Syndecan 3 Intramembrane Proteolysis Is Presenilin/γ-Secretase-dependent and Modulates Cytosolic Signaling*

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The syndecans play critical roles in several signal transduction pathways. The core proteins of these heparan sulfate proteoglycans are characterized by highly conserved transmembrane and intracellular domains which are required for signaling across the membrane and for interaction with cytosolic proteins. However, regulatory mechanisms controlling these functions remain largely unknown. Here we show that, upon ligand-induced primary proteolytic cleavage within the ectodomain, the intracellular domain of syndecan 3 is released by regulated intramembrane proteolysis. The cleavage is mediated by presenilin/γ-secretase complex and negatively regulates the plasma membrane targeting of the transcriptional cofactor CASK.

Heparan sulfate proteoglycans (HSPG)† are present on the surface of all adherent cells. Binding to a large number of ligands depends upon highly charged heparan sulfate chains, linear polysaccharide chains that can be modified by sequential enzymatic modifications. These modifications lead to enormous structural diversity (for review see Ref. 1). Although numerous functions for the heparan sulfate moiety of proteoglycans have been shown in vivo and in vitro, the roles of the core proteins remain largely elusive (2, 3). The syndecan family of HSPG, as opposed to the GPI-anchored glypicans or matrix-associated HSPG, contains a transmembrane and cytosolic domain that is highly conserved across homologues and species, suggesting an important role for this part of the protein (4). Indeed, a role in FGF signaling, neurite outgrowth, dendritic spine morphogenesis, and left-right axis formation has been demonstrated (5–8), but the regulatory mechanisms are incompletely understood. The cytosolic domain can be subdivided into a membrane-proximal C1 and a C-terminal C2 conserved region that is nearly identical in all syndecans and has a more variable V region in the middle. The most conserved residues are serines and tyrosines that at least partially undergo phosphorylation, a basic motif that binds nonreceptor tyrosine kinases and cytoskeletal proteins, and the C terminus that is required for interaction with PDZ proteins such as syndenin, CASK, synectin, or syndibin (for review see Ref. 4).

The heparan sulfate-bearing syndecan ectodomain has been shown to undergo ligand-activated or stress-induced proteolytic cleavage and shedding (9–11), but the fate of the C-terminal fragment (CTF) that remains associated with the membrane is unknown. We surmised that the remaining CTF is subject to further proteolytic degradation, ectodomain-shedding being a first step in an intracellular signaling cascade. Because regulated intramembrane proteolysis, a novel mechanism of signal transduction across the membrane (12), has been demonstrated to depend upon prior ectodomain cleavage of type I transmembrane protein substrates (13–22) and is mediated by presenilins (PS) as part of a larger so-called γ-secretase complex (23), we investigated whether syndecan 3 undergoes PS-dependent cleavage.

EXPERIMENTAL PROCEDURES

Materials—Pleiotrophin was purchased from R+D systems, lactacystin and threonine receptor agonist peptide from Calbiochem, ω-phenanthrolin, phorbol 12-myristate 13-acetate, carbacol, insulin-like growth factor II, platelet-derived growth factor AB, and forskolin from Sigma, FuGENE 6, bFGF, and epidermal growth factor from Roche Applied Science, and enterokinase from Invitrogen. The γ-secretase inhibitor was an aspartyl protease transition-state analog inhibitor (24).

Cell Culture—Generation and genotyping of PS1−/−, PS2−/−, and PS1−/−PS2−/− mice and corresponding simian virus 40 large T antigen-transformed MEFs were described before (13, 14, 25). Primary MEFs were derived from E17 embryos and used after one passage. All cells were kept in Dulbecco’s modified Eagle’s medium/P12 with 10% fetal calf serum. For serum starvation, cells were kept in Dulbeco’s modified Eagle’s medium/P12 overnight.

