Gao, J. H. Weaver, *J. Vac. Sci. Technol. A* 7, 865 (1989).
11. C. M. Aldao, M. Vos, I. M. Vitomirov, G. D. Waddill, J. H. Weaver, *Phys. Rev. B* **42**, 2878 (1990).
12. E. H. Rhoderick and R. H. Williams, *Metal-Semiconductor Contacts* (Oxford Scientific Publications, Oxford, 1988).
13. J. N. Israelachvili, *Intermolecular and Surface Forces* (Academic Press, New York, 1985).
14. G. D. Waddill, I. M. Vitomirov, C. M. Aldao, J. H. Weaver, *Phys. Rev. Lett.* **62**, 1568 (1989); Z. Liliental-Weber, E. R. Weber, J. Washburn, J. H. Weaver, *Appl. Phys. Lett.* **56**, 2507 (1990).
15. G. D. Waddill *et al.*, *Phys. Rev. B* **41**, 5293 (1990).
16. T. R. Ohno *et al.*, *ibid.*, p.11677.
17. T. R. Ohno, Y.-N. Yang, J. H. Weaver, Y. Kimachi, T. Hidaka, *Appl. Phys. Lett.* **57**, 718 (1990).
18. D. J. Chadi, *Phys. Rev. B* **18**, 1800 (1978).
19. Studies of cluster assembly have been supported by the Office of Naval Research. Investigations of overlayer growth have been supported by the National Science Foundation and the Army Research Office. Special thanks to I. M. Vitomirov, C. M. Aldao, T. R. Ohno, and Z. Liliental-Weber for their many contributions. The STM images for Ag/GaAs(110) were generously provided by B. M. Trafas and Y.-N. Yang before publication.

Cadherin Cell Adhesion Receptors as a Morphogenetic Regulator

MASATOSHI TAKEICHI

Cadherins are a family of cell adhesion receptors that are crucial for the mutual association of vertebrate cells. Through their homophilic binding interactions, cadherins play a role in cell-sorting mechanisms, conferring adhesion specificities on cells. The regulated expression of cadherins also controls cell polarity and tissue morphology. Cadherins are thus considered to be important regulators of morphogenesis. Moreover, pathological examinations suggest that the down-regulation of cadherin expression is associated with the invasiveness of tumor cells.

AMONG VARIOUS ASPECTS OF ADHESION-MEDIATED CONTROL of cell behaviors, the adhesion selectivity is especially important in regulating morphogenesis. Selective cell adhesion or cell sorting is observed in a wide variety of developmental and pathological events where specific cells are connected only to particular cell types (for example, egg-sperm interactions, neuronal connections, and lymphocyte homing). Essentially all types of animal cells appear to have such adhesive properties, as suggested by classical findings that cells derived from any one particular tissue can be sorted from those of other tissues when mixed (*1*). It is thus likely that cell adhesion selectivity is a general property of cells and participates in the entire process of morphogenesis.

Cell-sorting behaviors in vitro were often theoretically explained by various models such as the differential adhesion hypothesis (*2*). With the recent progress in identification of cell adhesion receptors, we are now unraveling the molecular basis of the selectivity of cell adhesion. The receptors required for cell adhesion are classified into several groups, of which two major groups are the immunoglobulin (Ig) superfamily and the integrin superfamily. Many members of the Ig superfamily specifically bind to other molecules identical to themselves (*3*). This phenomenon is called homophilic binding, and it suggests that the members of the Ig superfamily may be involved in specific cell-cell interactions. Some members of the integrin superfamily bind to particular members of the Ig superfamily expressed on the surface of certain cell types and thus act as mediators for specific cell-cell binding interactions, especially in the immune system (*4*). In addition to these molecular families, selectins are also crucial for specific lymphocyte adhesions (*4*). The *Drosophila* molecules fasciclins I and III also show homophilic cell binding specificities (*5*).

Although these classes of molecules participate in events that occur in particular cell systems, they may not be involved in the general phenomenon of cell adhesion specificity. Cadherins are another protein family of cell-cell adhesion receptors (*6*). All cell types that form solid tissues express some members of this molecular family, and each member displays a homophilic binding specificity. Therefore, cadherins could define adhesion specificities for the majority of cell types. Moreover, cadherins may take part in other cell-cell interaction phenomena, such as the formation of a junctional complex, cell polarization, or tumor invasion. In this article, the properties of cadherins are summarized, and the mechanisms by which this molecular family regulates morphogenetic and neoplastic cell behaviors are discussed.

