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REVIEW

Common Principles in Cell Adhesion

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INTRODUCTION

There are two principle kinds of cell adhesion: In cell–cell adhesion physical bonds are formed between adjacent cells, and in cell–matrix adhesion those bonds bind cells to adhesive proteins in extracellular matrices. Both kinds of cell adhesion are involved in a variety of basic processes in multicellular organisms (Fig. 1).

By guiding cells into their appropriate locations in the body and by anchoring them there, adhesive interactions are thought to play a major role in the construction of the body plan of multicellular organisms during development. Adhesion is also important in the maintenance of the body plan; tumor cells are able to loosen their attachment to leave their original location and become lodged at distant sites. Several families of adhesion molecules, many with a large number of members, have been discovered and characterized during the past several years. In addition to mediating adhesive interactions, the "classical" adhesion molecules also serve as signaling molecules. Conversely, certain cell surface proteins that resemble growth factor receptors in their structure have adhesive functions. Despite the bewildering number of these molecules, certain unifying themes have begun to emerge. Moreover, the potential applications of the field in tissue reconstruction, cancer, and many other diseases is receiving increasing attention. The purpose of this review is to outline some of the unifying principles in cell adhesion.

COMMON STRUCTURAL MOTIF IN MANY ADHESION MOLECULES

A striking unifying property of cell adhesion molecules is that many of them share structural features; the adhesive domains in fibronectin, immunoglobulin (Ig) type cell–cell adhesion proteins, and cadherins are all structurally related and serve in various combinations as building blocks in many adhesion proteins.

Fibronectin and some other matrix molecules, which are ligands for the integrin family of adhesion receptors, contain multiple repeats of a 90-amino-acid domain known as fibronectin type III (FNIII) domains; some of these contain sites for cell attachment. The structures of the FNIII domains that contain the RGD cell attachment site of fibronectin and tenascin have been determined. NMR and crystallographic analyses show that the domains consist of two β sheets, one with four β strands and the other with three [1–3]. The RGD site [4] resides in an exposed turn connecting two of the β strands in this structure. The basic structure of the FNIII domain resembles closely the domain that is characteristic of the immunoglobulin superfamily of molecules, the Ig fold [5, 6]. Like the FNIII domains, Ig domains are common in adhesion molecules; they are most often found in cell–cell adhesion molecules, often together with FNIII domains. Thus, the classical Ig superfamily cell–cell adhesion molecules, such as N-CAM, contain both Ig and FNIII domains, as do the Eph family of tyrosine kinases [7, 8] and tyrosine phosphatases that function as cell adhesion molecules [9].

Quite recently the repeating units of another major family of adhesion proteins, the cadherins, have been found to be related to the Ig and FNIII repeats [10, 11]. Among the other main families of adhesion proteins, integrins and selectins do not appear to contain domains related to the Ig fold, although most of their detailed structure remains to be determined. However, many of the integrin ligands belong to one of the Ig fold protein families. Moreover, the ligand binding sites of integrins and selectins have some similarities (see below).

The prevalence of the Ig fold in adhesion proteins suggests that the same primordial recognition unit may have given rise to many of the binding structures of present day cell adhesion molecules, as well as to those of the immune system. Alternatively, some features of the Ig fold may make it particularly well suited for cell adhesion functions and that may have driven

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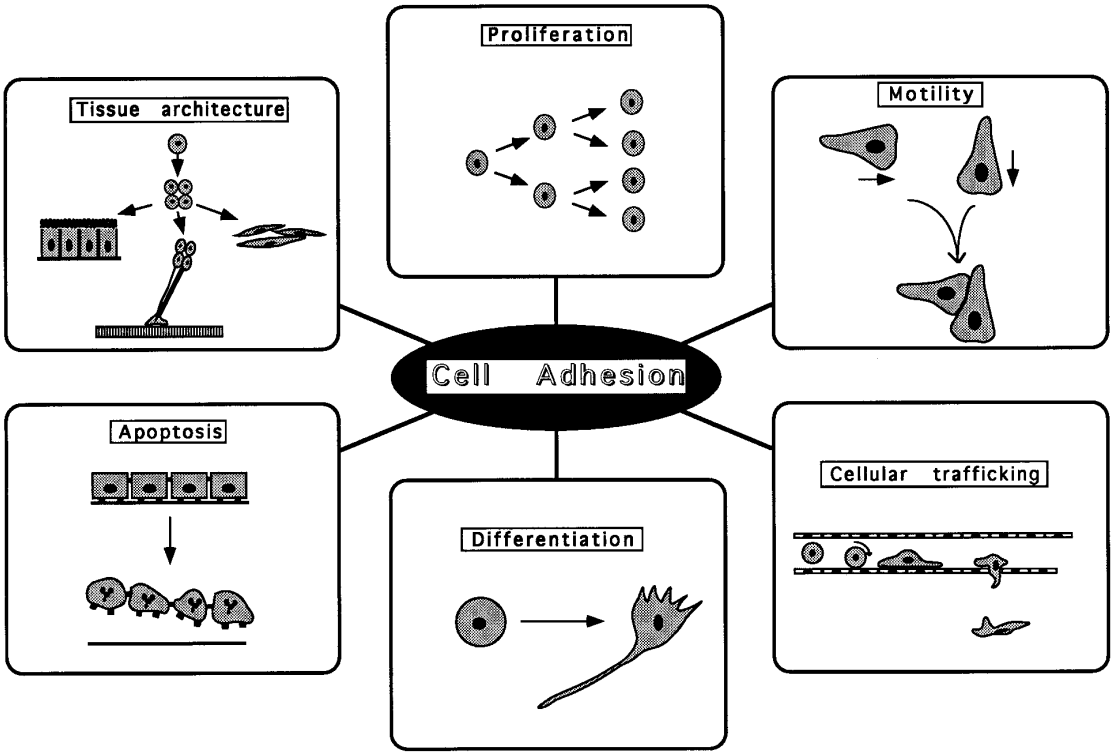

