health care provision. This is why I know that you need someone like me to explain about competition. It works in the high street because suppliers are trying to sell more washing machines and videos than there are customers wishing to buy them; the firms are therefore forced to compete on both price and quality, to the benefit of the consumer. In the NHS the reverse is true: demand exceeds supply and, what is more, the suppliers are working within strict cash limits. Competition and purchaser pressure may have forced hospitals to give more attention to some of the easily measurable quality issues such as waiting times and patient information leaflets—and a good thing too—but this will not increase efficiency. Indeed, the net result may well be to consume resources without producing any improvement in more important but less readily quantifiable criteria of outcome. Hospitals should be cooperating, not competing.

When Kenneth Clarke first told us of his ideas these and other flaws were so obvious that many of us assumed that either we had analysed the situation incorrectly or that he too had spotted the pitfalls and had the solutions up his sleeve. We now realise that this was not the case. The NHS did need a kick up the backside, and a lot of us were (and still are) far more prepared than you realise to promote any scheme that looks halfway decent. Sadly, there was no discussion or consultation, and the present confrontational atmosphere was allowed to develop. It is depressing to see the predicted problems materialising one after another, and even more damaging to morale when it becomes apparent that the message we are trying to get across—that a so called free market is no way to ensure the satisfactory provision of health care to an aging population—has not been appreciated by those in a position to make a difference.

I work in a trust hospital which, as far as I can tell, has made a successful transition from directly managed status. Nevertheless, like everyone else we wonder how we can ever afford to replace the time expired capital equipment and infrastructure which was our legacy from the past 20 years of neglect. But if we are doing well someone else is doing badly—that is what free markets are like. We cannot afford to have failures in a health system which needs to use every hospital and every health care worker if it is to cope with the demands of the twenty first century.

Please listen to the arguments of those of us who are doing our best to make the new system work. The reforms are not all bad, and many of us can see opportunities opening up which we are eager to grab. Don't assume that we are all Luddite malcontents, afraid of change. Like you, we are committed to the NHS, and there is an enormous reserve of goodwill that you could be harnessing; just show some evidence that you appreciate the nature of the problems we are facing, and we can all work together to establish the quality service that our patients rightly demand.

Basic Molecular and Cell Biology

Cell to cell and cell to matrix adhesion

D R Garrod

This article will be in the second edition of the book "Basic Molecular and Cell Biology," which is to be published in April this year

The structure and organisation of body tissues is dependent on maintenance of contact between cells and their neighbours and between cells and the extracellular matrix. In simple epithelia, such as the lining of the intestine or the kidney tubule, the individual cells have surfaces with three different sets of adhesive properties. The apical or luminal surface is non-adhesive, the lateral surface is specialised for adhesion to adjacent cells, and the basal surface is specialised for adhesion to the underlying matrix, the basement membrane.

In a stratified epithelium, such as epidermis, the cells in the basal layer adhere to the basement membrane below, to each other laterally, and to suprabasal cells apically. The suprabasal cells have lost adhesion to the matrix and instead adhere to similar cells on all sides. Apically this mutual adhesion is also lost and cells are sloughed off.

Other cell types—leucocytes and blood platelets—spend much of their time circulating freely and thus showing no adhesive interactions. Lymphocytes, however, show quite specific recirculation patterns in which particular subsets leave the blood circulation by first adhering to high endothelial venule cells at specific sites—for example, peripheral lymph nodes or mucosal associated lymphoid tissue. They then migrate into the lymphoid tissue and eventually return to the blood circulation. Endothelial adhesion by leucocytes is also the first step in a range of adhesive interactions required in their tissue invasive response to inflammation. Blood platelets respond to injury by a whole set of adhesive interactions with endothelial cells, with the matrix of the clot and endothelial basement membrane, and with each other.

Thus cells of any particular type possess a set of adhesive properties that may be both spatially and temporally regulated. A considerable amount is now known about the molecular mechanisms that mediate these properties.[1-4]

Families of cell adhesion molecules

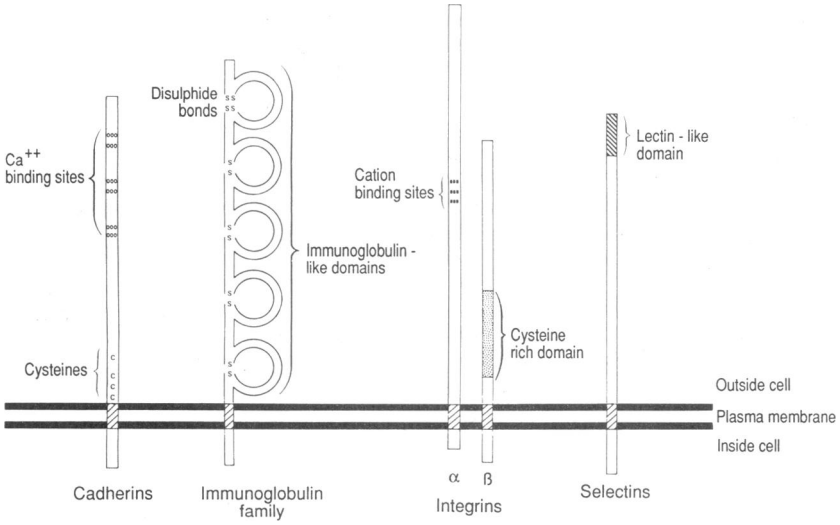
Many different cell adhesion molecules have been described. Most of them belong to one of a small number of families of related molecules in which the individual members share the same basic molecular structure but are subtly different from each other (figure).

