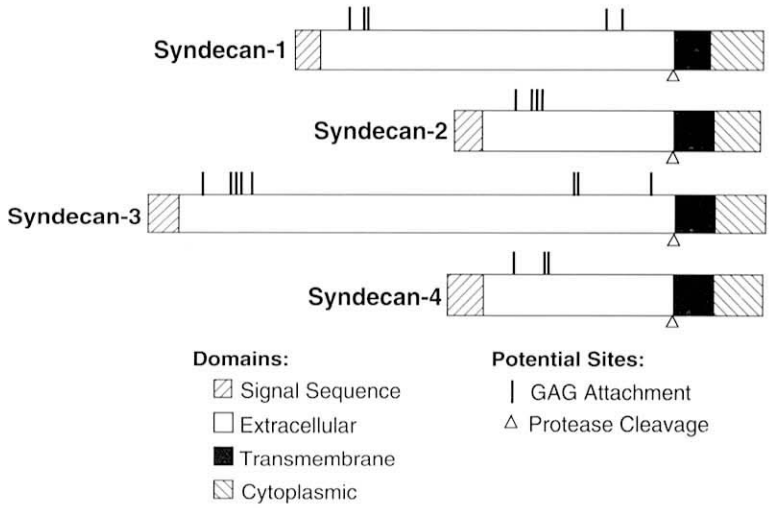

Fig. 1. Core proteins of the syndecan family. Diagrams showing the core protein domain structures and location of potential glycosaminoglycan and protease cleavage sites deduced from the cDNA sequences of the mammalian syndecans. The proteins are aligned at the start of the putative transmembrane domain. See Table 2 for citations.

Table 2. The syndecan family of transmembrane heparan sulfate proteoglycans

Origin of cDNA	Designation	Reference
Syndecan-1		
mouse, human mammary epithelia	*syndecan*	Saunders et al., 1989; Mali et al., 1990
hamster kidney (BHK-21) fibroblasts	*FGF-binding HSPG*	Keifer et al., 1990
rat microvascular endothelia	*syndecan*	Kojima et al., 1992
rat aorta	*syndecan*	Cizmeci-Smith et al., 1992
Syndecan-2		
human fetal lung fibroblasts	*48K5 fibroglycan*	Marynen et al., 1989
rat liver	*major rat liver membrane HSPG*	Pierce et al., 1992
Syndecan-3		
chick embryo limb buds	*syndecan-3*	Gould et al., 1992
rat newborn Schwann cells	*N-syndecan*	Carey et al., 1992
Syndecan-4		
chick 14 day embryos	*syndecan-4*	Baciu et al., 1991
rat microvascular endothelia	*ryudocan*	Kojima et al., 1992
human lung fibroblasts	*amphiglycan*	David et al., 1992

SYNDECAN EXPRESSION IS HIGHLY REGULATED

Expression during mouse development

Syndecan-1 expression is highly regulated developmentally. It is first detected by immunostaining soon after fertilization during mouse development, apparently due to post-zygotic gene activation, and localizes in the blastula on the inner cell mass (Sutherland et al., 1991). It is expressed on the primitive ectoderm, retained on the definitive ectoderm and endoderm, and persists on the mesodermal cells emerging following gastrulation. However, in late primitive streak embryos, syndecan-1 is lost from the neural plate. The chordamesenchyme and precardiac mesenchyme lose syndecan-1 expression and subsequently expression is lost from the mesenchyme anterior to the otic sulcus, resulting in an anterior (low) to posterior and lateral (high) gradient of syndecan-1 expression in mesenchyme (Sutherland et al., 1991) . Later, syndecan-1 is lost from the lateral plate mesenchyme when it becomes predominantly epithelial in distribution, appearing at the basal surfaces of the sheets and tubes of various epithelial organs and of the somites (Trautman et al., 1991).

Epithelia undergoing developmental changes in cell shape often show reduced levels of syndecan-1 while concurrently inducing it on their closely associated mesenchyme (Trautman et al., 1991). This mesenchymal induction is transient; syndecan-1 expression is lost as the morphogenesis ceases. Syndecan-1 expression is also lost during the transformation of epithelia to mesenchyme, as at the medial edge epithelium of the palate (Fitchett et al., 1990) and during the dispersion of the somites. Taken together, syndecan-1 expression follows morphogenetic rather than histologic boundaries, thus showing characteristics of a molecule involved in the organization of cells into tissues and organs.

