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Mini Review

Shedding; towards a new paradigm of syndecan function in cancer

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Syndecans, cell surface heparansulfate proteoglycans, have been proposed to act as cell surface receptors and/or coreceptors to play critical roles in multiple cellular functions. However, recent reports suggest that the function of syndecans can be further extended through shedding, a cleavage of extracellular domain. Shedding constitutes an additional level for controlling the function of syndecans, providing a means to attenuate and/or regulate amplitude and duration of syndecan signals by modulating the activity of syndecans as cell surface receptors. Whether these remaining cleavage products are still capable of functioning as cell surface receptors to efficiently transduce signals inside of cells is not clear. However, shedding transforms cell surface receptor syndecans into soluble forms, which, like growth factors, may act as novel ligands to induce cellular responses by association with other cell surface receptors. It is becoming interestingly evident that shed syndecans also contribute significantly to syndecan functions in cancer biology. This review presents current knowledge about syndecan shedding and its functional significance, particularly in the context of cancer. [BMB reports 2010; 43(5): 305-310]

INTRODUCTION

Shedding is defined as "releasing and/or separating something". The phenomenon of shedding can be found in biological systems, exemplified by viral shedding and receptor shedding. Viral shedding is the process of expelling virus particles from the body, whereas receptor shedding is the process whereby the extracellular domain of transmembrane proteins is cleaved (separated) and released from the cell surface. Receptor shedding has been implicated in a number of common regulatory mechanisms. For example, epidermal growth factor receptor (EGFR) ligands are synthesized as transmembrane proteins, and shedding of the extracellular domain (ectodomain) is required for the release of EGF and the regulation of diverse functions, including development, growth, and differentiation (1). The ectodomain shedding of membrane-tethered EGFR ligands are mediated by protease TACE/ADAM17 (2) and ADAM12 (3). During osteoclastogenesis, receptor activator of NF-κB ligand (RANKL) is cleaved proteolytically and released from the cell surface by tumor necrosis factor-α (TNF-α)-converting enzyme (4). Extracellular domain shedding is also a characteristic of other growth factors, such as transforming growth factor-α (TGF-α) and TNF-α as well as cell adhesion molecules, including L-selectin (5) and E-cadherin (6). Thus, the process of shedding is an important mechanism for controlling diverse cellular functions.

Recently, receptor shedding has been identified as a common mechanism in various diseases, including cancer and cardiovascular disease. For example, proteolysis of the receptor for advanced glycation end products (RAGE) (7-9) is able to suppress the development of Alzheimer's disease; therefore, the modulation of RAGE proteolysis is considered a potential novel therapeutic target for the treatment of Alzheimer's disease (9, 10). Stimulation of platelet 5-hydroxytryptamine (5-HT) receptors (5-HT2ARs) by circulating serotonin (5-HT) induces TACE-mediated shedding of GPIbα, which is capable of modulating cardiovascular disease (11). A high level of the P-cadherin soluble fragment, which is possibly released via extracellular domain shedding, has been correlated with an increased risk for breast cancer (12). A soluble fragment of the Type III TGF-β receptor generated by ectodomain shedding has been shown to suppress the invasion of non-small cell lung cancer (13), and the progression of pancreatic cancer (14). In addition, the shed soluble domain of the endothelial-specific Tie2 receptor might be a prognostic indicator in patients with acute myeloid leukemia (15); and serum soluble interleukin 2 receptor might act as a new biochemical marker of neoplasm activity in adults and children (16). On the other hand, tissue inhibitor metalloproteinases-3 (TIMP-3), which inhibits the shedding of TNF-α receptors, Fas, and p55TNF receptor 1, might facilitate apoptosis of cancer cells. Although is uncertain whether shedding is a direct cause of cancer, it is clear that shedding is an important regulatory mechanism in carcinogenesis.