Basic Properties of Cadherins

Cadherins are Ca^{2+}-dependent cell-cell adhesion receptors that have been identified in vertebrates. They bind cells by means of homophilic interactions. As expected from the importance of Ca^{2+} in cell-cell adhesion, cadherins are important for establishing and maintaining intercellular connections. Generally, cells with fewer cadherin molecules are less adhesive. However, when cadherin-deficient cells are transfected with complementary DNA (cDNA) that codes for cadherins, they acquire the Ca^{2+}-dependent, cadherin-mediated adhesive activity (*6*). In addition, cell morphology is generally altered, for example, from the fibroblastic cell type to the epithelial cell type, which reflects increases in the cell's adhesiveness. Treatment of cell layers that express cadherins with antibodies to these cadherins induces dispersion of cells (*6*). As long as cadherins are functioning, inactivation of other adhesion systems has little effect on cell-cell adhesion (*7*). Cadherins are therefore the cell-cell adhesion receptors that are most important for the formation of physical cell-cell associations.

Cadherins are divided into subclasses, all of which share a common basic structure (Fig. 1). Four subclasses are well charac-

The author is in the Department of Biophysics, Faculty of Science, Kyoto University, Kitashirakawa, Sakyo-ku, Kyoto 606, Japan.

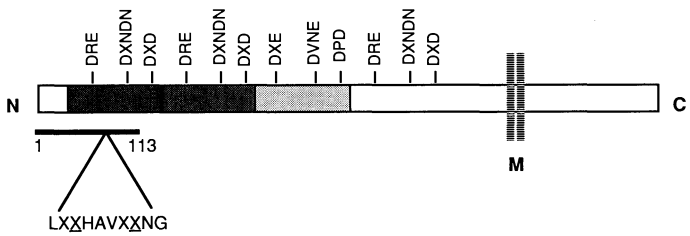

Fig. 1. The basic structure of cadherins. The three shaded segments on the drawing represent three repeated domains in the molecule. Lighter shading in the third repeat indicates that this repeat is less similar to the first two repeats than they are to each other. Some of the repeated sequences conserved in most members of the cadherin family are also shown; the amino acid clusters DXNDN and DXD were proposed to be involved in Ca^{2+}-binding (*9*), and the amino acid clusters DRE and DXNDN were detected in some molecules in *Drosophila* (*18*). The NH_2-terminal 113–amino acid region is responsible for the binding specificities of these molecules, within which the underlined nonconserved amino acid residues are most important in determining the interaction specificity. N, NH_2 terminus; M, membrane-spanning region; C, COOH-terminus; D, aspartic acid; R, arginine; E, glutamic acid; N, asparagine; V, valine; P, proline; and X, an amino acid not conserved among different members of the family.

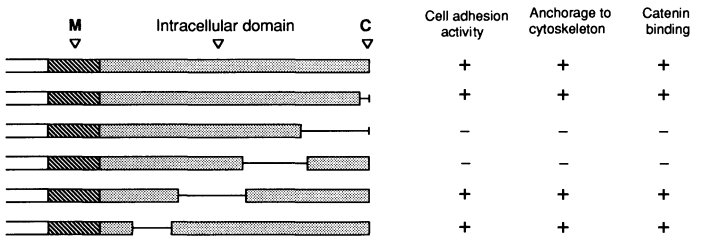

Fig. 2. Effect of deletions in the intracellular domain on the cell-binding function of E-cadherin and on its binding to the cytoplasmic components. Properties of the mutated E-cadherins were analyzed with mouse L cells transfected with the corresponding cDNAs. Deleted regions are represented by thin lines. M, membrane-spanning region; C, COOH-terminus.

terized at the molecular level. They are E-cadherin (epithelial cadherin or uvomorulin) (*8, 9*), P-cadherin (placental cadherin) (*10*), N-cadherin (neural cadherin) (*11–13*), and L-CAM (liver cell adhesion molecule) (*14*). Other subclasses have also been characterized (*15, 16*). Among the subclasses, about 50% of the amino acids are conserved when compared within a single species. The extent of conservation varies with the region of the molecules; the highest percent of conservation is found in the intracellular domain. Homologous cadherin subclasses identified across species are generally well conserved. Each of the subclasses displays a unique pattern of tissue distribution, and in many types of cells multiple cadherin subclasses are coexpressed in varying combinations (*6*). Each cell type thus can be characterized by the expression of a particular cadherin subclass or set of cadherin subclasses.

