FEBS Letters 586 (2012) 2207–2211

journal homepage: www.FEBSLetters.org

Review

Syndecans play dual roles as cell adhesion receptors and docking receptors

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ARTICLE INFO

Article history:
Received 3 February 2012
Revised 3 May 2012
Accepted 22 May 2012
Available online 31 May 2012

Edited by Veli-Pekka Lehto

Keywords:
Syndecan
Adhesion receptor
Docking receptor
Extracellular matrix
Cell adhesion
Signal transduction

ABSTRACT

Syndecan are a family of cell surface heparan sulfate proteoglycans that act as cell surface receptors. Most cell surface receptors have a limited number and type of ligand interactions, responding only to the binding of (a) specific ligand(s). In contrast, syndecans can interact with various numbers and types of ligands, and thus play more diverse roles than others. Various syndecan functions have not yet been fully classified and categorized, but we herein review previous studies suggesting that syndecans play dual function as cell surface receptors by acting as both adhesion receptors and docking receptors. Through this dual regulatory function, syndecans are capable of regulating both intra- and extracellular activities, potentially altering a variety of cell behaviors.

1. Introduction

Syndecan cell surface heparan sulfate proteoglycans are a family of type I transmembrane proteins [1] whose extracellular domains interact with various soluble and insoluble factors in the extracellular matrix (ECM) [2]. These interactions activate syndecans, allowing them to regulate various signaling events both inside and outside the cell [3]. Syndecans are typical cell surface receptors, in that they typically respond to the binding of extracellular ligands. Unlike other receptors, such as those for growth factors and cytokines, however, syndecans have additional, unique characteristics. Through glycosaminoglycan chains attached to the core protein, syndecans can interact with a various number of extracellular ligands, and the possible number of bound ligands per syndecan molecule is much higher than that of growth factor receptors. Syndecans can also interact with many different types of soluble and insoluble proteins, lipids, and even microorganisms [1]. These characteristics together with other structural features allow syndecans to fulfill more diverse functions than other receptors. However, if we look carefully at syndecan-mediated regulatory signaling, there appear to be some common regulatory mechanisms. Here, we discuss two ways in which syndecans act as cell surface receptors: as adhesion receptors, and as docking receptors. In the context of an adhesion receptor, the interaction of the extracellular domain of a syndecan with a ligand triggers the transduction of signals from the extracellular environment to the cytosol, leading to changes in the intracellular environment. As a docking receptor, in contrast, a syndecan can mediate several extracellular events. Through these dual regulatory mechanisms, syndecans are capable of regulating both intracellular and extracellular events, in turn leading to changes in a variety of cell behaviors (Fig. 1).

2. Syndecan as a cell adhesion receptor

The adhesion of cells to the ECM provides physical support, regulates cell positioning and transduces signals to initiate proper responses [4]; this adhesion occurs via cell adhesion receptors,

Abbreviations: CXCR1, CXC chemokine receptor-1; ECM, extracellular matrix; EGF, epidermal growth factor; FGF, fibroblast growth factor; FGFR, FGF receptor; GAG, glycosaminoglycan; GM-CSF, granulocyte-macrophage colony-stimulation factor; HGF, hepatocyte growth factor; HS, heparan sulfate; HSPGs, heparan sulfate proteoglycans; IL-8, interleukin-8; MMPs, matrix metalloproteinases; PDGF, platelet derived growth factor; PKA, protein kinase A; PKCα, protein kinase Cα; RANTES, regulated on activation normal T cell expressed and secreted; ROS, reactive oxygen species; TGFβ1, transforming growth factor β1; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor-2

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0014-5793
http://dx.doi.org/10.1016/j.febslet.2012.05.037

