Syndecan-4 Regulates ATF-2 Transcriptional Activity in a Rac1-dependent Manner*

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Syndecan-4 is a transmembrane heparan sulfate proteoglycan that co-operates with integrins during cell-matrix interactions for the assembly of focal adhesions and actin stress fibers and in the phosphorylation of focal adhesion kinase (FAK) on Tyr397. These cellular events are regulated by the small GTPase Rho, and in the absence of syndecan-4 ligation, cellular levels of GTP-bound Rho are decreased implicating syndecan-4 in the regulation of the small GTPases. In the present study we report that, compared with wild type cells, fibronectin-adherent syndecan-4-null fibroblasts showed enhanced lamellipodia and increased Rac1 activity that could be down-regulated by re-expression of syndecan-4 in the mutant cells. Consistent with the role for Rac1 in activating p38 and JNK signaling, syndecan-4-null cells display higher levels of active p38 MAPK and JNK that were abolished by the expression of a dominant-negative RacN17 mutant. Since p38 and JNK regulate gene expression by phosphorylating and activating transcription factors, we compared both the phosphorylation state and the transcriptional activity of the ATF-2 transcription factor, as a direct p38 and JNK target in syndecan-4-null and wild type cells. In the absence of syndecan-4, both ATF-2 phosphorylation and transcriptional activity were significantly more elevated compared with wild type cells, and both activities were decreased either by the re-expression of syndecan-4 or by the expression of RacN17. Our results reveal a novel function for syndecan-4 in modulating nuclear transcriptional activity and indicate an underlying mechanism that acts at the level of Rac1-p38/JNK signaling.

The syndecans make up a family of four transmembrane heparan sulfate proteoglycans that, by virtue of their heparan sulfate side chains, can bind insoluble ligands such as extracellular matrix (ECM) molecules and soluble ligands such as growth factors (1). Of all the syndecans, syndecan-4 is the most ubiquitously expressed. Of the remaining family members, syndecan-1 is primarily expressed in epithelia, syndecan-2 in connective tissue, and syndecan-3 in nervous tissues. A number of studies have shown that syndecan-4 is important in adapting to physiological stresses. Its expression is up-regulated in response to hypoxia (2) and to mechanical stress (3, 4). Loss of syndecan-4 in mice results in defective renal function (5), increased mortality due to septic shock (6), and in delayed wound healing due to a reduction in cell migration and impaired angiogenesis in the granulation tissue (7).

A number of studies implicate syndecan-4 in the regulation of the small GTPase Rho in events associated with cell attachment and migration. First, syndecan-4 co-operates, in a Rho-mediated manner, with integrins in the assembly of focal adhesions and actin stress fibers when cells adhere to the ECM molecule fibronectin (FN) (8). Focal adhesions are macromolecular complexes that are composed of transmembrane receptors and structural and signaling cytoplasmic molecules. Integrins and syndecan-4 are the two transmembrane receptors of focal adhesions (9). Furthermore, syndecan-4 ligation is necessary for the phosphorylation of Tyr397 of focal adhesion kinase (FAK). The syndecan-4 dependent phosphorylation of FAK-Tyr397 is also Rho-dependent and we have shown that syndecan-4-null cells have reduced levels of activated Rho (10).

FAK participates in the activation of the mitogen-activated protein kinases (MAPKs) ERK and JNK (11), and integrin ligation is a critical step in these events (12–14). The activation of JNK and p38 in cells exposed to inflammatory cytokines and a variety of cellular stresses is regulated by the Rho GTPases Rac and Cdc42 but not Rho (15–17). Although a role of syndecan-4 in the activation of the three major MAPKs has not been systematically investigated, it has been shown that syndecan-4 ligation is not involved in the activation of ERK (18).

We have observed that syndecan-4-null fibroblasts plated on FN display a morphology that suggests an alteration in Rac1 signaling. Since Rac1 regulates the activation of JNK and p38, we tested the hypothesis that syndecan-4 may regulate the activity of Rac1 and the stress responsive MAPKs JNK and p38 leading to changes in nuclear signaling. We report that syndecan-4-null fibroblasts have elevated levels of GTP-bound Rac1. They also have elevated levels of the activated forms of p38, JNK, and increased ATF-2 transcriptional activity. The introduction of a dominant-negative construct of Rac1 or the re-expression of syndecan-4 in the syndecan-4-null cells lowers the activation states of the two MAPKs as well as the ATF-2 transcriptional activity.
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MATERIALS AND METHODS