FIG. 1. Role of cell adhesion in basic multicellular processes.

convergent evolution of various adhesion protein families toward the Ig structure. The ability to serve as building blocks for elongated, relatively rigid molecules could be such a feature: it would allow the adhesive site to project away from the cell membrane or from other binding sites in the same protein molecule.

COMMON FEATURES OF LIGAND RECOGNITION

Heterophilic and homophilic binding. The primary binding mode of the cadherins and Ig family adhesion proteins is homophilic self-association, whereas the integrins and selectins recognize other types of molecules in a heterophilic binding mode [12, 13]. However, Ig family members, cadherins, and apparently other integrins can all serve as integrin ligands [14–17], and integrin–integrin binding may also mediate cell–cell adhesion [18, 19]; however, see also [20]. Thus, the distinction between homophilic and heterophilic adhesion molecules is somewhat arbitrary. Moreover, as discussed next, the recognition by integrins of their ligands may well have its origins in homophilic binding.

The key amino acid residue in integrin ligands is an aspartic acid or, sometimes, a glutamic acid [4, 21]. Similarly, aspartate residues play a key role on the integrin side; the binding sites in the integrin subunits each contain aspartic acid residues in a 23-amino-acid ligand binding segment, and mutations in these residues impairs ligand binding [22]. Moreover, a peptide has been identified from a random peptide library that recognizes the RGD sequence in a manner similar to the integrins, and this peptide contains a pair of aspartic acid residues embedded in an otherwise hydrophobic sequence [23]. Mutational analyses have also shown that certain aspartic acid residues in integrin α subunits are important in ligand binding [24–26].

A short peptide that incorporates both this RGD binding motif and the RGD sequence binds to itself [23]. Thus, the integrin ligand recognition may have evolved from a self-complementary binding structure centered around an aspartic acid residue, the homophilic nature of which would resemble the present day cell–cell adhesion systems. The crystal structure of a ligand binding site in one of the integrins has been determined [27]; a complete structure is eagerly awaited to provide a full structural explanation for the integrin–ligand binding.

Dependency on divalent cations. Among the adhesion protein families, integrins, cadherins, and selectins are divalent cation dependent in their ligand binding. The ligand binding sites in the integrin α subunits contain binding sites for divalent cations that resemble EF hands but differ from canonical EF hands in that one coordination site is absent. It has been proposed

that the critical aspartic acid residues in the ligand and receptor binding sites enable the ligand and receptor to jointly coordinate a divalent cation [28]. However, it has also been shown that the divalent cation is extruded from the $\alpha_{IIb}\beta_3$ integrin as it binds its ligand [22], and a peptide that mimics the ligand binding site in the β_3 subunit binds RGD-containing ligands in a divalent cation-independent manner [23]. These results suggest that if the joint coordination hypothesis is correct, the cation–ligand complex may be transient.

The X-ray and NMR structures of cadherin homophilic binding domains indicate that the divalent cation (Ca^{2+}) binding site is spatially separated from the presumed ligand binding site [10, 11], but is needed for the ligand binding activity. The situation may be similar in integrins; the peptide from the β3 subunit that is capable of divalent cation-independent ligand binding [23] is structurally constrained by cyclization, and this may force it into a conformation compatible with ligand binding. In the intact integrin it may be the cation that provides similar folding constraint. In the cadherin polypeptide, the cation stiffens the joint between adjacent modules [11], perhaps allowing the molecule to extend farther from the cell membrane than would be the case otherwise.

The role of divalent cations in the ligand binding by α-mannose binding lectin, which like the selectins is a member of the family of C-type lectins, has been clarified by protein crystallography [29]. One of the two Ca^{2+} ions of this lectin is jointly coordinated by two hydroxyl groups from the ligand, mannose, and by five amino acid side chains from the lectin. However, four of the five amino acid side chains are also engaged in hydrogen bonds with the two mannose hydroxyl groups. Thus, the binding arrangement may not be that different from that in integrins.

