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Cell adhesion: old and new questions

Richard O. Hynes

Metazoans clearly need cell adhesion to hold themselves together, but adhesion does much more than that. Adhesion receptors make transmembrane connections, linking extracellular matrix and adjacent cells to the intracellular cytoskeleton, and they also serve as signal transducers. In this article, I briefly summarize our present understanding of the molecular basis and biological consequences of cell adhesion and discuss how our current knowledge sheds light on questions of specificity of cell adhesion. I offer some thoughts and speculations about the evolution of cell-adhesion molecules and processes, consider their inter-relationships with other forms of cell–cell communication and discuss unresolved questions ripe for investigation as we enter the postgenomic era.

Even a cursory consideration of metazoan anatomy and development forces the realization that the associations of cells in epithelia, their attachment to basement membranes and the migrations of cells and projections of neurons all require selective adhesion of cells to one another and to extracellular matrices (ECMs). Recognition of this requirement led to a spirited debate between proponents of a large number of highly selective adhesion receptors, and advocates of models in which quantitative differences in adhesive strength, without necessarily a large spectrum of individual specificities, were invoked to explain differential cell adhesion. Similarly, the phenomenon of induction, in which one tissue influences the developmental fate of adjacent tissues, clearly relies on cell–cell interactions, and experimental embryologists attempted to define whether induction relies on diffusible signals or on cell–cell or cell–matrix contacts. Neither the issue of specificity of cell adhesion nor the question of the mechanistic bases of induction could be resolved without molecular biology. Now, with the benefit of a couple of decades of molecular analysis, we can see that there is some truth to all of the earlier models. The specificity of cell adhesion comes from combinatorial expression and interactions among a large, but not unlimited, number of adhesion receptors, and induction relies on diffusible ligands binding to receptors, on cell–cell contacts and on cell–matrix adhesion. The distinctions among these three mechanisms are not actually that great – adhesion receptors signal much like receptors for growth factors and should be considered in parallel with them.

Before considering the biological functions of cell adhesion, we need to define the players. Figure I in Box 1 diagrams the structures of representative cell–cell adhesion receptors. Fortunately, many adhesion receptors fall into a relatively small number of families, the major ones being shown in Fig. I. Other families of adhesion receptors, such as syndecans and other membrane-bound proteoglycans, the disintegrin family and others are less well understood at this time. In addition to their roles in binding cells to their neighbours (Fig. I) or to ECM (Fig. 1), engagement of cell-adhesion receptors has major effects on many aspects of cell behaviour – cell shape and polarization, cytoskeletal organization, cell motility, proliferation, survival and differentiation. How do they accomplish all these functions?

Cytoskeletal connections

Crucial to the effects of adhesion receptors on intracellular organization and cell motility is the fact that their cytoplasmic domains connect to the cytoskeleton. Figure 1a shows how integrins bind to linker proteins, which in turn make direct and indirect connections to F-actin filaments, thus establishing a mechanical link between the fibrils of the ECM and the filaments of the cytoskeleton[9,10]. The connection of classic cadherins to the actin cytoskeleton that occurs at cell–cell junctions is analogous, although the molecules involved are different (Fig. 2a)[1,11,12]. Although integrins appear to be the major receptors for ECM, they are not the only ones. One well-studied example, of considerable interest because of its involvement in

Richard O. Hynes
rohynes@mit.edu

Howard Hughes Medical Institute and Center for Cancer Research, Dept of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA.

