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REVIEW

Role of syndecan-2 in osteoblast biology and pathology

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Syndecans 1–4 are a family of transmembrane proteins composed of a core protein and glycosaminoglycan chains. Although the four syndecans have common functions, they appear to be connected to different signaling pathways, and their expression occurs in a cell- and development-specific pattern. In contrast to other syndecans, syndecan-2 expression increases during osteoblast differentiation. Mechanistically, syndecan-2 exerts multiple functions in cells of the osteoblast lineage as it serves as a co-receptor for fibroblast growth factors and Wnt proteins and controls cell adhesion, proliferation, differentiation and apoptosis. Recent studies indicate that syndecan-2 also contributes to osteosarcoma cell response to cytotoxic agents through interactions with Wnt/β-catenin signaling. Here we summarize our current understanding of the role of syndecan-2 in the control of osteoblast biology and pathology and discuss how syndecan-2 acts as a modulator of the bone cell microenvironment.

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Introduction

Bone development and remodeling require the coordinated action of osteoclasts, osteoblasts and osteocytes. These bone cells communicate with each other to regulate bone resorption or formation through various signaling mechanisms. This includes soluble factors such as growth factors that are produced by osteoblasts or released by osteoclasts during bone resorption and cytokines that are expressed in the bone marrow. The biological activity of these soluble molecules is highly dependent on their interactions with different components of the bone microenvironment, such as syndecans. Syndecans belong to a family of transmembrane proteoglycans composed of four members (syndecans 1–4) that arise from two rounds of gene duplication.[1] The core protein of syndecan-2 comprises an N-terminal ectodomain with a signal peptide for translocation, glycosaminoglycan (GAG) chain attachment sites and a dibasic peptide motif adjacent to the plasma membrane, which is a protease sensitive sequence important for shedding (**Figure 1**).[2] The transmembrane domain is highly conserved among syndecans and comprises a GXXXG motif that drives oligomerization.[3] The cytoplasmic tail comprises two conserved domains (C1 and C2) and a more specific one (V). The sequence of the V domain comprises two serine residues that are phosphorylated by PKCγ in a tissue-specific manner.[4] The C2 domain consists in an EFYA motif that binds type II postsynaptic density 95/disc-large/Zona occludens (PDZ) domain proteins including synbindin, synectin and CASK/LIN-2[5] (**Figure 1**). An essential feature of syndecans is the attachment in the Golgi area of GAG chains on serine in the consensus motif of the extracellular domain.[4] Syndecan-2 bears 3–5 heparan sulfate chains but may also bear chondroitin or dermatan chains. The heparin sulfate chains consist in N-acetylglucosamine and glucuronic acid disaccharide repeats that are modified by uronic acid epimerization and 2-*O*-sulfation and glucosamine *N*- and 6-*O*-sulfation (**Figure 1**). These complex modifications are regulated by transferases and other enzymes that are part of the cell machinery regulating transmembrane proteins.[2] These processes result in specific alternation of highly and poorly sulfated saccharides with different affinity for the heparin-binding proteins. Hence, the GAG composition defines the ligand directory and constitutes an important level for the regulation of syndecan-2 activities in different cell types.[6,7]

Syndecan-2 exerts various functions in different cell types (**Figure 2**).[6] It is a co-receptor for soluble ligands, such as enzymes, growth factors or cytokines, and serves for docking, protection and concentration of these molecules at the proximity of the membrane surface. Once shed from the cell surface, syndecan-2 contributes to the formation of cytokine gradients. Syndecan-2 may also interact with high affinity receptors and integrins to modulate intracellular signaling.[8,9] It can also participate in endocytosis/internalization processes and in receptor recycling.[8] In addition, syndecan-2 is involved in matrix assembly and remodeling.[9] Thanks to these various functions, syndecan-2 was found to control cell proliferation, differentiation, adhesion and migration during development,