Low affinity. One other ligand binding feature that is shared by most, if not all, adhesion proteins is their relatively low affinity for their ligands. For example, the K_d of the $\alpha_5\beta_1$ integrin binding to fibronectin is in the order of 10^{-7} M [30], and the K_d for homophilic binding of polysialylated N-CAM is in the order of 10^{-6} M [31]. By comparison, N-CAM binds to heparin with a K_d of about 10^{-8} M [32]. The reason for the low affinities appears to be that adhesion proteins are designed to function coordinately as a part of a multimolecular zipper, rather than individually [11]. As some extracellular matrix adhesion proteins—notably fibronectin and vitronectin—exist also as soluble proteins in the blood, high receptor affinities would tend to cause the receptors to be blocked by the soluble ligand, preventing cell adhesion.

REGULATION OF ADHESION RECEPTOR AFFINITY—INSIDE-OUT SIGNALING

The ligand binding activity of adhesion receptors is regulated by the cells that express them. This process has been termed inside-out signaling. The regulation of integrin activity in cells circulating in the blood is a particularly good example of inside-out signaling. The $\alpha_{IIb}\beta_3$ integrin in platelets and the β_2 integrins of white blood cells are expressed at the cell surface, but in a configuration that does not bind ligand. The activation of ligand binding allows a cell to respond quickly to a change in environment. Thus, blood clotting is initiated by platelets, the $\alpha_{IIb}\beta_3$ integrin of which has become activated causing platelet aggregation. Similarly, leukocytes attach to blood vessel walls through β_2 integrins that have been activated by inflammatory signals [33]. Among adherent cells integrin activity is modulated at least in keratinocytes [34] and some neuronal cells [35]. The molecular mechanisms of integrin activation are not well understood, but are thought to be mediated by the integrin cytoplasmic domains and involve heterotrimeric G-proteins, phospholipids, and protein kinases [33]. In src-transformed cells the ligand binding activity of integrins can be downregulated through tyrosine phosphorylation of the β_1 cytoplasmic domain by the src kinase [36]. On the cytoplasmic side, the binding of talin, one of the connections of the integrins to the actin cytoskeleton, is lost upon the tyrosine phosphorylation, and the phosphorylated β subunit is no longer associated with focal adhesions [36, 37]. This and other evidence [12] emphasizes the strong dependence of integrin function on the connection to the actin cytoskeleton, but other regulatory interactions are also likely to exist.

Cadherins also have cytoplasmic companion proteins that connect these receptors to actin filaments and signaling systems. These proteins, catenins, are necessary for the homophilic binding activity of cadherins, and their adhesion-supporting activity is regulated by phosphorylation [38]. A newly discovered adhesion protein, trophinin, is similarly dependent on a cytoskeletal protein for its adhesive activity [39]. Among the Ig superfamily adhesion proteins, C-CAM is regulated by calmodulin, which binds to the cytoplasmic domain of C-CAM [40] and PECAM activity is regulated by TGF-β [41].

In some cases, the ligand specificity of an adhesion receptor can also be regulated. Thus, the $\alpha_2\beta_1$ integrin can be induced from being totally inactive to becoming a collagen receptor and further to acquiring also the ability to bind laminin [42]. Clearly, the ability of adhesion receptors to be regulated in their activity and specificity adds a great deal to the versatility of cell adhesion.

PHYSICAL CONSEQUENCES OF ADHESION MOLECULE ENGAGEMENT

The main families of adhesion receptors connect to the cytoskeleton inside the cell. Integrins and cadher-

ins are associated with the actin microfilament system. The actin association of integrins is mediated by talin and α-actinin [43, 44], while α-catenin and β-catenin serve in that role for the cadherins [45]. However, at least one integrin, $\alpha_6\beta_4$ and the cadherin-related desmosomal proteins, desmogleins and desmocollins, are associated with intermediate filaments rather than the actin microfilaments [46–48]. Less is known about the cytoskeletal associations of the Ig superfamily and selectin family members. Evidence for association with the cytoskeleton has been presented both for N-CAM [49] and for C-CAM [50], and both I-CAM-1 and P-selectin have been shown to bind to α-actinin [51, 52], which in turn could connect these adhesion molecules to vinculin and actin. This arrangement is similar to the binding of the integrin cytoplasmic domains to the actin microfilament system. Many Ig type adhesion proteins are GPI-linked to the cell membrane, lacking a cytoplasmic domain that could mediate direct binding to cytoskeletal elements. GPI-linked proteins are generally insoluble in non-ionic detergents [53, 54], but this seems to reflect the composition of the associated lipids rather than association with the cytoskeleton. In general, integrins and cadherins would appear to be mediating strong adhesive interactions through the cytoskeletally connected adhesion plaques they form, whereas the Ig superfamily members are more likely to serve in fine-tuning of adhesion and guidance of cell migration.