Cell Culture— Fibroblasts derived from mice null for the syndecan-4 core protein gene (7) or wild type mice have been described (10). These cells are referred to as syndecan-4-WT and syndecan-4-null. Cells were maintained in Dulbecco’s modified Eagle’s medium (DMEM; Invitrogen), supplemented with 10% fetal bovine serum (FBS; Invitrogen) and 1× antibiotic-antimycotic (Invitrogen). For experimental analyses, 6 × 10^5 cells/100-mm tissue culture dishes were seeded in DMEM with 10% FBS overnight and subsequently switched to serum-free medium (SFM) for 24 h. At this point they were washed three times with phosphate-buffered saline minus calcium chloride and magnesium chloride (PBS, Invitrogen), detached with a 1:1 dilution of PBS/EDTA, and 0.05% trypsin (Invitrogen), and maintained in suspension at 37°C in SFM before plating either on tissue culture plates or on glass coverslips that were coated with 10 μg/ml of FN (BD Biosciences) diluted in PBS for 1 h at 37°C. The plates and coverslips were washed with PBS before the fibroblasts were allowed to attach and spread for the indicated time in SFM.

DNA and Viral Constructs— pCMV-SPORT6-54, a mouse syndecan-4 core protein encoding cDNA (GenBank accession number BC002312) was from ATCC. A syndecan-4 recombinant adenovirus (AdS4) was generated by subcloning the mouse cDNA for syndecan-4 into the pAdTrack-CMV expression vector, which already carries a cDNA for the GFP, and used as a shuttle vector for the generation of replication-defective adenovirus as described by He et al. (19). The plasmid expression vector for the Rac1 dominant-negative mutant RacN17 was provided by S. Gutkind (15). The fusion trans-activator plasmid pATF-2 and the reporter plasmid pPR-Luc was from Stratagene, and the reporter plasmid pRL-TK (GenBank accession number AF362545) was from Promega.

Syndecan-4 Recombinant Adenovirus Infection and Transfections—AdS4 and the control virus, AdGFP, were purified by double banding on sucrose gradients and used at a multiplicity of infection of 50. Infection of primary fibroblasts was performed in DMEM for 1 h, followed by a further incubation for 24 h in complete medium and 24 h in DMEM. Transient transfection of primary syndecan-4-WT and syndecan-4-null fibroblasts were performed with the indicated expression constructs using LipofectAMINE 2000 (Invitrogen) according to the manufacturer’s protocol, and cell extracts were analyzed after 24 h in SFM.

Immunofluorescence— Fibroblasts of both genotypes were seeded for 1 h on FN-coated glass slides, fixed and permeabilized with 4% paraformaldehyde, 0.1% Triton X-100 in PBS for 15 min, and stained for Rac1 or actin. The Rac1 monoclonal antibody (Upstate Biotechnology Inc.) was used at a 1/50 dilution. To visualize the primary antibody staining, the slides were incubated with a 1/100 dilution of Cy5-conjugated anti-mouse antibodies (Jackson ImmunoResearch Laboratories, Inc., West Grove, PA) for 45 min at 37°C. Fluorescein isothiocyanate-phalloidin (Molecular Probes) was used for actin staining according to the manufacturer’s instructions. Immunocytochemical analysis was done with a Leica TCS NT4D confocal microscope (Leica, Heidelberg, Germany). The lack of bleed-through between channels in the double labeling experiments was verified experimentally.

Rac1 Activation Assay— Levels of GTP-bound Rac1 were determined in syndecan-4-null and WT fibroblasts adherent to FN-coated tissue culture dishes using the Rac1 Activation Assay kit (Upstate Biotechnology Inc.) according to manufacturer’s instructions. Briefly, cell lysates were incubated with a fusion protein of GST with the PDB domain of human PAK-1 that selectively binds the GTP-bound form of Rac1. Bound proteins were washed and eluted with boiling sample buffer before electrophoresis on 12% SDS-PAGE. Rac1 proteins were detected by immunoblotting with a monoclonal Rac1 antibody (Upstate Biotechnology Inc.). A fraction of the cell lysates used in the Rac1 activation assay was directly assayed by immunoblotting assay normaliz-ation. The blots were washed, incubated with the appropriate secondary antibody, and developed with the West Pico chemiluminescent reagent (Pierce).