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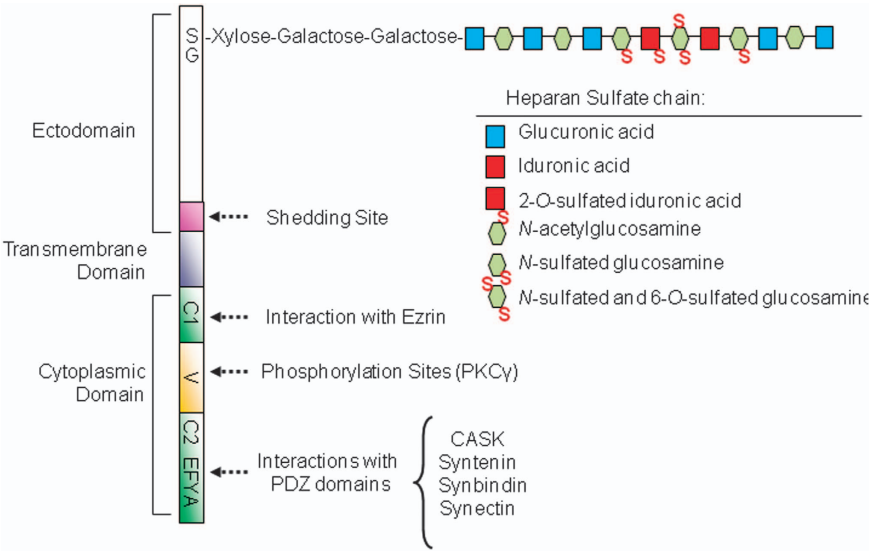

Figure 1 Structure of syndecan-2. The core protein of syndecan-2 comprises a unique transmembrane domain. The cytoplasmic tail is composed of a conserved domain near the membrane (C1) that interacts with the ERM molecules, a more specific domain (V) that does not resemble to other syndecans and that contains phosphorylable residues and a C-terminal domain with the EFYA motif that interacts with PDZ domains of cytoplasmic proteins. The ectodomain can be shed from the cell surface through its MMP-sensitive sequence. One to three heparan sulfate chains can be added to the protein on the serine residues that have an adjacent glycine residue. These GAG chains are bound on a xylose–galactose–galactose primer and are composed of disaccharide repeats of N-acetylglucosamine (green) and glucuronic acid (blue) that can be modified by uronic acid epimerization (red) and 2-*O*-sulfation and glucosamine *N*- and 6-O-sulfation (red S).

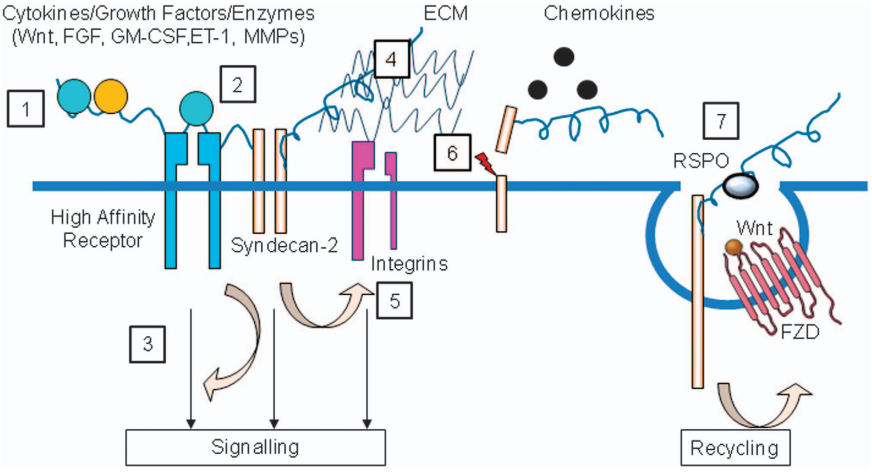

Figure 2 Functions of syndecan-2. Syndecan-2 can oligomerize at the cell surface to protect and concentrate various enzymes, growth factors and cytokines, thereby controlling their biological availability (1). Syndecan-2 can modulate the activation of its ligands, their presentation to high affinity receptors (2) and the subsequent intracellular signaling (3). Syndecan-2 can interact with extracellular matrix (ECM) proteins (4) and cooperate with integrins through intracellular signals (5). In addition, syndecan-2 can be shed from the cell surface and thereby participate in the formation of cytokine gradients in the extracellular compartment (6). Finally, syndecan-2 can also participate in endocytosis processes (7).

wound healing, angiogenesis, inflammation, infection and tumorigenesis.[10] In the skeleton, some syndecans may display redundant functions, and deletion of one syndecan can induce a compensatory upregulation of other syndecans as exemplified in syndecan-4 knockout mice during cartilage development.[11] However, syndecan-2 and -4 are, respectively, down- and upregulated in response to cytokines and growth factor stimulation, and syndecan-2 is specifically regulated during the differentiation of cells of the osteoblast lineage, which predicts particular functions of syndecan-2 in these cells.[11] Current studies suggest that syndecan-2 may have specific roles in bone as compared with other syndecans. In this review, we summarize our knowledge on the role of syndecan-2 in osteoblast biology and pathology and discuss the recent evidence that syndecan-2 may act as a regulator in the bone cell microenvironment.