CADHERINS

In most tissues a major contribution to cell to cell adhesion is made by calcium dependent cell adhesion molecules known as cadherins.[3] In general these are simple transmembrane glycoproteins. The extracellular domain has an adhesion site towards the N-terminal region and several calcium binding sites. Adhesive binding is homophilic: a cadherin molecule on one cell binds to another cadherin molecule of the same type on the next cell. Linkage of the cytoplasmic domain to the cytoskeleton through proteins known as catenins is necessary for cadherin function. The best characterised is epithelial cadherin, E-cadherin or uvomorulin. This appears very early in development, when it is involved in compaction of the eight cell embryo and cell polarisation. In adult epithelia—for example, intestinal epithelium—it is present on the lateral cell surfaces but is concentrated in intercellular junctions known as the zonulae adherentes, which ring the cells in the apicolateral region. The zonula adherens is characterised by a cortical ring of

Cancer Research Campaign Epithelial Morphogenesis Group, Department of Cell and Structural Biology, University of Manchester, Manchester M13 9PT

BMJ 1993;306:703-5



Molecular structure of families of cell adhesion molecules

cytoskeleton, the major component of which is actin.

The adhesive glycoproteins of the other major intercellular junctions of epithelia, the desmosomes, are members of the cadherin family. Their extracellular domains are very like those of cadherin but their cytoplasmic domains differ, being specialised for forming desmosomal plaques and, thereby, attachment to the keratin intermediate filament cytoskeleton rather than to actin.

A cell adhesion molecule known as neural cadherin (N-cadherin) is expressed predominantly in the nervous system, where it is implicated in neuronal migration during development.

IMMUNOGLOBULIN SUPERFAMILY

The other major group of cell to cell adhesion molecules is part of the immunoglobulin superfamily.[4] The extracellular portions are characterised by the presence of at least one, and usually multiple, immunoglobulin-like domains. Included in this group are several nervous system adhesion molecules such as the neural cell adhesion molecule (N-CAM), L1, and TAG, which are involved in neuronal guidance and fasciculation. Several members of the immunoglobulin family are concerned with antigen recognition and adhesion in T lymphocytes. These include the T cell receptor (CD3) and its coreceptors CD4 and CD8, which together recognise complexes of antigen peptide and major histocompatibility complex on other cells; the major histocompatibility complex molecules themselves; and lymphocyte function-related antigen 2 (LFA-2 or CD2), a receptor for another immunoglobulin-like molecule, LFA3, expressed on other cells. Another group of immunoglobulin-like cell adhesion molecules includes the so called intercellular adhesion molecules, ICAM-1 and ICAM-2, which are more widely expressed, for example, on epithelial and endothelial cells, and V-CAM, which is expressed on endothelial cells. These three are involved in the inflammatory response.

The immunoglobulin superfamily is large and diverse probably because the basic structure of the immunoglobulin domain is versatile and readily adaptable to different binding functions. Among these molecules, however, only the T cell receptor and the immunoglobulins themselves have somatically variable domains necessary for antigen recognition. Members of the superfamily are present in insects, where they are involved in forming nerve connections; thus the association of immunoglobulin-like domains in cellular recognition preceded the immune system in evolution.

INTEGRINS

Both cell to cell and cell to matrix receptors are contained within the remaining large family of adhesion molecules, the integrins.[2] These are heterodimers consisting of one α chain and one β chain, both of which are necessary for adhesive binding. Thirteen different α chains and eight different β chains are now known. Integrins may be classified into subfamilies according to which β subunit is involved in the complex. Thus β1 integrin may associate with one of eight different α subunits to give a series of matrix receptors. The β2 integrins on the other hand are a family of cell to cell adhesion molecules of lymphoid cells with three alternative α subunits. The classification is made more complicated because some α subunits can associate with different β subunits (for example, α6β1 and α6β4).