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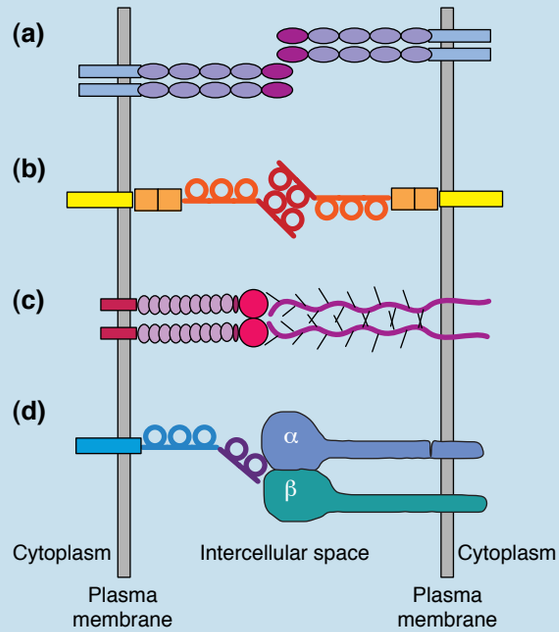
BOX 1. Major classes of cell-adhesion receptors

(a) Cadherins

Cadherins are primarily and centrally involved in cell–cell adhesion (Fig. I). The so-called classic cadherins (shown) currently number ~20 in vertebrates[1]. Their extracellular domains contain five characteristic cadherin repeats, each comprising a sandwich of β sheets. Cadherins mediate Ca^{2+}-dependent homophilic (like-with-like) adhesion between cells through the most distal cadherin repeats. Classic cadherins share homologous cytoplasmic domains that link to the actin cytoskeleton. Both structural and functional analyses suggest that the functional unit is a dimer as shown. As for other adhesion receptors, clustering of cadherins is important for their functions, and multiple dimer–dimer interactions are believed to provide sufficient local avidity to mediate cell–cell adhesion. Desmosomal cadherins (desmocollins, desmogleins), although related to classic cadherins in their extracellular domains, have distinct cytoplasmic domains that link to intermediate filaments. Other subclasses of the cadherin superfamily are known as protocadherins[2,3], and these typically have six cadherin repeats. Unlike classic and desmosomal cadherins, each of which is encoded by a separate genetic locus, protocadherins appear to be encoded by complex genetic loci with multiple (15–22) tandem exons each encoding one entire extracellular and transmembrane domain upstream of a single common cytoplasmic domain[3]. Each protocadherin subfamily is encoded by one such complex locus, but the mechanisms by which individual family members are generated remain unclear.



(b) Immunoglobulin superfamily

The second major class of adhesion receptors comprises the immunoglobulin superfamily (Ig-SF), characterized by the presence of varying numbers of Ig-related domains[4]. Like cadherin domains, these are sandwiches of two β sheets held together by hydrophobic interactions. This is a stable structure that occurs also in another domain common among adhesion molecules: fibronectin type III (Fn3) domains (boxes), which frequently occur in tandem with Ig domains (circles) in cell-adhesion receptors. Fn3 domains also occur in adhesive proteins of the extracellular matrix (ECM) such as fibronectin and tenascin and in the ligand-binding domains of cytokine receptors. Since homologous Ig/Fn3 receptors occur in insects, nematodes and vertebrates, this arrangement is clearly evolutionarily ancient. Indeed, these two domains probably originated in the context of cell-adhesion receptors early in metazoan evolution; their later appearance in immunoglobulins and fibronectin appears restricted to chordates.

The Ig superfamily is diverse, numbering well over 100 members in vertebrates. In addition to adhesion receptors containing both Ig and Fn3 repeats such as N-CAM (b), numerous molecules with one or more Ig domains play roles in cell–cell interactions in the immune system and elsewhere. Different Ig-SF members participate in homophilic interactions, as shown here for N-CAM, or in heterophilic interactions with other Ig-SF members, with integrins [see panel (d) and below] or with ECM proteins (e.g. DCC-netrins, see article by Tessier-Lavigne and Goodman in this issue). Where they have been mapped, the interaction sites typically are in the distal Ig domains. There are fewer data on dimerization, clustering and cytoskeletal connections than for cadherins, although some evidence suggests that such interactions also contribute to the functions of Ig-SF receptors.

(c) Selectins

Another well-studied group of cell adhesion receptors comprises the selectins and their counter-receptors[5,6]. The figure shows a heterophilic interaction between a selectin (P selectin) and its counterreceptor, a heavily glycosylated protein (PSGL-1). Binding is through the C-type lectin domain (pink) in the selectin, which recognizes specific carbohydrate groupings in the counter-receptor/ligand.