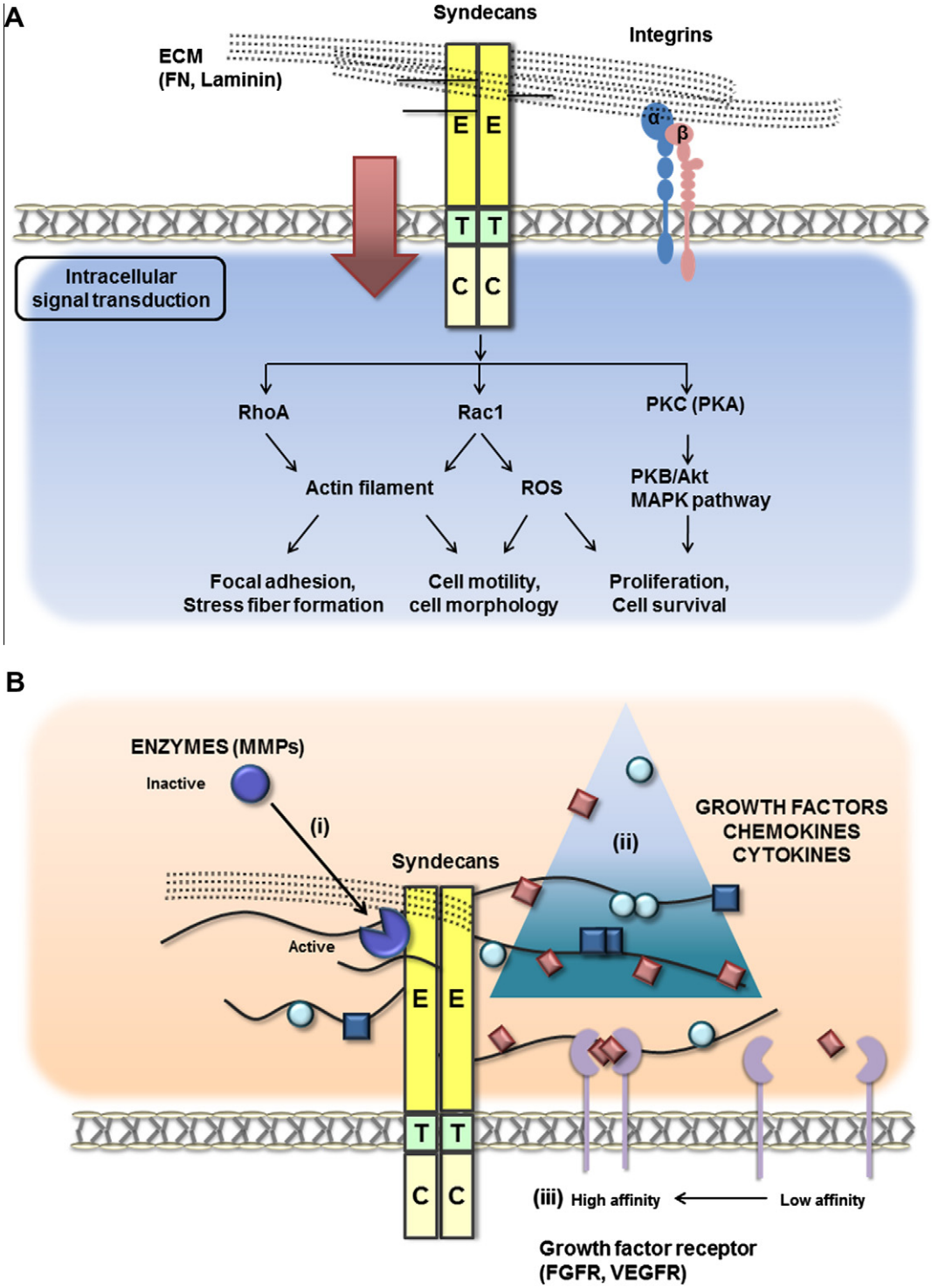

Fig. 1. The dual regulatory mechanisms of syndecans. Syndecans play dual roles as cell surface receptors. (A) In the context of an adhesion receptor, the extracellular domain of a syndecan transduces signals from the extracellular environment to the cytosol, thereby regulating intracellular signaling events such as cytoskeletal organization, morphological changes in migrating cells and proliferation. (B) As a docking receptor, a syndecan can regulate extracellular events. When extracellular ligands bind to syndecan, (i) extracellular enzymes such as MMPs become activated, (ii) soluble ligands are diluted much less and can achieve high local concentrations, and (iii) extracellular ligands such as growth factors bind with high affinities to their receptors. Through these dual regulatory mechanisms, syndecans can regulate events both inside and outside the cell. E, extracellular domain; T, transmembrane domain; and C, cytoplasmic domain.

such as integrins. The interaction of the extracellular domain of an integrin with the ECM is tightly linked to the phosphorylation states and activities of cytosolic tyrosine kinases, such as focal adhesion kinase and Src family kinases, which subsequently regulate other kinases, scaffolding proteins and intracellular signal transduction. This is the typical example of adhesion receptor-mediated signal transduction, such as that by integrin family members. Integrins and syndecans both regulate many cellular events, such as gene expression, proliferation, differentiation, cell morphology and motility [1,5].

