p120-independent Modulation of E-cadherin Adhesion Activity by the Membrane-proximal Region of the Cytoplasmic Domain*

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Cadherins are transmembrane glycoproteins that function as Ca\(^{2+}\)-dependent cell-cell adhesion molecules and are linked to the actin cytoskeleton via catenins. Previously, we showed that although E-cadherin lacking its cytoplasmic tail is active in aggregation assays, partially truncated E-cadherin lacking the carboxy-terminal catenin-binding site is not. Contrary to this observation, a similar N-cadherin construct is found to be functional. Chimeric constructs, in which the membrane-proximal region of the partially truncated E-cadherin was replaced by that of N-cadherin, are active in aggregation assays. N-cadherin constructs in the opposite manner are nonfunctional. Although deletion of the membrane-proximal region, which eliminates the binding site for p120, results in activation of the nonfunctional E-cadherin mutant polypeptides, substitutions in the membrane-proximal region, which uncouple p120 binding, do not. The p120 uncoupling could not activate a full-length E-cadherin construct, which was β-catenin-uncoupled by amino acid substitutions in the catenin-binding site. These results indicate that the membrane-proximal region determines the activity of these cadherin constructs but that p120 does not seem directly involved in the modulation of E-cadherin activity.

The classic cadherins (e.g. E-, N-, and P-cadherins) are transmembrane proteins that function as Ca\(^{2+}\)-dependent cell-cell adhesion molecules (1–4). Ca\(^{2+}\) protects the extracellular domains of cadherins from proteolytic degradation, and this ion is necessary for their function. The extracellular domain of cadherins is responsible for specific homophilic binding (5), whereas the conserved carboxy-terminal cytoplasmic domain interacts with intracellular proteins termed catenins (6–8). Each cadherin molecule can bind to either β-catenin or plakoglobin (γ-catenin), which in turn binds to α-catenin (9–11). α-Catenin is an actin-binding protein (12) and interacts with other actin-binding proteins, i.e. α-actinin (13), vinculin (14), ZO-1 (15), and Ajuba (16). These interactions link cadherins to the actin cytoskeleton.

Partial truncation of the cytoplasmic domain of E-cadherin, which removes the catenin-binding site from the domain, results in a loss of function, despite its continued expression on the cell surface (7, 17, 18). Cells expressing E-cadherin with further deletions that eliminate the membrane-proximal region of the cytoplasmic domain showed E-cadherin-dependent aggregation (19). Thus, deletion of the membrane-proximal region results in activation of nonfunctional E-cadherin polypeptides. Consequently, it appears that the binding of the cadherin-catenin complexes to the actin cytoskeleton is not an absolute requirement for the binding activity.

The capacity of the membrane-proximal portion of the E-cadherin cytoplasmic domain to negatively regulate its aggregation activity may be due to its interaction with an intracellular partner. Since p120, which was originally identified as a Src substrate, binds to the membrane-proximal region of cadherins (19–22), p120 has been suggested to play a role in regulating the adhesive activity of cadherins. p120 likely affects the strength of cadherin-mediated cell adhesion by influencing the dimerization or clustering of cadherins or by changing the organization of the actin cytoskeleton (23–26).

Although the membrane-proximal region of cadherins and p120 appears to be important for the control of the activity of multiple cadherin family members, some reports have provided conflicting evidence with E-cadherin. A mutant VE-cadherin polypeptide lacking the carboxy-terminal catenin-binding site but still having the membrane-proximal region expressed on CHO cells is able to promote cell aggregation (27). Similarly, a C-cadherin deletion mutant retaining a juxtamembrane 94-amino-acid region of the cytoplasmic tail expressed on CHO cells displays adhesive activity (21). Although the observed differences between E-cadherin and VE- and C-cadherin may arise from the different cadherin subtypes analyzed in the different studies, this remains to be determined. Since the cell adhesion activity of cadherins is under the control of cell physiology such as protein phosphorylation (23, 24), the activity of any cadherin expressed on L cells and CHO cells could vary significantly.