Immunoprecipitation—Cells were lysed in 1% Triton X-100, 10 mM Tris, pH 8.0, 140 mM NaCl, 0.025% NaN₃, complete protease inhibitor tablet (Roche Applied Science) for 30 min at 4 °C and spun for 15 min at 13,000 × g. Supernatants containing equal amounts of protein were incubated for 90 min with mAb 2E9-Sepharose beads (26). Beads were washed, and bound antigen was eluted in boiling sample buffer. For
RESULTS

Presentin-dependent Turnover of Syndecan CTF—First, we probed for endogenous syndecan CTF in PS1+/-, PS1-/-, and PS1-/- primary fibroblasts derived from littermate embryos, using the syndecan1/3 C terminus-specific monoclonal antibody 2E9 (26). Although the amount of full-length syndecan core protein was unchanged (SDS-stable dimers of syndecan 1 (S1) and 3 (S3) running at 80 and 120 kDa, respectively), CTFs of 10 and 12 kDa accumulated in large amounts in all PS1-/- fibroblast lines (Fig. 1A). The appearance of CTFs with different mobility might be due to posttranslational modification or to alternative ectodomain cleavage sites (see also Ref. 10). Because both PS1 and -2 have been shown to be involved in intramembrane proteolysis, we investigated the relative contribution of each to syndecan processing. Syndecan CTF accumulated strongly in PS1-/- and PS1-/- PS2/-/- MEF cell lines, whereas PS2-/- cells showed only minor differences compared with wild type (WT) cells (Fig. 1B). This finding is in accordance with data on PS-dependent processing of Notch and amyloid precursor protein (APP), where the absence of PS1 also has a much more pronounced effect than that of PS2 (25, 30).

To differentiate between increased generation and decreased turnover of syndecan CTF in PS-deficient cells, we trypsinized WT and PS1-/- MEF at 4 °C to cleave cell surface syndecans, generating a pool of “trypsin-CTF” that can be differentiated from endogenous CTF by the difference in mobility (see also Ref. 10). After trypsin washout and within 60 min of incubation at 37 °C, the pool of trypsin-CTF was completely turned over in WT cells, while there was basically no turnover in PS1-/- cells (Fig. 1C). Interestingly, endogenous CTF levels are stable during the chase in WT but accumulate further in PS1-/- cells (Fig. 1C). Under the same conditions, frizzled, a seven-pass plasma membrane protein involved in Wnt signaling, did not accumulate in PS1-/- cells (not shown). The results with the trypsin-CTF indicate that syndecan CTF accumulate in PS1-deficient cells as a consequence of decreased processing and not increased generation. Consistently, immunofluorescence microscopy revealed rapid clearance of endogenous syndecan from the cell surface in trypsinized WT but not PS1-/- cells (Fig. 1D).

To prove further that the failure to cleave syndecan CTF in PS-deficient cells was the consequence of the loss of PS, we reintroduced PS1 into PS1-/- MEF. The newly expressed human PS1 protein was detected with both C- and N-terminal antibody specific for human PS1 (Fig. 1E). Confirming the role of PS, accumulation of the syndecan CTF was completely reversed in PS1-rescued but not in mock-transduced cells.

Independent evidence that syndecan is processed by the PS/γ-secretase complex was obtained with the γ-secretase inhibitor l-685,458 that binds to PS and inhibits γ-processing of APP and Notch in the nanomolar range (24). Syndecan CTF processing was inhibited at similarly low concentrations of inhibitor (Fig. 1F).

Generation of Further Syndecan Fragments—If syndecan CTFs undergo restricted intramembrane cleavage (as opposed to random degradation), two fragments of lower Mr than the CTF should be detectable in cells or media: one fragment ranging from the extracellular to the transmembrane cleavage site and a second fragment representing the released syndecan intracellular domain (SIDC) (Fig. 2A). We were not able to detect SIDC in cell extracts from MEF, even when these cells over-expressed syndecan 3 (S3-MEF). This was not entirely unexpected, because, as for other substrates γ-secretase, it is extremely difficult to detect ICD, probably because of rapid digestion.
intracellular turnover (31, 32). Yet, several groups have developed cell-free assays, allowing them to demonstrate ICD generation from APP by γ-secretase (28, 33–36). Using a similar assay for syndecan, we detected a 7-kDa fragment that was continuously released over a period of at least 4 h into the supernatant of S3-MEF membranes (Fig. 2E), suggesting that intramembrane cleavage of syndecan 3 occurs in vivo.

PS-mediated APP processing is involved in the generation of the amyloid peptide that is believed to be central in the pathological cascade causing Alzheimer’s disease (37). To analyze whether syndecan processing yields a comparable extracellular fragment, we transduced MEF with an HA-antibody in the medium of WT but not PS1−/− MEF (Fig. 2F). Although this fragment is generated by PS/γ-secretase, its apparent size is larger than expected. We surmise abnormal migration could be a consequence of the hydrophobicity of the fragment or of dimerization.