Syndecans act as adhesion receptors, as shown in studies of focal adhesion formation on fibronectin-coated cells [6]. Although the extracellular domain of integrin is sufficient for the attachment and spreading of primary fibroblasts, it is not sufficient to direct focal adhesion and stress fiber formation. Instead, the formation and maturation of adhesion complexes requires the glycosaminoglycan (GAG) chains of syndecan-4 and/or the core syndecan-4 protein, which bind the heparin-binding domain II of fibronectin [6,7], triggering the activation of protein kinase Cα (PKCα) [6,8] and the subsequent modulation of the Rho GTPases [9]. In this case, the interaction of syndecan-4 with an extracellular ligand, fibronectin, induces and stabilizes the oligomerization of the syndecan-4 transmembrane domain, transduces an extracellular signal to the cytosol, and ultimately regulates intracellular events, such as cytoskeletal rearrangement and the formation of focal adhesions. Recent studies on fibronectin-coated cells have revealed that syndecan-4 cooperates with integrin α5β1 to activate Rac, a major regulator of cell migration [9,10], and induce directional cell migration [11]. Two other interacting proteins, paxillin [12] and Tiam-1 might be also associated with the syndecan-4-containing protein complex and could support the activation of Rac1 [13]. Interaction of syndecan-4 with laminin 332, particularly via the C-terminal globular domain of the former protein, is involved in regulation of keratinocyte migration during epidermal repair [14]. As an adhesion receptor, syndecan-4 is also likely to be involved in the generation of reactive oxygen species (ROS) [15] during cell spreading and adhesion, probably through the activation of Rac1 [16].

Similarly, studies have shown that syndecan-2 and integrins appear to cooperate in the formation of stress fibers. Knockdown of syndecan-2 with an antisense oligonucleotide inhibited the formation of actin stress fibers, and syndecan-2 was shown to interact with fibronectin and cooperate with integrin α5β1 to regulate actin stress fiber formation in Lewis lung carcinoma-derived P29 cells [17]. In P29 cells, syndecan-2 cooperated with α5β1 integrin to form actin stress fibers on a fibronectin substratum, whereas cells expressing syndecan-2 alone formed filopodia [18]. Cooperation between syndecan-2 and α2β1 integrin has also been reported during cell adhesion and migration in normal epithelial cells and colon cancer cells [19]. Similar to the interaction of PKCα with syndecan-4, protein kinase A (PKA) activity is related to syndecan-2-mediated intracellular signaling in HEK cells and cultured hippocampal neurons, where it triggers the formation of filopodia and dendritic spines [20]. Syndecan-2 is known to be essential for angiogenesis [21] and can regulate the tumorigenic activity of HT1080 fibrosarcoma cells [14], but future work will be required to assess the mechanisms through which extracellular ligands regulate syndecan-2 in these cases.

Various studies have shown that syndecan-1 regulates αvβ3 integrin [22], modulates αvβ5 integrin during cell adhesion to vitronectin [23], and promotes cell adhesion to laminin-332 by inhibiting the phosphorylation of β_4 integrin [24]. In addition, syndecan-1 acts as a critical regulator of the αvβ3 and αvβ5 integrins during angiogenesis and tumorigenesis [25]. Cooperative regulation between syndecan-1 and α2β1 integrin has been suggested during cell adhesion to collagen [26], which negatively modulates cancer cell movement [27]. The interaction between syndecan-1 and collagen I was shown to control the Rho GTPases, activating and suppressing the activities of RhoA and Rac1, respectively [28]. The activation of RhoA by the binding of syndecan-1 to collagen I was found to induce focal adhesions and reduce cell motility, whereas the suppression of Rac1 by syndecan-1 triggered the formation of lamellipodia and the directed migration of cells [27]. In A431 human squamous carcinoma cells plated on laminin 332, syndecan-1 formed a complex with α6β4 integrin, which activated PI3K-Akt-mediated signaling and protected the cells against apoptosis [28]. As syndecan family members share several signaling molecules, there might be functional redundancy and/or a synergistic effect of syndecans and integrins on cell adhesion and migration. However, it is also possible that the various syndecans might play unique roles in specific environment. Therefore, future studies will be warranted to investigate which syndecans are primarily responsible for responding to diverse changes in the cellular environment, and which signaling networks are involved in the synergistic signaling of syndecans and integrins during cell adhesion.

