Syndecan-2 Affects the Basal and Chemotherapy-Induced Apoptosis in Osteosarcoma

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Abstract

Syndecans are transmembrane heparan sulfate proteoglycans controlling cell adhesion, migration, and proliferation. We previously showed that syndecan-2 is involved in the control of apoptosis in cultured osteosarcoma cells. These data led us to the hypothesis that syndecan-2 may play a role in the apoptotic signaling in bone tumors. We immunohistochemically analyzed tissue sections from biopsies from 21 patients with well-characterized osteosarcoma. These tissues expressed low levels of syndecan-2 compared with osteoblasts and osteocytes in normal bone. Cultured human osteosarcoma cells also produced lower mRNA levels of syndecan-2 than normal osteoblastic cells. Moreover, the presence of syndecan-2 correlated with spontaneous apoptosis in osteosarcoma tissues as assessed by detection of DNA fragmentation in situ. Overexpression of syndecan-2 resulted in decreased number of migrating and invading U2OS osteosarcoma cells in Matrigel. In addition, overexpression of syndecan-2 sensitized human osteosarcoma cells to chemotherapy-induced apoptosis, increasing the response to methotrexate, doxorubicin, and cisplatin. Consistently, knockdown of the proteoglycan using a plasmid coding small interfering RNA resulted in inhibition of chemotherapy-induced apoptosis. Analysis of syndecan-2 expression both in biopsies and in corresponding postchemotherapy–resected tumors, as well as in cells treated with methotrexate or doxorubicin, showed that the cytotoxic action of chemotherapy can be associated with an increase in syndecan-2. These results provide support for a tumor-suppressor function for syndecan-2 and suggest that dysregulation of apoptosis may be related to abnormal syndecan-2 expression or induction in osteosarcoma. Moreover, our data identify syndecan-2 as a new factor mediating the anticongenic effect of chemotherapeutic drugs. [Cancer Res 2007;67(8):3708–15]

Introduction

Osteosarcoma is the most common primary bone cancer occurring mainly in children (1, 2). Aggressive chemotherapies and surgical treatment are currently done to achieve a disease-free state. However, overall 2-year survival rate in patients with osteosarcoma remains below 66% because a significant portion of patients respond poorly to chemotherapeutic protocols and because of frequent metastases occurring in lung and brain (2, 3). In cancer cells, dysregulation of apoptotic processes are believed to contribute to metastatic potential and to drug resistance (4, 5). Although such dysregulation may represent a potent source of new therapeutic targets, the molecular mechanisms that control osteosarcoma cell fate are largely unknown.

Syndecans are transmembrane heparan sulfate proteoglycans that serve as low-affinity receptors for various extracellular soluble and matrix components (6). They modulate the binding and availability of factors, thereby inducing downstream signaling pathways that control cell adhesion, migration, differentiation, and proliferation. Both tumor suppressor and tumor growth promoter activities have been reported for syndecans depending on the type of cancer (7–9). Syndecan-2 cooperates with integrins in lung carcinoma cells (10) to induce adhesion and was found associated with an antimetastatic effect (11). In contrast, syndecan-2, which is highly expressed in several colon cancer cell lines, is also involved in the adhesion and proliferation of these cells and promotes their tumorigenic activity (12, 13). It was shown that syndecan-2 expression occurs during mouse embryonic skeletal development and persists in differentiated bone structures (14). Moreover, human adult normal osteoblastic cells express high level of this proteoglycan (15). In contrast, some osteosarcoma cell lines were found to produce very low level of syndecan-2 (16). We recently reported that syndecan-2 is involved in the control of apoptosis in osteosarcoma cells. Indeed, overexpression of syndecan-2 in osteosarcoma cells induced signaling modifications such as inhibition of protein kinase Cδ and extracellular signal-regulated kinase as well as activation of c-Jun-NH2-kinase, resulting in cell death (16, 17). These data led us to hypothesize that syndecan-2 may play a role in the apoptotic signaling in bone tumors and may control osteosarcoma cell fate in vivo. Here, we examined the expression and role of syndecan-2 in osteosarcoma cells in vivo. We show that syndecan-2 expression is low in bone tumors and this correlates with spontaneous apoptosis. To determine whether syndecan-2 could modulate the apoptotic response to chemotherapeutic drugs, we used methotrexate, doxorubicin, and cisplatin, drugs that are currently used in chemotherapeutic protocols to treat osteosarcoma. We show here that syndecan-2 sensitizes osteosarcoma cells to chemotherapy-induced apoptosis and that chemotherapeutic drugs can promote syndecan-2 expression. These results indicate that syndecan-2 may contribute to the anticongenic effect of chemotherapeutic drugs in osteosarcoma.