Immunodetection of Proteins— Cells were washed twice in ice-cold PBS and lysed in boiling SDS-sample buffer before electrophoresis on 12% SDS-PAGE. Rac1 proteins were detected by immunoblotting with a monoclonal Rac1 antibody (Upstate Biotechnology Inc.). A fraction of the cell lysates used in the Rac1 activation assay was directly assayed by immunoblotting assay normaliz-ation. The blots were washed, incubated with the appropriate secondary antibody, and developed with the West Pico chemiluminescent reagent (Pierce).

RESULTS AND DISCUSSION

Syndecan-4-null Fibroblasts Display Enhanced Lamellipodia, Altered Subcellular Localization of Rac1, and Increased Rac1 Activity— When syndecan-4-null and WT fibroblasts were plated on FN for 1 h, the mutant cells displayed enhanced membrane ruffles and lamellipodia compared with the WT cells. Such a cellular morphology is usually associated with Rac1 function early in the cell adhesion process (21–24). The translocation of Rac1 to the plasma membrane is essential for activating downstream effectors and important for Rac1 signaling during the adhesion of cells to the ECM (25–27). Immunocytochemical analysis for the localization of Rac1 revealed a pronounced sublocalization of the small GTPase in the membrane lamellipodia and ruffles of the syndecan-4-null cells compared with WT cells. In addition, a punctate perinuclear staining pattern of Rac1 was more pronounced in the mutant cells (Fig 1A). These data suggest a functional link between syndecan-4 and Rac1 during cell-matrix interactions. The small GTPase Rac1 cycles between a GTP-bound active and a GDP-bound inactive state (28). To test whether the altered cell morphology and localization of Rac1 in the syndecan-4-null fibroblasts reflects alterations in Rac1 activity, we analyzed the levels of GTP-bound Rac1 in syndecan-4-null and WT fibroblasts that had adhered to FN for 1 h. We found that the level of GTP-bound Rac1 in syndecan-4-null and WT fibroblasts was 4.6-fold higher in syndecan-4-null cells compared with WT cells relative to the total amount of Rac1 protein (Fig 1B). The level of GTP-bound Rac1 in syndecan-4-null cells was still elevated after 3 h of attachment to FN, whereas the level in the WT cells had diminished (data not shown). These results are consistent with the possibility that the enhanced lamellipodia in the syndecan-4-null cells are associated with an increased Rac1 activity. To test directly whether the elevated level of GTP-bound Rac1 in the syndecan-4-null cells results from the absence of syndecan-4, syndecan-4 was re-introduced in the mutant cells using an adenoviral delivery system. The effectiveness of the re-expression of syndecan-4 in syndecan-4-null fibroblasts was evident when extracts from cells infected with the AdS4 virus, but not from extracts of cells infected with the control AdGFP virus, are immunoblotted with syndecan-4 antibodies (Fig 1C). When adenovirally delivered syndecan-4 was re-expressed in the syndecan-4-null fibroblasts, the enhanced lamellipodia in the syndecan-4-null cells were not observed (Fig 1D). These results suggest that the syndecan-4-null cells generated increased lamellipodia in the presence of diminished syndecan-4 in order to maintain Rac1 activation, which is important in the early phase of cell adhesion.

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decan-4-null cells, the levels of GTP-bound Rac1 were 3.6-fold lower compared with the levels seen in mutant cells infected with the control virus (Fig. 1D). These cells also showed a concomitant decrease in lamellipodia (data not shown). These data indicate a role for syndecan-4 in modulating the activation status of Rac and its targeting to the cell membrane.

**The Levels of p38, JNK, and ATF-2 Phosphorylation Are Elevated in Syndecan-4-null Fibroblasts through a Rac1-dependent Mechanism**—The Rho GTPases play a role in transducing cell surface originated signals intracellularly and in the regulation of gene expression through the activation of the MAPKs, p38, SAPK/JNK, and ERK (15–17). Specifically, activated Rac1 has been shown to activate p38 and JNK but not MAPKs, p38, SAPK/JNK, and ERK (15–17). Consistent with the elevated levels of active p38 and JNK seen in syndecan-4-null cells, the syndecan-4-null cells exhibited a 2.7-fold higher level of ATF-2 phosphorylation levels compared with the levels in mutant cells infected with the AdS4 virus. However, actin stress fibers were absent from cells infected with the AdS4 virus. This indicates enhanced membrane ruffles and lamellipodia that depict a pronounced Rac1 sublocalization at these cellular structures in the syndecan-4-null cells compared with the WT counterparts. The images are representative of at least 30 fields analyzed for each genotype in at least three additional independent experiments. The levels of GTP-bound Rac1 and total Rac1 were analyzed in syndecan-4-WT and null fibroblasts plated on FN for 1 h. After fixation, cells were doubly stained for actin fibers (green) and Rac1 protein (red) with fluorescein isothiocyanate-conjugated phalloidin and Rac1 antibodies followed by TRITC-conjugated secondary antibodies (Rac1), respectively. Arrows indicate enhanced membrane ruffles and lamellipodia that depict a pronounced Rac1 sublocalization at these cellular structures in the syndecan-4-null cells compared with the WT counterparts. The images are representative of at least 30 fields analyzed for each genotype in at least three additional independent experiments.