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Syndecans and cancer

Syndecans, a family of cell surface heparansulfate proteoglycans, are known to play critical roles in cancer cell biology. The biological functions of syndecans as cell surface receptors have been well summarized in several excellent reviews (17-19). Each syndecan appears to have different role in the regulation of cancer-related processes. Syndecan-1 plays an important role in the growth, survival, vasculogenesis, and metastasis of various cancers, including myelomas (20) and breast (21), bladder (22), ovary (23), prostate (24) and colon cancers (25). For instance, knockdown of syndecan-1 using small interfering RNAs (shRNA) promotes apoptosis of myeloma cells and dramatically diminishes tumor cell growth (20). Knockdown of syndecan-1 also decreases vascular endothelial growth factor-A (VEGF-A) levels and vasculogenesis in mouse models (20). Consistent with this, overexpression of syndecan-1 has bee shown to induce approximately a twofold increase in the proliferation of endometrial cancer cells (26). Syndecan-1 mRNA levels are up-regulated in pancreatic cancer in association with accelerated tumor growth, as determined by in situ hybridization and immunohistochemistry (27).

In contrast to syndecan-1, which has been implicated in a variety of cancer types, the role of syndecan-2 seems to be limited to melanomas and colon and prostate cancers. Syndecan-2 is dramatically overexpressed in melanomas and several colon carcinoma cell types, and up-regulation of syndecan-2 is believed to increase the tumorigenic activity of these cells. Moreover, colon cancer cells cultured on syndecan-2 ectodomain or syndecan-2 antibody show increased adhesion and spreading (28). Syndecan-2 is also overexpressed in about 90% of prostate cancer patients, and the increased syndecan-2 expression enhances the growth of prostate tumor cells (29). In contrast to other syndecans, which generally function as tumor promoters, syndecan-4 apparently functions as a tumor suppressor. Syndecan-4 promotes focal adhesion formation, resulting in increased cell adhesion but decreased cell migration, effects that collectively reduce cancer cell activity (30). Those reports have all shown that syndecans play a critical role as cell surface receptors in cancer cells. Interestingly, the presence of a dibasic peptide sequence adjacent to the plasma membrane in all syndecans predicted that the extracellular domain of syndecan could be cleaved by extracellular proteases. This has since been experimentally demonstrated and recent evidence points to shedding of the extracellular domain as a prominent aspect of the function of syndecans. Considered in light of the function of syndecans as cell surface receptors, syndecan shedding seemingly poses a dilemma. However, syndecan shedding might constitute an additional level for controlling the function of syndecans, providing a means to attenuate and/or regulate the amplitude and/or duration of syndecan signals by modulating the activity of syndecans as cell surface receptors.

Syndecan shedding enzymes

Since syndecan shedding involves releases of the extracellular domain, it would most likely be mediated by extracellular proteases. Several matrix metalloproteases (MMPs), zinc-dependent endopetidases that play an important role at different stages of cancer progression, have been reported to regulate the shedding of syndecans. MMP-9 has been implicated in the stromal cell-derived factor-1 (SDF-1)-induced shedding of syndecan-1 and syndecan-4 in HeLa cervical cancer cells (31). In these cells, siRNA-mediated knockdown of MMP-9 reduced shedding of syndecan-1 and syndecan-4, despite the continued presence of SDF-1, confirming that MMP-9 mediates shedding of syndecan-1 and syndecan-4. There is also evidence for the involvement of other MMPs. For example, Chen et al showed that epithelial injury induced syndecan-1 shedding from the epithelium of wild-type mice but not from the epithelium of MMP-7 knockout mice (32); and Endo et al showed that membrane type matrix metalloproteinase-1 (MT1-MMP) promoted syndecan-1 shedding through the preferential cleavage of syndecan-1 core protein Gly245-Leu246 peptide bond. Indeed syndecan-1 contains a general consensus sequence for cleavage by MMP-7, MMP-9 and MT1-MMP (33). The shedding of syndecan-3 has also been reported in Schwann cells obtained from the sciatic nerves of 2-4 day-old rats (34). This shedding is reduced in cells treated with the MMP inhibitor Batimastat (BB-94) (34), providing evidence for the involvement of MMPs in mediating syndecan-3 shedding.