**Structural Requirements for Intramembrane Cleavage**—To demonstrate that the PS-dependent cleavage site of syndecan 3 is within the transmembrane region, we labeled S3-MEF with [35S]methionine and determined the position of the single methionine within the putative SICD relative to the N terminus of this fragment. N-terminal Edman degradation of the immunoprecipitated 7-kDa fragment released several peaks of radioactivity, encompassing cycles 6–8. This result indicates that cleavage of syndecan 3 occurs between the transmembrane amino acids Leu403, Val404, Thr405, and Leu406 (Fig. 3A). The largest peak eluted after eight cycles, indicating a major cleavage between Leu405 and Val404.

To investigate the importance of Val404 for syndecan 3 processing, we introduced a V404G mutation. A V1744G mutation at P1′ has been shown to strongly interfere with γ-secretase processing of Notch (38), whereas a V646G mutation at P1′ of APP is without effect (28, 33, 34). Surprisingly, the syndecan V404G mutation caused a marked increase in γ-secretase cleavage, as judged by an increased ratio of SICD to CTF (Fig. 3B, lane 2). It is unlikely that this effect is due to an increased SICD stability, because the experiment was performed in cell-free conditions in the presence of protease inhibitors (28).

To evaluate whether transmembrane residues remote from the predicted cleavage site influence intramembrane processing of syndecan, we mutated the highly conserved Gly396 that is...
part of a GXXXG motif located in the center of the transmembrane region. The GXXXG motif is involved in high affinity dimeric association of transmembrane helices by permitting helix proximity (39) and is also present in the dimeric association of transmembrane helices by permitting helix proximity (39) and is also present in the dimeric association of transmembrane helices by permitting helix proximity (39). 

The GXXXG motif is involved in high affinity dimeric association of transmembrane helices by permitting helix proximity (39) and is also present in the dimeric association of transmembrane helices by permitting helix proximity (39). Introducing a G396L mutation to disrupt the syndecan GXXXG motif was not sufficient to monomerize CTF (Fig. 3B, lane 3; see also Ref. 40), but γ-secretase processing became less efficient (Fig. 3B, lane 3). Additional substitutions of the two other transmembrane glycine residues did not change processing or dimerization of syndecan 3 CTF any further (Fig. 3B, lanes 4–5). Interestingly, a G → L point mutation within the GXXXG motif of a glycophorin A chimeric construct favors γ-secretase cleavage and disrupts dimerization (41).

**Ligand-induced SICD Generation**—To assess SICD release in living cells, we transiently transfected HEK293 cells with syndecan containing a Gal4BD-VP16 sequence in the cytosolic domain and a reporter vector expressing luciferase under the control of a Gal4 upstream activating sequence. Transfection of the cells with PS inhibitor dose-dependently reduced luciferase activity by 80% (Fig. 4A); treatment with the second messenger activators phorbol 12-myristate 13-acetate or forskolin caused an 18- or 28-fold increase, respectively (Fig. 4B). To test whether extracellular ligands can induce SICD generation, we used a panel of different agents. Carbachol, pleiotrophin, insulin-like growth factor II, thrombin receptor agonist peptide, and platelet-derived growth factor had no effect, epidermal growth factor caused a small but consistent 1.5-fold increase, whereas bFGF caused a 10-fold increase. To show that syndecan ectodomain release is sufficient to initiate SICD release, we introduced an enterokinase cleavage site in the ectodomain of syndecan (29). A dose-dependent effect of enterokinase in the medium on SICD generation was observed for syndecan containing an enterokinase cleavage site (Fig. 4C), but there was no effect at all for WT syndecan (not shown).

**Syndecan-processing and Subcellular Distribution of CASK**—The cytosolic multidomain protein CASK is alternatively targeted to the plasma membrane via binding to the C terminus of syndecan or to the nucleus via binding to the transcription factor thr-1 (42). CASK contains an N-terminal calcium/calmodulin-dependent kinase-like domain and a C-terminal guanylate kinase domain, both of which appear to be enzymatically inactive. Two L27 domains, a PDZ, a SH3, and a CK2 domain form the middle part of the molecule. The PDZ domain of CASK is required for syndecan binding, whereas the guanylate kinase domain is required for binding to thr-1 (42, 43). The mechanism by which the subcellular distribution of CASK is regulated remains unknown. We hypothesized that syndecan transmembrane processing might play a role in that regulation.