Recently, novel cadherin-like molecules have been identified that share similar amino acid sequences with the original cadherins but have different overall structures. For example, desmoglein, an intercellular component of desmosomes, has amino acid deletions at a proximal region of the extracellular domain and an additional amino acid tail at the COOH-terminus (*17*). In *Drosophila*, proteins that have cadherin-like amino acid sequences were found (*18*); one of these proteins has a cluster of cadherin-like sequences repeated 34 times in its extracellular domain (the vertebrate cadherins have only three to four repeats of the corresponding sequences) (Fig. 1). These *Drosophila* proteins are implicated in growth control of imaginal disks. We thus need to extend the cadherin family to include a wider group of related molecules with diverse functions.

Cadherin-Mediated Cell Adhesion Specificities

An important property of cadherins is their binding specificities. When cells expressing different cadherins are mixed, they aggregate separately (*19*). These observations were recently confirmed by genetic approaches; cells transfected with cDNAs of different cadherins segregated from each other when mixed, indicating that cadherins are involved in cell adhesion selectivity. Cadherins connect cells to each other by means of their homophilic interactions. In these interactions, they selectively bind to identical cadherin types (*12, 20*). For example, E-cadherin binds selectively to E-cadherin. Therefore, homotypic cell aggregation should occur more efficiently than heterotypic cell aggregation when cell types expressing different cadherins are mixed. These findings now provide a solution, at least in part, to the classical problem of the mechanism of preferential adhesion between homotypic cells.

The above findings led investigators to realize that homotypic cell adhesion specificities are generated by molecular diversification of a single gene family of adhesion receptors. The number of members of the cadherin family is increasing, and cells generally coexpress multiple subclasses of cadherins. Therefore, a wide range of adhesion specificities could be created by combinations of different cadherin molecules.

To determine the molecular sites responsible for binding specificities of cadherins, Takeichi and associates constructed chimeric molecules that consisted of P- and E-cadherin and examined their binding properties (*21*). These analyses showed that the NH_2-terminal 113–amino acid region was essential for their specificities (Fig. 1). The majority of the amino acids in this region are conserved among different members of the cadherin family, but some of them are not conserved. Site-directed mutagenesis of the nonconserved sequences in this region of E-cadherin revealed that mutations at only two amino acid residues altered its binding specificity (Fig. 1); an E-cadherin that has P-cadherin–type amino acid residues at these two sites can interact with both E- and P-cadherin. Therefore, although these residues are essential, cooperation of other sites is necessary for complete binding specificity. Antibodies capable of blocking cadherin activity recognize epitopes localized close to the NH_2 terminus. These observations suggest that the NH_2-terminal regions of cadherins are important in their specific binding interactions.

The finding that cadherins mediate specific cell adhesions does not preclude the differential adhesion hypothesis; this hypothesis attempted to explain the sorting behaviors of cells by assuming only quantitative differences in adhesiveness between cells (*2*). It has been shown that cell lines expressing different amounts of the same type of cadherin segregated from each other in their mixtures (*20*). Therefore, both qualitative and quantitative differences in cellular cadherin expression could contribute to cell sorting. Other adhesion receptors must also be considered if we are to achieve total understanding of cell-sorting mechanisms.

Transmembrane Interaction of Cadherins with Cytoskeletons

The intracellular domain of cadherins is the most conserved region in this molecular family, implying that this domain has an important function. The importance of the intracellular domain was clearly demonstrated by partial or complete deletion of this domain (*22–26*). E- or N-cadherin with the COOH-terminal half of the intracellular domain deleted cannot function as a cell-cell adhesion receptor, even though the extracellular domain remains intact (Fig.

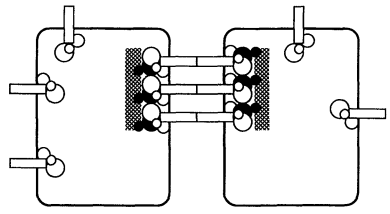

Fig. 3. Schematic representation of cadherin-mediated cell-cell adhesion. Cadherins are always associated with catenins, and the catenin-cadherin complexes are further associated with cytoskeletal components at cell-cell junctions. Open rectangles, cadherins; open circles, catenins; filled circles, other cytoskeletal components; and shaded rectangles, actin bundles.

