Cadherins Mediate Both the Association between PS1 and β-Catenin and the Effects of PS1 on β-Catenin Stability*

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Presenilin1 (PS1), a protein involved in cellular development, forms functional complexes with β-catenin, a regulator of Wnt signaling and cell-cell adhesion. In addition, both proteins have been shown to play important roles in disease including cancer and Alzheimer disease. Although PS1 and β-catenin are found in the same complexes, it is not clear whether they bind directly to each other or a third complex component, like cadherin, may mediate their interactions. Here we show that PS1 and β-catenin form no detectable complexes in cells that express no cadherin. In contrast, these complexes are readily found in E-cadherin containing cells. Furthermore, binding of both PS1 and β-catenin to E-cadherin is necessary for the formation of PS1/β-catenin complexes. Importantly, our data show that binding of PS1 to cadherin mediates the effects of PS1 on the phosphorylation, ubiquitination, and destabilization of β-catenin. Thus, cadherins mediate both the association of PS1 and β-catenin and the effects of PS1 on the cellular levels of β-catenin.

Cytosolic β-catenin is an important mediator of Wnt signaling, a pathway that plays crucial roles in development and in disease including cancer (1). The cellular levels of this catenin are regulated by an axin-dependent multiprotein complex that includes adenomatous polyposis coli factor and glycogen synthase kinase-3β (GSK-3β). In the absence of Wnt stimulation, the axin complex promotes the GSK-3β-dependent phosphorylation at β-catenin residues 33, 37, and 41. Phosphorylated β-catenin is then ubiquitinated and degraded by the proteasome (2, 3). Binding of Wnt to its cell surface receptor results in the inactivation of the axin complex and the accumulation of cytosolic β-catenin, which then translocates to the nucleus where it activates gene transcription (4). In addition to its role in Wnt signaling, β-catenin is a component of the cadherin-based adherens junction complexes formed at cell-cell adhesion sites. β-Catenin binds the cytoplasmic domain of E-cadherin distal to the membrane at residues 833–862 and acts as a structural protein by linking cell surface cadherins to the actin cytoskeleton (5–7). By sequestering β-catenin at the membrane, cadherins affect the signaling properties of cytosolic β-catenin, which may act as a communicator between Wnt signaling and cell-cell adhesion (6–9).

Recent reports show that PS1, a protein that plays critical roles in Alzheimer disease pathogenesis, binds E-cadherin at amino acids 760–771 close to the membrane/cytosol interface (juxtamembrane region). In addition, PS1 forms complexes with the cadherin/catenin-based adherens junction at the plasma membrane where it functions to stabilize the catenin/β-catenin association and to promote cell-cell adhesion (10, 11). Under apoptotic or Ca2+-influx conditions, however, PS1 promotes cleavage of the cytoplasmic domain of cadherins and the release of the cadherin-associated β-catenin to the cytosol (12, 13). Due to the importance of both PS1 and β-catenin in cell development and in disease, their interactions and potential functional consequences have been the subject of intense investigation. PS1 has been found in multimolecular complexes with β-catenin (10, 14–17), and it has been suggested that the two proteins bind directly to each other (16). However, although the homologous armadillo proteins δ-catenin and p0071 have been found by the two-hybrid technology to bind directly to PS1 (14, 18), no clear evidence exists that β-catenin binds directly to PS1. In addition, the effects of PS1 on the stability of β-catenin have been controversial as some researchers reported that PS1 stabilizes detergent-soluble β-catenin (17), while others reported that PS1 destabilizes β-catenin and inhibits its transactivation activity (16, 19–21). Furthermore, it has been suggested that the complexes between FAD mutants of presenilin and β-catenin play a part in the pathogenesis of FAD (22) and that FAD mutations reduce the ability of PS1 to stabilize β-catenin (17). Additional reports suggest that PS1 facilitates β-catenin phosphorylation and degradation independent of the Wnt-controlled axin complex (23). However, since both PS1 and β-catenin bind at distinct sites of the cytoplasmic domain of cadherins (11, 12), we examined the role cadherins may play in the association of PS1 and β-catenin. Our data show that cadherins are necessary for this association. Furthermore, binding of both PS1 and β-catenin to E-cadherin is necessary for the formation of PS1/β-catenin complexes. Importantly, E-cadherin mediates the effects of PS1 on β-catenin phosphorylation, ubiquitination, and destabilization.