It has been shown that two major cadherins in endothelial cells, VE-cadherin and N-cadherin, are differentially targeted to membranes; i.e. VE-cadherin is clustered at cell-cell junctions, whereas N-cadherin remains diffusely distributed on the cell membrane (20, 28). The membrane-proximal region of VE-cadherin has been shown to have the ability to exclude N-cadherin from intercellular junctions (20). Therefore, it is possible that the membrane-proximal region of each cadherin

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exhibits specific functional features depending on the subtype, despite a certain degree of homology.

In this study, I expressed hemagglutinin (HA)-tagged full-length, partially truncated, and tail-less N-cadherin constructs on L cells and found that each construct is active in aggregation assays. Since the partially truncated N-cadherin construct was designed to retain the cytoplasmic amino acid residues similar to the N-cadherin, it was partially truncated nonfunctional E-cadherin construct, I wanted to know the biological basis for these functional differences. A similar amount of p120 is coprecipitated with these constructs. Substitution of residues in the nonfunctional E-cadherin construct with homologous residues from functional N-cadherin demonstrated that the region containing the p120-binding site is responsible for the suppression of aggregation of truncated E-cadherin. Uncoupling of p120 binding by amino acid substitutions did not confer adhesive function, however, raising the possibility that p120 is not directly involved in the modulation of cadherin activity.

EXPERIMENTAL PROCEDURES

cDNA Construction—A cDNA encoding full-length mouse E-cadherin was described previously (6). A cDNA encoding full-length human N-cadherin was kindly provided by Dr. S. T. Suzuki (Department of Biosciences, School of Science and Technology, Kwansei Gakuin University, Mita, Japan). All constructs used were cloned into the expression vector pcAGGSneo (30) (a gift from Dr. K. Yamamura, Institute of Molecular Embryology and Genetics, Kumamoto University, Kumamoto, Japan).

To compare the amounts of the expressed constructs directly, all the cadherin constructs were fused to an HA epitope at their carboxyl termini. The cDNAs encoding the HA-tagged full-length E-cadherin (ECF), a mutant E-cadherin protein with a carboxyl-terminal deletion of 70 amino acids (EC81), and the tail-less protein (EC0) were described previously (7). In brief, cells were incubated for 10 min at 37 °C in Hepes-buffered saline containing 0.1% trypsin (type XI, Sigma) and 2 mM CaCl2. After the addition of soybean trypsin inhibitor (Boehringer Mannheim) and the cells were washed, resuspended, incubated for 30 min at 37 °C with constant rotation at 70 rpm.

Fluorescence Microscopy—Immunofluorescence staining of cells was performed as described previously (24). Cells were fixed with 3% paraformaldehyde in phosphate-buffered saline for 20 min at room temperature. After three washes with phosphate-buffered saline containing 50 mM NH4Cl, the cells were soaked in a blocking solution (phosphate-buffered saline containing 5% fetal calf serum) for 15 min and then incubated with DECMA-1 diluted with the blocking solution for 30 min. The cells were then washed three times with phosphate-buffered saline and incubated with fluorescein isothiocyanate-conjugated rabbit anti-rat IgG (Jackson ImmunoResearch Laboratories). Cells were analyzed on a conventional Olympus fluorescence microscope (Tokyo, Japan) equipped with a CCD camera CoolSNAP (Nippon Roper). Clustering was defined as one or several intense spots or regions of fluorescence on the cell surface. Cells that displayed a homogeneous distribution of fluorescence throughout the membrane were recorded as negative for clustering. In each experiment, the presence or absence of clustering in at least 100 randomly chosen cells was scored.

RESULTS

Partial Cytoplasmic Truncation of E-cadherin, but Not N-cadherin, Inhibits Cell Aggregation—E-cadherin and N-cadherin constructs encoding full-length proteins (ECF or NCF) (Fig. 1), partially truncated constructs lacking the catenin-binding region (EC81 or NC91), or constructs lacking the entire cytoplasmic domain (EC0 or NCO) were introduced into L cells, and stable transfectants were established. E-cadherin has a cytoplasmic domain of 151 amino acid residues, and N-cadherin has a cytoplasmic domain of 160 residues. Alignment of amino acid sequence of the cytoplasmic domain of ECF and NC91 shows that there are insertions of 10 amino acid residues in the NC91 sequence, but there is a certain degree of identity.
L cells expressing EC81, with a carboxyl-terminal deletion of 70 amino acid residues eliminating the catenin-binding site but retaining the membrane-proximal region, showed almost no aggregation (Fig. 4). Cells expressing EC0, with the further deletion of 151 amino acid residues, showed Ca\textsuperscript{2+}-dependent aggregation. These results confirm our previous observations that deletion of the membrane-proximal region results in the activation of nonfunctional E-cadherin polypeptides (19). Contrary to the observations with E-cadherin, all three N-cadherin constructs, NCF, NC91, and NC0, are active in aggregation assays (Fig. 4). These results surprised me and prompted me to explore why NC91 is active but EC81 is not.