2). Thus, particular regions of the intracellular domain are necessary for the cell-binding function of the extracellular domain.

Wild-type cadherins are concentrated at the contact sites between cells, and these functional proteins localized to the cell junctions cannot be extracted with nonionic detergents, although cadherins localized to other regions can be extracted (*27, 28*). The nonfunctional mutant cadherins with deletions in the intracellular domain are not concentrated at cell-cell contact sites, and all of them can be extracted with nonionic detergents. These observations suggest that intact cadherins, but not the mutant cadherins, are associated with the cytoskeletal components at cell-cell contact sites. In fact, the detergent-insoluble, junctional cadherins were found to be located with cortical actin bundles when researchers examined cells by immunostaining techniques (*27, 29*). Thus, the association of cadherin with the cytoskeleton by means of its intracellular domain may be crucial for its cell-binding function.

The soluble forms of functional cadherins are associated with cytoplasmic proteins, termed catenin α, β, and γ (*23–25, 28*). These molecules precipitate with E-cadherin upon immunoprecipitation. Catenins do not bind to the mutant E-cadherins with COOH-terminal deletions. Moreover, the catenin-binding sites in the intracellular domain of E-cadherin coincide with the sites that are essential for cell-cell and cytoskeletal binding (Fig. 2) (*24, 25*). The catenin-associated form of E-cadherin can bind to globular actin, but the COOH-terminal mutant forms of E-cadherin cannot (*25*). It appears, therefore, that only the catenin-associated forms of cadherins can be associated with the cytoskeleton, and that the formation of these molecular complexes is a prerequisite for the function of cadherins (Fig. 3).

How the cytoskeletal system is involved in the cell-binding function of the extracellular domain of cadherins is not known. Possibly, interactions between individual cadherin molecules are too weak to connect cells. If so, cadherins may need to aggregate laterally at cell-cell contact sites to achieve sufficient cell-cell binding forces. The cytoskeleton might support these lateral interactions of cadherins, or it might anchor these molecules to the cell-cell contact sites. Such processes may be crucial for cadherins to function as cell adhesion receptors. However, certain observations suggest that the extracellular domain of cadherins has a binding ability in the absence of the authentic intracellular domain or the cytoplasmic elements. (i) Fragments of the extracellular domain can interfere with cadherin-mediated cell-cell adhesion (*30*). (ii) Neurons that express N-cadherin show an adhesive response to culture dishes coated with purified N-cadherin (*31*). (iii) When the intracellular domain of L-CAM was replaced by the intracellular domain of N-CAM (a member of the Ig superfamily of adhesion molecules) the recombinant L-CAM functioned in cellular aggregation (*32*). Therefore, the intracellular domain is not required for some of the activities attributed to the extracellular domain.

At the ultrastructural level, cadherins are concentrated at the zonula adherens junctions, which are characterized by underlying cytoplasmic plaques. These plaques contain multiple classes of proteins, such as vinculin, α-actinin, radixin, and actin filaments (*33*). The intracellular domain of cadherins is believed to interact with these molecules, directly or indirectly. Recent studies with isolated adherens junctions demonstrated that three members of the *src* proto-oncogene family, *src*, *yes*, and *lyn*, have gene products that are concentrated at these junctions, suggesting that the zonula adherens provides a center for the action of these kinases (*34*). Tyrosine kinases may regulate the function of the cadherin-cytoskeleton complex, or they may mediate transmission of intercellular signals at zonula adherens junctions. Cadherins are known to be phosphorylated (*35*).

It will be important to elucidate how cadherin-bearing junctions achieve a polarized distribution in cells; zonula adherens junctions are generally localized at the apical portions of cells (*36*). A related question is whether cadherin-bearing junctions are structurally associated with other junctional structures. The activity of cadherins influences the formation of tight, gap, and desmosome junctions, suggesting some structural interactions between them (*37*). A recent study demonstrated that the transfection of a fibroblast line with E-cadherin cDNA causes the polarized distribution of Na^+,K^+–adenosine triphosphatase (*38*). These findings suggest a function for the cadherin system in the establishment of cell polarities.

