E-cadherin has been termed an “invasion suppressor,” yet the mechanism of this suppression is not known. In contrast, several reports indicate N-cadherin does not suppress but, rather, promotes cell motility and invasion. Here, by characterizing a series of chimeric cadherins we defined a previously uncharacterized region consisting of the transmembrane domain and an adjacent portion of the cytoplasmic segment that is responsible for the difference in ability of E- and N-cadherin to suppress movement of mammary carcinoma cells, as quantified from time-lapse video recordings. A mutation in this region enabled N-cadherin to suppress motility, indicating that both E- and N-cadherin can suppress, but the activity of N-cadherin is latent, presumably repressed by binding of a specific inhibitor. To define regions common to E- and N-cadherin that are required for suppression, we analyzed a series of deletion mutants. We found that suppression of movement requires E-cadherin amino acids 699–710. Strikingly, β-catenin binding is not sufficient for and p120ctn is not involved in suppression of these mammary carcinoma cells. Furthermore, the comparable region of N-cadherin can substitute for this required region in E-cadherin and is required for suppression by the mutant form of N-cadherin that is capable of suppressing. Variations in expression of factors that bind to the two regions we have identified may explain previously observed differences in response of tumor cells to cadherins.

The cadherin family of calcium-dependent adhesion molecules plays important roles in differentiation and morphogenesis (1). Alterations in cadherin expression also have been found to be an important determinant of tumor behavior (2). E-cadherin suppresses cell movement (3, 4), whereas loss of E-cadherin correlates with acquisition of invasive capacity in vitro (5, 6) and in carcinomas (7). Restoration of E-cadherin expression suppresses invasion in vitro (5, 6) and in a mouse tumor model (8). For these reasons, E-cadherin has been termed an invasion suppressor, but the mechanisms mediating these effects are poorly understood. In contrast, N-cadherin promotes rather than suppresses cell motility and invasion (9, 10), apparently by triggering or enhancing activation of the fibroblast growth factor receptor (9, 11). Because cadherins might suppress invasion through mechanical restraint or through alterations in cell behavior induced by signaling, the roles of adhesion and signaling in suppression of invasion have been the subject of substantial investigation.

These investigations have focused upon the cytoplasmic domain, which is highly conserved among classic cadherins and crucial for mediating cadherin function. Proteins that bind to the cadherin cytoplasmic domain in roughly stoichiometric amounts were termed catenins (12). β-Catenin binds to a C-terminal region of cadherins referred to as the catenin binding domain (13) and also to α-catenin, which interacts with the actin cytoskeleton (14). A related molecule, p120ctn, binds to a second region close to the plasma membrane (15, 16). Both regions contribute to adhesion, although there is substantial cell type variation in precise roles (see (14, 17)). The catenin binding and p120ctn binding domains are highly conserved between E- and N-cadherin.

We investigated the role of these cytoplasmic domains in suppression of motility and found that the p120ctn binding domain was essential for E-cadherin to suppress motility of a rat astrocyte-like cell line (4). Three groups found that cytoplasmic p120ctn induced changes in cell morphology and small GTPase activity and suggested that E-cadherin may suppress motility by sequestering p120ctn (18–20). In contrast, Wong and Gumbiner (21) recently reported that p120ctn is not involved and instead suggest that modulation of β-catenin association is responsible for control of cell invasion by E-cadherin. Activated β-catenin stimulates motility of epithelial cells (22). There are apparent inconsistencies in these findings, and none of these studies offers an obvious explanation for the difference in suppressing capacity of E- and N-cadherin.

To explore the basis for this difference and to investigate the mechanisms by which E-cadherin suppresses cell movement, we have analyzed the effects of a series of E/N chimeric cadherins and deletion mutants on the motility of mammary carcinoma cells. This work revealed a region common to both E- and N-cadherin that is essential for suppression of the movement of these cells and a second region responsible for the difference in suppression capacity of E- and N-cadherin. Surprisingly, we found that N-cadherin is capable of suppressing motility, but this capacity is normally repressed or latent.