An important aspect of adhesion receptor function is the clustering of these receptors that results from contact with the ligand. Integrins accumulate in focal adhesions and extracellular matrix contacts [55], and the cadherins assemble in specialized cell–cell contacts, adherence junctions [38]. These are sites where the cytoskeletal filaments make their connection to the adhesion apparatus. Perhaps more significant is the resulting clustering of various signaling molecules at the interface of the adhesion receptors and the connecting cytoskeleton. Thus, focal adhesions appear to contain one of the highest concentrations of proteins phosphorylated at tyrosine residues, a hallmark of signaling molecules [56]. The high concentration of signaling molecules at focal adhesions makes possible molecular interactions that would not take place in more dilute solutions because of insufficient affinities. This concentration factor, and proximities of multiple components necessary to complete signal transduction through complex pathways, facilitate efficient signaling. One important proximity is likely to be that of the cell membrane, as many signaling molecules require membrane association to be active (e.g., ras) or have their enzymatic substrates in the membrane (e.g., PI-3 kinase).

One other phenomenon that is greatly influenced by the physical parameters of adhesion is cell migration. Traction from integrin-mediated adhesion to extracellular matrix is necessary for migration, but strong matrix adhesion and cadherin-mediated cell–cell adhesion can inhibit migration (see below).

CELL ADHESION AND SIGNALING

Exciting developments have taken place in this particular aspect of adhesion research. It has become clear that adhesion is intimately coupled to signal transduction, and that most, if not all, adhesion receptors function also as signaling molecules (Fig. 2). The signaling pathways of the various adhesion molecules are incompletely understood, but two general principles have emerged: First, the various adhesion receptors are closely linked to protein kinases and phosphatases; in fact, some adhesion proteins are kinases or phosphatases. Second, adhesion receptors cooperate with growth factor receptors through physical linkages between the two kinds of receptors and through convergence of signaling pathways. Important cell biological phenomena, such as anchorage dependence of growth and contact inhibition of growth are turning out to be linked to adhesion receptor signaling. Among the adhesion receptors, integrins have been studied in greatest detail regarding their signaling functions.

Signaling pathways. Integrin ligation leads to the assembly of focal adhesions, which are specialized substrate contacts containing high concentrations of integrins, cytoskeletal proteins and various signaling molecules; these structures are thought to be the principal sites of integrin signaling. The formation of focal adhesions induces tyrosine phosphorylation of a number of cytoskeletal components and signaling molecules at the cytoplasmic surface of the cell membrane. As discussed above, the concentration of various signaling molecules into focal adhesions and the resulting proximities of multiple components are likely to facilitate efficient signaling at focal adhesions.

A number of protein tyrosine kinases are activated in focal adhesions as a result of integrin ligation. Particularly central to integrin signaling is focal adhesion kinase (FAK), which appears to bind directly to integrins [57]. FAK becomes activated through autophosphorylation when cells attach through an integrin and is then phosphorylated further by the src kinase [58]. A number of other signaling molecules subsequently bind to FAK and are phosphorylated by it, including Grb-2, which links FAK to the ras pathway, and the 85-kDa subunit of PI-3 kinase [58–60]. The proteins that become phosphorylated include the src substrates $p130^{Cas}$ and the cytoskeleton-associated proteins paxillin, tensin, and cortactin [61–65].

There are striking parallels between the integrin signaling pathways described above and those associated with cadherins. The cell–cell contacts formed

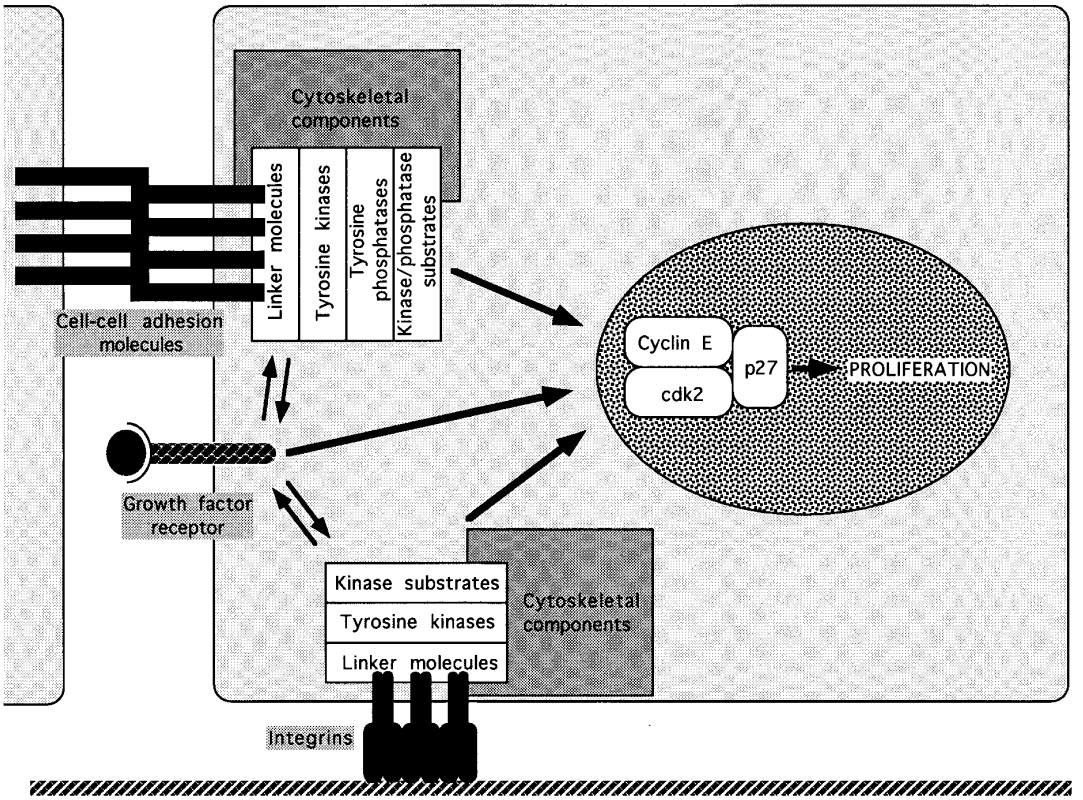

FIG. 2. Signaling pathways of cell adhesion receptors.