Where multiple syndecan family members are examined by in situ hybridization during development, complementary expression patterns are seen (Gallo et al., 1993). In the 8.5- to 10.5-day mouse embryo, syndecan-1 and syndecan-3 mRNA seem to be expressed either in adjacent tissues or sequentially. Examples include syndecan-1 mRNA in the peripheral mesenchyme of the first branchial arch while syndecan-3 mRNA is in the central core mesenchyme, or syndecan-1 mRNA within the somites while syndecan-3 mRNA surrounds the somites, or diffuse syndecan-1 within limb bud mesenchyme and absent from the apical ectodermal ridge, while syndecan-3 mRNA appears later, is densely concentrated in the mesenchyme and is expressed in the apical ectodermal ridge. Expression of syndecan-2 and -4 is delayed until at least 10.5 days.

Expression during wound repair

Syndecan-1 expression is also highly regulated during the repair of cutaneous wounds (Elenius et al., 1991). Within 24 hours following an incision in mouse skin, the epidermal keratinocytes at the wound edge show reduced immunostaining. At the same time, the keratinocytes more distant from the injury site show slightly enhanced staining. More dramatically, however, dermal endothelial cells and fibroblasts, which show no apparent stain in unperturbed skin, now express syndecan-1 in granulation tissue. These changes in expression are transient, beginning within 24 hours following injury and returning to physiological levels once the repair is complete. Thus, as during development, changes in syndecan-1 expression parallel changes in cell behavior.

Tissue-specific patterns of glycosylation

Mature tissues show syndecan-1 in three isoforms that differ in size due to differences in the size, and possibly number, of their glycosaminoglycan chains (Sanderson and Bernfield, 1988). The smallest isoform surrounds cells, as on stratified keratinocytes (Sanderson and Bernfield, 1988) and plasma cells (Sanderson et al., 1989). The intermediate-sized isoform is at the basolateral surfaces of epithelia (Sanderson and Bernfield, 1988), and the largest isoform is predominantly within fibroblasts (Kato and Bernfield, 1989) and endothelial cells (Lose, 1991). In addition to these differences in size, the heparan sulfate chains on syndecan-1 also show cell-type specific differences in disaccharide composition and in ligand binding properties (Kato et al., 1991). Changes in GAG chain composition can also be induced by growth factors (Rasmussan and Rapraeger, 1988), embryonic inductions (Boutin et al., 1991), and can be elicited during keratinocyte differentiation (Sanderson et al., 1992). The size of the syndecan-1 heparan sulfate chains decreases during lung organogenesis (Brauker et al., 1991). The basis for these differences in glycosylation is unclear, but could be to modify the binding properties of the proteoglycan.

THE SYNDECANS MAY FUNCTION AS CORECEPTORS FOR COMPONENTS OF THE CELLULAR MICROENVIRONMENT

We have proposed that the syndecans bind ligands to the cell surface where they function as coreceptors (Bernfield et al., 1992). In this model, the proteoglycan together with another cell surface molecule constitute a receptor complex that binds the ligand and mediates its action. Ligand binding to cell surface heparan sulfate can concentrate, change the conformation or reduce the degradation of the ligand. Moreover, cell surface heparan sulfate can bind directly with the signal-transducing receptor (Kan et al., 1993). Thus, the syndecans can enhance or enable the interactions of ligands with their receptors.

This coreceptor mechanism is potentially involved in the action of many ligands, but the best evidence for a ternary complex with cell surface heparan sulfate is for bFGF (Kan et al., 1993; Rapraeger et al., 1991; Yayon et al., 1991) and for fibronectin (Guan et al., 1991; Woods and Couchman, 1988; Woods et al., 1993). With bFGF and fibronectin the cellular response entirely depends on an interaction of the ligand with cell surface heparan sulfate. Hence, regulation of cell surface heparan sulfate can be critical to the response of the cells.

An analysis of the developmental expression of several heparin-binding extracellular matrix molecules and growth factors, or their receptors, reveals a pattern of coincident

expression with syndecan-1. This pattern supports the coreceptor model because simultaneous expression is essential for ternary complex formation. We will cite a few examples of such expression with syndecan-1 in embryonic mesenchyme.