**EXPERIMENTAL PROCEDURES**

**CELL CULTURE**—MDA-MB-435 cells and MDA-MB-231 cells were obtained from Michael Kinch (MedImmune) and grown in Dulbecco’s modified Eagle’s medium plus 10% fetal bovine serum and 60 μg/ml...
Suppression of Cell Motility by Cadherins

| Chimera  | Amino acid junctiona | Amino acid numbersb | Parent vector |
|---------|----------------------|---------------------|-------------|
| NEE     | TDVDR/AIVGA          | Ncd-555/Ead-544     | pBATMNC     |
| ENN     | NNCMI/AIVGAG         | Ead-543/Ncd-556     | pBATEM2     |
| ENE     | LLLFL/RRRKK          | Ead-577/Ncd-559     | pBATM2      |
| NNE     | PVVWW/AIVGAG         | Ncd-557/Ead-578     | pBATMNC     |
| NEN     | TDVDR/IVAAAG         | Ncd-555/Ead-546     | pBATMNC     |
| LLLFL/RRRKK | Ead-577/Ncd-588 | pBATM2      |
| ENNE    | NNCMI/AIVGAG         | Ead-543/Ncd-556     | pBATEM2     |
| ENE     | PVVWW/AIVGAG         | Ncd-557/Ead-578     | pBATMNC     |
| E615N   | DLSQL/QQPD'T         | Ead-618/Ncd-632     | pBATEM2     |
| E657N   | DEIGN/FINEG          | Ead-657/Ncd-676     | pBATEM2     |

a E-cadherin sequences are in bold.
b Ead, E-cadherin; Ncd, N-cadherin.

1 The abbreviations used are: HA, hemagglutinin; PIPES, 1,4-piperazineethanesulfonic acid; TMS, transmembrane segment; GFP, green fluorescent protein.
Suppression of Cell Motility by Cadherins

Fig. 1. Exogenous cadherin expression increases aggregation of MDA-MB-435 mammary carcinoma cells. MDA-MB-435 cells expressing a control vector (Control), an E-cadherin expression vector (E-cadherin), or an N-cadherin expression vector (N-cadherin) were allowed to aggregate in the presence of calcium for 60 min as described under “Experimental Procedures.” Although control cells could form small aggregates, expression of E-cadherin or N-cadherin greatly increased the extent of cell aggregation. Bar = 100 µm.

Fig. 2. E-cadherin, but not N-cadherin, suppresses movement of MDA-MB-435 cells. The panels illustrate the movement of MDA-MB-435 control cells and cells expressing E- or N-cadherin into wounds. Each panel shows two overlapping images of sheets of cells. In each case, the darker image represents the sheet of cells 1 h after the wound was produced. The lighter image shows the same field 14 h later. Tracks of selected cells, determined from video recordings, are superimposed on the pictures. Bar = 100 µm.

Table II

| Vector        | x axis | y axis | Total track |
|---------------|--------|--------|-------------|
|               | µm/h   | µm/h   | µm/h        |
| Control       | 10.93  | 10.79  | 17.83       |
| E-cadherin    | 6.01   | 9.34   | 12.89       |
| N-cadherin    | 15.31  | 14.03  | 23.53       |

* Mean rate of x axis movement (parallel to the direction of the wound) and S.D. for eight selected cells from each of two video recordings for one clonal isolate of cells transfected with the indicated vectors.

+ Mean rate of y axis movement (perpendicular to the direction of the wound) and S.D. for eight selected cells from each of two video recordings for one clonal isolate of cells transfected with the indicated vectors.

+ Mean rate of total movement and S.D. for eight selected cells from each of two video recordings for one clonal isolate of cells transfected with the indicated vectors.

* Significantly different from control (p < 0.0001).

* Significantly different from control (p = 0.0076).

* Significantly different from control (p = 0.0143) and from E-cadherin (p < 0.0001).