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

Materials and Methods

Clinical samples. Slices of formalin-fixed and paraffin-embedded osteosarcoma tissues were obtained from biopsies in 21 patients. These samples were fixed in 10% buffered formalin, processed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Postchemotherapy–resected tumors were obtained from patients who received chemotherapy and surgical treatment are currently done to achieve a disease-free state. These samples were used for immunohistochemistry and transcriptional analysis. Bones were fixed in 10% buffered formalin, decalcified in 10% nitric acid, processed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissue slices were obtained from 21 patients who received chemotherapy and surgical treatment are currently done to achieve a disease-free state. These samples were used for immunohistochemistry and transcriptional analysis.
biopsies have been histologically characterized by pathologists. For five patients, samples were also obtained from surgically resected tumors after preoperative chemotherapy. Informed consent was obtained from each patient or the patient’s guardian.

**Immunohistochemistry.** Tissue sections were deparaffinized with xylene and rehydrated in decreasing concentrations of ethanol to distilled water. The sections were then washed in PBS containing 0.1% Tween 20 (pH 7.6). Background labeling was reduced by heparitinase III and chondroitinase ABC digestion (Sigma-Aldrich, Saint Louis, MO). Endogenous peroxidase activity was blocked with 0.3% hydrogen peroxide in methanol. After multiple rinses in PBS and antigen blocking serum, 2 μg of rabbit anti-syndecan-2 antibody that react with the cytoplasmic domain of syndecan-2 were added (Zymed, San Francisco, CA). Sections were then sequentially incubated in secondary biotinylated antirabbit antibody, in biotin-avidin amplification system, and finally with diaminobenzidine (DAB) substrate. The sections were counterstained with 0.1% methylene blue for tissue morphology, dehydrated with xylene, and mounted using Entelan. Tissue sections treated with DNase for 30 min served as positive controls for detecting DNA fragmentation and negative controls included tissue sections processed with 10% FCS and antibiotics (100 IU/mL penicillin and 100 μg/mL streptomycin), served as normal controls. All cells were maintained in DMEM supplemented with 10% FCS and antibiotics (100 IU/mL penicillin and 100 μg/mL streptomycin).

**Cell transfection and transduction.** TRIP-GFP, a gift from Pierre Charneau, is a lentiviral HIV-1–derived vector expressing enhanced green fluorescent protein (EGFP) from the cytomegalovirus immediate-early promoter (20). Syndecan-2 sequence was subcloned into this vector, replacing the GFP sequence between the promotormRNA sequences. Syndecan-2 was produced was solubilized in DMSO and absorbance measured at 540 nm. Statistical analysis. Each experiment was done at least thrice each time and in triplicates. Two-tailed Student’s t test and two-way ANOVA were done.

**Results**

Osteosarcoma cells express lower syndecan-2 levels than normal osteoblasts *in vivo*. To determine whether syndecan-2 is
expressed in osteosarcomas, we immunohistochemically analyzed tissue sections from biopsies from 21 patients with well-characterized osteosarcoma. In normal bone structures present in biopsies and in sections of nontransformed adult bone, both osteoblasts and osteocytes displayed a strong staining for syndecan-2 (Fig. 1A, a, b). In contrast, in most osteosarcoma tissues, only a faint or no syndecan-2 labeling was present (Fig. 1A, c, d). When expressed at all, syndecan-2 was detected only in localized spotted areas. The proteoglycan appeared both in osteogenic and chondrogenic osteosarcomas. Syndecan-2 expression level was graded from 0.5 to 4, combining percentage and staining intensity of positive cells in cancerous bone and in normal bone. Results presented in Fig. 1B show that in 18 osteosarcomas out of 21, syndecan-2 expression was lower than in normal bone. Low levels of syndecan-2 was found both in high- and low-grade tumors (Fig. 1B). Consistent with these observations, osteosarcoma cells expressed 3- to 20-fold less syndecan-2 than normal human osteoblastic cells as measured by qRT-PCR (Fig. 1C).