Tenascin is an extracellular matrix glycoprotein that binds syndecan-1 (Salmivirta et al., 1991), interacts with the cell surface and is thought to be involved in extracellular matrix assembly (Chiquet-Ehrismann, 1991). Tenascin and syndecan-1 are both expressed in the condensed mesenchyme of developing organs such as the tooth, mammary gland, hair follicles, kidney, limb and lung (Aufderheide et al., 1987; Chiquet-Ehrismann et al., 1988; Mackie et al., 1987; Thesleff et al., 1987). Double immunostaining for syndecan-1 and tenascin during tooth development and in recombination cultures of dental mesenchyme and epithelium (Vainio and Thesleff, 1992a,b) shows their coincident expression in the mesenchyme condensing around the forming epithelial bud and at the late bud stage. However, subsequently, at the cap stage, mesenchymal expression of tenascin decreases while that of syndecan-1 persists briefly.

Members of the fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) families are involved in mesenchymal cell proliferation, migration and differentiation (Baird and Böhlen, 1991; Ferns et al., 1991; Stephenson et al., 1991). bFGF binds syndecan-1 (Bernfield and Hooper, 1991; Elenius et al., 1992; Kiefer et al., 1990) and cell surface heparan sulfate is thought to be involved in the receptor interaction (Rapraeger et al., 1991). The expression patterns of these growth factor receptors in mouse embryonic mesenchyme are striking for their similarity to syndecan-1 expression. For example, the FGFR-1/*flg* receptor, which binds aFGF, bFGF, and FGF-5 with equal affinity, is expressed in presomitic and limb bud mesenchyme (Orr-Urtreger et al., 1991; Yamaguchi et al., 1992) (see Fig. 2). The PDGF-A receptor (*pdgfra*), which interacts with the heparin-binding PDGF-A chain, is expressed at these sites at similar developmental stages (Orr-Urtreger et al., 1992; Orr-Urtreger and Lonai, 1992). These expression patterns are identical to those of syndecan-1. At other stages, however, the expression patterns of these molecules diverge.

MECHANISMS OF SYNDECAN-1 REGULATION

Thus far, we have reviewed evidence indicating that the expression of syndecan-1 is dynamic and tissue-specific during development and wound repair, and that this expression may be coordinated with that of its putative ligands and coreceptors. These expression patterns must be explained in terms of the molecular mechanisms controlling syndecan-1 gene expression. Hence, we have attempted to identify soluble extracellular factor(s) that induce syndecan-1 expression as well as to identify transcription factors that might activate the syndecan-1 promoter.

Syndecan-1 is induced by tissue interactions

Inductive interactions between cells are mediated via direct cell-cell contact, deposition and/or modification of extracellular matrix, or release of soluble factors. Induction of syndecan-1 in developing mesenchyme depends on association with an inducing tissue, as seen by immunostaining of recombinant cultures of mouse dermal mesenchyme with chick epidermis (Solursh et al., 1990) and of mouse nephrogenic mesenchyme with rat spinal cord (Vainio et al., 1989). In these and other inductive interactions, e.g. dental mesenchyme induced by tooth bud epithelium (Vainio and Thesleff, 1992b), the intensity of syndecan-1 expression decreases as the distance from the inducer increases. This mesenchymal induction of syndecan-1 is transient and depends on the continuous presence of the inducer, consistent with the action of a soluble factor released by the inducing tissue. Although members of the FGF and TGFβ families are expressed in developing mesenchymal tissues and a combination of bFGF and TGFβ at high concentrations can increase syndecan-1 expression in NIH 3T3 cells (Elenius et al., 1992), the factor(s) participating in syndecan-1 induction during in vivo tissue interactions are not known.

The cutaneous wound environment is a potential source of inductive factor(s). Immunostaining of mouse skin wounds has shown that dermal mesenchymal cells at the wound edge express syndecan-1 transiently while these cells in unperturbed dermis show no expression (Elenius et al., 1991). Therefore, we hypothesized that an inductive factor(s) may be released during wound repair. Fluid collected aseptically from partial-thickness skin wounds in pigs was assayed for its ability to increase cell surface syndecan-1 in cultured cells. Cell surface syndecan-1 in NIH 3T3 cells increased 2- to 4-fold in response to partially purified fluid collected during the first 5-7 days of wound repair (Gallo et al., 1992), the time period of syndecan-1 induction in murine wounds (Elenius et al., 1991). However syndecan-1 was not induced by late phase wound fluid, amniotic fluid, crude chick or mouse embryo extracts, serum from wounded pigs, conditioned culture media from several cell types, or several purified growth factors. Further purification identified the inductive activity in wound fluid as residing in a basic protein that does not bind to heparin and thus is not a member of the FGF family (Gallo et al., 1992).