* Significantly different from control (p < 0.0001).
or control cells. Examples of selected cell tracks determined from video recordings are shown in Fig. 3, and quantification of movement calculated from these tracks indicated the difference in movement of E-cadherin cells, and control or N-cadherin cells was statistically significant. In contrast to its effect in wounding assays, N-cadherin did not promote motility relative to control cells in intact monolayers (Fig. 3).

The Transmembrane Sequence and Juxtamembrane Domain Determine Ability to Suppress Motility—To investigate the basis for the differing effects on motility of E- and N-cadherin, we constructed and tested chimeric cadherins (Fig. 4) (for convenience, these chimeras are referred to by a three-letter designation, such as NEE, signifying the derivation of the extracellular, transmembrane, and cytoplasmic segments from E- or N-cadherin). The overall structure and function of these chimeric molecules was not disrupted, as in each case we verified that the chimeric proteins were correctly localized to the cell surface, and adhesive activity was preserved. This strategy had the potential to reveal regions within E-cadherin that mediate suppression or regions within N-cadherin that overcome or inhibit suppression. An NEE chimera suppressed the motility of MDA-MB-435 cells, but an ENN chimera did not (Fig. 4), as shown both by the morphology of wound edges and by quantitative analysis of video recordings (x axis movement of NEE was significantly less than control, \( p < 0.0001 \)). Therefore, the ability to suppress motility is dictated by the transmembrane and/or cytoplasmic domains of these cadherins.

To further define the region involved in controlling motility, the three segments derived from E- or N-cadherin were linked in all possible combinations, introduced into MDA-MB-435 cells, and analyzed for effects on motility by comparing morphology of the wound edges 18–24 h after wounding. The motility of cells expressing the first four constructs listed was also assayed by quantitative analysis of individual cell tracks determined from time-lapse video recording. Aggregation was also assayed as described under “Experimental Procedures” and scored positive or negative by comparison to aggregation of control or E-cadherin-expressing cells as shown in Fig. 1.

**Fig. 4. Analysis of chimeric cadherins defines a region responsible for the difference between E- and N-cadherin in suppression of motility.** The diagram shows the structures of chimeric cadherins in which the extracellular domain, TMS, or portions of the cytoplasmic domain of mouse E- or N-cadherin were fused in various combinations (“Experimental Procedures” and Table I). Each construct was transfected into MDA-MB-435 cells, and the resultant lines were characterized and assayed for the ability to suppress motility by the qualitative assessment of the morphology of wound edges 18–24 h after wounding. The motility of cells expressing the first four constructs discussed previously, narrowing the sequences that define the difference in suppression ability of E- and N-cadherin to the transmembrane segment (TMS). As this finding would predict, the chimeric cadherin produced by replacing the TMS of N-cadherin with E-cadherin sequences (NEN) also suppressed movement. Unexpectedly, however, two constructs with TMS sequences derived from N-cadherin, an ENE construct and an NNE construct, also suppressed. In short, when results from all eight chimeric constructs were compared, we found that any construct with an E-cadherin TMS or an E-cadherin cytoplasmic domain suppressed, whereas only constructs in which both the TMS and cytoplasmic domains are derived from N-cadherin failed to suppress (Fig. 4). One interpretation of these findings is that the TMS and cytoplasmic regions of E-cadherin possess redundant activities, either one of which is sufficient to suppress motility.