by cadherins are also rich in phosphotyrosine, this phosphotyrosine is contained in src substrate proteins, and a FAK-related protein has recently been discovered in these structures [66–68]. Moreover, β-catenin is likely to be a regulatory and signaling molecule; the colon cancer tumor suppressor protein APC competes with cadherin for β-catenin binding, and β-catenin has been found to be capable of translocating into the cell nucleus [48, 69].

Less is known about the signaling properties of the Ig superfamily adhesion proteins, but some of them also appear to be associated with src family kinases. One indication is that src-related kinases are concentrated in growth cones [70], and src-negative but not fyn- or yes-negative cerebellar cells extend shorter neurites when grown on substrates containing the adhesion molecule L1 *in vitro* [71]. However, $p59^{fyn}$ seems to be essential for N-CAM-dependent neurite outgrowth [72]. Moreover, it has been found that extracellular interactions of N-CAM and L1 regulate cellular calcium fluxes, probably via interactions with the FGF receptor (see below). Another demonstration of transmembrane signaling mediated by Ig superfamily adhesion proteins is the finding that transmembrane N-CAM, but not GPI-linked N-CAM, downregulates the expression of matrix metalloproteinases [73]. Integrins also regulate the expression of metalloproteinase genes [74]. A direct interaction with nonreceptor kinases has been demonstrated for the Ig superfamily adhesion molecule C-CAM. Thus, tyrosine phosphorylation of the large cytoplasmic domain isoform of C-CAM leads to binding and activation of $pp60^{c\text{-}src}$ [75]. This is the same C-CAM isoform that has growth regulatory and tumor suppressor properties (see below).

As mentioned earlier, many Ig type adhesion proteins are GPI-linked to the cell membrane. However, there are a number of observations suggesting that GPI-linked surface glycoproteins are capable of mediating cell activation and that the GPI anchor is a structure capable of facilitating signal transduction. Antibody-induced cross-linking of GPI-linked molecules leads to T-cell activation [76, 77] and to calcium fluxes and oxidative burst in monocytes and granulocytes [78]. Moreover, it has been found that in several types of leukocytes src-like protein tyrosine kinases, such as $p53/p56^{lyn}$ and $p56^{lck}$, are physically associated with GPI-linked surface proteins, suggesting a potential mechanism for signal transduction [54, 79].

The adhesion receptor–growth factor connection. It has been known for some time that extracellular matrices, mostly through their proteoglycan component, can regulate the activities of growth factors. A prime exam-

ple is fibroblast growth factor (FGF), which binds to the heparan sulfate component of proteoglycans and which actually requires heparan sulfate as a cofactor to bind to the receptor that transmits its growth signal into the cell [80].

More recent is the realization that adhesion receptors cooperate closely with growth factor receptors. Thus, one of the integrins, $\alpha_v\beta_3$ is associated with insulin receptor substrate-1 (IRS-1), which is a cytoplasmic signal transduction mediator of the insulin and insulin-like growth factor (IGF) receptors [81]. Growth stimulation by insulin is enhanced in cells that have attached to a substrate through the $\alpha_v\beta_3$ integrin. Platelet derived growth factor (PDGF) may cooperate with the $\alpha_v\beta_3$ integrin in an analogous manner, because a protein phosphorylated in cells treated with PDGF binds to this integrin [82]. The Ig superfamily member, C-CAM, is one of the main proteins that become phosphorylated on tyrosine in insulin-stimulated hepatocytes [83]. It remains to be seen whether C-CAM might modify insulin signaling in a manner similar to the $\alpha_v\beta_3$ integrin and whether insulin might affect the functions of C-CAM.

N-CAM and L-1, as well as N-cadherin, can activate the FGF receptor [84]. These adhesion molecules appear to serve as pseudoligands for the FGF receptor, binding to it at recognition sequences that resemble their own homophilic recognition sites. Finally, E-cadherin is physically associated with the EGF receptor [85], suggesting a possible functional link between these receptors.

Thus, many, if not all, growth factor receptors have their specific adhesion receptor partner or partners. These circumstances may, at least partly, explain the effects of cell adhesion in various growth-related phenomena.