3. Syndecan as a docking receptor

Another way for the syndecans to mediate the information flow between the cell and its environment is through their activities as docking receptors [29–31], which allows them to regulate extracellular events rather than transduce the signals to the interior of the cell. The heparan sulfate (HS) chains of syndecans play a critical role in this function [32,33], as they are responsible for recruiting soluble growth factors, such as fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF), platelet derived growth factor (PDGF), and transforming growth factor β1 (TGFβ1) to the membrane, and subsequently allowing them to bind to their receptors [34–39]. FGF-2 has been thoroughly investigated in this context, and is a good model for the docking-receptor function of syndecans. David and co-workers reported that syndecan-1, -2, and -4 supported the interaction of FGF-2 with FGF receptor (FGFR), and also increased FGFR1 activation [40]. The binding of FGF-2 to syndecan achieves high local concentration of FGF-2 at the cell surface. However, this interaction does not transduce an intracellular signal, but rather helps FGF-2 bind to FGFR with higher affinity than FGF-2 in itself, which then transduces the signal [41]. A similar relationship has been identified between VEGF and syndecan-2, in that $VEGF_{165}$ can bind syndecan through a heparin-binding site [42], which then enhances the binding of $VEGF_{165}$ to VEGF receptor-2 (VEFGR2) and activates VEGFR2 [42]. Syndecan-2, which is known to be required for sprouting angiogenesis in zebrafish development, is believed to mediate the interaction between VEGF and VEGF receptor [21]. Syndecan-1 has been reported to mediate HGF- and EGF-related signaling in multiple myeloma [43–47], and HGF and EGF family members were shown to associate with syndecan-1 for promotion of cell survival and proliferation [43,46]. The interaction of syndecan-1 with HGF has been shown to trigger clustering and activation of HGF receptor/MET, and the interaction of syndecan-1 with EGF is known to activate EGF receptor in a similar manner [43,46].

In addition to interacting with growth factors, the HS chains of syndecans mediate recruitment of various cytokines and chemokines at the cell surface. Syndecans 1, 2, and 3 interact with interleukin-8 (IL-8) on the surface of endothelial cells [48–50]. As an inflammatory response is mounted, interaction of syndecan with IL-8 generates an IL-8 gradient at the HUVEC cell surface; this mediates neutrophil recruitment to the site of inflammation [48]. In addition, interactions of syndecan HS chains with IL-8 protect IL-8 from proteolytic degradation [51]. IL-8 stability is thus maintained and the IL-8-mediated cell response sustained. Granulocyte–macrophage colony-stimulating factor (GM-CSF), a heparin-binding cytokine, binds to syndecan-2 on the surface of osteoblastic cells; syndecan-2 mediates functional interaction between GM-CSF and the GM-CSF receptor [52]. In addition, syndecan may interact with other cytokines and chemokines that bind HS chains. These interactions may contribute to establishment of chemokine/cytokine concentration gradients on cell surfaces, raising the binding affinities of such materials to their cognate receptors. In summary, studies to date have revealed that various growth factors and cytokines may bind to the HS chains of syndecans, thereby enhancing local concentrations of the former materials and/or the binding thereof to receptors.

Some of the matrix metalloproteinases (MMPs) also appear to be recruited to the cell membrane by syndecans [53]. Yu and Woessner [54] showed that heparan sulfate proteoglycans (HSPGs) might provide anchoring sites for MMP-7, while other studies have showed binding between HSPGs and MMP-2, -9, and -13 [55–58]. Berton and co-workers reported that modulation of HSPG levels decreased the membrane-binding and enzymatic activities of MMP-7 [59], while other groups showed that MMP-7 can trigger the shedding of syndecan-1 ectodomains in vivo from the surface of activated airway epithelia in mice [60,61]. Thus, it is possible that syndecan-1 docks MMP-7 to the cell surface via its HS chains and thus exposes itself to MMP-7 as a substrate. Syndecan-2 has been shown to trigger the processing of pro-MMP-7 into active MMP-7 [31], suggesting that some syndecans may tether specific MMPs and accelerate their activation. In contrast, however, syndecan-2 was found to suppress MMP-2 activation and decrease metastasis in a Lewis lung carcinoma cell line, whereas a mutated syndecan-2 lacking the GAG sites did not [56]. This indicates that the HS chains of syndecan-2 recruit MMP-2 and inhibit activation thereof. Thus, syndecan may tether extracellular proteases at the cell surface, either positively or negatively regulating the activities of these enzymes. It is not yet clear how the syndecans facilitate the interaction of growth factors with their receptors or seize and act upon other molecules near the cell surface, but these effects may involve the establishment of a concentration gradient, protection from inhibitory or proteolytic molecules, or the formation of appropriate orientations. In the future, it will be critical for us to better understand the binding mechanisms of syndecans with other extracellular ligands.

4. Conclusions

The communication between a cell and its environment is very important, since cells must respond to change or alter their surroundings in order to adapt and survive. Syndecans are among the receptor proteins responsible for mediating such signaling, and are unusual in that they play diverse roles. As summarized in our prior review [5], their functional diversity might arise at least in part from their structural diversity. However, syndecans may also utilize different regulatory mechanisms to perform their diverse functions.