EXPERIMENTAL PROCEDURES

Antibodies and Plasmids—Mouse monoclonal antibody 33B10 against residues 331–350 of the large loop of PS1 has been described (10). A polyclonal antibody against PS1 C-terminal fragment (PS1/CTF) purchased from Sigma was used to detect PS1 in cell lysates. Antibodies to β-catenin, p0071, and wild type.

1Cell Culture and Transfections—all cell lines were grown in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine

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Cadherin Is Required for PS1/β-Catenin Interaction

serum, penicillin, and streptomycin in 5% CO₂ at 37 °C. Transfection of the cells was done using either Lipofectamine (Invitrogen) for A431D cells or FuGENE (Roche Diagnostics) for the Phoenix α cells according to the recommended protocols. For retroviral gene transfer of pMX vectors, vesicular stomatitis virus glycoprotein pseudo-typed murine leukemia virus particles were prepared using Phoenix α cells according to standard procedures. For transduction target cells (6 x 10⁶ cells/60-mm dish) were incubated with the virus particles for 6–8 h in the presence of polybrene (10 μg/ml). 48 h after transduction GFP-positive cells were sorted using a MoFlo cell sorter.

Cell Lysis for β-Catenin Determination—to assess the PS1 effect on the amount of detergent soluble β-catenin, cells were lysed in 1% CHAPS lysis buffer or 1% SDS containing 50 mM Tris (pH 8.0), 150 mM NaCl, 0.02% sodium azide, 200 mM microcystin-LR, 0.5 mM sodium vanadate, and 1× protease inhibitor mixture (Roche Diagnostics). Lysates were incubated with rotation for 2 h at 4 °C and centrifuged at 16,000 x g for 20 min at 4 °C. The supernatant was collected, and protein concentration was determined. Soluble β-catenin antibody.

Western Blots (WBs) and Immunoprecipitations—For Western blot analysis cells were washed with PBS and solubilized in 1% SDS solubilization buffer. For immunoprecipitation, cells were solubilized in HEPES buffer (25 mM HEPES (pH 7.4), 150 mM NaCl, 1× complete protease inhibitor mixture), containing 1% Triton X-100. Following centrifugation at 16,000 x g for 10 min, supernatants (2–3 mg of protein) were precleared with either non-immune serum and Protein A or Protein G (Pierce) for 2 h at 4 °C. Supernatants were incubated with antibodies overnight at 4 °C and treated for 2 h with Protein A or Protein G. Immunoprecipitates were washed with HEPES buffer containing 1% Triton X-100 and analyzed by SDS-PAGE as described (10, 11).

β-Catenin Ubiquitination—Cells treated with Me₂SO, 30 μM MG132, or 10 μM lactacystin were lysed in buffer A (100 mM Tris-HCl (pH 7.4), 0.25 M sucrose, 2 mM EDTA, 10 mM EGTA, 5 mM sodium vanadate, 20 mM sodium fluoride, 1 mM sodium pyrophosphate, 0.1 μM microcystin, and 1× protease inhibitor mixture), and the extent of β-catenin ubiquitination was assayed as described (23). Briefly, cell lysates were passed 10 times through each needle of 19, 22, and 25 gauge and centrifuged at 500 x g for 10 min at 4 °C. The resulting supernatants were centrifuged at 120,000 x g for 45 min at 4 °C to separate the cytosolic and crude membrane fractions. The cytosolic fraction was subjected to IP using anti-β-catenin antibodies and analyzed on Western blots for ubiquitin or β-catenin. The crude membrane fraction was washed twice with buffer A, resuspended by sonication in buffer A containing 1% Triton X-100, and incubated at 4 °C for 30 min. The suspension was centrifuged at 120,000 x g for 45 min at 4 °C to isolate the membrane fraction from Triton X-100-insoluble fraction. The membrane fraction was subjected to immuno blot with anti-PS1 antibody 33B10. Each experiment has been replicated at least twice.