B. The level of GTP-bound Rac1 in syndecan-4-null fibroblasts was detected by antibody against Rac1. A fraction of the lysates used for the pull-down assay were processed for the Rac1 pull-down assay, and the amounts of GTP-bound Rac1 were 3.6-fold higher compared with the levels seen in mutant cells infected with the AdS4 virus. Loading equivalence was assessed from re-probing the same membranes with antibodies against actin (Actin). C. Validation of the syndecan-4 adenoviral delivery system. Syndecan-4-null cells were infected with an adenoviral vector harboring the mouse syndecan-4 core protein cDNA (AdS4) or with a control adenovirus that harbors the green fluorescent protein cDNA (AdGFP). WT cells were infected only with AdGFP, 48 h after infection, cells were lysed, and where indicated (+), cell lysates were digested with heparitinase (Hep-ase) to remove the heparan sulfate side chains. The core protein was visualized by immunoblotting with anti-syndecan-4 antibodies (Syndecan-4). Adenovirally delivered syndecan-4 core protein was evident in the heparitinase treated syndecan-4-null lysates, whereas the protein was absent from cell lysates infected with the AdGFP. Endogenous syndecan-4 core protein was also evident in the heparitinase-treated lysates of the WT cells infected with the control AdGFP virus. Loading equivalence was assessed from re-probing the membrane with antibodies against actin (Actin). D. Syndecan-4-null fibroblasts were infected either with the AdGFP or with the AdS4 viruses; 48 h post-infection, cells were trypsinized and replated on FN for 1 h. Cell extracts were processed for the Rac1 pull-down assay as in B. The level of GTP-bound Rac1 was found to be 3.6-fold lower in the AdS4-infected cells compared with the same cells infected with the AdGFP control virus.

Since syndecan-4 co-operates with integrins in cells adherent to FN (8), and in light of the observation that the absence of syndecan-4 results in elevated levels of GTP-bound Rac1, we analyzed the possible contribution of syndecan-4 to MAPK signaling in cells adherent to FN for 3 h. These analyses indicated that the levels of phosphorylated, active p38 MAPK and JNK are, respectively, 2.4- and 2.2-fold higher in cells lacking syndecan-4 compared with WT cells (Fig. 2, A and B). These results suggest that syndecan-4 signaling may negatively regulate the stress-activated p38 and JNK MAPK cascades. The activation level of ERK in syndecan-4-null cells did not differ from that of syndecan-4 WT cells in three independent tests (Fig. 2C). This observation is consistent with the results obtained by Kim et al. (18) who showed that syndecan-4 does not co-operate with integrins in modulating ERK signaling during cell-FN adhesion.

Activation of MAPKs results in their translocation to the nucleus where they phosphorylate and activate transcription factors (31–33). We tested whether the elevated levels of p38 and JNK might be reflected in changes in the activity of transcription factors. As a representative transcription factor, we analyzed the ATF-2 protein, which can be phosphorylated and activated by both p38 and JNK (34–36). For this purpose we compared syndecan-4-null and WT cells for their levels of dually phosphorylated Thr547 of ATF-2, which represent the p38 and JNK phosphorylation sites of this transcription factor. Consistent with the elevated levels of active p38 and JNK seen in the mutant cells, the syndecan-4-null cells exhibited a 2.7-fold higher level of ATF-2 phosphorylation levels compared with WT cells (Fig. 2D). The results shown in Fig. 2 were obtained with cells adherent to FN for 3 h, and identical data were obtained with cells adherent to FN for as long as 24 h or with cells seeded in serum (data not shown). An identical pattern of activation for p38, JNK, and ATF-2 is also observed between syndecan-4-null and WT cells transfected with an empty expression vector and subjected to the same culture conditions. Under these conditions the levels of activation for p38, JNK, and ATF-2 in the syndecan-4-null cells were 3.1, 2.1, and 2.2, respectively, compared with WT cells (Fig. 3, A–C). These data suggest a novel role for syndecan-4 in the integration of signals from the cell surface to the nucleus at the level of MAPK signaling. To test whether the elevated level of active,
phosphorylated p38, JNK, and ATF-2 detected in syndecan-4-null cells depends on Rac1 signaling, syndecan-4-null and WT fibroblasts were transiently transfected with a dominant-negative RacN17 mutant (A′–C′). Cells were harvested after 48 h of transfection and 24 h in SFM, and cell lysates were analyzed by immunoblotting with phospho-specific antibodies for the activated forms of p38 (P-p38), JNK (P-JNK), ATF-2 (P-ATF-2) (upper panels) or antibodies directed against the corresponding total proteins (p38, JNK, ATF-2) (lower panels).