I postulated that the inability of EC81 to mediate cell adhesion could be ascribed to the association of p120 to the protein (24). To identify whether NC91 is associated with p120 or not, L cells expressing EC81 or NC91 were subjected to immunoprecipitation with anti-HA antibodies followed by immunoblotting with anti-p120 (Fig. 3B). p120 was detected in both EC81 and NC91 immunoprecipitates. Coprecipitation of similar amounts of p120 in EC81 and NC91 indicates that there is not a substantial difference between the degree of association of p120 with these constructs. The amount of p120 associated with these constructs cannot explain the differences in aggregation activity of the E- and N-cadherin constructs.

**EC81 Constructs Substituted by the Cytoplasmic Domain of NC91 Are Active**—To define the molecular domain responsible for the suppressed activity of EC81, I prepared a series of EC81 or NC91 cytoplasmic domain chimeric constructs (Fig. 1). These constructs were introduced into L cells, and stable clones
were isolated. Aggregation assays of L cell clones expressing these constructs revealed that constructs having the cytoplasmic domain of N-cadherin (E/NC91 and E/NTMC91), like NC91, are active in the assays, whereas the constructs having the cytoplasmic domain of E-cadherin (EC81, N/EC81, and N/ETMC81) are not (Fig. 4).

Lack of activity does not seem to be due to failed cell surface transport because immunofluorescence microscopy revealed that all constructs are expressed on the cell surface (data not shown). Trypsin digestion (0.01%) in the presence of 1 mM EGTA, which would remove all Ca\(^{2+}\) from the system, revealed that significant portions of these constructs were degraded and thus were expressed on cell surfaces (Fig. 5A). In the presence of 2 mM Ca\(^{2+}\), these constructs were protected from trypsin and remained on the surface after digestion.

To know the association status of these constructs with p120, these constructs were collected by immunoprecipitation using anti-HA antibodies, and coprecipitated-p120 was detected by immunoblot analysis (Fig. 6A). No difference in the amount of coprecipitated p120 was detected among the active and inactive constructs, indicating that the degree of p120 association with these constructs is similar, if not identical.

To define the region involved in suppression of the adhesion activity of EC81, two additional constructs, EC88E/N and EC84N/E, were prepared. EC88E/N has a cytoplasmic domain composed of residues 1–41 of the E-cadherin cytoplasmic domain and residues 45–91 of the N-cadherin cytoplasmic domain. EC84N/E has a cytoplasmic domain composed of residues 1–44 of the E-cadherin cytoplasmic domain and residues 42–81 of the E-cadherin cytoplasmic domain (Fig. 1). These constructs were introduced into L cells, and stable transfectants were isolated. Aggregation assays with L cell clones expressing these constructs revealed that EC84N/E is active in the assays, whereas EC88E/N is inactive (Fig. 4).

These constructs were expressed on the surface, as shown by the sensitivity of the protein to trypsin digestion in the absence of Ca\(^{2+}\) but not in its presence (Fig. 5B). Similar amounts of p120 coprecipitated with the constructs, as revealed by immunoblot analysis with anti-p120 antibodies of the material immunoprecipitated with anti-E-cadherin (Fig. 6B).

**Fig. 5.** Cell surface expression of the E-cadherin and N-cadherin constructs. A, cells expressing EC81 and NC91 and their derivatives were incubated with 0.01% trypsin for 10 min at 37°C in the presence of 2 mM Ca\(^{2+}\) (TC) or 1 mM EGTA (TE). Proteins were detected by anti-HA mAb (3F10). The slowly migrating protein bands correspond to the intracellular, incompletely processed proteins having the precursor segment. In B, cells expressing EC81 and its derivatives were incubated with 0.01% trypsin for 10 min at 37°C in the presence of 2 mM Ca\(^{2+}\) (TC) or 1 mM EGTA (TE). Proteins were detected by anti-E-cadherin mAb (DECMA-1).