**N-cadherin Can Suppress Motility, but This Ability Is Inhibited**—A simpler explanation is that N-cadherin actually has the ability to suppress motility, but the TMS and adjacent cytoplasmic sequences comprise a binding site for a component that restricts or prevents this ability. This possibility was tested by introducing a mutation that might be expected to disrupt the binding of such a regulatory component. Amino acids 591 through 599 of mature N-cadherin were replaced with a 9-amino acid HA tag (Fig. 5A) (32). This construct, termed N-HA, was transfected into MDA-MB-435 and MDA-MB-231 cells, and several stable lines were isolated. All N-HA
lines isolated displayed good aggregation similar to that of N-cadherin-expressing cells (not shown). Immunoprecipitation experiments showed that the HA insertion did not affect the ability of N-HA to associate with p120ctn or β-catenin (Fig. 5C). Motility was suppressed in all three independent MDA-MB-435 cell lines isolated displayed good aggregation similar to that of control and N-HA (Fig. 7A), supporting the hypothesis that N-cadherin possesses the ability to suppress motility but that this ability is latent, suppressed by a mechanism that involves amino acids 591–599. This region is referred to subsequently as the M domain, for modulation of movement.

**Identification of a Cadherin Cytoplasmic Domain Region That Is Required for Suppression of Cell Motility**—Although we focused initially on differences between E- and N-cadherin, the finding that N-cadherin shares with E-cadherin the ability to suppress mammary carcinoma cell motility caused us to examine conserved regions in the two cadherins that might be essential. We, therefore, produced and characterized permanently transfected lines of MDA-MB-435 cells expressing the E-cadherin deletion mutants shown in Fig. 6A. These mutant forms, which centered around the p120ctn and β-catenin binding regions, were tested by co-immunoprecipitation for their ability to associate with these two known cadherin binding partners. Full-length E-cadherin and Δ699–710 co-immunoprecipitate both p120ctn and β-catenin, Δ581–593 and Δ594–618 co-immunoprecipitate β-catenin but not p120ctn, and 692T co-immunoprecipitates p120ctn but not β-catenin (Fig. 6C). The Δ699–710 and 692T molecules did not mediate effective aggregation, whereas cells expressing the other mutant molecules aggregated similarly to full-length E-cadherin (Fig. 6A).

The motility of the MDA-MB-435 cell lines expressing mutant forms of cadherin was then assayed by time lapse recording of wound-filling (Fig. 6B). Deletion of the entire cytoplasmic domain abolished suppression, as did a truncation that deleted the catenin binding domain and remaining C-terminal sequences. Deletion of amino acids 699–710, a small region that is just C-terminal to the catenin binding domain, also abolished the ability to suppress (Fig. 6A), as the x axis motility of all three of these mutant forms differed significantly from that of E-cadherin with p < 0.0001. We termed the region containing these essential amino acids the S domain, for suppression of motility. Deletion of the S domain had no effect on association of β-catenin or p120ctn, and two deletions (Δ581–593 and Δ594–618) that abolish p120ctn binding had no effect on suppression, suggesting β-catenin is not sufficient, and p120ctn plays little, if any, role in suppression in these cells.

Recently, cytoplasmic but not membrane-associated p120ctn has been found to induce a dendritic morphology in several cell types and to affect the activity of small GTPases, leading to the suggestion that E-cadherin suppresses motility by sequestering p120ctn at the membrane (18–20). This does not appear to be the case in MDA-MB-435 cells, however, because there was no correlation between the cellular localization of endogenous p120ctn and effects on movement in several of our cadherin-transfected cell lines (Fig. 7A) even though overexpression of p120ctn induced a dendritic phenotype in these cells (Fig. 7B). For example, motility was suppressed in the Δ594–618 cell line, but not in control MDA-MB-435 cells, even though these cells expressed similar, relatively high amounts of p120ctn in the cytoplasm. Furthermore, the motility of E-cadherin and N-cadherin-expressing cells differed even though the cytoplasm of these lines contained comparable, low amounts of p120ctn (Fig. 7A).

Because the amino acid sequence of the S domain is highly conserved among cadherins, including N-cadherin (Fig. 8), we investigated whether this region in N-cadherin performs the same function as in E-cadherin. We concluded that the N-cadherin region can substitute for the E-cadherin region, as the chimeric molecules EEN, E618N, and E657N, in which C-terminal sequences of the E-cadherin cytoplasmic domain were replaced with N-cadherin sequences, did suppress motility (Fig. 4). Furthermore, when the region (amino acids 720–731) that is homologous to the E-cadherin S domain was deleted...
from the N-HA mutant of N-cadherin, which is capable of suppressing, its ability to suppress was abolished (Fig. 5B).