In order to respond to external stress, a cell must properly modulate both its internal and external environment. Thus, it would be useful for a single cell surface receptor to efficiently perform both of these functions. In this review, we propose that syndecans play dual roles as cell adhesion receptors and docking receptors, enhancing their ability to recognize and efficiently respond to external stimuli. As cell adhesion receptors, syndecans transduce ‘outside-in’ signals, taking information from the cell exterior and using it to regulate intracellular events. As docking receptors, syndecans regulate proper external cellular responses to the environment. The ligand specificities of these roles are not yet clear, but it seems likely that syndecans use these two different mechanisms to govern adequate cellular responses. Future studies may reveal how syndecans select their ligands and the signal direction under various conditions.

Acknowledgements

This study was supported by a grant of the Korea Healthcare technology R&D Projects, Ministry for Health, Welfare, and Family Affairs, Republic of Korea (A090615 to ESO) and in part by Grant No. R15-2006-020 from the NCRC program of the MEST and the KOSEF through the Center for Cell Signaling and Drug Discovery Research at Ewha Womans University.

References

[1] Tkachenko, E., Rhodes, J.M. and Simons, M. (2005) Syndecans: new kids on the signaling block. Circ. Res. 96, 488–500.
[2] Lambaerts, K., Wilcox-Adelman, S.A. and Zimmermann, P. (2009) The signaling mechanisms of syndecan heparan sulfate proteoglycans. Curr. Opin. Cell Biol. 21, 662–669.
[3] Rapraeger, A.C. (2000) Syndecan-regulated receptor signaling. J. Cell. Biol. 149, 995–998.
[4] Morgan, M.R., Humphries, M.J. and Bass, M.D. (2007) Synergistic control of cell adhesion by integrins and syndecans. Nat. Rev. Mol. Cell. Biol. 8, 957–969.
[5] Choi, Y., Chung, H., Jung, H., Couchman, J.R. and Oh, E.S. (2011) Syndecans as cell surface receptors: unique structure equates with functional diversity. Matrix. Biol. 30, 93–99.
[6] Woods, A., Longley, R.L., Tumova, S. and Couchman, J.R. (2000) Syndecan-4 binding to the high affinity heparin-binding domain of fibronectin drives focal adhesion formation in fibroblasts. Arch. Biochem. Biophys. 374, 66–72.
[7] Mahalingam, Y., Gallagher, J.T. and Couchman, J.R. (2007) Cellular adhesion responses to the heparin-binding (HepII) domain of fibronectin require heparan sulfate with specific properties. J. Biol. Chem. 282, 3221–3230.
[8] Lim, S.T., Longley, R.L., Couchman, J.R. and Woods, A. (2003) Direct binding of syndecan-4 cytoplasmic domain to the catalytic domain of protein kinase Cα (PKCα) increases focal adhesion localization of PKCα. J. Biol. Chem. 278, 13795–13802.
[9] Mahoney, C.M., Morgan, M.R., Harrison, A., Humphries, M.J. and Bass, M.D. (2009) Therapeutic ultrasound bypasses canonical syndecan-4 signaling to activate rac1. J. Biol. Chem. 284, 8898–8909.
[10] Humphries, M.J., Mostafavi-Pour, Z., Morgan, M.R., Deakin, N.O., Massent, A.J. and Bass, M.D. (2005) Integrin-syndecan cooperation governs the assembly of signaling complexes during cell spreading. Novartis. Found. Symp. 269, 178–188.
[11] Bass, M.D., Roach, K.A., Morgan, M.R., Mostafavi-Pour, Z., Schoen, T., Muramatsu, T., Mayer, U., Ballestrem, C., Spatz, J.P. and Humphries, M.J. (2007) Syndecan-4–dependent Rac1 regulation determines directional migration in response to the extracellular matrix. J. Cell Biol. 177, 527–538.