Morphogenetic Roles of Cadherins

Expression of cadherins is developmentally regulated. The switching on and off of cadherin expression correlates with a variety of morphogenetic events that involve cell aggregation or disaggregation (*6*). For example, presumptive neural crest cells express E-cadherin (or L-CAM in the chicken) when they are part of the ectoderm but they lose any detectable cadherins when converted into a migratory form. However, they again acquire cadherins when aggregating to form peripheral ganglia. Conversely, the somites, whose cells are connected tightly to each other to form epithelial spheres, strongly express N-cadherin, but, when part of the somites are converted to migrating cells and differentiate into the sclerotome, they cease to express this cadherin. In these phenomena, there is a clear correlation between cadherin expression and adhesive cell behavior; the closely aggregating cells show greater amounts of cadherin expression, whereas the nonaggregating cells show lesser amounts.

Another interesting feature of cadherin expression is observed in the morphogenetic processes that involve the segregation of cell layers (*6*). For example, in the development of the neural tube, the ectoderm originally expresses E-cadherin (or L-CAM in chicken) in the entire region, but the part of the ectoderm that differentiates into the neural tube gradually turns off expression of this cadherin and begins to express N-cadherin. Eventually, the neural tube expresses only N-cadherin, whereas the overlying ectoderm continues to express E-cadherin. Also, neural crest cells that separate from the ectoderm stop expressing all of the cadherins. Thus, three different cell groups that originate from one cell layer exhibit distinct patterns of cadherin expression when separating from each other. Similar changes in the pattern of cadherin expression associated with cell-layer segregation occur in other morphogenetic events, such as gastrulation, lens vesicle formation, and epidermal differentiation. In all of these cases, when a single cell layer gives rise to multiple layers, these layers begin to express different types of cadherins. Observing these phenomena, Takeichi proposed that a switching of cadherin expression is involved in the segregation of cell layers (*6*).

The idea that cadherins are involved in morphogenesis was tested by an artificial perturbation of their original pattern of expression in embryos; this was achieved by the injection of N-cadherin messenger RNA into *Xenopus* fertilized eggs (*13, 26*). Exogenous N-cad-

herin was detected in various regions of the injected embryos, generally showing a mosaic distribution pattern. In these embryos, various effects of ectopic N-cadherin expression during morphogenesis were observed. When this molecule was strongly expressed in the epidermis, the epithelial layer became thicker than in the control, and cell morphology was converted from the squamous type to the cuboidal or columnar type. When the high ectopic expression of N-cadherin occurred in parts of the neural tube or the mesoderm, disorganized tissue morphologies were observed; cells in these regions condensed into clumps and formed sharp boundaries with adjacent cells that expressed only endogenous N-cadherin. These observations provide evidence that the amount of cadherins expressed has a direct effect on the morphology of tissues. The thickening of the epidermis is probably a result of increases in lateral adhesiveness between cells, and, likewise, the condensation of cells is induced by increases in their mutual adhesiveness. Thus, quantitative differences in cadherin expression affect tissue morphology.

Another effect of ectopic N-cadherin expression is observed when it occurs both in the dorsal epidermis and in the neural tube. In this case, the neural tube cannot separate from the epidermis but remains partly fused. In normal development, the epidermis that separates from the neural tube does not express N-cadherin. Therefore, the failure of these two structures to separate can be ascribed to the aberrant pattern of N-cadherin expression. Thus, the spatiotemporal regulation of cadherin expression at both quantitative and qualitative levels is essential in controlling morphogenesis.

In elucidating the function of specific cell-cell adhesion in morphogenesis, researchers found that the nervous system provides still more complex phenomena to investigate. It contains many different types of neurons and glia, which are interconnected in a specific manner. Do cadherins participate in controlling such specific neural cell connections? Neural tissues express N-cadherin, and its expression begins during the formation of the neural tube and the peripheral ganglia (*39*). The pattern of distribution of N-cadherin, however, changes during development. For example, in the chicken embryonic retina, all cells express N-cadherin in the early undifferentiated stages, but this expression becomes restricted to particular layers during development and eventually ceases by the time of hatching (except at the outer limiting layer) (*40*). Consistent with the developmental change in the distribution of N-cadherin, antibodies to this protein can destroy the structure of the retina almost completely at the early stage, but only partially at the later stages (*40*). If cadherins are essential to neural morphogenesis throughout development, the disappearance of N-cadherin from differentiated retina raises the possibility of the presence of other cadherin subclasses. In fact, recent studies have identified several novel neural cadherins (*15, 41*), and it has also been found that E-cadherin, which is distributed mostly in epithelial tissues, is present in some types of neurons and glia (*41*).