ADAMTS1, a member of the disintegrin-like and metalloprotease with thrombospondin type-1 motifs family is also known to cleave the syndecan-4 ectodomain. After co-transfecting 293T cells with ADAMTS1 and an N-terminally HA-tagged full-length syndecan-4 construct, a soluble fragment (approximately 6-7 kDa) of HA-tagged syndecan-4 extracellular domain was detected in conditioned media (35). This shedding of syndecan-4 was reduced by BB-94, a metalloprotease inhibitor that partially inhibits the protease activity of ADAMTS1 (35). Moreover, shedding of both syndecan-1 and -4 was blocked by the peptide hydroxamates BB-2116 and BB-1101 (36), which are compounds that were originally designed to inhibit zinc-dependent MMPs.

ADAM17, a disintegrin and metalloproteinase family members, is also known to cleave syndecans. Production of soluble syndecan-1 and -4 was reduced in both ECV304 bladder carcinoma epithelial cells and A549 lung carcinoma epithelial cells by treatment with GW280264, an inhibitor of ADAM17 and ADAM10, but not by the ADAM10 inhibitor GI254023 (37). Similarly, the shedding of syndecan-1 and syndecan-4 is stimulated by the recombinant ADAM17 catalytic domain (37). In addition, siRNA-mediated knockdown of ADAM17 reduced shedding of syndecan-1 and syndecan-4 in ECV304 cells and A549 cells (37). ADAM17 activation also mediates release of soluble syndecan-1 and -4 into the bronchoalveolar fluid of

mice, as evidenced by the fact that both constitutive and induced syndecan shedding could be prevented by inhibiting ADAM17 (37). The pseudomonas virulence factor LasA, an M23 metallopeptidase related to autolytic glycylglycine endopeptidases, is known for stimulating ectodomain shedding of syndecan-1 (38, 39). Collectively, these observations establish that shedding of syndecans is mediated by a number of factors, including MMP-9, MMP-7, MT1-MMP, ADMTS1, ADAM17, and LasA.

Regulation of syndecan shedding

Syndecan shedding is regulated by several factors, one of which is growth factors. Subramanian et al. showed that EGF increased the shedding of syndecan-1 and syndecan-4 in a concentration-dependent manner, and demonstrated that other EGF family members, such as EGF, HB-EGF, TGF-α and amphiregulin, produce the same effects (40). Ding et al showed that FGF-2 enhances the shedding of syndecan-1 in PANC-1 pancreatic carcinoma cells (41). Interestingly, it is known that MMP7 (matrilysin) is frequently overexpressed by pancreatic cancer cells (42), and fibroblast growth factor (FGF)-2 induces expression and activation of MMP7 together with syndecan-1 shedding (41). Increased levels of serum syndecan-1 have been observed in patients with type 2 diabetes treated with insulin (43). The fact that this association represents a causal linkage is supported by the observation that exogenous insulin promotes time-dependent shedding of syndecan-1 into the serum (43). In 3T3-L1 adipocytes, insulin has been shown to induce a dose- and time-dependent shedding of syndecan-1 and syndecan-4 that is also metalloproteinase-dependent (44). Growth factors are also involved in the regulation of syndecan-2 shedding. Fears et al reported that treatment of microvascular endothelial cells with EGF, FGF-2, or VEGF induced shedding of syndecan-2 (17).