Unlike cadherins and Ig-SF members, which are evolutionarily ancient and widely expressed, selectins are currently known only in cells of the vertebrate circulation (endothelium and blood cells), although other lectins are widely distributed. Given the great potential for specificity that lies in carbohydrate structures, it seems likely that additional carbohydrate-specific receptors, such as galectins and the C-type lectins expressed by natural killer cells, will be increasingly recognized to be important.

Selectins and their ligands play a crucial role in the adhesion of leukocytes to endothelium, where their cooperation with integrins and Ig-SF receptors is one of the best-understood examples of cell-adhesion specificity, which arises from tightly regulated display and interaction among a limited number of receptors[5,6].

(d) Integrins

The final major family of adhesion receptors is the integrins[7,8]. Unlike all the others, these are heterodimers. In mammals, there are genes for eighteen α and eight β integrins; many α–β combinations fail to occur but at least two dozen are well defined. Most integrins are predominantly or exclusively receptors for ECM proteins such as fibronectins, laminins and collagens (Fig. 1a), but a few also play important roles in heterotypic cell adhesion, most notably of leukocytes, where they bind to counter-receptors of the Ig superfamily (ICAMs, VCAM-1, MAdCAM-1) or, in one case, a cadherin (αEβ7–E-cadherin). The figure shows a heterophilic interaction between an Ig-SF receptor (ICAM-1) and an integrin; the binding site is in the distal Ig repeats in ICAM-1 and partakes of both subunits in the integrin. Integrins play a central role in cell adhesion to basement membranes, in the polarization of cells induced by that adhesion and in cell migration upon and through ECM.

muscular dystrophies, is the dystroglycan complex, which connects dystrophin/actin inside the cell to laminin and/or agrin in the extracellular matrix (Fig. 1b)[13]. Although studied most extensively in muscle cells, analogous dystroglycan complexes clearly function in other cells.

Transmembrane structural connections, as shown in Fig. 1 and also demonstrated for other adhesion receptors [e.g. hyaluronan/CD44/ezrin–radixin–moesin (ERM) proteins], appear to be a common feature. There are preliminary indications that some immunoglobulin superfamily (Ig-SF) receptors also make cytoskeletal