Anchorage dependence and contact inhibition of growth. An important new development is the recent realization that integrin-mediated adhesion and signaling is responsible for anchorage dependence of growth and cell survival (Fig. 3). In fibroblasts, detachment from substrate causes a cessation of growth. The block is in the G1 phase, and it is apparently caused by loss of activity of the cyclinE/cdk2 complexes [86]. Epithelial and endothelial cells are not only incapable of proliferating when denied attachment, they undergo apoptosis [87–90]. This apoptosis mechanism has been termed anoikis.

Only integrin-mediated attachment circumvents anoikis; attachment to antibodies against the main histocompatibility complex proteins, or to a polylysine substrate, fails to rescue the cells. Moreover, it may not suffice that cells attach to the substrate through any integrin; Chinese hamster ovary cells and human osteosarcoma cells, when cultured under serum-free conditions, survived only if they attached through the $\alpha_5\beta_1$ integrin, whereas some other integrins, while supporting cell attachment, could not rescue the cells from apoptosis [91]. Other types of cells may depend on other integrins for survival [92–94], and cellular dependence on a given integrin may shift to another integrin depending on the circumstances. Thus, a long-known cell biological phenomenon, anchorage dependence, seems to have found a partial molecular explanation; of course, the signaling pathways utilized by the integrins to govern anchorage dependence will have to be elucidated.

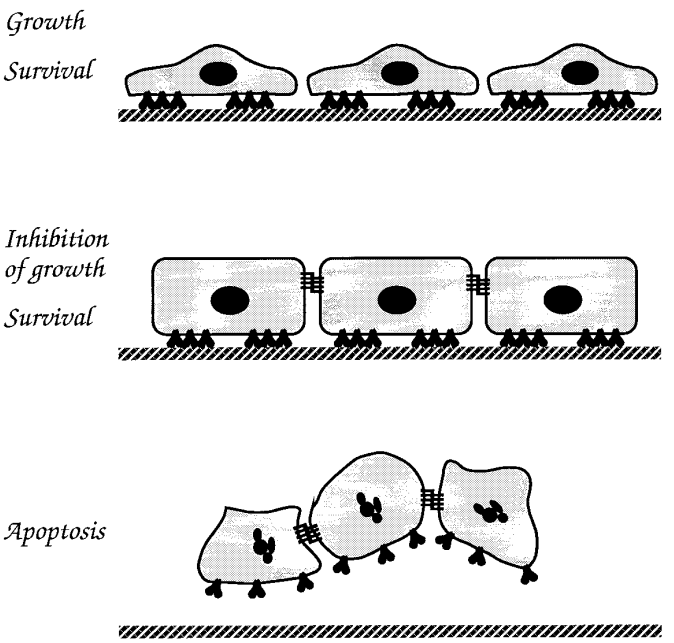

FIG. 3. Cell adhesion in anchorage dependence, contact inhibition of growth, and apoptosis.

While anchorage dependence of growth appears to be an integrin-related phenomenon, it may be that contact inhibition of growth is mediated by cell–cell adhesion molecules. N-CAM is directly growth inhibitory; antibodies against N-CAM, soluble N-CAM itself, and peptide mimetics of N-CAM all can inhibit the growth of astrocytes in primary culture [95]. These findings indicate that cell–cell contacts mediated by homophilic N-CAM binding trigger growth inhibitory signals.

C-CAM may be a negative regulator of epithelial cell proliferation. That this is the case is suggested by its expression pattern: C-CAM is expressed in normal liver, prostate, and colon epithelia, but is lost when these tissues turn malignant [96–99]. Moreover, when introduced into tumor cells derived from prostate or colon, C-CAM suppresses tumor growth [100, 101]. Thus, it seems that Ig superfamily adhesion proteins may be contact inhibitory molecules.

The signaling pathways influenced by these growth

inhibitory cell adhesion molecules are not known, but they might include activation of protein tyrosine phosphatases (PTPs) that can counteract growth stimulatory signals mediated by protein tyrosine kinases. An increased PTP activity has been found associated with the cytoplasmic face of the plasma membrane in contact inhibited fibroblasts [102]. It has also been found that transmembrane PTPs become activated in density-inhibited cells [103]. Moreover, receptor protein tyrosine phosphatases can associate with cadherins and catenins [104]. The cyclin E/cdk2 activity is shut down in contact inhibited cells by an increased activity of cyclin E/cdk2 inhibitor $p27^{Kip1}$ [105], suggesting a possible mediator pathway for the growth inhibitory effects of cellular contact.

Thus, cellular growth may be regulated by a balance between growth stimulatory integrins and growth inhibitory cell–cell adhesion molecules that influence the cyclin E/cdk2 effector system in opposite ways. There may also be other connections between the contact inhibition caused by cell–cell adhesion and the integrin-mediated anchorage dependence, because cell–cell contact has been found to sensitize epithelial cells to the apoptosis-inducing effects of loss of substrate attachment [88].

CELL MIGRATION

Cell adhesion receptors and their ligands provide traction and stimulus for cell migration. Migration depends on a delicate balance of cell adhesion and detachment. In general, most adhesion molecules are capable of mediating cell migration and most cells in the body have a potential for using them for translocation.