**Fig. 6.** Coprecipitation of p120 with partially truncated non-functional and functional cadherin constructs except for p120-uncoupled constructs. In A, materials collected by immunoprecipitation (IP) with anti-HA mAb from L cell transfectants expressing EC81, NC91, and their derivatives were detected by HA and p120 antibodies. In B, materials collected by immunoprecipitation with polyclonal anti-E-cadherin antiserum from L cell transfectants expressing EC81 and its derivatives were detected by anti-E-cadherin and anti-p120 antibodies.

Uncoupling of p120 from E-cadherin Is Not Sufficient for the Activation of Nonfunctional E-cadherin—The region identified in the above experiments contains the p120-binding site. Three amino acid substitutions to alanine in this region have been shown to uncoat the E-cadherin-p120 interaction (25). I introduced the same substitutions; a conserved triple glycine, Gly (605)-Gly-Gly (Fig. 2), to alanine, or a conserved Glu (608)-Glu-Gly sequence to alanine, in EC81 constructs yielded EC81GA and EC81EA (Fig. 1). L cells were transfected with these constructs, and stable cell clones expressing these constructs were isolated. Aggregation assays revealed that these constructs remained inactive. Trypsin digestion in the presence of 1 mM EGTA showed that a significant fraction of E-cadherin was expressed on the surface of the cells (Fig. 5B). Absence of p120 in immunoprecipitates argues for the successful uncoupling of the interaction of these constructs with p120 (Fig. 6B).

All the experiments described above were carried out using truncated constructs. I was interested to know whether uncoupling of p120 binding would activate catenin-uncoupled full-length E-cadherin. Substitution of the conserved 8 serine residues in the catenin-binding site of E-cadherin to alanine residues (Fig. 2) has been shown to uncoat the interaction with catenins and inactivate the mutant protein (8). I introduced the same substitutions in the full-length E-cadherin construct yielding ECFS8A. The Glu (608) ED to AAA substitution was then introduced into wild-type (ECF) and ECFS8A constructs yielding ECFEA and ECFEASSA, respectively. L cells were transfected with these constructs, and stable transfectants were isolated (Fig. 7A). Despite its cell surface expression (Fig. 7B), ECFEASSA is inactive as assessed by aggregation assay (Fig. 8), consistent with the previous report (8). This construct does not associate with β-catenin as β-catenin was not detected by immunoprecipitation (Fig. 7C). Thus, uncoupling of β-catenin from E-cadherin resulted in inactivation of the latter molecule. The construct uncoupled with both β-catenin and p120 (ECFEASSA) was expressed on the surface of cells (Fig. 7B) and was no longer associated with β-catenin and p120 (Fig. 7C). Cells expressing this construct (ECFEASSAL) showed no aggregation (Fig. 8). The additional uncoupling of p120 from β-catenin-uncoupled E-cadherin did not activate the
resulted in no coprecipitation of p120 and/or H9252 (C). Proteins were detected by anti-E-cadherin mAb. In TE46018 bars represent S.D.

1.4. Partial Truncations of E-Cadherin and C-Cadherin Are Active Aggregation Assays

In the presence of 2 mM CaCl2 and were allowed to aggregate for 30 min, either uncoupled and /H9252 and /H9252, L cells expressing ECF (ECFL) and its p120-uncoupled (ECFEAL and ECFGAFL), catenin-uncoupled (ECFS8AL), and both p120 and catenin-uncoupled derivatives (ECFEAS8AL) were subjected to immunoblot detection of the constructs. Proteins were detected by anti-E-cadherin mAb (DECMA-1). In B, cells were incubated with 0.01% trypsin for 10 min at 37 °C in the presence of 2 mM Ca2+ (TC) or 1 mM EGTA (TE). Proteins were detected by anti-E-cadherin mAb. In C, uncoupling resulted in no coprecipitation of p120 and/or catenin with the constructs. Materials precipitated by polyclonal E-cadherin antiserum were detected by immunoblotting (IB) with E-cadherin, catenin, and p120 antibodies.