Syndecan-2 Expression and Regulation in Skeletal Cells

In mineralized tissues, syndecans are expressed in a cell- and development-specific pattern. Syndecan-1 is only transiently expressed at early stages of skeletal development, syndecan-3 expression is restricted to cartilage and has a role in limb development, whereas syndecan-4 expression is more ubiquitous.[12] During mouse development, syndecan-2 is restricted to mesenchymal tissues and connective tissues.[13]

Syndecan-2 expression is high in the condensing pre-chondrogenic core and in the periochondrium and decreases during chondrocyte differentiation.[14] Syndecan-2 is also expressed in the periosteum at the onset of osteogenesis, but its expression increases during osteoblast differentiation.[15] Thus, in contrast to other syndecans, syndecan-2 expression is tightly associated with osteoblastogenesis.

Syndecan-2 is regulated by multiple factors in bone cells. Its expression is induced in myoblasts during differentiation into osteoblasts by bone morphogenic protein-2.[16] In addition, Runx2 enhances syndecan-2 expression in mouse calvaria osteoprogenitor cells.[17] In prostate cancer cells, aberrant expression of Runx2 is also associated with high syndecan-2 levels.[18] A strong expression of syndecan-2 was found in mature human osteoblasts, whereas osteosarcoma cells express low levels.[19,20] In osteoblasts, syndecan-2 messenger RNA is upregulated in response to transforming growth factor-β1 (TGF-β1) and interleukin-1. However, prolonged exposure to interleukin-1 inhibits the TGF-β-dependent upregulation of syndecan-2.[21] Fibroblast growth factor-2 (FGF-2) also modulates syndecan-2 expression according to the differentiation stage of the cells. In mouse osteoblast precursors, FGF-2 reduces syndecan-2 expression in the absence of Runx2, and this inhibitory action is suppressed in the presence of Runx2.[17] In osteosarcoma cells, Wnt proteins and IL-6 are negative regulators of syndecan-2 expression.[22] We have shown that both canonical Wnt/β-catenin/TCF and noncanonical Wnt/RhoA pathways mediate the inhibition of syndecan-2 expression in osteosarcoma cells through direct repression of syndecan-2 transcription or increased protein shedding from the cell surface.[23] In addition, in response to cell stress, syndecan-2 contributes to the promotion of its own transcription in osteosarcoma cells through modulation of diverse signaling pathways including RhoA, JNK, PI3K and Wnt/β-catenin/TCF.[23,24] Thus, syndecan-2 expression in osteoblastic cells is tightly regulated by Wnts, FGF and TGF-β signaling. Interestingly, recent data suggest that syndecan-2 expression is also regulated by mechanical loading. Thanks to a global gene transcriptome analysis that aimed to show molecular variations associated with bone architecture resulting from different mechanical and functional demands, syndecan-2 was found to be upregulated in osteoblasts and osteocytes in trabecular bone subjected to a high mechanical load.[25] Although no mouse model is currently available to determine the precise role of syndecan-2 in normal bone cells *in vivo*, the fine regulation of syndecan-2 during osteoblast differentiation suggests that this proteoglycan may have specific functions during osteogenesis. In addition, there is evidence that syndecan-2 contributes to some pathological mechanisms.[10] In bone, we showed that syndecan-2 has a pro-apoptotic role in osteosarcoma cells.[19,26] In chemosensitive osteosarcoma cells, we found that cytotoxic drugs increase the expression of syndecan-2 through the activation of FoxO transcription factors, resulting in cell apoptosis.[27] These studies support the concept that syndecan-2 expression contributes to osteosarcoma pathogenesis and chemoresistance.