**Increased syndecan-2 expression results in decreased cell motility.** A weak expression of syndecan-2 was consistently found in all subsets of analyzed osteosarcomas irrespective of classification according to the grade of the tumor (Fig. 1B), their osteogenic or chondrogenic phenotype, age of the patients, localization of the tumor, and survival status. Because syndecan-2 was previously shown to be involved in tumorigenic activity in sarcomas (12), we checked whether modulation of the expression of syndecan-2 in osteosarcoma cells affects their motility and their invasive capacity in vitro. To modify syndecan-2, we used a lentiviral vector coding the proteoglycan (TRIP-SYND2) or the control empty vector (TRIP-EV). TRIP-SYND2 allowed increasing syndecan-2 expression by 3- to 5-fold in MG63 cells and U2OS cells (Fig. 2A–C). Then, we determined the capacity of transduced MG63 and U2OS cells to migrate, in response to chemoattractant medium containing 10% FCS, through a microporous membrane or a Matrigel-coated membrane. U2OS and MG63 cells exhibited very different motility and invasive capacities. U2OS cells migrated at a high rate through the membranes. In U2OS cells, overexpressing syndecan-2 resulted in a significant decrease in the number of migrating and invading cells (Fig. 2D). Although the same trend toward decreased motility was found, TRIP-SYND2 did not significantly modify this variable in MG63 cells. This was probably due to the very low basal capacity of migration of these cells. Overexpression of syndecan-2 did not render MG63 cells competent to invade Matrigel (Fig. 2D).

**Syndecan-2 expression in osteosarcoma tissues is related to the level of basal apoptosis.** To determine whether expression of syndecan-2 in vivo in osteosarcoma tissues is associated with apoptosis, we detected apoptotic cells in tissue slides consecutive to those used for the syndecan-2 immunostaining. We observed that most regions of the osteosarcoma tumors that exhibited no syndecan-2 staining also displayed a low number of apoptotic cells with fragmented DNA (Fig. 3A, a, b; arrowheads). In contrast, areas where syndecan-2 was detected was significantly higher number of apoptotic cells (Fig. 3A, c, d; asterisks). The number of apoptotic cells and the number of cells with immunoreactive syndecan-2 in 18 fields within different osteosarcoma tissues were enumerated. The Pearson coefficient between syndecan-2 expression and the spontaneous apoptosis that occurs in osteosarcoma was $r = 0.7$, indicating a link between syndecan-2 and occurrence of apoptosis in vivo (Fig. 3B).

**Syndecan-2 sensitizes osteosarcoma cells to cytotoxic drugs.** Together, the finding that syndecan-2 is associated with apoptosis in osteosarcoma tissues and our previous results showing that syndecan-2 is able to modify osteosarcoma cell signaling to induce cell death suggest that the proteoglycan could modulate responsiveness to cytotoxic drugs. We therefore investigated the effect of...
syndecan-2 overexpression on the induction of apoptosis by methotrexate, doxorubicin, and cisplatin in MG63 cells. These cells that express very low basal level of the proteoglycan were transduced with empty vector, TRIP-EV (a and c) or TRIP-SYND2 (b and d), and syndecan-2 level was analyzed by Western blot (A and B) and qRT-PCR (C). TRIP-SYND2 induced a significant increase in syndecan-2 expression \((P < 0.001)\). D, the effects of syndecan-2 overexpression on cell motility and invasive capacity were analyzed using transwell assays, counting the cells that migrate across a microporous membrane or across Matrigel, respectively. Columns, means; bars, SE. *, \(P < 0.01\), significant difference between cells transduced with TRIP-SYND2 and TRIP-EV.