DISCUSSION

Although the presence of the E-cadherin inner membrane-proximal region suppresses cell adhesion activity of partially truncated E-cadherin polypeptides, the corresponding sequence of N-cadherin does not suppress the activity of partially truncated N-cadherin polypeptides. Therefore, the membrane-proximal region of each cadherin exhibits different functional features despite a high degree of similarity. The removal of these amino acid residues from E-cadherin activates the nonfunctional E-cadherin polypeptides, but uncoupling of p120 binding from the nonfunctional E-cadherin does not. Therefore, it is not p120 binding that suppresses the activity of the partially truncated E-cadherin polypeptides.

Partial truncations of the E-cadherin cytoplasmic domain, which remove the distal catenin-binding site, result in inactivation of E-cadherin expressed on L cells or K562 leukemic cells (7, 17–19). Complete truncation or removal of the membrane-proximal region results in the activation of nonfunctional E-cadherin (19). These observations lead me to propose that the membrane-proximal region of E-cadherin negatively regulates adhesion activity (19). Contrary to our observations on E-cadherin, partially truncated VE-cadherin and C-cadherin retaining the membrane-proximal region expressed on CHO cells are active in aggregation assays (21, 27). Since the activity of cadherins is under the control of multiple mechanisms, the activity of any cadherin expressed on L cells and CHO cells could vary significantly. In the present study, I expressed E-cadherin and N-cadherin constructs on L cells and found that a partially truncated N-cadherin construct with the membrane-proximal region is functional. Therefore, it is possible that the membrane-proximal region of each cadherin exhibits different functions depending on the subtype, despite the relatively high degree of homology. In addition to the activities related to cell adhesion, the membrane-proximal region also appears to be involved in regulation of neuronal outgrowth mediated by N-cadherin (32), the selective exclusion of N-cadherin from junctions by VE-cadherin in endothelial cells (20), and the suppression of cell motility by E-cadherin (33). Recently, an ubiquitin-ligase, Hakai, has been shown to interact with the cytoplasmic domain of E-cadherin but not with that of N-cadherin or OB-cadherin. Phosphorylation of E-cadherin-specific tyrosine residues in the membrane-proximal region has been shown to be critical for its interaction with the ubiquitin-ligase and subsequent ubiquitination in v-Src-transformed cells (34).

It seemed less likely that p120 associated with the partially truncated E-cadherin polypeptides is responsible for the inability of the protein to act as an adhesion molecule (19) because p120 is associated not only with the nonfunctional mutant E-cadherin constructs but also with the functional mutant polypeptides of VE-cadherin and C-cadherin (21, 27). Later, however, I postulated that p120 is involved in the modulation of E-cadherin adhesion activity based on several observations (24). First, the p120-binding site was mapped to residues 596–628 of the E-cadherin cytoplasmic domain (which correspond to the residues 19–52 of the E-cadherin sequence in Fig. 2). Additionally, deletion of 11 amino acid residues in this region (corresponding to residues 27–37 of the E-cadherin sequence in Fig. 2) activated the partially truncated, nonfunctional E-cadherin polypeptides. Furthermore, expression of p120 proteins with the amino-terminal deletion partially activated the nonfunctional E-cadherin polypeptides. Finally, staurosporine, a compound that activated nonfunctional E-cadherin polypeptides, induced dephosphorylation of p120 associated with the polypeptides. The data obtained in the present study, however, argue against this earlier postulation. Experiments with chimeric constructs composed of E-cadherin and N-cadherin revealed that the region including the p120-binding site determines whether the construct is active or not. There is, however,
no correlation between the amount of p120 associated with a construct and the activity of that construct in aggregation assays. To clarify the role of p120 in modulation of cadherin function, I introduced three amino acid alanine substitutions, which were used to uncouple the E-cadherin-p120 interaction with minimal conformational effect and high selectivity (25). Although the removal of the membrane-proximal region activated the nonfunctional E-cadherin polypeptides, the uncoupling of p120 binding did not activate the partially truncated nonfunctional E-cadherin polypeptides. These results indicate that p120 is not directly involved in the suppression of the adhesion activity of the mutant polypeptides. I assume that the deletion of 11 amino acid residues in the membrane-proximal domain might have introduced conformational changes and uncoupled interactions with other proteins in addition to p120. The reason why the truncated mutant E-cadherin polypeptides were partially activated by the expression of the amino-terminally deleted p120 but not by the wild-type p120 is unknown at present.