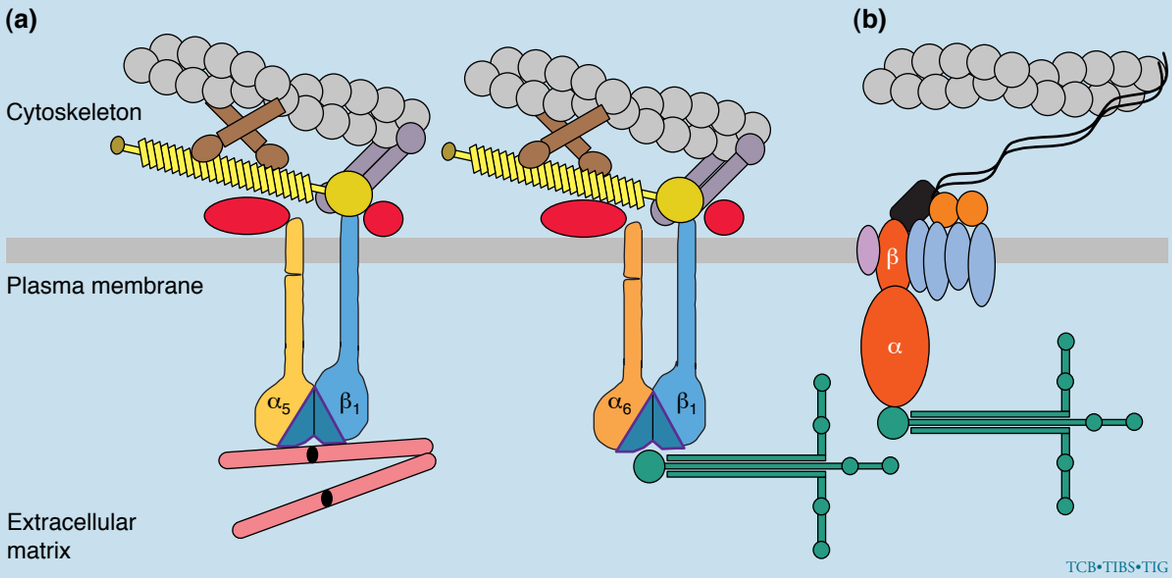


FIGURE 1. Transmembrane connections between the extracellular matrix (ECM) and the cytoskeleton. (a) Integrins (α5β1, α6β1) comprise the major receptors for ECM proteins, such as fibronectin (pink) and laminins (green), as shown here. Their extracellular domains bind to specific sites in the ECM proteins. Their cytoplasmic domains bind to submembranous cytoskeletal proteins such as talin (yellow) and α-actinin (lilac) and, through them, to other linkers such as vinculin (brown) or to actin microfilaments (grey). Additional cytoplasmic proteins (red) are also recruited; many of these function in signalling (see Fig. 2b). (b) Dystroglycan (αβ) together with sarcoglycans (blue) form another transmembrane link to laminin or to agrin (not shown) and bind via dystrophin (black) to actin filaments. Classic cadherins also link to the actin cytoskeleton via catenins (see Fig. 2a). For both integrins and cadherins, variant members of the families with divergent cytoplasmic domains (α6β4 integrin, desmogleins and desmocollins) connect instead to intermediate filaments via desmoplakins and other linker proteins.

connections (e.g. N-CAM/fodrin, ICAMs/ERM proteins) and that selectins or their counter-receptors might make similar connections that lead to their clustering on microvilli. The connections to the cytoskeleton affect not only intracellular organization but also cell adhesion itself. The adhesive functions of integrins and cadherins depend upon these cytoskeletal connections. Some of this dependence is presumably related to the clustering necessary to provide sufficient local avidity for stable cell adhesion. However, at least for integrins and possibly for other adhesion receptors, there can be more to it than that. Connection to the cytoskeleton can 'activate' integrins, changing their conformation and increasing their ability to bind to ligands. This ability to control the affinity and/or avidity of integrins is crucial to proper cell adhesion and is known as 'inside-out' signalling[7,14]. As we will see in the next section, integrins and cadherins are in fact two-way signalling receptors, and the same might be true for most adhesion receptors.

Signal transduction by adhesion receptors

A fundamental advance in the past decade has been the demonstration that cell-adhesion receptors transduce signals. This is best understood for integrins, which display a repertoire of signal-transduction capabilities at least as diverse as most growth-factor receptors (Fig. 2b)[14–16]. Their effects include activation of Rho-family GTPases leading to changes in cytoskeletal organization, activation of mitogen-activated protein (MAP) kinase pathways and activation of an array of protein and lipid kinases. These signalling pathways allow integrins to influence cell-cycle progression, cell survival and gene expression in addition to their effects on cell adhesion and morphology. In fact, most cells will not proliferate or survive unless they are adhering to a substrate – so-called anchorage dependence. Provision of soluble growth factors such as epidermal growth factor (EGF) or platelet-derived growth factor (PDGF) is not sufficient; input from integrin signalling is also necessary, and there is considerable crosstalk and cooperation between integrins and growth-factor receptors. This cooperation occurs at many levels, ranging from membrane-proximal interactions, in which the different types of receptor influence each other's activity, to multiple inputs into common pathways. Indeed, it is not realistic to consider either adhesion receptors or growth-factor receptors separately – they are part of an integrated system.

This integration is clearly demonstrated by the cadherin/β-catenin system[11,12]. β-catenin is a cytoskeletal connector of classic cadherins, but it is also a central player in signal transduction, functioning as a transcriptional activator whose levels are elevated in response to Wnt signalling (Fig. 2a). The interplay between cell–cell adhesion and the Wnt signalling pathway is complex, with each affecting the other, just like the interplay between integrins and tyrosine kinase receptors. Other members of the cadherin superfamily presumably affect different signalling pathways; protocadherins fall into subfamilies, each with a distinct cytoplasmic domain, and one protocadherin subclass was first identified by its interactions with the Src-family kinase Fyn[2].