The wound fluid activity has features that are reminiscent of syndecan-1 induction in embryonic tissue interactions. Syndecan-1 induction by the wound fluid factor(s) occurs in mesenchymal, but not epithelial cells, is accompanied by loss of epithelial syndecan-1 expression in the associated epithelium, requires the continuous presence of the inducing activity, is not species-specific and shows increased syndecan-1 mRNA levels and reduced size of the syndecan-1 heparan sulfate chains. Thus it is tempting to speculate that the factor(s) that influence syndecan-1 expression in the wound may be similar to the factor(s) responsible for the syndecan-1 inductions of embryonic tissue interactions.

Syndecan-1 is regulated by transcriptional mechanisms

Syndecan-1 gene expression is regulated at multiple levels, including post-transcriptional (Sanderson et al., 1992; Vainio et al., 1992; Yeaman and Rapraeger, 1993) and post-translational (Sanderson and Bernfield, 1988), yet there is ample evidence for transcriptional control during morphogenesis and differentiation. For example, changes in syndecan-1 transcript levels correlate directly with protein

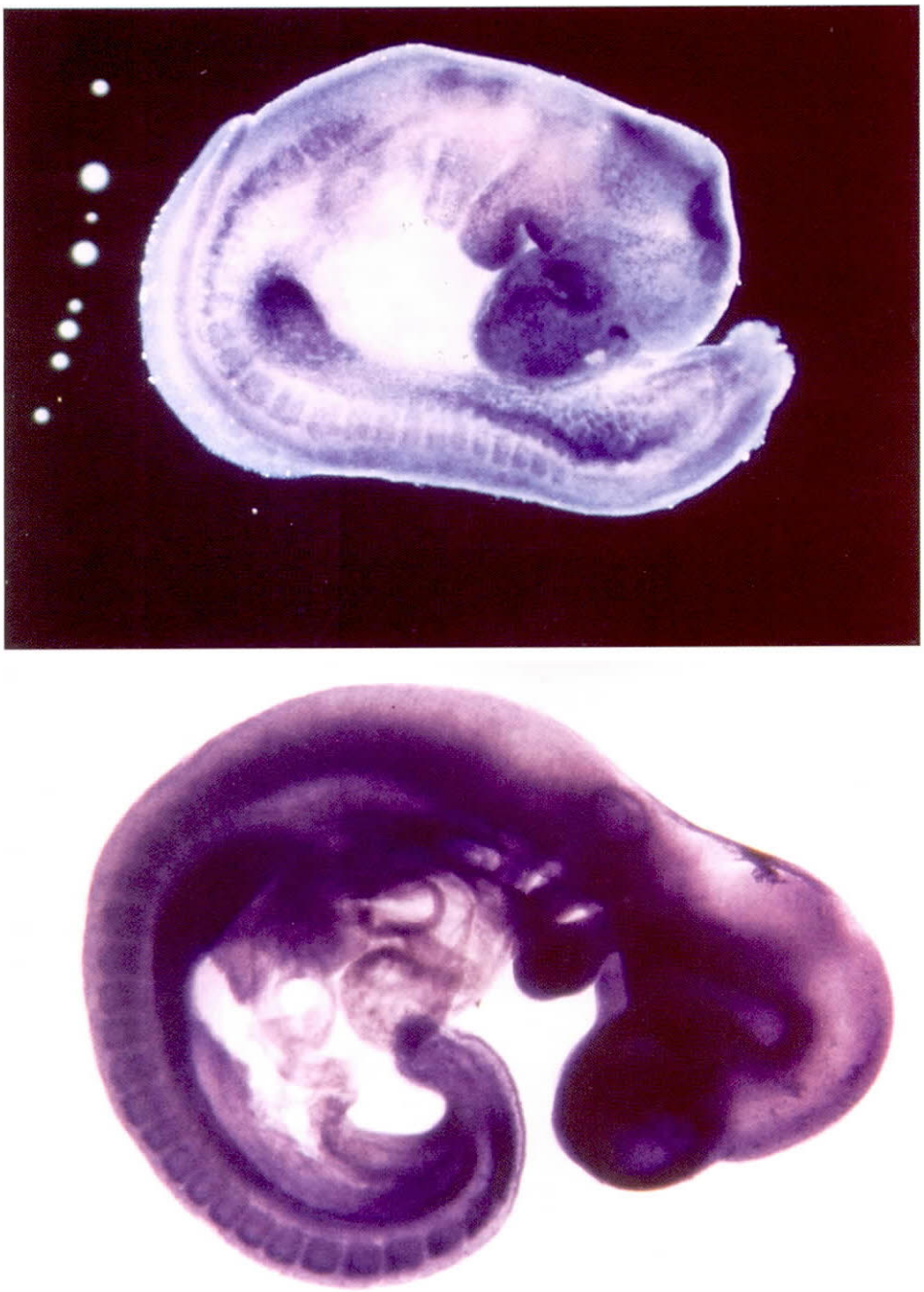

Fig. 2. Whole-mount in situ hybridization analysis of *Synd-1* (top, darkfield) and FGFR-1 (bottom, brightfield) expression in E9-9.5 mouse embryos. Note similar expression in developing forelimb, branchial arches and somites. Staining of head region is artifactual. FGFR-1 photo courtesy of Dr R. A. Conlon (Yamaguchi et al., 1992).

expression in condensing dental mesenchyme (Vainio et al., 1991), keratinocytes and granulation tissue from healing cutaneous wounds (Elenius et al., 1991), and during muscle differentiation (Olwin and Rapraeger, 1992; Saunders et al., 1989).

In an effort to assess transcriptional regulation of syndecan-1, we have examined the features of the murine syndecan-1 gene and its promoter (Hinkes et al., 1993). This gene (*Synd-1*) is about 19.5 kb in size and has five exons and four introns. Sequences upstream of the first exon demonstrate promoter activity and display an array of consensus transcription factor binding sites. These sites, which include Antennapedia, MyoD (E box), NF-kB, Sp1 (GC box) and TATA and CAAT boxes, provide possible mechanisms for the diverse modes of syndecan-1 regulation.