Figure 2. Syndecan-2 overexpression in osteosarcoma cells results in decreased cell motility. MG63 and U2OS cells were transduced with empty vector, TRIP-EV (a and c) or TRIP-SYND2 (b and d), and syndecan-2 level was analyzed by Western blot (A and B) and qRT-PCR (C). TRIP-SYND2 induced a significant increase in syndecan-2 expression \((P < 0.001)\). D, the effects of syndecan-2 overexpression on cell motility and invasive capacity were analyzed using transwell assays, counting the cells that migrate across a microporous membrane or across Matrigel, respectively. Columns, means; bars, SE. *, \(P < 0.01\), significant difference between cells transduced with TRIP-SYND2 and TRIP-EV.

Knockdown of syndecan-2 results in inhibition of apoptosis induction by drugs in osteosarcoma cells. To further document the role of syndecan-2 in the apoptotic response to chemotherapeutic drugs, we used U2OS cells, which express higher level of the proteoglycan and which are more sensitive to doxorubicin and to cisplatin than MG63 cells. Indeed, very low dosages of the two drugs induced apoptosis in U2OS (Fig. 5C and D). We analyzed U2OS cell population expressing a siRNA sequence targeted against syndecan-2 (psiSYND2). In these cells, syndecan-2 level was reduced by 7- to 10-fold compared with the control cell population stably transfected with a scramble siRNA sequence (psiscramble; Fig. 5A and B). Inhibition of syndecan-2 expression resulted in a clear decrease in U2OS sensitivity to doxorubicin and cisplatin.

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Figure 3. Syndecan-2 expression in osteosarcoma tissues is related to the level of basal apoptosis. A, apoptotic cells were stained using an in situ TdT-mediated nick-end labeling assay in paraffin-embedded tissue sections of osteosarcoma tumors. Fragmented DNA in nuclei of apoptotic cells appears as a brown staining. The corresponding fields were located in adjacent tissue sections stained for syndecan-2 by immunohistochemistry. Representative fields with (*) or without (arrowheads) syndecan-2 expression (b and d) and the corresponding fields stained for apoptotic cells (a and c). B, the number of apoptotic cells and syndecan-2-positive cells in the corresponding fields of adjacent tissue slides was counted. \(r\) is the Pearson correlation coefficient.
from the same patient (Fig. 6A). In three other patients, a very weak or no difference in the syndecan-2 level was found in tissues obtained before and after treatment (data not shown). A striking result was that the increased syndecan-2 expression after induction chemotherapy was associated with the strongest histologic responses (50% and 42% of necrotic cells present after treatment in tumors) compared with the three patients characterized as very poor responders (20%, <10%, and <10% of necrotic cells, respectively) and who did not display any change in syndecan-2 expression postchemotherapy. These results suggest that the cytotoxic activity of the chemotherapeutic drugs may be associated with an induction of syndecan-2 in osteosarcoma. To confirm this finding, we measured syndecan-2 mRNA expression in osteosarcoma cells after 24-h exposure to various concentrations of

(Fig. 5C and D). These results suggest that syndecan-2 contributes to drug-induced apoptosis.

The cytotoxic action of chemotherapeutic drugs is associated with increased syndecan-2 expression. Although syndecan-2 seems to be crucial for the cytotoxic activity of doxorubicin and cisplatin in U2OS cells as well as rendering MG63 cells sensitive to methotrexate, there was no clear correlation between the level of syndecan-2 found in tumors and the histologic response to chemotherapy as evaluated in situ by the pathologists (Fig. 1B). We therefore investigated whether chemotherapeutic drugs could modify syndecan-2 expression. We examined the presence of immunoreactive syndecan-2 in biopsies and in corresponding osteosarcoma tissues obtained from the surgical resection after a preoperative chemotherapy in five patients. We found that the level of syndecan-2 was higher in two samples of postchemotherapy-resected tumors compared with biopsies obtained pretreatment