Syndecan-2 and Matrix Proteins

Syndecan-2 interacts with heparin-binding domains of matrix proteins with specific differences between cells. Notably, syndecan-2 produced by lung carcinoma cells binds fibronectin, whereas syndecan-2 produced by osteoblastic cells does not.[28,29] The interactions of syndecan-2 with matrix proteins involve several mechanisms. Syndecan-2 contributes to osteoblast adhesion to fibronectin–transglutaminase complexes through actin regulation downstream of syndecan-4-dependent activation of PKCα.[29] The cross-linking enzyme tissue transglutaminase-2 is secreted by osteoblasts and is deposited into the matrix where it forms complexes with fibronectin.[29,30] This complex supports osteoblast adhesion and spreading and rescues from the RGD peptide-induced loss of cell adhesion and cell death by anoikis in a syndecan- and integrin-β1-dependent manner.[31] Although syndecan-2 has synergic functions with integrin-mediated adhesion,[29] proteomic analyses failed to identify syndecans in integrin complexes, suggesting that the cooperation between the two membrane molecules does not depend on physical interactions.[32] Consistently, heparan sulfate chains make syndecans spread out at a minimal distance of 40 mm from the cell surface, whereas the distance between plasma membrane and the matrix is <10 nm in focal adhesions. It was therefore proposed that syndecans are excluded from the focal adhesion because of spatial constraints.[32] Interestingly, the unglycosylated ectodomain of syndecan-2 was shown to promote integrin-mediated adhesion through indirect activation of β1 integrin,[7] indicating that syndecan-2/integrin crosstalk relies on intracellular signaling. In this context, the C1 domain of syndecan-2 can interact with proteins of the ERM (ezrin, radixin and moesin) family, which control the organization of actin and are responsible for the activation of focal adhesion kinase.[33] According to this concept, syndecan-2 overexpression results in stress fiber formation.[28] Mechanistically, syndecan-2 induces actin polymerization through a signal pathway that involves neurofibromin-dependent activation of Protein Kinase A (PKA) and enabled/vasodilator-stimulated phosphoprotein as PKA effectors[34] (**Figure 2**). It can be therefore hypothesized that syndecan-2 not only controls cell morphology but is responsible for the organization of membrane micro-domains with signaling complexes involved in the regulation of the cytoskeleton.[35]

Syndecan-2 can also modulate the cell microenvironment through the regulation of matrix assembly. For example, the expression of a dominant-negative syndecan-2 blocks fibronectin fibrillogenesis in CHO cells[9] and *Xenopus* cap ectoderm.[4] Syndecan-2 may also regulate extracellular matrix remodeling through the control of metalloprotease activity. Indeed, syndecan-2 was shown to trigger the processing of pro-MMP-7 into active MMP-7[36] and, in contrast, to suppress MMP-2 activation in lung carcinoma cells.[37] Through these various mechanisms, syndecan-2 may influence the cell environment and thereby the behavior of neighboring cells, and this concept needs to be further determined in cells of the osteoblast lineage.

Syndecan-2: A Regulator of Growth Factor Actions in Bone

Syndecan-2 was shown to functionally contribute to the mitogenic action of granulocyte–macrophage colony-stimulating factor and thereby to control the proliferation of cells of the osteoblast lineage.[38] Other studies showed that syndecan-2 can also modulate the activity of other key factors involved in osteoblastogenesis, such as FGFs and Wnt proteins.

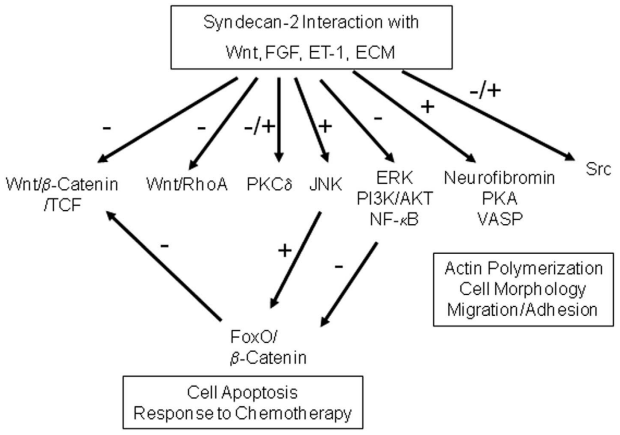

Figure 3 Syndecan-2 modulates multiple signaling pathways in osteoblastic cells. Syndecan-2 was found to modulate cell signaling induced by Wnts, FGF, endothelin-1 (ET-1) and extracellular matrix (ECM) to influence cell apoptosis and actin cytoskeleton. + indicates a positive regulation; − indicates an inhibitory effect and ± indicates dual effects.

Syndecan-2 and FGF Signaling

FGFs are the prototypes of heparin-dependent factor family that includes vascular endothelial growth factor and heparin-binding epidermal growth factor-like factors. Syndecan-2 acts as a co-receptor for FGF receptors (FGFRs) during chondrogenesis and osteogenesis.[15] As such, syndecan-2 is essential for the biological response to FGF-2 during osteogenic differentiation.[39] Consistently, exogenous heparin was found to increase FGF-2 affinity binding to FGFR-1.[40] Several mechanisms have been evoked to explain the cooperation between syndecan-2 and FGF/FGFRs[6] (**Figure 2**). First, FGF binding to heparan sulfate chains results in growth factor dimerization that facilitates presentation to and interaction with its receptors.[41] Second, syndecan-2 can interact with FGFR to form a tertiary complex with FGFs and then serves as a co-receptor that directly modifies cell signaling. Third, syndecan-2 may be involved in membrane trafficking. In particular, syndecan-2 associates with FGFR along the recycling pathway mediated by syntenin, in a heparin sulfate- and FGF-dependent manner.[42] Fourth, syndecan-2 may induce signaling independently of its interaction with high affinity FGF receptors[5] (**Figure 2**). Thus, the presence of syndecan-2 at the surface of osteoblasts not only accounts for FGF availability, storage and protection but also strongly influences the cell response to this growth factor.

