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Molecular organisation of cell–matrix contacts: essential multiprotein assemblies in cell and tissue function

Josephine Clare Adams

The adhesion of cells to their surrounding extracellular matrix has vital roles in embryonic development, inflammatory responses, wound healing and adult tissue homeostasis. Cells attach to extracellular matrix by specific cell-surface receptors, of which the integrins and transmembrane proteoglycans are major representatives. The engagement of adhesion receptors triggers assembly of functional matrix contacts, in which bound matrix components, adhesion receptors and associated intracellular cytoskeletal and signalling molecules form large, localised multiprotein complexes. This review discusses the functional categories of matrix contacts, examples of the biological roles of matrix contacts in normal physiology, and examples of the ways in which abnormalities of matrix contacts are associated with major human diseases.

Cell–matrix contacts are specialised zones at the cell surface, where activated or clustered adhesion receptors bind to their extracellular matrix (ECM) ligands and link intracellularly to components of the cytoskeleton. Cell–matrix contacts thus bridge the extracellular and intracellular milieux and are fundamental features of the cells and tissues of multicellular organisms. Different cell–matrix contacts have been characterised by their morphology or by biochemical composition, or a combination of both criteria. However, the variation in size, prevalence and dynamics of different types of cell–matrix contacts has made some much more accessible to recognition and experimental study than others. Thus, the overall level of knowledge of different cell–matrix contacts is patchy and widely varying in sophistication.

This review presents an overview of the molecular composition of different contacts and sets out definitions for major types of cell–matrix contacts that are based on functional criteria. Cell–matrix contacts have essential roles in normal physiology and there are many contexts

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in which abnormalities of cell–matrix contacts lead to chronic and life-threatening diseases. The review discusses examples of the normal roles of matrix contacts, the molecular basis of selected pathological abnormalities of matrix contacts in different cell types, and prospects for understanding and controlling the cellular coordination of matrix contacts, which could have therapeutic possibilities.

General features and categories of cell–matrix contacts

Individual forms of cell–matrix contacts are currently recognised by a combination of their morphological features and molecular composition – the latter with regard to the matrix ligands, cell-surface adhesion receptors, cytoplasmic linker proteins and cytoskeletal filament system involved. These characterisations are listed in Tables 1–3. It can be seen that the level of precision in these definitions varies widely: for some contacts, the level of biochemical knowledge is much more comprehensive and detailed than for others.

The array of matrix contacts can also be divided into three categories according to their functional characteristics: protrusive, contractile or mechanically supportive. *Protrusive* contacts (Table 1) are those in which outward extensions of the plasma membrane make contact with matrix. These regions can be very localised and of highly defined shape, as in the case of filopodia, spikes or podosomes, or occupy broad regions of the plasma membrane as in the case of pseudopodia, invadopodia or lamellipodia (see glossary in Box 1, on page 22). Although the adhesive receptors in these structures are linked to the actin cytoskeleton by various types of linker complex (Table 1), protrusive contacts develop little tension on the matrix (Refs 1, 2) and are usually associated with rapid membrane remodelling, transient matrix adhesions, exploratory cell movements and cell locomotion.

Contractile contacts (Table 2) are those in which adhesive receptors make physically closer or longer-lived contacts with the ECM and are connected to the contractile actomyosin filament system. This results in the development of isometric tension across the plasma membrane that enables cells to maintain spreading on a rigid ECM (as prepared by coating matrix onto a plastic dish) or to exert tension on a deformable ECM (as prepared by coating matrix onto flexible silicone rubber sheets or polyacrylamide, or by use of three-dimensional matrix; Refs 3, 4, 5, 6). This type of contact is exemplified by focal adhesions, collagen matrix assembly sites, fibrillar adhesions, fibrillin microfibril contact sites and the dystroglycan contact.