One of the novel cadherins is R-cadherin (*41*). This cadherin was identified from chicken retina, and its expression increases during retinal development, in contrast to N-cadherin expression. At the later stages of development, R-cadherin becomes the predominant retinal cadherin, and its distribution is complementary to that of N-cadherin in the retina. Although the expression of this and other novel neural cadherins has not been extensively studied, it is expected that they, too, will show distinct tissue distributions. Thus, we can imagine that neural tissues are a mosaic of various cell types that express distinct cadherins. Future studies should test the function of cadherins in sorting neural cells during the development of the nervous system.

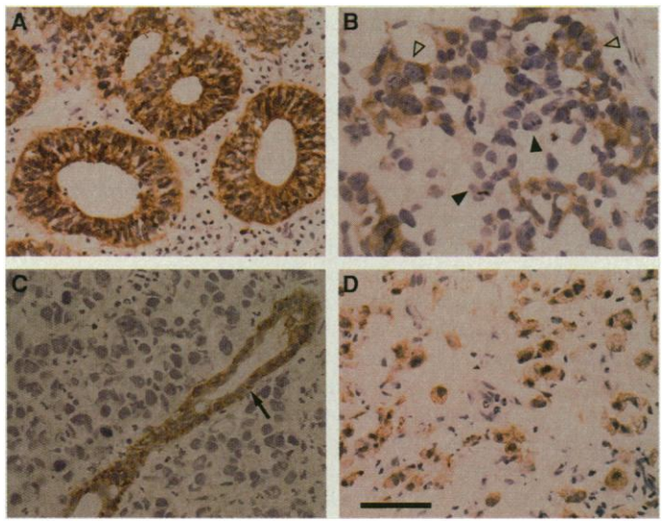

Fig. 4. Four different patterns of E-cadherin expression in human gastric adenocarcinoma. (**A**) E-cadherin is expressed in all tumor cells. Most of the differentiated-type tumors exhibit this type of pattern. (**B**) E-cadherin–positive and –negative cells are mixed. Open and filled arrowheads indicate some of the positive and negative cells, respectively. (**C**) E-cadherin is not detected throughout the tumor. Arrow indicates staining of the normal gastric epithelia. (**D**) E-cadherin–positive cells are scattered and do not aggregate. The peroxidase-diaminobenzidine reaction was used for the detection of E-cadherin. Bar, 50 μm. [Photographs by H. Oka and H. Shiozaki, Osaka University Medical School.]

Possible Implications of Cadherins in Tumor Invasion and Metastasis

The initial step of cancer metastasis is the detachment of cells from the primary tumor mass. In general, when cadherins are sufficiently active, cells, especially epithelial ones, are unable to disrupt their mutual connections; it is only when cadherins are inactivated that cells can be freed from their adhesive constraints and migrate out of their parent colonies. Therefore, the suppression of cadherin activity might trigger the release of tumor cells. This could occur either by the suppression of cadherin gene expression or by the loss of function of the expressed cadherin molecules.

Malignant transformation does not necessarily affect cadherin activity. However, when comparisons were made between tumor cells with higher and lower activities of spontaneous metastasis, differences were observed in cadherin expression. For example, an ovarian tumor line with a high spontaneous metastatic activity showed a very low amount of E-cadherin expression, as compared with the control line, which had a lower metastatic activity (*42*). Moreover, E-cadherin expression was unstable and varied with cell culture conditions in the highly metastatic line (*42*). These in vitro findings suggest that metastasis is enhanced by the down-regulation of cadherin expression. This is consistent with the results of other studies that indicate that inhibition of cadherins with antibodies promotes the invasion of normal tissues by tumor cells (*43*).

The most important question is, however, whether cadherin expression is altered in human cancers. Extensive studies are under way to examine cadherin expression in various human carcinomas. The results obtained at this point are intriguing (*44*). In gastric carcinoma, highly differentiated tumors generally maintain homogeneous, strong expressions of E-cadherin (Fig. 4A), as do all normal gastric epithelial cells. In poorly differentiated tumors, cadherin expression is altered; E-cadherin–positive and –negative cells can be mixed (Fig. 4B), or in extreme cases, E-cadherin expression can be virtually suppressed throughout the tumor (Fig. 4C). Pathological examination of these samples suggests that tumors

that lose E-cadherin tend to be more invasive. In another type of tumor, cells do express E-cadherin, but they are scattered and do not form close contacts with each other (Fig. 4D), suggesting that the cadherins are not functioning normally. Such cells also appear to be highly invasive. The observation that the expression or activity of cadherins is down-regulated in many human carcinomas is consistent with the idea that the invasiveness of tumor cells is associated with aberrant cadherin function.