Integrins mediate migration of adherent cells, such as fibroblasts and epithelial cells on extracellular matrix. The regulation of integrin ligand binding activity and integrin interactions with the actin microfilament system are believed to be crucial [106]. As discussed above, the affinity of integrins is relatively low. This means that multivalent binding between membrane-bound adhesion receptors and surface-bound ligand molecules is required for a productive interaction to occur. A cell can either adhere to a surface (matrix or another cell) in such a way that it becomes immobilized or it can use the surface to migrate. The outcome appears to depend largely on the strength of the attachment; weak or moderate strength of attachment favors migration, whereas strong attachment tends to immobilize the cell.

A correlation between the strength of adhesion and impared migration has been observed with fibronectin receptors. Fibronectin is generally a favorable substrate for cells to migrate on both *in vitro* and *in vivo.* However, very strong adhesion appears to bring migration to a halt; *in vitro,* both overexpression of the $\alpha_5\beta_1$ integrin and enhanced deposition of matrix containing its ligand fibronectin curtail cell migration [107, 108]. Moreover, substrates formed from high-affinity antibodies to $\alpha_5\beta_1$, or from high-affinity fibronectin, allow less migration than a low-affinity antibody or ordinary fibronectin [107, 109]. While the strength of attachment is clearly an important factor in migration, regulation of integrin activity and subcellular localization is a prerequisite for migration. Integrins are internalized by cells; they are taken in at the trailing end of the cell and inserted at the leading edge; the process is controlled by subcellular changes in calcium concentration and the calcium-dependent phosphatase, calcineurin, [106] and results in the cell being moved forward much as the tracks move a tank.

Another way of controlling migration through the strength of adhesion is evident in experimental models for leukocyte rolling on the endothelial cell lining of capillaries. The rolling is mediated by selectins. It is thought that a fast on-rate of the selectin ligand binding makes it possible for selectins to slow down the leukocyte relative to the blood flow and that a fast off-rate ensures the rapid detachment: the end result is rolling [16]. Strong attachment and the traction for the subsequent exit of the rolling leukocytes from the circulation is provided by β_2 integrins.

Cell–cell adhesion molecules are also involved in the regulation of cell migration; like integrins, they can either promote or inhibit migration. PECAM, an Ig superfamily cell–cell adhesion protein, is necessary for the penetration of leukocytes through capillary walls when they exit circulation [110]. The outgrowth of nerve cell processes (neurites), which is a form of cell migration, is mediated by N-cadherin, the Ig superfamily molecules N-CAM and L1, as well as by integrins [111, 112]. Neurite outgrowth triggered by N-cadherin, N-CAM, and L1 involves their homophilic binding to molecules on adjacent cells, on which the neurites extend. However, the homophilic bonding is not thought to physically pull out the neurites; rather, calcium influxes triggered in the neurons activate the cellular motility machinery [111]. The calcium channel activation is mediated by the FGF receptor, which in turn is activated by N-cadherin, N-CAM, and L1, as described in the preceding section [84]. Neurite outgrowth is also influenced by receptor tyrosine kinases, which will be discussed in the next section.

Contact inhibition of movement results when migrating cells touch other cells and a contact-mediated paralysis of the motility machinery of the cells results. In migrating fibroblasts cell contacts result in a rapid formation of submembraneous actin filament bundles at the contact areas [48, 113]. L-cells expressing E-cadherin or P-cadherin from transfected cDNA have been shown to exhibit classical contact inhibition of movement [114, 115]. Moreover, cells with functional E-

cadherin are less motile in an *in vitro* invasion assay than cells with compromised or missing E-cadherin [116, 117]. Thus, it seems likely that cadherins, via their interactions with the actin filament system, can negatively regulate cell motility.

In conclusion, all major types of adhesion receptors can both trigger and inhibit migration. Whether a given cell in a given situation remains stationary or migrates is likely to depend on cooperation and cross-talk between different adhesion receptors.

CELL ADHESION IN DEVELOPMENT

Cell adhesion is crucial in the formation and maintenance of coherent multicellular structures. The essence of embryonic development is the formation of tissues and organs, each consisting of billions of cells, from a single original cell. The cellular processes governing the chain of events that lead to mature tissues are proliferation, differentiation, migration, and apoptosis; cell adhesion influences each of these processes, as well as provides physical bonding of cells to one another and to extracellular matrices.

The most important cell adhesion molecules involved in the formation of strong physical bonds are the cadherins and the integrins. Thus, null mutants of both E-cadherin [118] and β_1 integrin [119] are lethal; the embryos disassemble around the time of implantation. At a more refined level, differences in cellular affinities lead to both association of some cell types and segregation of others, initiating specific tissue architectures. This aspect of cell adhesion has been studied in detail by employing *in vitro* cell sorting experiments [120]. Both cells expressing different cadherins and cells expressing different amounts of the same cadherin segregate into separate cellular populations [121–123]. There is no direct evidence that changes in cadherin expression would lead to cellular regrouping *in vivo,* but dynamic changes of the expression of various kinds of adhesion molecules correlate with cellular rearrangements during a number of developmental processes including gastrulation, neurulation and placode formation [124, 125]. The developmental progression of neural crest cells is a well-studied example of such an event [126]. The emergence of these cells from the neural crest is preceded by a downregulation of E-cadherin, N-cadherin, and N-CAM. During the migratory phase the cells' affinity to fibronectin, the substrate they migrate on is upregulated. When the cells reach their destinations their affinity for fibronectin decreases, their affinity for laminin increases, and they reexpress N-cadherin and N-CAM. During the subsequent differentiation stage, new adhesion molecules, such as Ng-CAM (L1), are also expressed.