ATF-2 Transcriptional Activity Is Elevated in Syndecan-4-null Cells—To verify whether the increased Thr^69/71 phosphorylation of ATF-2 in the syndecan-4-null cells represents an increase in ATF-2 dependent transcription, we quantified the transcriptional activity of ATF-2 in syndecan-4-WT and null fibroblasts using a luciferase-based assay. Syndecan-4-null cells showed a 6.7-fold increase in ATF-2-dependent luciferase activity compared with WT cells (Fig. 3A, A′–C′). Thus, the elevated levels of activated p38, JNK, and ATF-2 seen in syndecan-4-null cells depend on Rac1 signaling.

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ATF-2 Transcriptional Activity Observed in the Mutant Cells—To assess whether the elevated ATF-2 activation and transcriptional activity seen in syndecan-4-null cells is truly syndecan-4-dependent, we measured ATF-2 phosphorylation and transcriptional activity in syndecan-4-null cells in which syndecan-4 was re-expressed either by infection with the AdS4 virus or by transient transfection with a plasmid expression vector that harbors the mouse syndecan-4 cDNA. The re-expression of syndecan-4 in the mutant cells resulted in a 2.1-fold reduction of Thr^69/71 ATF-2 phosphorylation compared with control virus-infected cells (Fig. 4C). In the experiments designed to measure the effect of re-expressing syndecan-4 on ATF-2 transcriptional activity we observe a 6.6-fold higher activity in the mock-transfected syndecan-4-null cells compared with mock-transfected WT cells. Upon transfection of the syndecan-4 construct,
we observed a reduction in ATF-2 activity to 0.45 in the WT cells and to 2.45 in the syndecan-4-null cells relative to the levels measured in the mock-transfected WT cells (Fig. 4D). The reduction in ATF-2 transcriptional activity seen in the mutant cells has not reached levels of activity seen in WT cells. This may result from a limited efficiency of syndecan-4 expression by transient transfection. Consistent with this view is the observation that when mutant cells are transfected with a lower concentration of the syndecan-4 construct, we observe less of a reduction in ATF-2 transcriptional activity. Together, these results indicate that the elevated levels of ATF-2 phosphorylation and transcriptional activity in syndecan-4-null fibroblasts are substantially diminished by the re-expression of syndecan-4.

Conclusion—In the present study we have demonstrated that fibroblasts that lack syndecan-4 have elevated levels of GTP-bound Rac1 and as a result elevated levels of the activated forms of the stress-activated MAPKs p38 and JNK and the transcription factor ATF-2. We also demonstrate an increased transcriptional activity of ATF-2. ATF-2 is a transcription factor that is involved in a number of biological functions such as growth factor signaling, cell cycle regulation, differentiation, and in the regulation of stress responsive genes (34). The syndecan-4-dependent, and Rac1-mediated, regulation of ATF-2 transcriptional activity represents a novel function for this cell surface proteoglycan.

There is increasing evidence that suggests that syndecan-4 mRNA and syndecan-4 levels are up-regulated in physiological stress situations. In addition, in the absence of syndecan-4 there is a decreased ability of adapting to physiological stress situation (reviewed in Ref. 9). It is tempting to speculate that the elevated levels of GTP-bound Rac1, p38, JNK, and ATF-2 in the syndecan-4-null cells documented in the present study may be a reflection of a deregulation of signaling pathways that are normally controlled by syndecan-4 during stress situations. The exact mechanisms of such regulation remain to be elucidated.

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