Some integrins are apparently quite specific in their ligand-binding properties—for example, α5β1 for the arginine, glycine, and aspartic acid (-arg-gly-asp-) tripetide sequence of fibronectin—whereas others are promiscuous—for example, αvβ3, once regarded as the vitronectin receptor, also binds fibronectin, fibrinogen, von Willebrand factor, thrombospondin, and osteopontin. An interesting example is α4β1, which binds both the IIICS domain of fibronectin and the immunoglobulin-like molecule V-CAM on endothelial cells. To complicate matters further individual cell types usually express multiple integrins. A good example to consider here is the blood platelet that expresses predominantly αIIbβ3 (GPIIb/IIIa), which binds fibrinogen, fibronectin, von Willebrand factor, and vitronectin but also lesser amounts of αVβ3, α5β1, α2β1 (collagen), and α6β1 (laminin).

SELECTINS

Most cellular adhesive interactions seem to entail homophilic or heterophilic protein to protein binding. However, the final, as yet small, family of cell adhesion molecules bind to carbohydrate. These are the selectins, which have lectin-like domains at their extracellular N-terminal extremities. One of these, L-selectin (previously LAM-1/Mel-14), is a "homing receptor," mediating specific adhesion of lymphocytes to endothelium in peripheral lymph nodes. This molecule is also involved in the adhesion of neutrophils to endothelium during the inflammatory response. The other two members of this family, E-selectin (previously ELAM-1 endothelial leucocyte adhesion molecule) and P-selectin (previously GMP-140, PADGEM or CD62), are also involved in the inflammatory response. E-selectin is up regulated on endothelial cells over a period of hours after stimulation by inflammatory mediators. P-selectin is contained within Wiebel-Palade bodies of endothelial cells and platelet α granules, from which it is rapidly mobilised on activation or clotting, mediating adhesion to neutrophils and monocytes.

Cell adhesion and disease

ADHESION MOLECULE DEFICIENCY

A number of rare diseases result from specific defects in adhesion molecules. The inherited immunodeficiency disease leucocyte adhesion deficiency is characterised by pronounced granulocytosis, lack of pus formation, mobilisation of neutrophils and monocytes to inflammatory sites, severe gingivitis, and recurrent or progressive soft tissue infections. It is caused by defects in the common β2 subunit of the lymphocyte integrins, resulting for example, in deficient expression of the αβ heterodimers at the cell surface with the result that adhesion of lymphocytes is impaired. Defects in β2 may be either mutations, which affect the structure of the protein, or greatly reduced expression or absence of mRNA. In its most severe form the disease causes death in early childhood from overwhelming infection.

It has been shown recently that adhesiveness of lymphocytes from patients with leucocyte adhesion deficiency can be restored by transfection with an expression vector continuing the complementary DNA for the normal β2 subunit.[5] Thus gene therapy may be feasible for these patients.

Mutation of the β3 subunit of the platelet integrin GPIIb/IIIa results in the bleeding disorder Glanzmann's thrombasthenia. The Bernard-Soulier syndrome entails a deficiency of the non-integrin platelet adhesion receptor GPIb/IX and von Willebrand's disease abnormalities of von Willebrand factor.

PEMPHIGUS

In pemphigus, the group of autoimmune diseases that cause epidermal blistering, patients' serum contains autoantibodies to desmosomes, the cadherin-like glycoproteins of the epidermal intercellular junctions. The autoantibodies cause the junctions to break down and the keratinocytes to separate (acantholysis) giving rise to the formation of blisters. Breakdown of desmosomes by another mechanism (possibly protease activity) gives rise to the inherited Darier's disease and Hailey-Hailey disease, which are similar but probably unrelated.

Failure of adhesion between the epidermis and its underlying basement membrane occurs in bullous pemphigoid, in which autoantibodies to cytoplasmic protein components of the matrix adhesive junctions known as hemidesmosomes are found in serum.[6] The hemidesmosomes adhesion receptor is another integrin, α6β4. The matrix ligand for this may be a newly discovered trimeric basement membrane component known as BM-600, nicein, kalinin, or epiligrin. (Like many new proteins this has been discovered by different groups, which have given it different names.) Another group of blistering diseases, epidermolysis bullosa, results from failure of epidermis to adhere to basement membrane. The most severe form of junctional epidermolysis bullosa is fatal in early childhood. It involves defects in hemidesmosomes possibly resulting from defective interaction between the integrin and its ligand.