Syndecan shedding is also affected by other factors, including inflammatory cytokines, bacterial toxins, oxidative stress and others. For example, chronic inflammation promotes shedding of syndecan-1 into serum (41); *Staphylococcus aureus* beta-toxin stimulates ectodomain shedding of syndecan-1, which induces neutrophil-mediated lung injury; and oxidative stress induces syndecan-1 shedding, which causes neutrophil chemotaxis and abnormal wound healing (45). Phorbol 12- myristate 13-acetate (PMA), an activator of protein kinase C (PKC), also enhances shedding of syndecan-1 from the surface of human myeloma cells (46). The effects of PMA on syndecan-1 shedding presumably involve PKC-dependent activation of the appropriate protease, but the pathway has yet been established. Interestingly, the cell surface heparansulfate chains of syndecans greatly affect syndecan shedding. The expression of heparanase-1, an endoglycosidase that degrades heparansulfate chains in the extracellular matrix and cell surface, is rare in normal tissues. However, heparanase-1 is up-regulated in many human tumors in association with an increase in the angiogenic and metastatic potential of tumor cells (47). In myeloma cells, syndecan-1 shedding is promoted by expression of heparanase-1 (48) and by treatment with recombinant heparanase (48). In addition, serum levels of shed syndecan1 are elevated in animals bearing tumors derived from heparanase-transfected CAG cells (48). Clearly, MMPs are not the only mediators of syndecan shedding; several other factors act cooperatively to regulate syndecan shedding.

The function of shed syndecans in cancer

The cleaved extracellular domain of syndecan plays a role in multiple pathologies. The most important and well-studied function of shed syndecans are their role(s) in tumorigenesis. MT1-MMP promotes syndecan-1 shedding, and shed syndecan-1 stimulates HEK293T cell migration (33), T47D breast carcinoma cell proliferation (49), and breast carcinoma cell growth in three-dimensional co-culture (33). Overexpression of shed syndecan-1 also promotes an invasive phenotype in MCF-7 breast cancer cells (50). Heparanase-mediated syndecan-1 shedding within the tumor microenvironment appears to be associated with an aggressive tumor phenotype. Serum levels of soluble syndecan-1 are much higher in animals with tumors formed from heparanase-transfected cells, and these animals have a significantly higher tumor burden than animals bearing tumors from control-transfected cells (51). Heparanase up-regulation stimulates enhanced ERK signaling, which acts through upregulation of MMP-9 and uPA/uPAR to enhance syndecan-1 shedding. Such shed syndecan-1 stimulates a dramatic increase in the aggressive behavior of myeloma tumors (51). Treatment of human umbilical vein endothelial cells with conditioned media from heparanase-transfected myeloma cells significantly stimulates syndecan-1 shedding and VEGF expression. Heparansulfate chains of shed syndecan-1 mediate interaction with VEGF, resulting in formation of a syndecan-1/VEGF complex that activates integrin and VEGF receptors, and thereby stimulates endothelial invasion (48). Similar to shed syndecan-1, the extracellular domains of syndecan-2 and syndecan-4 are also known to increase endothelial cell-mediated angiogenesis. Recombinant syndecan-2 ectodomain promotes membrane capillary tube formation in mouse brain microvascular endothelial cells (44), and the ectodomain of syndecan-4 cleaved by secreted ADAMTS1 causes altered distribution of cytoskeleton components, functional loss of adhesion, gain of migratory capacity, and angiogenesis (35).

Anti-tumorigenic effects of shed syndecans have also been reported. The membrane-bound syndecan-1 promotes proliferation of MCF-7 breast cancer cells; overexpression of constitutively shed syndecan-1 inhibits MCF-7 proliferation (50). In addition, shed syndecan-1 inhibits alveolar epithelial wound healing and promotes fibrogenesis (45), and decreases invasion of TIMP-1-sensitive breast cancer cell invasion (50). Moreover, treatment of human endothelial cells with syndecan-1 ectodomain decreases vitronectin attachment and angio-

genesis (52). Although there are controversies surrounding the various proposed roles of shed syndecans in cancer, it is clear that shed syndecans serve multiple functions, and may differentially and variably affect various cellular behaviors.