It is also becoming clear that integrins, at least, do not signal by themselves; they are frequently associated with accessory transmembrane molecules (tetraspanins, CD47, caveolin, syndecans) that contribute to the diversity of their signalling capacities[17]. It is possible to draw an analogy with the well-analysed T- and B-cell receptors and their multiple associated signalling molecules[18,19]. There are also indications that other adhesion receptors function as constituents of complexes involving multiple signalling molecules. One can readily extrapolate from the current data and postulate that most or all signal transduction relies on associations among multiple receptors, including both adhesion receptors and receptors for soluble ligands.

A receptor continuum: soluble ligands to ECM to cell–cell contact

There is, in fact, little or no justification for drawing a distinction between adhesion receptors and receptors for soluble ligands; both signal, often affecting the same signal-transduction pathways. Indeed many 'soluble' growth factors often do not function as truly soluble

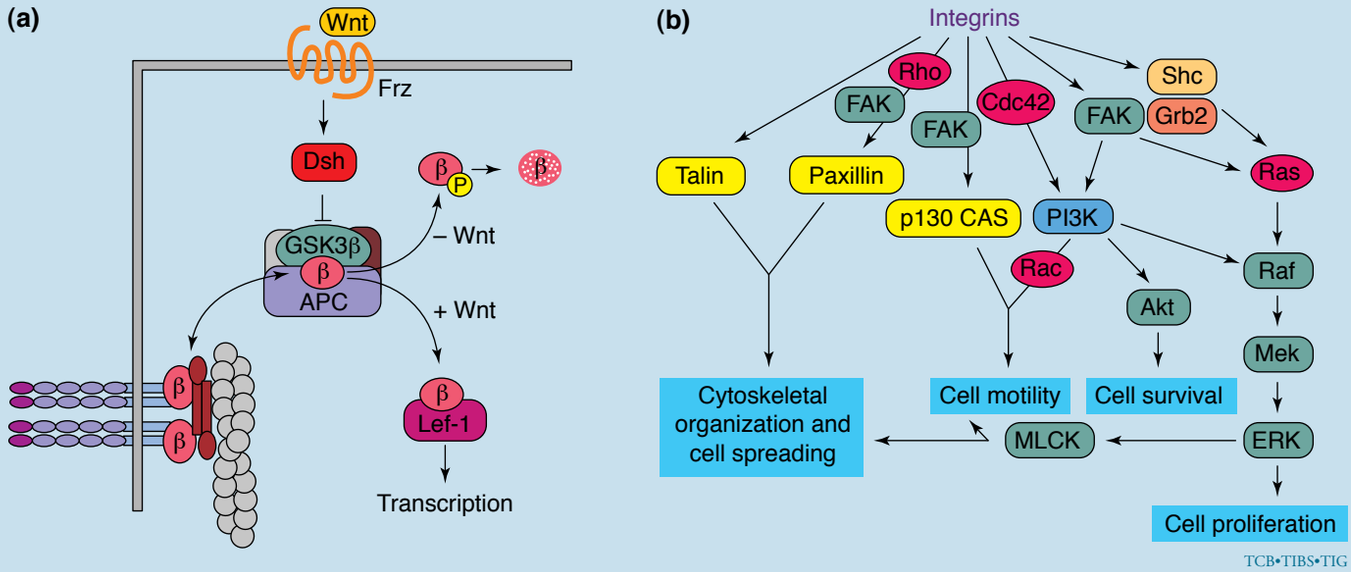


FIGURE 2. Signalling mediated by adhesion receptors. (a) Classic cadherins bind to β-catenin through their cytoplasmic domains. β-catenin can link via α-actinin to the actin cytoskeleton or it can bind to a large protein complex containing adenomatous polyposis coli (APC) and the serine/threonine kinase glycogen synthase kinase 3β (GSK3β). The latter phosphorylates β-catenin, targeting it for degradation by the proteasome. Wnt binding to its receptor, Frizzled (Frz), leads to inhibition of GSK3β, allowing β-catenin to accumulate and bind to the transcription factor Lef-1/TCF. The β-catenin–Lef-1 complex moves to the nucleus and activates transcription. Thus, the balance between cadherin association, degradation and Wnt signalling controls the level of β-catenin–Lef-1. (b) Integrins activate a large array of signalling intermediates, including small GTPases (red), protein kinases (green), cytoskeletal proteins (yellow) and others. Acting through these intermediates, which can also be activated by various growth-factor receptors, integrins can greatly affect many biological responses (blue boxes). Abbreviations: FAK, focal-adhesion kinase; MLCK, myosin light chain kinase; PI3K, phosphoinositide 3-kinase.

molecules. Many (transforming growth factor β, fibroblast growth factors, Wnts, Hedgehogs) bind in one way or another to the ECM and are presented to their signal-transduction receptors as insoluble mediators. The whole concept of morphogenetic gradients incorporates the idea that morphogens are both soluble and anchored. So the boundary between soluble ligands and ECM ligands is blurred. Similarly, receptors that mediate cell–cell contacts such as the T-cell receptor[18] have much in