METASTATIC BEHAVIOUR

Defective cell adhesion has long been thought to play a part in the invasive and metastatic behaviour of neoplastic cells. Invasive cells spread into the tissues surrounding the primary tumour; penetrate into blood vessels, lymphatics, or body cavities; and become dispersed to distant areas. Some may become trapped at new sites, extravasate, and form secondary tumours. This is a complex series of events that may involve various altered cellular properties, such as secretion of proteolytic enzymes, alterations in cell motility, and altered growth properties, as well as possible changes in adhesiveness. However, some interesting observations have been made in relation to adhesion and tumour spread. For example, formation of secondary tumours by injected melanoma cells in mice was inhibited by simultaneous injection of a short synthetic peptide containing the -arg-gly-asp-tripeptide that blocks integrin α5β1 binding to fibronectin,[7] strongly suggesting a role for matrix adhesion in the formation of metastases. A series of small, cysteine rich peptides that contain -arg-gly-asp- (which are called disintegrins) has been identified in viper venom.[8] These peptides are much more potent inhibitors of β1 and β3 integrins than synthetic peptides and inhibit tumour metastasis in mice, as well as platelet aggregation.

In a series of human tumour cell lines invasion into collagen gels was inversely related to expression of E-cadherin and inhibition of invasion was achieved in a breast carcinoma cell line by transfection with a vector expressing E-cadherin.[9] This suggests a possible tumour suppressor function for this cell adhesion molecule. In a detailed study of the genetic deletions found in colorectal cancer one of the commonly deleted genes (DCC) was found to code for a protein homologous to the immunoglobulin superfamily of cell adhesion molecules, again suggesting a possible tumour suppressor function.[10]

VIRUSES AND PARASITIC DISEASES

Cell adhesion molecules are also involved in some infectious and parasitic diseases, in which the invading organisms use the normal tissue molecules for binding. Thus the rhinoviruses—RNA viruses responsible for about a half of common colds—bind to intercellular adhesion molecules on respiratory epithelium. Of more sinister significance the binding of human immunodeficiency virus (HIV) during infection of T lymphocytes is mediated by binding of the viral gp120 protein to CD4, the immunoglobulin-like T cell co-receptor. Intercellular adhesive molecules are also implicated in the adhesion of red blood cells infected with *Plasmodium falciparum* to capillary endothelium in the pathogenesis of severe malaria.[11] Cytokine mediated up regulation of endothelial intercellular adhesion molecules may be associated with severity of the disease.

OTHER IMPORTANT FUNCTIONS

An important function of cell adhesion molecules in addition to adhesive binding is transmission of signals across cell membranes. Study of this has so far been limited, but several aspects have emerged. Members of all three of the large families of cell adhesion molecules —the cadherins, integrins, and immunoglobulin-like superfamily—have been shown to participate in signalling. Signals can be transmitted from the outside to the inside of cells in response to ligand binding, affecting second messengers and gene transcription, or from the inside to the outside of cells, modulating the binding affinity of cell adhesion molecules. Add to this the quantitative regulation of expression of cell adhesion molecules in response, for example, to inflammatory mediators and associated with changes in cellular differentiation, and we find a complex and highly responsive set of cellular adhesion mechanisms whose role in normal tissue formation and disease is only beginning to be understood.

I thank Dr J Sweetenham for helpful comments on the manuscript.

1 Edelman GM, Thiery JP, Cunningham BA, eds. *Morphoregulatory molecules*. New York: John Wiley, 1990.
2 Hynes RO. The complexity of platelet adhesion to extracellular matrices. *Thrombosis and Haemostasis* 1991;**66**:40-3.
3 Takeichi M. Cadherins: a molecular family important in selective cell-cell adhesion. *Ann Rev Biochem* 1990;**59**:237-52.
4 Springer TA. Adhesion receptors of the immune system. *Nature* 1990;**346**: 425-34.
5 Hibbs ML, Wardlaw AJ, Stacker SA, Anderson DC, Lee A, Roberts TM, *et al.* Transfection of cells from patient with leukocyte adhesion deficiency with an integrin β subunit (CD18) restores lymphocyte function—associated antigen-1 expression and function. *J Clin Invest* 1990;**85**:674-81.
6 Legan PK, Collins JE, Garrod DR. The molecular biology of desmosomes and hemidesmosomes: "What's in a name?" *BioEssays* (in press).
7 Humphries MJ, Olden K, Yamada KM. A synthetic peptide from fibronectin inhibits experimental metastasis of murine melanoma cells. *Science* 1986; **223**:467-9.
8 Gould RJ, Polokoff MA, Friedman PA, Huang TF, Holt JC, Cook JJ, *et al.* Disintegrins: A family of integrin inhibiting proteins from viper venom. *Proc Soc Exp Biol Med* 1990;**195**:168-71.
9 Frixen UH, Behrens J, Sachs M, Eberle G, Voss B, Warda A, *et al.* E-cadherin-mediated cell-cell adhesion prevents invasiveness of human carcinoma cells. *J Cell Biol* 1991;**113**:173-85.
10 Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990;**61**:759-67.
11 Berendt AR, Simmons DC, Tansey J, Newbold CI, Marsh K. Intercellular adhesion molecule-1 in an endothelial cell adhesion receptor for Plasmodium falciparum. *Nature* 1989;**341**:57-9.