Mechanically supportive contacts (Table 3) are stable, large-scale adhesions that stabilise the plasma membrane and enable cells to resist deformation from mechanical forces during normal tissue function. The prime example is the hemidesmosome, in which a specialised matrix-adhesion receptor, the α6β4 integrin, stably attaches epithelial or endothelial cells to their underlying basement membrane and is linked intracellularly to the non-contractile keratin filament system (Refs 7, 8; Fig. 1a). Retraction fibres are poorly understood branching projections that are apparent in tissue culture under conditions of strong matrix adhesion or in association with mitotic cells (Refs 9, 10, 11). In interphase cells, retraction fibres maintain cell spreading and matrix adhesion at rear or lateral cell margins during contraction or forward movement of the cell body, and are enriched for the proteoglycan NG2 (Ref. 12; Table 3). Although dystroglycan contacts are contractile, they can also be considered as mechanically supportive contacts in that they mediate the constant attachment of myotubes, cardiomyocytes and epithelial cells to their basement membrane under conditions of varying mechanical load, and in addition stabilise the plasma membrane and participate in basement membrane assembly (Ref. 13).

Whereas some matrix contacts, such as hemidesmosomes, are specific to particular differentiated cell types, others, such as spikes and filopodia, occur in many cell types (Table 1). Individual cells commonly form multiple contact types simultaneously, at different points on the cell surface. For example, fibroblasts or leukocytes in connective tissue organise matrix assembly sites and several types of protrusive contacts to attach to, organise and move through the fibrillar matrix (Refs 14, 15; Fig. 2). The array of contact types that is formed is important for the functional state of cells. For instance, macrophages polarised and motile in a chemoattractant gradient show filopodia at the leading edge and arrays of podosomes along other cell margins.

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Table 1. Characteristics of protrusive cell–matrix contacts (tab001jal)

Contact type	Cell context	Characteristics	Molecular components
Filopodium	Many cell types, especially growth cones, early embryonic cells	Finger-like shape: 0.2–0.5 μm diameter, 10–200 μm length	M: LN, HB-GAM CS: β1 integrins, syndecan 1 or 3 L: Mena/VASP, vinculin, ptyr, N-WASP, cofilin F: actin, bundled by fascin or filamin
Invadopodium	Cancer cells	Sites of matrix degradation implicated in motility in 3-D matrix	M: collagen, FN + ND CS: α3β1 integrin, seprase, gelatinase A L: $pp60^{v\text{-}src}$, ptyr, p190RhoGAP, cortactin, paxillin, PKC F: actin network
Lamella/ lamelipodium	Many cell types	Broad protrusion of leading edge; edge can roll back to form ruffle	M: FN (transient), TSP-1, FN-CCB, hep II fragment, PF4 (stable) CS: β1 integrins, layilin L: talin, zyxin, Mena/VASP, ERM, Rac, Arp2/3 F: actin network
Podosome	Monocytes/ macrophages, osteoclasts, virally transformed fibroblasts	0.4 μm diameter protrusions, rapid turnover	M: LN + ? CS: β1 and β2 integrins, αvβ3 L: vinculin, talin, α-actinin, gelsolin, ptyr, Arp2/3, PYK2, $p130^{cas}$ F: actin core, bundled by fimbrin
Pseudopodium	Cancer cells, early blastocytes, extravasating leukocytes, fibroblasts	Lobular, smooth-edged protrusion of leading edge in culture; cylindrical structure with marginal spikes and ruffles in 3-D matrix	M: FN, LNs, collagen CS: β1 integrin, CD44 L: ezrin + ND F: actin network
Spike/ microspike	Many cell types, growth cones	Projection: 0.2–0.5 μm diameter, 2–10 μm length	M: TSP-1, TN-C, LN (stable), FN (transient) CS: syndecan 1, α6β4 (context dependent) L: Rac, Cdc42 + ND F: actin, bundled by fascin

Abbreviations for molecular components: M, matrix components; CS, cell-surface components; L, linker complex components; F, associated cytoskeletal filament system.
Abbreviations for molecules: Arp2/3, actin-related proteins 2/3 complex; ERM, ezrin–radixin–moesin family of proteins; FN, fibronectin; FN-CCB, FN central cell-binding domain; hep II, heparin-binding site II of FN; HB-GAM, heparin-binding growth-associated molecule; GAP, GTPase-activating protein; LN, laminin; Mena/VASP, mouse enabled-like/vasodilator-stimulated phosphoprotein family of proteins; N-WASP, neuronal Wiskott–Aldrich syndrome protein; PF4, platelet factor 4; PKC, protein kinase C; ptyr, phosphotyrosine-containing proteins; PYK2, proline-rich tyrosine kinase 2; TSP-1, thrombospondin 1; TN-C, tenascin-C. ND, not determined.'Transient' and 'stable' refer to the dynamics of turnover of the contact.