Concluding Remarks

The data presented above indicate that cadherins are important in morphogenetic processes. The number of cadherin molecules expressed in a cell directly affects its adhesiveness, which consequently modulates the overall morphology of its cell group. Furthermore, cadherins confer selective adhesiveness on cells, which may function in the segregation of these cells during morphogenesis. Cadherins are thus important determinants of tissue morphology. New subclasses of cadherins that have been identified in the nervous system may contribute to the sorting of neural cells.

Another important aspect of the function of cadherins is that they form a complex with the cytoskeleton and that the tyrosine kinases of the *src* family are localized to this complex. This raises the possibility that cadherin-mediated cell-cell junctions might be used for intercellular signaling. Finally, cadherin expression or function was found to be perturbed in human invasive carcinoma. Although further analyses are necessary to confirm the causal relations between the altered cadherin activity and tumor invasiveness, the results presented here indicate that consideration should be given to cadherins in the elucidation of the molecular basis of tumor invasion and metastasis.

REFERENCES AND NOTES

1. P. L. Townes and J. Holtfreter, *J. Exp. Zool.* **128**, 53 (1955); P. B. Armstrong, *CRC Crit. Rev. Biochem. Mol. Biol.* **24**, 119 (1989).
2. M. S. Steinberg, *Science* **141**, 401 (1963).
3. B. A. Cunningham *et al.*, *ibid.* **236**, 799 (1987); S. Benchimol *et al.*, *Cell* **57**, 327 (1989).
4. T. A. Springer, *Nature* **346**, 425 (1990).
5. T. Elkins, M. Hortsch, A. J. Bieber, C. S. Goodman, *J. Cell Biol.* **110**, 1825 (1990).
6. M. Takeichi, *Development* **102**, 639 (1988); *Annu. Rev. Biochem.* **59**, 237 (1990).
7. J.-L. Duband *et al.*, *J. Cell Biol.* **104**, 1361 (1987); H. Larjava *et al.*, *ibid.* **110**, 803 (1990).
8. A. Nagafuchi, Y. Shirayoshi, K. Okazaki, K. Yasuda, M. Takeichi, *Nature* **329**, 341 (1987); A. Masouri, N. Spurr, P. N. Goodfellow, R. Kemler, *Differentiation* **38**, 67 (1988).
9. M. Ringwald *et al.*, *EMBO J.* **6**, 3647 (1987).
10. A. Nose, A. Nagafuchi, M. Takeichi, *ibid.*, p. 3655; Y. Shimoyama *et al.*, *Cancer Res.* **49**, 2128 (1989).
11. K. Hatta, A. Nose, A. Nagafuchi, M. Takeichi, *J. Cell Biol.* **106**, 873 (1988).
12. S. Miyatani *et al.*, *Science* **245**, 631 (1989).
13. R. J. Detrick, D. Dickey, C. R. Kintner, *Neuron* **4**, 493 (1990).
14. W. J. Gallin, B. C. Sorkin, G. M. Edelman, B. A. Cunningham, *Proc. Natl. Acad. Sci. U.S.A.* **84**, 2808 (1987).
15. B. Ranscht and M. T. Dours, *Soc. Neurosci. Abstr.* **15**, 959 (1989); L. F. Reichardt *et al.*, *Cold Spring Harbor Symp. Quant. Biol.*, in press; S. Suzuki, K. Sano, H. Tanihara, *Cell Regul.*, in press.
16. R. L. Heimark, M. Degner, S. M. Schwartz, *J. Cell Biol.* **110**, 1745 (1990).
17. P. J. Koch *et al.*, *Eur. J. Cell Biol.* **53**, 1 (1990).
18. P. A. Mahoney *et al.*, in preparation.
19. M. Takeichi, T. Atsumi, C. Yoshida, K. Uno, T. S. Okada, *Dev. Biol.* **87**, 340 (1981); M. Takeichi, K. Hatta, A. Nagafuchi, in *Molecular Determinants of Animal Form*, G. M. Edelman, Ed. (Liss, New York, 1985), pp. 223–233.