common with those binding soluble or bound antigen or antibody (B-cell receptor, Fc receptor)[19]. Receptor pairs such as the eph/ephrin[20] and Notch/Delta/Serrate families[21], Sevenless/Boss and receptor tyrosine phosphatases[22] all share domains and signal-transduction mechanisms, or both, with growth factors, ECM or classical growth-factor receptors. In some cases, these receptors have been shown to mediate cell–cell adhesion. In other words, there is considerable commonality of evolution and function among the different types of receptors.

If we return to the question of embryonic induction first raised 70 years ago by experimental embryologists and reconsider the debate as to whether induction relies on soluble factors, extracellular matrix or cell–cell contact, that question now seems somewhat moot. The answer is that all three can, and typically do, contribute, but they are part of a continuum, and all feed into a common network of intracellular signals with much synergy and crosstalk among them. A major challenge ahead of us is to understand the integration of all these inputs to generate coherent responses.

Where do we stand and where do we go from here?

Given what we now know about adhesion receptors, what can we say about the specificity of cell adhesion? Is it due to a very large number of receptors, sufficient for example to confer identity on each retinal axon or synapse? How many adhesion receptors are there in the genome? With the sequence of the first metazoan genome, that of *Caenorhabditis elegans* [see articles in *Science* (1998) 282, 2011–2046], we can begin to answer these questions – some of the answers are surprising.

One striking result from the *C. elegans* sequence is the discovery of a very large number of genes that encode ECM proteins. What are all these proteins for? They could serve purely structural roles or act as docking sites for presentation of growth factors, gradients of morphogens or chemoattractants. The ECM performs such functions in vertebrates, and even well-studied matrix proteins such as fibronectin, tenascin and agrin contain many highly conserved segments whose functions remain completely obscure. There is clearly a great deal that we do not understand about the functions of the ECM. Will a similar plethora of putative matrix proteins emerge from the fly and vertebrate genome sequences? There is every reason to believe that they will; the discovery of new matrix proteins continues apace even before the flood of genomic sequence data. One recent example is the discovery of netrins[23] as axonal guidance molecules. The large number of matrix proteins is not matched by a large number of integrins. Does this mean that the integrins are very promiscuous, that other matrix receptors exist or that these putative matrix proteins do not interact directly with cells?