![Figure 5. Syndecan-2 silencing results in inhibition of apoptosis induction by drugs in osteosarcoma cells. U2OS cells were transfected with psiRNA plasmid containing a sequence coding for siRNA against syndecan-2 (psi SYND2) or a scrambled sequence as control (psi Scramble) and selected for stable expression. The level of syndecan-2 in transfected cells was determined by Western blot (A) and qRT-PCR (B). C and D, apoptosis induced by cisplatin or doxorubicin was measured by colorimetric detection of Apop percentage dye uptake in psi Scramble– and psi SYND2–expressing cells. Points, mean; bars, SE. The slopes of the regression lines for the two conditions (psi Scramble and psi SYND2) differ significantly (P < 0.001).](image)
methotrexate or doxorubicin. In MG63 and U2OS cells, methotrexate did not alter syndecan-2 expression. In contrast, doxorubicin induced a significant increase in syndecan-2 RNA (Fig. 6B). Syndecan-2 induction by doxorubicin was dose dependent in both cell lines and was of a greater magnitude in U2OS cells compared with MG63 cells. Experiments to evaluate the effect of the two drugs on cell viability in the same conditions indicated that the induction of syndecan-2 was related to the cytotoxic activity of the drugs in both MG63 and U2OS cells. Although methotrexate did not modify the viability of the two cell lines, doxorubicin induced a dose-dependent decrease in cell viability that was proportionately greater in U2OS than in MG63 cells (Fig. 6C). Overall, these results show that chemotherapeutic drugs are able to induce syndecan-2 expression in vivo and in vitro and that the induction of syndecan-2 may correlate with the cytotoxic effect of the drugs.

Discussion

Osteosarcoma is the most common malignant bone tumor in children (1, 2). Recent improvements in its treatment have resulted in long-term disease-free survival rates approaching 70% in patients with localized disease. However, a large portion of patients do not respond to chemotherapy protocols and go on to develop metastasis. These patients are at a higher risk of relapse and poor outcome. Intensified chemotherapies failed to overcome the tumor resistance in poor responders (21). Thus, it is crucial to understand the mechanisms that support this resistance to chemotherapy and to identify new targets to improve the management of osteosarcomas. In this study, we identified syndecan-2 as a new factor mediating basal and drug-induced apoptosis in osteosarcoma tissues and cells.

We show here that osteosarcoma tissues express very low levels of syndecan-2 compared with osteoblasts and osteocytes in normal bone. Consistent with this observation, we also found that cultured osteosarcoma cells produce low levels of syndecan-2 compared with normal human osteoblastic cells. Although the exact function of syndecan-2 in osteoblastic cells is not yet elucidated, reduced level of the proteoglycan could reflect a relatively undifferentiated phenotype in osteosarcomas. In support of this hypothesis, undifferentiated human bone marrow stromal cells (22) express lower syndecan-2 levels compared with more differentiated osteoblastic cells (data not shown). Moreover, syndecan-2 expression increases during conversion of myoblasts to osteoblasts in response to bone morphogenetic protein-2, suggesting that syndecan-2 expression is induced during osteogenic differentiation (23). Thus, the low expression of syndecan-2 may be an important event in osteosarcoma biology because terminal osteoblast differentiation is inhibited in osteosarcoma with decreased RUNX-2 and Osterix expression (24, 25) and because there is an inverse relationship between osteoblastic differentiation and tumorigenesis (24). Alteration of syndecan-1 expression was described in tumoral tissues and associated with loss of an antitumoral activity. For example, syndecan-1 was found to be down-regulated during epithelial cell transformation, resulting in the loss of the epithelial phenotype and acquisition of an invasive and metastatic phenotype (26, 27). We report here that overexpression of syndecan-2 results in decreased number of migrating and invading U2OS cells and does not render MG63 cells competent to invade Matrigel. These data support an antitumoral role for syndecan-2 in osteosarcoma. This is in contrast with the tumor promoter function that was described for the proteoglycan in colon cancer cells (28), but is in agreement with its ability to

Figure 6. Syndecan-2 expression can be induced in osteosarcoma tissues and cells after chemotherapy. A, syndecan-2 level was determined by immunohistochemistry in osteosarcoma tissue sections obtained before and after preoperative chemotherapy in two patients. Syndecan-2 staining was increased after chemotherapy. B, syndecan-2 mRNA level was determined by qRT-PCR in MG63 and U2OS cells treated by grading doses of methotrexate or doxorubicin (top). GAPDH served as reference gene. Columns, mean of fold changes against nontreated cells; bars, SE. C, the effects of methotrexate and doxorubicin on cell viability were measured using a MTT assay. Results are expressed as the mean level for each condition relative to the mean value obtained for untreated cells. *, P < 0.05, significant difference between treated and untreated cells.
mediate cell binding to collagen and to inhibit cell invasion in other types of cancer cells (29).