Therefore, we co-expressed CASK, fused to Gal4BD-VP16, with increasing doses of syndecan 3 to test whether syndecan expression reduces CASK nuclear translocation. For readout, we again used the luciferase assay. Administered in a 1:1 molar ratio, syndecan coexpression reduced CASK nuclear translocation down to 15% of control levels without ectopic syndecan expression (Fig. 5A). Consistent with a direct interaction of the two molecules, the PDZ domain was required, but, interestingly, so also was the SH3/Hook domain of CASK. Neither calcium/calmodulin-dependent kinase-like, nor L27, or guanylate kinase domains of CASK were necessary for this effect. In fact, the potency of syndecan to prevent CASK nuclear translocation did not change even in a triple deletion construct (dCamK/L27/GK) consisting of only the PDZ and SH3/Hook domains.

To show that PS-dependent transmembrane processing facilitates CASK nuclear translocation, we inhibited γ-secretase in cells expressing CASK-Gal4BD-VP16 fusion protein. Luciferase activity was dose-dependently reduced by 60% (Fig. 5B), suggesting that CASK subcellular distribution is regulated by
PS-/γ-secretase. To see whether syndecan transmembrane processing contributes to the regulation of CASK subcellular distribution, we compared the potency of full-length syndecan versus "activated" syndecan without ectodomain (NE syndecan). Syndecan without ectodomain should still bind CASK but should be less potent to keep CASK on the membrane because, due to its minimal ectodomain, it is a direct substrate of γ-secretase and turned over at a much faster rate than full-length syndecan (see Figs. 1C and 4C). Consistent with our assumption, NE syndecan at a maximum dose can bind CASK as efficiently as full-length syndecan, but it is required in doses 30-times higher than full-length syndecan to reduce soluble CASK by 50% (Fig. 5C).

DISCUSSION

The highly conserved cytosolic domains of the syndecans have been shown to play an important role in signaling across the membrane. For example, left-right development and dendritic spine morphogenesis depends upon phosphorylation of serine or tyrosine residues within the syndecan cytosolic domain, respectively (5, 6). Furthermore, the plasma membrane targeting of cytosolic proteins with a nuclear function, such as the PDZ proteins CASK or syntenin, is promoted via binding to the C terminus of syndecan. However, the regulatory mechanisms for these functions are poorly understood.

It has been shown before that syndecans are cleaved by ligand-inducible protease(s) that release the heparan sulfate-
bearing ectodomain and generate membrane-bound CTF (9–11). Our experiments now demonstrate that syndecan 3 is a
bona fide substrate for regulated intramembrane proteolysis.
Syndecan 3 CTFs are cleaved within the transmembrane re-
region by PS-dependent γ-secretase upon ectodomain shedding.
Two new fragments, putative SICD and transmembrane do-
main fragments, are generated and released from the mem-
brane. SICD generation occurs in intact cells, was detected at
endogenous levels, and was induced by extracellular ligands
and second messenger activators.

Structural Requirements for Intramembrane Cleavage—γ-
Secretase-mediated intramembrane cleavage of type I trans-
membrane proteins follows ectodomain shedding. It has been
suggested that the rate of cleavage is inversely related to
ectodomain size, whereas the amino acid sequence of the sub-
strate’s transmembrane domain influences the efficiency and
exact γ-cleavage site (41). By generating an inducible ectodo-
main cleavage site, we could demonstrate that ectodomain
 cleavage of syndecan 3 is sufficient to initiate further CTF
processing by γ-secretase. Based on the loose sequence speci-
icity of γ-secretase, the high homology of transmembrane and
cytoplasmic domains between syndecans 1–4, and the demon-
strated ectodomain shedding of syndecan 1 and 4 (10, 11), we
predict γ-cleavage of CTF derived from other syndecans as
well.