There appear to be only two integrins in *C. elegans*. Strikingly, the two integrin α genes appear related to two distinct subfamilies of vertebrate integrins, one that binds to laminins (α3, α6, α7) and one that binds to proteins containing the sequence RGD, such as fibronectin and vitronectin (α5, α8, αv, αIIb)[24]. *Drosophila* also contains clear representatives of each of these two integrin subfamilies[24]. Thus, these two subfamilies apparently evolved prior to the divergence of nematodes, arthropods and chordates. The same is true for laminin and type IV collagen, although not for fibronectin, which is absent from nematodes (and apparently also flies) and might be a vertebrate invention. It is plausible to argue that some very early metazoan evolved laminin and collagen to build a basement membrane and integrins for cells to attach to this membrane. During evolution, vertebrates have acquired multiple integrin genes. How many more will we find when the *Drosophila*, human and mouse

genomes are sequenced in the next few years? The limited repertoire in *C. elegans* might suggest not many. On the other hand, the number of known cadherin/ protocadherin genes has more than doubled in just the past year with the application of human genomic analyses. This provides a glimpse of what might be just around the corner.

The *C. elegans* genome has 18 genes that contain cadherin repeats; we already know of more than 70 in humans, and the number is rising fast. Why do we need so many more integrins and cadherins than worms do? One obvious suggestion might be the elaboration of our nervous system; many cadherins and protocadherins are expressed in the brain, apparently differentially in different brain regions or in individual neurons[2,25]. Could they provide selectivity in neuronal or synaptic adhesion along the lines of the chemoaffinity hypothesis proposed 60 years ago by Sperry[26]? Both classic and protocadherins, as well as integrins, are expressed at synapses[27–29]. The recent discovery of multiple genes encoding protocadherins raises the exciting possibility that a large number of adhesion receptors confer synaptic selectivity. If these protocadherins can form heterodimers or heteromultimers, then the number of potential combinations becomes very large[2]. The tantalizing organization of the protocadherin loci, with multiple variable exons and a common constant region is reminiscent of immunoglobulins or T-cell receptors[3]. There is currently no evidence for DNA rearrangements at these loci, although mutations in some genes responsible for repair of double-strand breaks lead to selective apoptosis of early postmitotic neurons, encouraging speculation[30]. Even if DNA rearrangements were to occur, there is as yet no sign of the multiple combinatorial variation seen in the immune system. Nonetheless, the existence of >50 genes for protocadherins (conceivably 2500 heterodimers) offers a fair degree of variation.

Our current picture of leukocyte adhesion to the endothelium offers a good example of how a high degree of specificity in cell adhesion can be generated using only a limited number of not particularly selective adhesion receptors[5,6]. Three selectins and their ligands, three to five integrins and five to six Ig-SF receptors appear to be sufficient to target leukocytes specifically to multiple sites during inflammation or lymphocyte trafficking. This selectivity relies on tightly regulated expression and, importantly, on activation of the integrins through crosstalk from selectins and chemokine receptors. The specificity therefore relies more on spatiotemporal regulation, combinatorial expression and activation of several receptors than on the intrinsic specificity of individual receptors.

Therefore, in considering how to explain the specificity of cell–cell adhesion, we have a fairly large number of receptors (hundreds), and we will soon know exactly how many. Combinatorial display and the ability of these receptors to cooperate with each other and with 'classical' signalling receptors and to be fine-tuned in terms of their state of activation could provide enough potential spatiotemporal specificity. The challenge now will be to exploit our knowledge of the list of players to understand the complexity of individual biological systems.

While questions arising from developmental biology represented one impetus to understand cell adhesion, others came from a desire to understand pathological processes. Altered adhesion properties were recognized early as a feature of cancer cells, and the tightly regulated adhesion of blood cells is central to haemostasis, thrombosis, leukocyte trafficking and inflammation. A satisfying outcome of cell-adhesion research has been the discovery that most cell-adhesion events, be they developmental, physiological or pathological, rely on members of a limited number of families of cell-adhesion receptors. This realization has led to a very productive synergy among the originally separate areas of investigation. Molecular analyses of cell adhesion have revealed that adhesion has profound effects on cells that go far beyond merely sticking them together. Furthermore, detailed understanding of cell-adhesion receptors has opened the way to manipulating their functions, leading to therapeutic strategies applicable to pathological processes involving cell adhesion.

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