Both of these contacts are needed to achieve directed locomotion (Refs 16, 17, 18). Motile fibroblasts in culture show protrusive contacts at the leading edge and concentrations of focal adhesions towards the rear, which develop the cell body contractility needed to pull forward the rearmost part of the cell (Ref. 19; Fig. 2). An understanding of the mechanisms by which contacts are spatially and temporally coordinated, within and between cells, is thus fundamental to understanding the biological roles of cell adhesion and motility in health and disease. Selected examples of matrix-contact function in diverse cell types are discussed below.

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Table 2. Characteristics of contractile cell–matrix contacts (tab002jal)

Contact type	Cell context	Characteristics	Molecular components
Collagen matrix assembly site	Fibroblasts and other connective tissue cells	Initial fibril assembly site between narrow cytoplasmic projections	M: collagen I fibrils CS: α2β1, α1β1 integrins L : ND, ?similarities to focal contact F: actin stress fibres
Dystroglycan contact	Skeletal and cardiac muscle, epithelia, peripheral nerve	Basement membrane adhesion and assembly	M: LN, agrin, perlecan CS: dystroglycan α–β complex, sarcospan, sarcoglycan complex L: dystrophin (muscle), utrophin (epithelia and nerve) F: actin network
Fibrillar adhesion	Fibroblasts and other connective tissue cells	3–5 μm long; extended time course of formation; parallels actin microfilaments on ventral and dorsal cell surfaces	M: FN fibrils CS: α5β1, ?syndecan 2 + ? L: high tensin, low ptyr, + ?focal-contact-like F: actin stress fibres
Fibrillin microfibril attachment site	Fibroblasts, smooth muscle, chondrocytes	10–12 nm fibrils align on cell surface at termini of actin microfilaments	M: fibrillin-1 and -2, template for elastin polymerisation CS: αvβ3 integrin L: ND, ?similar to focal adhesion F: actin stress fibre
Focal contact or focal adhesion or adhesion plaque	Endothelial cells, activated platelets	0.25 μm wide x 1.5 μm long plaque; close matrix adhesion site at end of microfilament bundle	M: FN, VN, collagen, LN, PGs CS: β1 and β3 integrins, syndecan 4 L: large complex, high ptyr, low tensin F: actin microfilaments plus microtubule association

Abbreviations for molecular components: M, matrix components; CS, cell-surface components; L, linker complex components; F, associated cytoskeletal filament system.
Abbreviations for molecules: FN, fibronectin; LN, laminin; PGs, proteogylcans; ptyr, phosphotyrosine-containing proteins; VN, vitronectin. ND, not determined.

Roles of cell–matrix contacts in normal physiology and repair

Filopodia, spikes and other protrusive contacts

Surface protrusions of various lengths are present on many cell types in vivo and in tissue culture, and are thought to function in transient or exploratory cell adhesions and in environmental sampling and sensory guidance. These have been termed microspikes or spikes if less than 10 μm long, or filopodia if over 10 μm long (Ref. 20). The mesenchymal cells of sea urchin gastrulae have thin, dynamic filopodia that might be involved in cell positioning within the embryo and in the orientation of cells on fibrillar matrix (Ref. 21). Thoracic closure in *Drosophila* is mediated by filopodial-dependent crawling of imaginal cells (Ref. 22). Very long projections, termed cytonemes, are present within *Drosophila* wing imaginal discs and are thought to act as signalling centres that relay morphogenetic cues across the disc (Ref. 23). Highly active movements of filopodia have been documented in association with axon outgrowth and in the migration of neural crest cells in zebrafish and amphibian embryos (Refs 24, 25, 26). Contacts such as these are of obvious importance in the patterning of the nervous system and in the definition and maintenance of tissue organisation.