[12] Yoo, J., Jeong, M.J., Cho, H.J., Oh, E.S. and Han, M.Y. (2005) Dynamin II interacts with syndecan-4, a regulator of focal adhesion and stress-fiber formation. Biochem. Biophys. Res. Commun. 328, 424–431.
[13] Park, H., Han, I., Kwon, H.J. and Oh, E.S. (2005) Focal adhesion kinase regulates syndecan-2-mediated tumorigenic activity of HT-1080 fibrosarcoma cells. Cancer. Res. 65, 9899–9905.
[14] Carulli, S., Beck, K., Dayan, G., Boulesteix, S., Lortat-Jacob, H. and Rousselle, P. (2012) Cell surface proteoglycans syndecan-1 and -4 bind overlapping but distinct sites in laminin α3 LG45 protein domain. J. Biol. Chem. 287, 12204–12216.
[15] Kim, J., Lee, J.H., Park, H.S., Hwang, J., Han, I.O., Bae, Y.S. and Oh, E.S. (2008) Syndecan-4 regulates platelet-derived growth factor-mediated MAP kinase activation by altering intracellular reactive oxygen species. FEBS. Lett. 582, 2725–2730.
[16] Sundaresan, M., Yu, Z.X., Ferrans, V.J., Sulciner, D.J., Gutkind, J.S., Irani, K., Goldschmidt-clermont, P.J. and Finkel, T. (1996) Regulation of reactive-oxigen-species generation in fibroblasts by Rac1. Biochem. J. 318, 379–382.
[17] Kusano, Y., Oguri, K., Nagayasu, Y., Munesue, S., Ishihara, M., Saiki, I., Yonekura, H., Yamamoto, H. and Okayama, M. (2000) Participation of syndecan 2 in the induction of stress fiber formation in cooperation with integrin $\alpha_5\beta_1$: structural characteristics of heparan sulfate chains with avidity to COOH-terminal heparin-binding domain of fibronectin. Exp. Cell. Res. 256, 434–444.
[18] Munesue, S., Kusano, Y., Oguri, K., Itano, N., Yoshitomi, Y., Nakanishi, H., Yamashina, I. and Okayama, M. (2002) The role of syndecan-2 in regulation of actin-cytoskeletal organization of Lewis lung carcinoma-derived metastatic clones. Biochem. J. 363, 201–209.
[19] Choi, S., Kim, Y., Park, H., Han, I.O., Chung, E., Lee, S.Y., Kim, Y.B., Lee, J.W., Oh, E.S. and Yi, J.Y. (2009) Syndecan-2 overexpression regulates adhesion and migration through cooperation with integrin α_2. Biochem. Biophys. Res. Commun. 384, 231–235.
[20] Lin, Y.L., Lei, Y.T., Hong, C.J. and Hsueh, Y.P. (2007) Syndecan-2 induced filopodia and dendritic spine formation viz the neurofibromin-PKA-Ena/VASP pathway. J. Cell. Biol. 177, 829–841.
[21] Chen, E., Hermanson, S. and Ekker, S.C. (2004) Syndecan-2 is essential for angiogenic sprouting during zebrafish development. Blood 103, 1710–1719.
[22] Beauvais, D.M., Burbach, B.J. and Rapraeger, A.C. (2004) The syndecan-1 ectodomain regulates $\alpha_v\beta_3$ integrin activity in human mammary carcinoma cells. J. Cell. Biol. 167, 171–181.
[23] McQuade, K.J., Beauvais, D.M., Burbach, B.J. and Rapraeger, A.C. (2006) Syndecan-1 regulates $\alpha_v\beta_5$ integrin activity in B82L fibroblasts. J. Cell. Sci. 119, 2445–2456.
[24] Ogawa, T., Tsubota, Y., Hashimoto, J., Kariya, Y. and Miyazaki, K. (2007) The short arm of laminin γ2 chain of laminin-5 (laminin-332) binds syndecan-1 and regulates cellular adhesion and migration by suppressing phosphorylation of integrin β_4 chain. Mol. Biol. Cell. 18, 1621–1633.
[25] Beauvais, D.M., Ell, B.J., McWhorter, A.R. and Rapraeger, A.C. (2009) Syndecan-1 regulates $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin activation during angiogenesis and is blocked by synstatin, a novel peptide inhibitor. J. Exp. Med. 206, 691–705.