20. A. Nose, A. Nagafuchi, M. Takeichi, *Cell* **54**, 993 (1988); D. R. Friedlander, R. M. Mege, B. A. Cunningham, G. M. Edelman, *Proc. Natl. Acad. Sci. U.S.A.* **86**, 7043 (1989).
21. A. Nose, K. Tsuji, M. Takeichi, *Cell* **61**, 147 (1990).
22. A. Nagafuchi and M. Takeichi, *EMBO J.* **7**, 3679 (1988).
23. M. Ozawa, H. Baribault, R. Kemler, *ibid.* **8**, 1711 (1989).
24. A. Nagafuchi and M. Takeichi, *Cell Regul.* **1**, 37 (1990).
25. M. Ozawa, M. Ringwald, R. Kemler, *Proc. Natl. Acad. Sci. U.S.A.* **87**, 4246 (1990).
26. T. Fujimori, S. Miyatani, M. Takeichi, *Development* **110**, 97 (1990).
27. S. Hirano, A. Nose, K. Hatta, A. Kawakami, M. Takeichi, *J. Cell Biol.* **105**, 2501 (1987).
28. W. J. Nelson, E. M. Shore, A. Z. Wang, W. W. Hammerton, *ibid.* **110**, 349 (1990).
29. F. Matsuzaki *et al.*, *ibid.*, p. 1239.
30. M. J. Wheelock, C. A. Buck, K. B. Bechtol, C. H. Damsky, *J. Cell. Biochem.* **34**, 187 (1987).
31. J. L. Bixby and R. Zhang, *J. Cell Biol.* **110**, 1253 (1990).
32. S. H. Jaffe *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **87**, 3589 (1990).
33. B. Geiger, *Curr. Opin. Cell Biol.* **1**, 103 (1989).
34. Sh. Tsukita *et al.*, in preparation.
35. M. Hamaguchi and M. Takeichi, in preparation.
36. E. Rodriguez-Boulan and W. J. Nelson, *Science* **245**, 718 (1989).
37. Y. Kanno, Y. Sasaki, Y. Shiba, C. Yoshida-Noro, M. Takeichi, *Exp. Cell Res.* **152**, 270 (1984); B. Gumbiner and K. Simmons, *J. Cell Biol.* **102**, 457 (1986); B. Gumbiner, B. Stevenson, A. Grimaldi, *ibid.* **107**, 1575 (1988); R.-M. Mege *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **85**, 7274 (1988).
38. H. McNeill, M. Ozawa, R. Kemler, W. J. Nelson, *Cell* **62**, 309 (1990).
39. K. Hatta and M. Takeichi, *Nature* **320**, 447 (1986); K. Hatta, S. Takagi, H. Fujisawa, M. Takeichi, *Dev. Biol.* **120**, 215 (1987); M. Matsunaga, K. Hatta, A. Nagafuchi, M. Takeichi, *Nature* **334**, 62 (1988); K. J. Tomaselli, K. M. Neugebauer, J. L. Bixby, J. Lilien, L. Reichardt, *Neuron* **1**, 33 (1988); J.-L. Duband, T. Volberg, I. Sabanay, J. P. Thiery, B. Geiger, *Development* **103**, 325 (1988).
40. M. Matsunaga, K. Hatta, M. Takeichi, *Neuron* **1**, 289 (1988).
41. M. Takeichi, H. Inuzaka, K. Shimamura, T. Fujimori, A. Nagafuchi, *Cold Spring Harbor Symp. Quant. Biol.*, in press.
42. M. Hashimoto, O. Niwa, Y. Nitta, M. Takeichi, K. Yokoro, *Jpn. J. Cancer Res.* **80**, 459 (1989).
43. J. Behrens, M. M. Mareel, F. M. Van Roy, W. Birchmeier, *J. Cell Biol.* **108**, 2435 (1989).
44. H. Shiozaki *et al.*, in preparation; Y. Shimoyama and S. Hirohashi, in preparation.

45. I thank H. Shiozaki, H. Oka, and other members of Department of Surgery II, Osaka University Medical School; Y. Shimoyama and S. Hirohashi for communicating unpublished results on the cadherin expression in human carcinoma; L. Reichardt, W. W. Franke, P. Mahoney, and C. Goodman for communicating unpublished data; G. Radice for critical reading of the manuscript; and K. Fukusaki for preparing the manuscript. Supported by research grants from the Ministry of Education, Science, and Culture of Japan; the Special Coordination Fund of the Science and Technology Agency of the Japanese Government; and the Naito Foundation.