Molecular mechanisms of shed syndecan-mediated carcinogenesis

Shedding produces a soluble form of syndecan in the extracellular environment, and multiple lines of evidence suggest that shed syndecans are responsible for enhancing the activity of cancer cells. While the exact molecular mechanism(s) by which shed syndecans mediate tumorigenic activity in cancer cells remain unknown, the following four-point model describes a reasonable scenario.

First, shedding causes release of syndecan-bound signaling protein(s) to generate a new signal or modify an existing signal. Based on the promiscuous binding behavior of syndecans, it is possible that the extracellular domain of syndecan might bind to a variety of proteins and growth factors, some of which may regulate tumor growth (*i.e.* TGF-β). If shedding were to release syndecan-bound growth-inhibiting factors from normal cells, this would cause these confined factors to be released from the cell surface leading to disinhibition of cell proliferation. In this case, syndecan shedding would attenuate the function of the syndecan as a cell surface receptor, but enhance its caner-promoting activity.

Second, shed syndecan may not only release signaling proteins, but also enhance their activity. Because syndecan proteins contain heparansulfate chains, they may be capable of binding and regulating secreted signaling molecules, such as transforming growth factor and fibroblast growth factors, which promote proliferation of cancer cells. In addition, and perhaps more significantly, syndecan-2 may also regulate the activity of secreted proteins. It is quite possible that shed syndecan-2-bound FGF-2 more efficiently interacts with FGF receptor than FGF alone. As a result, syndecan-2 may enhance angiogenesis via FGF receptor signaling (53).

Third, shed syndecans may eliminate inhibitory soluble factors. Syndecan-1 shedding facilitates the resolution of neutrophilic inflammation by removing sequestered CXC chemokines. Consistent with this, treatment with a shedding inhibitor prevents the clearance of CXC chemokines and exacerbates disease (54). Therefore, shed syndecans may promote cancer by sequestrating inhibitory signals.

Fourth, shed syndecans could function as new soluble ligands. Because shed syndecan-2 expression is highly increased in colon cancer cells, these cells could presumably produce large amounts of soluble ectodomain polypeptide, which could bind to (unknown) carcinogenic receptors. These events could be dependent on or independent of glycosaminoglycan binding proteins. Affymetrix microarrays have shown that overexpression of shed syndecan-1 (soluble syndecan-1) induces expression of TIMP-1, furin, urokinase-type plasminogen activator (uPA) receptor and E-cadherin (50). These studies imply that shed syndecans might act as ligands to induce gene expression.

CONCLUSION

In this review, we have focused on the function of shed syndecans in carcinogenesis. Though carcinogenesis is clearly one context in which shedding of syndecans is enhanced, it should be noted that regulation of syndecan shedding may be equally important in other, as yet undefined, settings. Moreover, the importance of syndecan's function as adhesion receptors should not be underestimated. Each syndecan has its own role(s) in different aspects of cancer progression, but all are important regulators of human carcinogenesis in their capacity as cell surface receptors. However, the phenomenon of extracellular domain shedding adds a puzzling wrinkle to the effort to characterize the functions of syndecans. Is the importance of cell surface syndecans in controlling cancer cell activities related to their receptor functions, or is the shed extracellular domain of syndecans, acting as a ligand, the major player? In all likelihood, syndecans function as receptors as well as ligands in certain circumstances. Extracellular-domain shedding causes transformation of cell surface receptor syndecans into soluble ligand-like growth factors. Therefore, extracellular-domain shedding allows syndecans to contribute to carcinogenesis in many ways, and represents a new paradigm of syndecan functions in cancer. It is not clear yet whether syndecan shedding is directly involved in causing cancer, or whether the extracellular domain of shed syndecans plays positive or negative roles in carcinogenesis. However, what is clear is that further investigations to establish the detailed mechanism(s) underlying the process of syndecan shedding and precisely define the functions of syndecans are necessary if we are to understand how syndecans control carcinogenesis and develop novel syndecan-targeted cancer therapies.

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