Because syndecan-1 likely influences cell behavior during development, its expression may be governed by regulatory genes that are involved in generating the spatial arrangement of embryonic structures. These master genes encode transcription factors that are thought to act like molecular switches, turning on and off target genes, which in turn execute specific developmental programs. Thus it is not surprising that the *Synd-1* promoter has putative binding sites for two well known groups of regulatory genes, homeobox and MyoD.

Homeobox genes encode a helix-turn-helix DNA-binding

domain (the homeodomain) which is highly conserved in animals as diverse as fruit flies and humans (Hayashi and Scott, 1990). Although many transcription factors containing homeodomains (HD) have been discovered, their downstream target genes, which are directly responsible for tissue and organ phenotypes, are only beginning to be identified. For example, *N-CAM* (Hirsch et al., 1990); (Jones et al., 1992a) and *tenascin* (Jones et al., 1992b) have been shown to be targets for HD transcription factors. *Synd-1* may be a downstream target of HD proteins because its promoter contains a sequence [$(TAA)_{13}$] that resembles an overlapping tandem arrangement of the core DNA recognition site (TAAT) common to Antennapedia and other HD-containing transcription factors (Hayashi and Scott, 1990). Because many *Drosophila* HD genes can bind TAAT and because murine cognates and paralogs to these *Drosophila* genes are numerous (Scott, 1992), a variety of HD proteins might affect *syndecan-1* transcription.

One HD gene that is a candidate activator of *Synd-1* is *msx-1* (*Hox-7*), a murine cognate of the *Drosophila* muscle-specific homeodomain (*msh*) gene (Hill et al., 1989; Robert et al., 1989). Although simultaneous comparisons are unavailable, msx-1 and syndecan-1 expression correlate well in the developing tooth (Jowett et al., 1993; Vainio et al., 1991), eye (Monaghan et al., 1991; Trautman et al., 1991) and limb bud (Robert et al., 1989; Solursh et al., 1990), indicating that msx-1 could activate syndecan-1 in these tissues. In addition to msx-1, syndecan-1 expression overlaps with that of other HD-containing genes in these and other tissues. Therefore, the HD family of *trans* acting factors may govern *Synd-1* transcription in several developmental schemes.