RESULTS

E-cadherin Is Necessary for the Association of PS1 with β-Catenin—To examine the role cadherins may play in the association of PS1 with β-catenin we used the cadherin-negative cell line A431D (25) and asked whether PS1 and β-catenin are able to form complexes in the absence of cadherins. Since cells depleted of cadherins contain no detectable levels of β-catenin (25), we transfected A431D cells with the missense β-catenin mutant S33Y that is stable in the absence of cadherins. This mutant binds cadherins and has been used in β-catenin transactivation assays (26). Co-immunoprecipitation (co-IP) experiments (Fig. 1, a and b, lanes 1–3) showed that A431D cells expressing exogenous β-catenin contain no detectable PS1/β-catenin complexes. In contrast, reintroduction of WT E-cadherin in A431D cells (A431D-E) stimulated the formation of β-catenin complexes with both PS1 and E-cadherin (Fig. 1a, lanes 4–6) as well as the formation of PS1 complexes with E-cadherin and β-catenin (Fig. 1b, lanes 4–6). To examine whether binding of PS1 to E-cadherin plays a role in the association between PS1 and β-catenin, we transfected A431D cells with E-cadherin mutant 761 (A431D-E/761). This mutant contains a three-amino acid change (GGG759–761AAA) in the juxtamembrane region of the cytoplasmic domain of E-cadherin and is unable to bind PS1 (12). Fig. 1a, lanes 7–9, shows that although E-cadherin mutant 761 binds to β-catenin, no complexes are found between β-catenin and PS1. Furthermore, PS1 immunoprecipitates (IPs) contained neither β-catenin nor mutant E-cadherin (Fig. 1b, lanes 7–9). Since the E-cadherin-expressing A431D-E and A431D-E/761 cells contain detectable levels of endogenous β-catenin, we compared the levels of PS1/β-catenin complexes in these cells in the absence of exogenous β-catenin. In agreement with a critical role of the cadherin/PS1 binding, endogenous β-catenin associates with PS1 in A431D-E cells but not in A431D-E/761 cells (data not shown). Together, these data suggest that cadherins promote the association of PS1 and β-catenin and that binding of PS1 to cadherin may be critical for the formation of PS1/β-catenin complexes.

To exclude the possibility that our results are cell- or construct-specific we examined this question in L cells, a cadherin-negative cell line (5, 27, 28) transfected either with WT E-cadherin or with E-cadherin deletion mutant EΔ760–771 (Fig. 2a; see also Ref. 28). This mutant is also unable to bind PS1, but it still binds β-catenin (11). Fig. 2b shows that in the presence of WT E-cadherin, β-catenin forms complexes with both E-cadherin and PS1 (lanes 1–3). In the presence of the E-cadherin

![Figure 1](http://www.jbc.org)
mutant $\Delta 760–771$, however, $\beta$-catenin is unable to associate with PS1, although $\beta$-catenin still binds the mutant cadherin (Fig. 2b, lanes 4–6). Together, these data show that the cadherin/PS1 binding is critical for the formation of PS1/\(\beta\)-catenin complexes.

We next asked whether E-cadherin binding to $\beta$-catenin is necessary for the formation of PS1/\(\beta\)-catenin complexes. To answer this question we transfected the cadherin-negative L cells with E-cadherin mutant $\Delta 71$ lacking the 71 C-terminal amino acids that are critical for $\beta$-catenin binding (Fig. 2a). This mutant binds PS1 although it is unable to bind $\beta$-catenin (11, 27, 28). Co-IP experiments showed that $\beta$-catenin forms complexes neither with the mutant cadherin nor with PS1 (Fig. 2, lanes 7–9). That E-cadherin mutant $\Delta 71$ binds PS1 (11) even though it is unable to bind $\beta$-catenin independently of $\beta$-catenin. Conversely, E-cadherin mutants 761 and $\Delta 760–771$ bind $\beta$-catenin, although they are unable to bind PS1 (Fig. 1b, lanes 7–9, and Fig. 2b, lanes 4–6). Together, our data show that E-cadherin binds $\beta$-catenin and PS1 independent of each other and that E-cadherin binding to both PS1 and $\beta$-catenin is necessary for the formation of PS1/\(\beta\)-catenin complexes suggesting that cadherin organizes the PS1/\(\beta\)-catenin association.