Adhesion-dependent regulation of specific cell shapes, such as the polarization of epithelial cells and of axons and dendrites in neurons is an important part of morphogenetic processes. Both integrins and cadherins play essential roles in cell polarization [127–129].

The influence of the various adhesion receptors on cell migration, proliferation, and apoptosis has been discussed in the preceding section. These activities are thought to depend to a large extent on the role of these receptors as signaling molecules. There are also cell surface molecules that are structurally signaling molecules, but function in a similar manner as adhesion molecules, helping to set up specific cellular connections during development. An intriguing class of such molecules are the newly discovered transmembrane receptor tyrosine kinases of the Eph family. Activation of these receptors by their ligands, which are also cell surface-bound proteins, is instrumental in guiding neuronal processes in the developing central nervous system [130, 131]. Receptor activation guides axon migration by repelling axons from areas containing high ligand concentrations [7, 8, 132]. Similar interactions may in some cases be responsible for specific attraction of neuronal processes to certain locations.

Induction of cell differentiation can also be mediated by cell–cell contact, and transmembrane tyrosine kinases are also involved in these events. One well-studied example is the formation of the insect compound eye. The insect eye consists of a large number of functional units known as ommatidia. Each ommatidium contains eight neuronal cells. The development of the precursor of cell 7 to a neuronal cell depends on direct physical interaction with cell 8 [133]. This interaction is mediated by a transmembrane receptor kinase sev (coded for by the *sevenless* gene) on cell 7, binding to its ligand boss (bride of sevenless) on cell 8 [134, 135]. In null mutants of *sevenless,* cell 7 remains a supporting cell. Binding of boss to sev triggers the Ras–Raf signaling pathway and causes cell aggregation *in vitro* [136].

THE CANCER CONNECTION

Many cell adhesion molecules are tumor suppressors. Their genes may not be tumor suppressor genes in the traditional sense; the gene is not necessarily disabled in tumor cells as is the case with the classical tumor suppressors such as the retinoblastoma or p53 genes; rather, the function of the gene is compromised through downregulated gene expression or protein function. The first adhesion protein, fibronectin, was also the first protein of its kind to be found to be abnormal in tumor cells. The absence of a fibronectin matrix in virally transformed and other malignant cells created considerable enthusiasm in the mid-1970s, when it was first observed. However, many exceptions were soon found and the initial enthusiasm wained. Recent re-

sults suggest that the fibronectin system may be just as important in cancer as originally suspected.

The $\alpha_5\beta_1$ integrin, which is the main fibronectin receptor of most cells and which also directs the deposition of the fibronectin matrix, when transfected into various types of tumorigenic cells that have little or none of this integrin, can convert them into nontumorigenic cells [108]. Conversely, if this integrin is eliminated, increased tumorigenicity results. The effect of the $\alpha_5\beta_1$ integrin seems to be partly mediated by the enhanced fibronectin deposition mediated by this integrin [107], but inhibitory signals mediated by the integrin itself are also likely to play a role [137].

In some cells, $\alpha_2\beta_1$ can have a similar effect [138], but in other cells this integrin has been reported to increase tumorigenicity [139]. Syndecan, a membrane-associated heparan sulfate proteoglycan that functions as an auxiliary adhesion protein to the integrins, also suppresses tumorigenicity, even when provided to the tumor cells in the form of a soluble ectodomain [140]. A growth and migration inhibiting effect is by no means common to all integrins; the $\alpha_v\beta_3$ integrin has been associated both with tumor invasiveness and with the formation of new blood vessels that nurture the tumor [141].

E-cadherin appears to be both a classical tumor suppressor and one whose expression is downregulated in tumors. Recent studies have revealed a high frequency of E-cadherin mutations in certain tumors [142, 143]. In addition, some other tumors lack a functional α- or β-catenin [116, 144, 145]. Yet other tumors may simply downregulate E-cadherin expression; restoration of E-cadherin function in these types of tumor cells suppresses malignancy [114, 142]. A particularly intriguing link between the cadherins and tumor development is the APC tumor suppressor gene. The APC gene product competes with cadherins for β-catenin [146] and is, therefore, likely to affect the functioning of the cadherin system in some unknown way. One possibility is that APC and β-catenin are signaling molecules with functions related to suppression of cell proliferation or migration and invasion; that β-catenin can translocate in the nucleus [69] supports this suggestion.

Among the Ig superfamily adhesion proteins DCC (deleted in colon cancer) is a classical tumor suppressor [147] and at least one other, C-CAM, can suppress malignancy when transfected into tumorigenic cells [100, 101].

We may soon see application of these advances in the basic biology to the treatment of cancer and other diseases.

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