Using the chemical cross-linking reagent, 3,3'-dithiobisthioureasulfosuccinimidylpropionate, I observed that the active tail-less E-cadherin polypeptides could be cross-linked to form a dimer on the surface of cells, whereas the inactive polypeptides containing the membrane-proximal region could not (19). Therefore, I postulated that the membrane-proximal region participates in regulation of the adhesion activity by preventing lateral dimerization of the extracellular domain. Contrary to my initial postulation, both the functional tail-less construct and the nonfunctional polypeptides containing the membrane-proximal region on the cell surface exist as dimers, as revealed by immunoprecipitation assays (31). Therefore, the product of chemical cross-linking is not the dimer. It may reflect the presence of multimers or clusters of the proteins. Furthermore, activation of the partially truncated nonfunctional EC81 protein by staurosporine treatment did not change the degree of dimerization (31). Consistent with this idea, cell surface distribution of nonfunctional EC81 is homogeneous, and that of functional EC0 and E/N/C91 was found to be not homogeneous and to be clustered. The membrane-proximal region of the E-cadherin cytoplasmic domain may serve, therefore, to constrain the adhesion receptor in a default low affinity state by preventing lateral clustering of the extracellular domain. Thus, although the exact nature of clustered cadherin distribution is still unknown, this post-dimerization event seems to be critical for subsequent adhesive interactions and for the formation of adhesive structures (4).

Thorensen et al. (25) have reported that the p120-uncoupled E-cadherin mutants failed to mediate tight adhesion and were deficient in mediating cell-cell compaction, indicating that p120 is required for the E-cadherin-regulated transition from loose to tight adhesion. My results, however, argue that the association of p120 to the membrane-proximal region is not essential for compaction. Recently, a mutant variant of Drosophila epithelial cadherin (DE-cadherin) that is selectively uncoupled for p120 binding by the triple glycine to alanine substitution was shown to have the ability to substitute for endogenous DE-cadherin activity in multiple cadherin-dependent processes during Drosophila development and oogenesis (35). Thus, interaction with p120 does not appear to be required for DE-cadherin function in vivo. Furthermore, null alleles of p120 generated in Drosophila were found to be viable and fertile and have no substantial changes in junction structure or function (36). However, p120 mutations were reported to strongly enhance mutations in the genes encoding DE-cadherin or Armadillo, the β-catenin homologue, raising the possibility that p120 is an important positive modulator of adhesion but that it is not an essential core component of adherens junctions.

The capacity of the membrane-proximal portion of the E-cadherin cytoplasmic domain to negatively regulate its aggregation activity may be due to its interaction with an intracellular partner. The members of the p120 subfamily of Armadillo proteins that include p120, δ-catenin/neural plakophilin-related arm protein (37), p0071 (a ubiquitous isoform of δ-catenin/neural plakophilin-related arm protein) (38), and ARVC (Armadillo repeat gene deleted in velocardiofacial syndrome) (39) have been shown to bind to the membrane-proximal region of cadherins. Their association with cadherins was abrogated by the three amino acid alanine substitutions that uncouple p120 binding by the triple glycine to alanine substitution. Hence, the p120-uncoupled E-cadherin mutants failed to mediate tight adhesion and were deficient in mediating cell-cell compaction, indicating that p120 is required for the E-cadherin-regulated transition from loose to tight adhesion.

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REFERENCES

1. Takeichi, M. (1988) Development 102, 639–655
2. Geiger, B., and Ayalon, O. (1992) Annu. Rev. Cell Biol. 8, 307–332
3. Marrs, J. A., and Nelson, W. J. (1996) Int. Rev. Cytol. 165, 159–205
4. Gumbiner, B. M. (2000) J. Cell Biol. 148, 399–404
5. Nose, A., Tsuji, K., and Takeichi, M. (1990) Cell 61, 147–155
6. Ozawa, M., Baribault, H., and Kemler, R. (1989) EMBO J. 8, 1711–1717
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