Binding of PS1 to E-cadherin Mediates the Effects of PS1 on $\beta$-Catenin Destabilization—Recent reports show that PS1 destabilizes the detergent-soluble pool of $\beta$-catenin (16, 19–21). Our data that cadherins mediate the PS1/\(\beta\)-catenin association suggest that cadherins may play a critical role in the transmission of the PS1 effects on $\beta$-catenin, and Fig. 2a shows that exogenous PS1 reduces the levels of detergent-soluble $\beta$-catenin in A431D-E cells. These data are in agreement with recent reports that PS1 suppresses the levels of cellular $\beta$-catenin (16, 19, 23). In contrast, in A431D-E/761 cells that express mutant E-cadherin, PS1 has no effect on $\beta$-catenin levels (Fig. 3, b and c). These data indicate that binding of PS1 to cadherin may be crucial for the transmission of the PS1 effects on $\beta$-catenin stability. Recently it was reported that PS1 mutant $\Delta 330–360$ is able neither to associate with $\beta$-catenin nor to promote its degradation (Ref. 19; see also Fig. 3a, lane 3). Fig. 3d shows that this mutant is also unable to bind E-cadherin, a result consistent with the requirement of a cadherin/PS1 binding for the PS1-induced degradation of $\beta$-catenin. The negative effects of PS1 on $\beta$-catenin stability are not an artifact of the overexpression of PS1 because down-regulation of PS1 activity in PS1−/− cells results in increased $\beta$-catenin, but not $\gamma$-catenin, levels (Fig. 3e), a result consistent with the reported suppression of $\beta$-catenin by PS1 (23).

E-cadherin Mediates the Effects of PS1 on $\beta$-Catenin Phosphorylation and Ubiquitination—Recent evidence indicates that PS1 promotes the proteasomal degradation of $\beta$-catenin by facilitating a GSK-3$\beta$-dependent phosphorylation of $\beta$-catenin at residues 33, 37, and 41 (23). To examine whether PS1 binding to cadherin is necessary for the PS1-induced phosphorylation and ubiquitination of $\beta$-catenin we used A431D-E and A431D-E/761 cells. Fig. 4a shows that WT PS1 stimulates $\beta$-catenin phosphorylation at GSK-3$\beta$-dependent sites in A431D-E cells expressing WT E-cadherin but not in A431D-E/761 cells expressing mutant E-cadherin unable to bind PS1. In addition, PS1$\Delta 330–360$ that is unable to bind E-cadherin had no significant effects on $\beta$-catenin phosphorylation (data not shown, see also Refs. 19 and 23). PS1-induced phosphorylation of $\beta$-catenin is followed by its ubiquitination and pro-
FIGURE 3. PS1 effects on β-catenin destabilization are mediated by E-cadherin. a, A431D-E cells stably expressing WT E-cadherin (lanes 1–3) were transduced with vector (lane 1), WT PS1 (lane 2), or PS1Δ330–360 (lane 3). Cell extracts were prepared in 1% CHAPS and probed on Western blots for the proteins indicated at the right of figures. WTPS1 in lanes 1 and 2 were detected with antibody 33B10. PS1Δ330–360 in lane 3 was detected with Sigma antibody (see “Experimental Procedures”). b, A431D-E/761 cells expressing mutant E/761 were transduced either with vector (lane 1) or WT PS1 (lane 2). Cell extracts prepared as above were probed on WBs for the proteins indicated at the right of figures. PS1 was detected with antibody 33B10. c, densitometric quantification of β-catenin amounts from three independent experiments as described in a and b. Bars represent the mean ± S.E.; *, p < 0.05 (Student’s t test). d, cell extract prepared from A431D-E cells transduced either with WT PS1 or PS1Δ330–360 were IP with anti-PS1 antibodies or with non-immune serum (NI), and the resulting IPs were probed on Western blots with anti-E-cadherin (upper panel) or anti-PS1 (lower panel) antibodies. e, cell lysates from PS1+/+ or PS1−/− mouse fibroblasts prepared in 1% SDS were probed on WBs for β-catenin (upper panel) or γ-catenin (lower panel).
FIGURE 4. Effects of PS1 on β-catenin phosphorylation and ubiquitination are mediated by E-cadherin. a, A431D cells stably transfected with WT E-cadherin (lanes 1 and 2) or with E-cadherin mutant E/761 (lane 3) were transduced with vector (lane 1) or WT PS1 (lanes 2 and 3). Extracts prepared in lysis buffer (100 mM Tris-HCl (pH 7.5), 3% SDS, 8 M urea, 250 mM EDTA) were probed on Western blots using antibodies specific to P-33/37/41 β-catenin (upper panel), total β-catenin (middle panel), or PS1 (lower panel). For lanes used to detect phosphorylated and total β-catenin (upper two panels), the amounts of lysate loaded on each lane was adjusted so that all lanes contained similar levels of β-catenin. In last panel (panel 3) all lanes contained the same amount of lysate. b, A431D-E cells expressing WT E-cadherin (lanes 1–4) or A431D-E/761 cells expressing mutant E-cadherin (lanes 5 and 6) were transduced either with vector (lanes 1 and 2) or with WT PS1 (lanes 3–6). Confluent cultures were then treated for 100 min either with Me2SO (lanes 1, 3, and 5) or with 30 μM MG132 (lanes 2, 4, and 6). Cells were then lysed and separated into cytosolic and crude membrane fractions (see “Experimental Procedures”). Cytosolic fractions were IP with anti-β-catenin antibodies and analyzed on WBs for ubiquitin (upper panel) or for β-catenin (middle panel). Membrane fractions were treated with 1% Triton X-100, and the resulting detergent-soluble fractions were probed on WBs for PS1 (lower panel). c, A431D-E (lanes 1 and 2) or A431D-E/761 (lanes 3 and 4) cells transduced with WT PS1 were treated for 100 min either with Me2SO (lanes 1 and 3) or with 10 μM lactacystin (lanes 2 and 4). Cells were lysed, and cytosolic β-catenin was IP and analyzed for ubiquitin (upper panel) or for β-catenin (lower panel) as described above.