[26] Vuoriluoto, K., Jokinen, J., Kallio, K., Salmivirta, M., Heino, J. and Ivaska, J. (2008) Syndecan-1 supports integrin alpha2beta1-mediated adhesion to collagen. Exp. Cell. Res. 314, 3369–3381.
[27] Ishikawa, T. and Kramer, R.H. (2010) Sdc1 negatively modulated carcinoma cell motility and invasion. Exp. Cell. Res. 316, 951–965.
[28] Wang, H., Leavitt, L., Ramaswamy, R. and Rapraeger, A.C. (2010) Interaction of syndecan and alpha6beta4 integrin cytoplasmic domains: regulation of ErbB2-mediated integrin activation. J. Biol. Chem. 285, 13569–13579.
[29] Yu, Q. and Stamenkovic, I. (1999) Localization of matrix metalloproteinase 9 to the cell surface provides a mechanism for CD44-mediated tumor invasion. Genes Dev. 13, 35–48.
[30] Beauvais, D.M. and Rapraeger, A.C. (2010) Syndecan-1 couples the insulin-like growth factor-1 receptor to inside-out integrin activation. J. Cell. Sci. 123, 3796–3807.
[31] Ryu, H.Y., Lee, J., Yang, S., Park, H., Choi, S., Jung, K.C., Lee, S.T., Seong, J.K., Han, I.O. and Oh, E.S. (2009) Syndecan-2 functions as a docking receptor for pro-matrix metalloproteinase-7 in human colon cancer cells. J. Biol. Chem. 284, 35692–35701.
[32] Bernfield, M., Götte, M., Park, P.W., Reizes, O., Fitzgerald, M.L., Lincecum, J. and Zako, M. (1999) Functions of cell surface heparan sulfate proteoglycans. Annu. Rev. Biochem. 68, 729–777.
[33] Carey, D.J. (1997) Syndecans: multifunctional cell-surface co-receptors. Biochem. J. 327, 1–16.
[34] Burgess, W.H. and Maciag, T. (1989) The heparin-binding (Fibroblast) growth factor family of proteins. Annu. Rev. Biochem. 58, 575–606.
[35] Woods, A., Oh, E.S. and Couchman, J.R. (1998) Syndecan proteoglycans and cell adhesion. Matrix. Biol. 17, 477–483.
[36] Xian, X., Gopal, S. and Couchman, J.R. (2010) Syndecans as receptors and organizers of the extracellular matrix. Cell. Tissue Res. 339, 31–46.
[37] Cizmeci-Smith, G., Langan, E., Youkey, J., Showalter, L.J. and Carey, D.J. (1997) Syndecan-4 is a primary-response gene induced by basic fibroblast growth factor and arterial injury in vascular smooth muscle cells. Arterioscler. Thromb. Vasc. Biol. 17, 172–180.
[38] Elenius, K., Maatta, A., Salmivirta, M. and Jalkanen, M. (1992) Growth factors induce 3T3 cells to express bFGF-binding syndecan. J. Biol. Chem. 267, 6435–6441.
[39] Cizmeci-Smith, G., Stahl, R.C., Showalter, L.J. and Carey, D.J. (1993) Differential expression of transmembrane proteoglycans in vascular smooth muscle cells. J. Biol. Chem. 268, 18740–18747.
[40] Steinfeld, R., Berghe, H.V.D. and David, G. (1996) Stimulation of fibroblast growth factor receptor-1 occupancy and signaling by cell surface-associated syndecans and glypican. J. Cell. Biol. 133, 405–416.
[41] Reiland, J. and Rapraeger, A.C. (1993) Heparan sulfate proteoglycan and FGF receptor target basic FGF to different intracellular destinations. J. Cell Sci. 105, 1085–1093.
[42] Kajia, T., Yamamotoa, C., Oh-ia, M., Fujiwaraa, Y., Yamazakic, Y., Moritac, T., Plaasd, A.H. and Wighte, T.N. (2006) The vascular endothelial growth factor VEGF165 induces perlecan synthesis via VEGF receptor-2 in cultured human brain microvascular endothelial cells. Biochim. Biophys. Acta 1760, 1465–1474.
[43] Mahtouk, K., Cremer, F.W., Rème, T., Jourdan, M., Baudard, M., Moreaux, J., Requirand, G., Fiol, G., De Vos, J., Moos, M., Quittet, P., Goldschmidt, H., Rossi, J.F., Hose, D. and Klein, B. (2006) Heparansulphate proteoglycans are essential for the myeloma cell growth activity of EGF-family ligands in multiple myeloma. Oncogene 25, 7180–7191.
[44] Andersen, N.F., Standal, T., Nielsen, J.L., Heickendorff, L., Borset, M., Sørensen, F.B. and Abildgaard, N. (2005) Syndecan-1 and angiogenic cytokines in multiple myeloma: correlation with bone marrow angiogenesis and survival. Br. J. Haematol. 128, 210–217.
[45] Mahtouk, K., Jourdan, M., De Vos, J., Hertogh, C., Fiol, G., Jourdan, E., Rossi, J.F. and Klein, B. (2004) An inhibitor of the EGF receptor family blocks myeloma cell growth factor activity of HB-EGF and potentiates dexamethasone or anti-IL-6 antibody-induced apoptosis. Blood 103, 1829–1837.