The *Synd-1* promoter also contains five E boxes (CANNTG), which serve as binding sites for the MyoD family of transcription factors. MyoD family members (MyoD, myf-5, myogenin, mfr4-herculin-myf6) are basic-region helix-loop-helix (bHLH) proteins that control myoblast differentiation into mature myotubes by transactivating muscle-specific genes (Weintraub et al., 1991). bFGF is a potent inhibitor of myoblast differentiation (Clegg et al., 1987) and apparently acts by repressing MyoD function (Olson, 1992). This inhibition requires the presence of cell surface heparan sulfate proteoglycans (Olwin and Rapraeger, 1992; Rapraeger et al., 1991) acting as coreceptors of bFGF (Bernfield and Hooper, 1991; Rapraeger et al., 1991; Yayon et al., 1991). Because syndecan-1 is present on myoblasts but absent from skeletal muscle, syndecan-1 could be the heparan sulfate proteoglycan essential for mediating bFGF repression of myoblast differentiation. When myoblasts differentiate, perhaps MyoD (or a related family member) downregulates *Synd-1*, thereby preventing bFGF signaling and guaranteeing commitment of myoblasts to myotubes.

We have speculated above that msx-1 activates while MyoD inhibits syndecan-1 gene expression. The sequential appearance of msx-1 and MyoD in the developing limb bud is consistent with this possibility (Sassoon, 1993; Solursh et al., 1990). In early limb buds prior to muscle differentiation, msx-1 and syndecan-1 expression correlate spatiotemporally, whereas MyoD is absent. At later stages, syndecan-1 is lost as msx-1 diminishes and MyoD becomes prominent. Reciprocal effects of msx-1 and MyoD on the syndecan-1 promoter could be responsible for these changing expression patterns.

CONCLUSION

Increasing evidence for a variety of types of ligands, including extracellular matrix components, growth factors, proteases, anti-proteases, proteins involved in lipid metabolism and transport, and viral and microbial pathogens, implicates cell surface heparan sulfate in their interactions with cell surfaces. We have proposed that the syndecans, cell surface heparan sulfate proteoglycans, act as coreceptors in these interactions, enabling the ligands to occupy their specific receptors, thus mediating the action of the ligand. The syndecans belong to a class of cell surface proteins that interact with ligands and act to mediate their activity, but by themselves may not be involved in transmembrane signaling. In general, these coreceptors are more abundant but lower in ligand affinity than their ligand-specific receptor partners. They include the neurotrophins and p75 nerve growth factor receptor (Radeke et al., 1987), receptors for certain interleukins and hematopoetic cytokines (Honjo, 1991) and the TGFβ type III receptor (or betaglycan) (Lopez-Casillas et al., 1993).

Two features of the syndecans add complexity to their ligand interactions. First, they bind via heparan sulfate chains and these chains may vary in their selectivity for ligands. For example, the saccharide sequences and sulfation patterns in heparan sulfate that are responsible for binding bFGF (Turnbull et al., 1992) are distinct from those for binding aFGF (Mach et al., 1993); these differences could underlie the apparent switch in binding activity from basic to acidic FGF by heparan sulfate proteoglycans in developing neural epithelium (Nurcombe et al., 1993). Second, the syndecans represent a family of four distinct genes in mammals whose function appears to be that of presenting heparan sulfate chains at the cell surface. As proteins, these syndecans show tissue-specific expression and substantial differences in their patterns of developmental expression, raising the possibility that the individual syndecan molecules have distinct functions.

These features must be kept in mind when considering the modes of syndecan regulation during development and wound repair. We have reviewed here evidence indicating that syndecan-1 can be co-expressed with its ligands and with receptors for its ligands, that it is inducible by tissue interactions, potentially via the action of a soluble protein, and that the inductions are accompanied by changes in glycosylation. Based on the expression of its product and on the characteristics of its promoter, we have also suggested that *Synd-1* is a target for regulation by specific genes involved in pattern formation and tissue differentiation. Thus, the broad functional versatility of the syndecans seems to be matched by the multiple levels at which they are regulated.

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