Discussion

Recent studies revealed that PS1, β-catenin, and cadherins form complexes with important functions in cell development and in disease including cancer and Alzheimer disease (1, 8). Consequently, the exact structure, composition, and functions of the PS1/cadherin/β-catenin complexes have been the subjects of intense investigation. It has been suggested that PS1 binds β-catenin and promotes its degradation thus inhibiting β-catenin transactivation (16, 19–21, 23). However, the mechanism of PS1/β-catenin association is not clear and no evidence of a direct PS1/β-catenin binding has been presented. Since both PS1 and β-catenin bind cadherins at distinct sites (11, 12), we examined the role cadherins may play in the structure of the cadherin/β-catenin/PS1 complex. Our data show that binding of both PS1 and β-catenin to cadherins is necessary for the formation of stable complexes between PS1 and β-catenin indicating that cadherins mediate the interactions of PS1 and β-catenin. Furthermore, we show that binding of PS1 to cadherin is essential for the transmission of the PS1 effects on the destabilization, GSK-3β-dependent phosphorylation, and ubiquitination of β-catenin. By bringing together PS1 and β-catenin, cadherins may also mediate the effects of PS1 on β-catenin trafficking (22). Combined with recent data that PS1 forms complexes with both β-catenin and cadherins (10, 11, 12) and that PS1 binds the membrane proximal (juxtamembrane) region of cadherin (11, 12), while β-catenin binds the membrane distal cadherin sequence (5–7, 27), our data indicate that the mechanism by which PS1 transmits its effects on β-catenin phosphorylation, ubiquitination, and stability involves a complex containing all three proteins (10, 11). Furthermore, in contrast to reports that PS1 stabilizes β-catenin (17), our data provide further support for the theory that PS1 promotes β-catenin destabilization (16, 19–21).

Cadherin overexpression has been shown to antagonize β-catenin signaling in several systems (6, 29, 30), whereas reduction of cadherins in Drosophila enhances β-catenin signaling (31). Presently, however, it is not entirely clear how the functions of β-catenin in signaling and adhesion are coordinated as changes in cadherin are not always correlated with changes in β-catenin signaling (32). Our data suggest that the extent of PS1/cadherin/β-catenin association may regulate the amount of β-catenin marked for degradation, a function expected to affect β-catenin signaling. Consistent with this suggestion, in vivo data show that loss of either cadherins (31) or PS1 (21) may result in enhanced signaling of β-catenin. Although the mechanism by which the PS1/cadherin/β-catenin complex destabilizes β-catenin needs further investigation, formation of this complex seems to facilitate the post-translational modifications that mark β-catenin for degradation.
Cadherin Is Required for PS1/β-Catenin Interaction

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