[46] Derksen, P.W., Keehnen, R.M., Evers, L.M., van Oers, M.H., Spaargaren, M. and Pals, S.T. (2002) Cell surface proteoglycan syndecan-1 mediates hepatocyte growth factor binding and promotes Met signaling in multiple myeloma. Blood 99, 1405–1410.
[47] Seidel, C., Børset, M., Hjertner, O., Cao, D., Abildgaard, N., Hjorth-Hansen, H., Sanderson, R.D., Waage, A. and Sundan, A. (2000) High levels of soluble syndecan-1 in myeloma-derived bone marrow: modulation of hepatocyte growth factor activity. Blood 96, 3139–3146.
[48] Marshall, L.J., Ramdin, L.S., Brooks, T., Dphil, P.C. and Shute, J.K. (2003) Plasminogen activator inhibitor-1 supports IL-8-mediated neutrophil transendothelial migration by inhibition of the constitutive shedding of endothelial IL-8/heparan sulfate/syndecan-1 complexes. J. Immunol. 171, 2057–2065.
[49] Halden, Y., Rek, A., Atzenhofer, W., Szilak, L., Wabnig, A. and Kungl, A.J. (2004) Interleukin-8 binds to syndecan-2 on human endothelial cells. Biochem. J. 377, 533–538.
[50] Patterson, A.M., Gardner, L., Shaw, J., David, G., Loreau, E., Aguilar, L., Ashton, B.A. and Middleton, J. (2005) Induction of a CXCL8 binding site on endothelial syndecan-3 in rheumatoid synovium. Arthritis Rheum. 52, 2331–2342.
[51] Goger, B., Halden, Y., Rek, A., Mosl, R., Pye, D., Gallagher, J. and Kungl, A.J. (2002) Different affinities of glycosaminoglycan oligosaccharides for monomeric and dimeric interleukin-8: a model for chemokine regulation at inflammatory sites. Biochemistry 41, 1640–1646.
[52] Modrowski, D., Baslé, M., Lomri, A. and Marie, P.J. (2000) Syndecan-2 is involved in the mitogenic activity and signaling of granulocyte-macrophage colony-stimulating factor in osteoblasts. J. Biol. Chem. 275, 9178–9185.
[53] Li, Q., Park, P.W., Wilson, C.L. and Parks, W.C. (2002) Matrilysin shedding of syndecan-1 regulates chemokine mobilization and transepithelial efflux of neutrophils in acute lung injury. Cell 111, 635–646.
[54] Yu, W.H. and Woessner, J.F. (2000) Heparan sulfate proteoglycans as extracellular docking molecules for matrilysin (matrix metalloproteinase 7). J. Biol. Chem. 275, 4183–4191.
[55] Koyama, Y., Naruo, H., Yoshitomi, Y., Munesue, S., Kiyono, S., Kusano, Y., Hashimoto, K., Yokoi, T., Nakanishi, H., Shimizu, S., Okayama, M. and Oguri, K. (2008) Matrix metalloproteinase-9 associated with heparan sulphate chains of GPI-anchored cell surface proteoglycans mediates motility of murine colon adenocarcinoma cells. J. Biochem. 143, 581–592.
[56] Munesue, S., Yoshitomi, Y., Kusano, Y., Koyama, Y., Nishiyama, A., Nakanishi, H., Miyazaki, K., Ishimaru, T., Miyaura, S., Okayama, M. and Oguri, K. (2007) A novel function of syndecan-2, suppression of matrix metalloproteinase-2 activation, which causes suppression of metastasis. J. Biol. Chem. 282, 28164–28174.
[57] Brule, S., Charnaux, N., Sutton, A., Ledoux, D., Chaigneau, T., Saffar, L. and Gattegno, L. (2006) The shedding of syndecan-4 and syndecan-1 from HeLa cells and human primary macrophages is accelerated by SDF-1/CXCL12 and mediated by the matrix metalloproteinase-9. Glycobiology 16, 488–501.
[58] De Ceuninck, F., Allain, F., Caliez, A., Spik, G. and Vanhoutte, P.M. (2003) High binding capacity of cyclophilin B to chondrocyte heparan sulfate proteoglycans and its release from the cell surface by matrix metalloproteinases: Possible role as a proinflammatory mediator in arthritis. Arthritis. Rheum. 48, 2197–2206.
[59] Berton, A., Selvais, C., Lemoine, P., Henriet, P., Courtoy, P.J., Marbaix, E. and Emonard, H. (2007) Binding of matrilysin-1 to human epithelial cells promotes its activity. Cell. Mol. Life Sci. 64, 610–620.
[60] Chen, P., Abacherli, L.E., Nadler, S.T., Wang, Y., Li, Q. and Parks, W.C. (2009) MMP7 shedding of syndecan-1 facilitates re-epithelialization by affecting $\alpha_2\beta_1$ integrin activation. PLoS. ONE 4, e6565.
[61] Ding, K., Lopez-Burks, M., Sánchez-Duran, J.A., Korc, M. and Lander, A.D. (2005) Growth factor–induced shedding of syndecan-1 confers glypican-1 dependence on mitogenic responses of cancer cells. J. Cell. Biol. 171, 729–738.