Syndecan-2 and Wnt Signaling

Syndecans interact with Wnt effectors to positively or negatively modulate Wnt signaling. Several interactions between syndecans and Wnt signaling have been reported (**Figure 3**). Heparan sulfate proteoglycans are involved in the organization of the extracellular distribution of Wingless, a prototype of Wnt protein, and thereby contribute to its transport in the extracellular space.[43] Heparan sulfate chains also maintain Wnt solubility and prevent aggregation of these hydrophobic proteins in the extracellular environment.[44] Decreasing Wnt binding affinity to cell surface heparan sulfate chains with sulfatases leads to increased Wnt binding to Wnt receptor Frizzled and to increased Wnt signaling.[44] In addition, the C-terminal domain of Frizzled can interact with a PDZ domain of syntenin, which makes the link between syndecans and Wnt receptors, suggesting that this syndecan/syntenin complex controls Wnt receptors recycling.[45] Syndecans can also modulate Wnt signaling through binding with other Wnt effectors such as R-spondins or secreted FZD, which are heparin-binding proteins.[46] For example, syndecan-4 interaction with R-Spo3 results in Wnt/PCP signaling via clathrin-mediated endocytosis and is essential for Wnt/PCP-driven processes such as head cartilage morphogenesis.[47] Conversely, in osteosarcoma cells, we have shown that syndecan-2 acts as a negative modulator of Wnt signaling. Indeed, syndecan-2 overexpression in osteosarcoma cells antagonizes Wnt signaling by diverting β-catenin from T-cell factor- to Forkhead box *O*-mediated transcription (FoxO) factor, resulting in increased FoxO3a–β-catenin complexes at the expense of the Wnt/TCF pathway.[27] In this context, FoxO stabilization by syndecan-2 results from inhibition of PI3K, ERK and the NF-κB pathway and increased JUNK phosphorylation.[24,26] We also showed that syndecan-2 interacts with the Wnt/RhoA pathway in osteosarcoma cells. In these cells, syndecan-2 overexpression reduced the levels of RhoA associated with the membrane or linked to GTP and thereby increased p190RhoGAP activation.[23] Overall, these studies indicate that, in addition to control the localization and availability of Wnt effectors in the cell microenvironment via its heparan sulfate chains, syndecan-2 can modulate intracellular signals to modulate Wnt signaling (**Figure 3**).

Conclusion and Perspectives

Although syndecans may display redundant functions, syndecan-2 appears to have specific roles in bone cells as compared with other syndecans. It is now apparent that syndecan-2 has a regulatory role in the control of osteoprogenitor cell adhesion, proliferation, differentiation and survival in response to local factors and contributes to organize the cell and matrix microenvironment during normal bone formation. Recent studies also indicate that syndecan-2 is involved in osteosarcoma and other tumors development. Despite these significant advances in the role of syndecan-2 in bone biology and pathology, further researches are needed for a better elucidation of the specific function for syndecan-2 in osteoblasts. Notably, genetic models in mice are needed to elucidate the specific role of syndecan-2 in osteogenesis and to determine the specific role of the V domain of syndecan-2 in bone cells. Future studies are also required to determine whether the manipulation of syndecan-2 expression or function in cells of the osteoblast lineage may lead to correct the altered Wnt signaling in pathologic conditions such as age-related bone loss or osteosarcoma. In this context, several strategies are now available to modulate syndecan expression or function in nonskeletal cells. One therapeutic option is to target syndecan processing that alters its function using heparanase or sheddase inhibitors.[2,48] Syndecan functions can also be modulated by small heparan sulfate mimetics specifically targeting a particular component of heparan sulfate/heparin bioactivity, by using specific heparan sulfate proteoglycan antibodies or by syndecan-Fc hybrid molecule.[49,50] In the future, the development of such therapeutic strategies targeting syndecan-2 expression or function may allow modulating cell signaling in cells of the osteoblast lineage and thereby correct the abnormal cell functions in disorders of bone formation.

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