**DISCUSSION**

Our results indicate that two regions of the cadherin cytoplasmic domain are involved in suppressing the movement of mammary carcinoma cells. One region, defined by a mutant that lacks amino acids 699−710 of E-cadherin, was absolutely required for suppression of movement in these cells. The closely related sequence in N-cadherin was capable of substituting for this deleted region in E-cadherin, indicating both cadherins contain functionally equivalent domains, which we termed the S domain, for suppression of movement. These findings suggested that the failure of N-cadherin to suppress motility is not because it lacks the capability to do so but, rather, because this ability is masked or latent. Consistent with this interpretation, we identified a region within N-cadherin, consisting of the transmembrane segment and portion of the adjacent cytoplasmic segment that is required to restrict or repress the ability of N-cadherin to suppress movement. We termed this region the M domain, for modulation of movement.
Suppression of Cell Motility by Cadherins

Fig. 8. The S domain is highly conserved among cadherins. The figure shows C-terminal regions of mouse cadherins aligned with residues 690–728 of E-cadherin. Identical amino residues in the S domain (defined by deletion 699–710) are shaded. The sequences of all cadherins end at their C terminus (COOH), except cadherin 15, which extends an additional amino acid beyond those shown.

Table 1. Conformation of S domain

| S domain | COOH |
|----------|------|
| E-cad    | ...LSLNSSES... |
| N-cad    | ...LSLHTSAS... |
| P-cad    | ...LSLTSNAS... |
| R-cad    | ...VSLNSSES... |
| Cad-5    | ...LSSLSNES... |
| Cad-6    | ...LSTEKVT... |
| Cad-7    | ...LSLQSTS... |
| Cad-8    | ...LSLESTS... |
| Cad-9    | ...LSLQSTT... |
| Cad-11   | ...LSLQSTT... |
| Cad-12   | ...LSLQSTT... |
| Cad-15   | ...LSLQSTT... |
| Cad-16   | ...LSLQSTT... |

Reliable, quantitative assay. We evaluated suppression of movement by cadherins using in vitro wound-filling assays but found that the way these assays are usually scored (measuring the distance moved by the sheet of cells at the edge of the wound) did not give significant or reproducible results. Instead, we developed two alternative, more reliable scoring methods that entailed qualitative evaluation of wound edge morphology or quantitative analysis of individual cell tracks obtained from video recordings. The quantitative analyses confirmed that the degree of side-to-side movement of E-cadherin-expressing cells was consistently suppressed compared with control or N-cadherin-expressing cells, but these cells did not differ significantly in movement into the wound.

Other investigators (9, 10) report that N-cadherin promotes movement compared with control cells and link this effect to the activation of the fibroblast growth factor receptor (9, 10). We also observed a modest enhancement of movement promoted by N-cadherin during wound filling but not in intact, unwounded monolayers. Several differences in cells and procedures may account for the disparity between our results and those of others (9, 10). Different MDA-MB-435 cell isolates vary in expression of endogenous cadherins and EphA2 and may differ in expression of fibroblast growth factor receptor or other components involved in this effect. Additionally, different assays were used to assess cell movement in these studies. Nierman et al. (9) used a transwell assay with conditioned medium as a chemoattractant, which is likely to assess directional migration. The mechanisms controlling directional migration are known to differ from those controlling motility (33, 34).