Our finding that syndecan-2 levels correlate with spontaneous apoptosis in osteosarcoma tissues provides further support for a tumor-suppressor function for syndecan-2. This strengthens our previous in vitro data showing that syndecan-2 expression results in modifications of different signaling pathways that promote cell death (16, 17). Altogether, these data indicate that syndecan-2 is a key regulator of apoptosis in osteosarcoma cells and that low level of syndecan-2 may activate a default pathway resulting in apoptosis in these cancer cells.

Dysregulation of apoptosis due to alteration of p53 or phosphatidylinositol 3-kinase/AKT pathways or Bcl-2 overexpression have been previously shown to contribute to chemotherapeutic drug resistance, allowing cancer cells to escape stress effects induced by therapeutic agents (3). Here, we show that syndecan-2 level affects chemotherapeutic-induced apoptosis using methotrexate, doxorubicin, and cisplatin, drugs that are currently used in chemotherapy protocols to treat osteosarcoma. In MG63 cells that produce very low basal level of syndecan-2 and display none or only minimal response to the three drugs, increasing the expression of the proteoglycan results in a clear improvement in the apoptotic response to chemotherapeutic drugs. Moreover, in U2OS cells that express syndecan-2 at a higher basal level than MG63 cells, doxorubicin and cisplatin induced a much stronger apoptotic response than in MG63 cells. Silencing syndecan-2 expression in U2OS cells resulted in a clear inhibition of drug-induced apoptosis. Together, these results indicate that syndecan-2 is able to sensitize osteosarcoma cells to chemotherapy and contributes to apoptotic signaling propagation.

The level of syndecan-2 found in biopsies at diagnostic does not seem to be predictive of the histologic response to chemotherapy. However, we show here that syndecan-2 expression can be induced in osteosarcoma tissues after chemotherapy in some patients. Moreover, doxorubicin at dosages effective to reduce osteosarcoma cell viability also induced syndecan-2 expression in MG63 and U2OS cells, whereas methotrexate did not modify cell viability and syndecan-2 expression. Thus, syndecan-2 may represent a new target gene to improve chemotherapy. These data also suggest that induction of syndecan-2 is a key event mediating cytotoxic effects of chemotherapy. Consistent with our results, a positive relationship between syndecan-1 induction after chemotherapy and favorable prognosis was previously described in oral cancer (30). Others have also shown that syndecan-2 expression is decreased by interleukin-6, a cytokine that promotes osteoblastic cell survival and resistance to paclitaxel, an antimitotic agent, in osteosarcoma cells (31–33). Although larger studies are required to correlate syndecan-2 induction with various variables in osteosarcomas (grade, survival, metastasis), our data suggest that syndecan-2 may represent a new marker to evaluate the apoptotic response to preoperative chemotherapy.

In conclusion, our analysis of syndecan-2 expression in osteosarcoma tissues, supported by in vitro analysis in human osteosarcoma cell lines, clearly shows that this proteoglycan is involved in the control of cell death and affects the apoptotic response to chemotherapeutic agents in osteosarcoma.

Acknowledgments

Received 11/10/2006; revised 2/2/2007; accepted 2/14/2007.

Grant support: A Ph.D. studentship from ARC (JR/MLD/MDV/005/3) and a grant from Cancer and Solidarity Foundation, Geneva, Switzerland (A. Oroasco).

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We thank Drs. P. Charneau and E. Laplantine (Institut Pasteur, Paris, France) for the gift of the TRIP vector, Dr. B. Oyaobi (San Antonio, TX) for critical reading of the manuscript, and Prof. F. Debais (CHR Poitiers, Poitiers, France) for her help.

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