The apparent size of any full-length syndecan core protein in
SDS-gels is at least double the size that would be predicted
from the primary sequence, suggesting SDS-resistant dimer-
ization. For syndecan 3, dimerization has been demonstrated
in vitro; it requires the last four ectodomain residues and the
transmembrane region (40). Because the putative 38-amino
acid syndecan 3 ICD we detected runs at 7 kDa and syndecan
3 CFT runs at 10–12 kDa in SDS-gels, these fragments as well
may exist as dimers. Alternatively, low electrophoretic mobility
might be due to phosphorylation of highly conserved serine or
tyrosine residues (10). Dimerization of other syndecans has not
been addressed systematically, but the demonstration of a
6-kDa syndecan 1 CFT argues in favor of a monomeric synde-
can 1 CTF (10). To address the question whether dimerization
affects syndecan 3 CFT processing by γ-secretase, we disrupted
the transmembrane GXXG motif, a motif that is important for
dimeric proximity of transmembrane helices (39). Struhl
and Adachi (41) demonstrated that disruption of the GXXG motif
of glycoporin A favors PS/γ-processing in a reporter assay, but
the mutation is known to be sufficient to monomerize glycopho-
orin A. In contrast, PS/γ-processing was greatly reduced by
disrupting the transmembrane GXXG motif in syndecan 3,
while electrophoretic mobility and, therefore, dimerization was
unchanged (see also Ref. 40). Maybe PS/γ-cleavage is subject to
sterical limitations not only through ectodomain size but also
in the plane of the membrane, as it is efficient only for mono-
mers (APP and Notch) or tightly packed dimers (as shown here
for WT syndecan 3) but not for less tightly packed dimeric CFT
such as the mutant syndecan 3. In addition, no substrate with
more than one transmembrane domain has been described
until now. These data would fit the suggested ring structure
model of PS/γ-secretase (41, 44).

We also found that a V → G at P1′ abolishes γ-secretase
cleavage of Notch, whereas the same mutation does not affect
APP γ-secretase processing. We show that the V → G mutation
at P1′ of syndecan 3 even favors γ-secretase cleavage of syn-
decan 3 and conclude that valine at P1′ is neither necessary nor
necessarily in favor of processing by γ-secretase. This result is
in agreement with previous studies on APP, showing loose
sequence specificity for γ-cleavage, which seems to be deter-
mined by structural properties of the transmembrane domain
such as length or α-helix content (45–47).

Implications for Syndecan Intracellular Function—Although
the function of heparan sulfate proteoglycans has been attrib-
uted largely to the heparan sulfate chains, in syndecans it is
the cytosolic domain that is most conserved. Recent studies
have demonstrated a critical role for this domain (5, 6), al-
though the mechanisms are not clear. We were not able to
detect SICD in intact cells, nor could we detect transactivation
in a reporter assay when integrating a Gal4BD at various sites
within the syndecan cytoplasmic domain. This result suggests
rapid turnover of SICD and argues against a direct transcrip-
tional role, although we cannot exclude that a cofactor required
for stabilization and transcriptional activation, like Fe65 and
tip60 for APP (32), was missing in our cellular model.

Here we propose a role for SICD release in regulating the
subcellular distribution of CASK, similar to what has been
proposed for E-cadherin processing and α/β-catenin membrane
release (21). CASK is a multidomain cytosolic protein and
transcriptional cofactor that colocalizes with syndecan at the
plasma membrane of polarized cells (43, 48). Both proteins
could be coimmunoprecipitated from rat brain extracts (48).
Although the T-box transcription factor tbr-1 promotes CASK
translocation to the nucleus to regulate reelin expression,
syndecan has been shown to bind CASK to the plasma mem-
brane and prevent nuclear translocation even in the presence of tbr-1
(42). However, a regulatory mechanism for the differential
subcellular targeting of CASK is not known (49).

We show that syndecan-dependent CASK membrane target-
ing is modulated by γ-secretase processing of syndecan, which
may, therefore, provide such a mechanism. This does not ex-
clude other mechanisms to disrupt syndecan-CASK interaction
nor that alternative PDZ binding partners for CASK are
involved.

PDZ and SH3/Hook domains of CASK together are necessary

![Figure 5](http://www.jbc.org/Downloaded from July 22, 2018)
for CASK expression vector, G. Degeest, G. Reekmans, and I. Leenaerts for help with retroviral transduction, D. Dominguez and neuronal migration deficits (50, 51), raising the possibility that similar detrimental properties as ‘mer transmembrane processing (our data). In respect to Alzheimer-deficient activity of growth factors such as bFGF that not only

ding and provides a mechanism to terminate syndecan trans-

generation and release is a physiological mechanism that fol-

views that consider these molecules only as coreceptors. SICD

migration in the developing brain by favoring translocation of

Notch knockout animals support the idea that PS/substrates other than Notch contribute to the PS phenotype

— aggregatable and neurotoxic –secretase cleavage product of

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