To define the region(s) required for suppressing the motility of these mammary carcinoma cells, we used the wound-filling assay to test the effect of deletion mutants. Surprisingly, the p120ctn binding region was not required, which differed from results obtained previously with rat astrocyte-like cells (4). Rather, a region near the C terminus of cadherin, the S domain, was found to be required. The specific reason for this variation in mechanism of suppression remains unclear, but it extends cell type-specific differences in cadherin function seen in other studies (14, 17).

p120ctn has recently been suggested to play a key role in suppression of motility (15–20). Cytoplasmic, but not membrane-asso ciated p120ctn induces a dendritic morphology in several cell types and affects the activity of small GTPases, leading to the suggestion that E-cadherin suppresses motility by sequestering p120ctn at the membrane. This does not appear to be the case in MDA-MB-435 cells, however, because the cellular localization of endogenous p120ctn did not correlate with its effects on movement in several of our cadherin-expressed cell lines even though a dendritic phenotype was induced in these cells by overexpression of p120ctn as in other cell types (18–20).

Deletion of the S domain abolished suppression and compromised cell aggregation, but several results indicated that adhesion alone does not suppress movement. For example, N-cadherin, the ENN chimera, and the 584T mutant all mediate effective adhesion but are unable to suppress motility, and insertion of an HA tag into the M domain of N-cadherin enabled suppression of movement without discernable effects on adhesion. It is likely, therefore, that cell movement is affected by signaling events initiated by cadherins rather than adhesion per se.

Four components, Shc (35), the heterotrimeric G-protein subunit G(i) (36), and the protein-tyrosine phosphatases PTP1B (38) and PTP(2) (39), have been reported to interact with cadherins within the region of the S domain, although the generality and significance of these interactions has not yet been firmly established. Suppression is abolished by overexpression of activated G(i) (37), suggesting this molecule could play a significant role, possibly by modulating release of β-catenin. β-Catenin has been suggested to induce invasion (21) and motility (22, 39). Substantial amounts of β-catenin remain bound to cadherins lacking the S domain, however, suggesting that sequestration of β-catenin is not sufficient to suppress motility. Alternatively, the S domain might be required to generate or modulate tyrosine phosphorylation cascades triggered by E-cadherin (40), which could be regulated by PTP1B or PTP(2). Shc is unlikely to be involved because mutation of tyrosine 705, which is necessary for Shc binding (41), does not affect the ability of E-cadherin to suppress motility.

The S domain sequences of E- and N-cadherin are nearly identical, and motility was suppressed by several chimeric cadherins in which this portion of E-cadherin was replaced by N-cadherin sequences, indicating that N-cadherin possesses a fully competent S domain. Mutational analysis of N-cadherin showed that the region we termed the M domain disrupts the N-cadherin ability to suppress. The studies of Horikawa and Takeichi (42) also suggest a new function for this region of N-cadherin. They found that overexpression of N-cadherin had no effect on the spreading of myotome precursor cells, but expression of N-cadherin with a deletion of the p120ctn binding domain prevented this spread. This was not due to disruption of p120ctn binding, however, as point mutations that specifically abolish p120ctn binding did not produce the same effects as the deletion, suggesting the spread of myotome cells is affected by some other component that binds to this region (42). Similarly, Ozawa (43) recently observed that this membrane-proximal region differentially regulates adhesion of E- and N-cadherin, but again, p120 is not involved. It is possible that the HA-tag mutation we introduced disrupts binding of a component(s) involved in these activities.

Our findings suggest several ways in which diversity in cadherin effects might arise in different cell types. If the M domain and S domain each act by generating intracellular signals, different cells might respond to the same signal in different ways. Variations also would be expected if cells differ in expression of molecules that bind to the S and M domains.

† M. Fedor-Chaiken, unpublished observations.
For example, N-cadherin does not suppress the movement of MDA-MB-435 cells but would be expected to suppress the movement of any cells that do not express key M domain binding partners. One example may be LMS mouse osteosarcoma cells, as migration and metastasis of these cells is inhibited by expression of N-cadherin (44). Furthermore, expression of E-cadherin induces robust adhesion in some cells without suppressing movement (4, 45), raising the intriguing possibility that these cells may express regulators that bind to E-cadherin, permitting adhesion but preventing suppression.

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