The functional roles of filopodia have been most widely studied in neuronal cells. On surfaces patterned with different matrix proteins, growth cone motility and neurite outgrowth are positively or negatively affected according to the specific matrix: for example, laminin or

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Table 3. Characteristics of mechanical support cell–matrix contacts (tab003jal)

Contact type	Cell context	Characteristics	Molecular components
Hemidesmosome	Stratified epithelia, endothelia, Schwann cells	Basement membrane adhesion; elaborate adhesion plaque under electron microscope	M: LN CS: α6β4 integrin, BP180 L: plectin, BPAG1 F: keratin
Retraction fibre	Mesenchymal cells, endothelial cells, transformed cells undergoing strong or rigid matrix adhesion	Branching projections: 0.5 μm diameter, 2–100 μm length	M: FN CS: NG2 L: ND F: actin microfilaments

Abbreviations for molecular components: M, matrix components; CS, cell-surface components; L, linker complex components; F, associated cytoskeletal filament system.
Abbreviations for molecules: BPAG1, bullous pemphigoid antigen 1; BP180, bullous pemphigoid antigen 180 kDa protein; FN, fibronectin, LN, laminin; NG2, NG2 proteoglycan. ND, not determined.

thrombospondin 1 (TSP-1) promotes neurite outgrowth, whereas boundaries of chondroitin sulphate proteoglycans repel growth cones (Refs 27, 28). Time-lapse studies indicate that these outcomes are mediated primarily by effects on filopodial sampling of the substratum and subsequent matrix attachment by filopodia; indeed, experimental ablation of filopodia inhibits growth cone navigation and motility (Refs 29, 30).

In the cellular contexts in which filopodia have been studied, spikes are also apparent as short projections from cell surfaces or at the margins of growth cones (Refs 29, 31; Table 1). Spikes are present at the surface of tissue culture cells during initial spreading, on the lamellipodial margins of migratory cells, and at the outer margins of post-mitotic cells (Refs 32, 33, 34). Several types of spikes have been studied in different experimental systems. For many cell types, spreading on TSP-1 or tenascin-C drives the formation of spikes that contain the actin-crosslinking protein fascin (Refs 35, 36). In the case of TSP-1, spike formation is transduced by the transmembrane proteoglycan syndecan 1 (Ref. 37). The assembly of these spikes is positively regulated by the GTPases Cdc42 and Rac, and is negatively regulated by protein kinase C activity (Refs 38, 39). Functional perturbation of the actin–fascin interaction and overexpression of wild-type or actin-binding mutants of fascin have uncovered roles for fascin spikes in matrix adhesion and cell locomotion (Refs 34, 39). The motility of certain carcinoma cells on laminin depends on spikes that are enriched for the α6β4 integrin (Ref. 40; see below).

As stated above, current definitions that distinguish filopodia from spikes or microspikes are based on the actual lengths of the projections (Table 1). Detailed time-lapse studies of neuronal cell growth cones demonstrate that the dynamic movements of individual filopodia occur in conjunction with a general lateral movement and regression of filopodia under membrane retrograde flow (Ref. 41). Thus, the different lengths of projections documented in static images could reflect either different stages of protrusion and withdrawal of a single highly dynamic type of contact structure or the compartmentalised formation of different types of protrusive structures. Although there is mounting direct evidence for roles of filopodia and spikes in matrix adhesion, motility and cell guidance, it is not yet clear how the structures studied in different systems (i.e. growth cones versus fibroblasts versus tumour cells or embryonic cells) relate to one another. Comparative biochemical and real-time tracking studies of cell-surface projections across different cell types are now needed to rationalise existing definitions and establish clear commonalities or differences as a basis for future research.

Podosomes and osteoclast function

The mass and form of bone is regulated throughout life by the actions of osteoblasts, which secrete and deposit bone ECM, and osteoclasts, which resorb bone (Ref. 42). The end balance of the actions of these two cell types is termed bone remodelling. Osteoclasts exist in two functional states – the migratory state and

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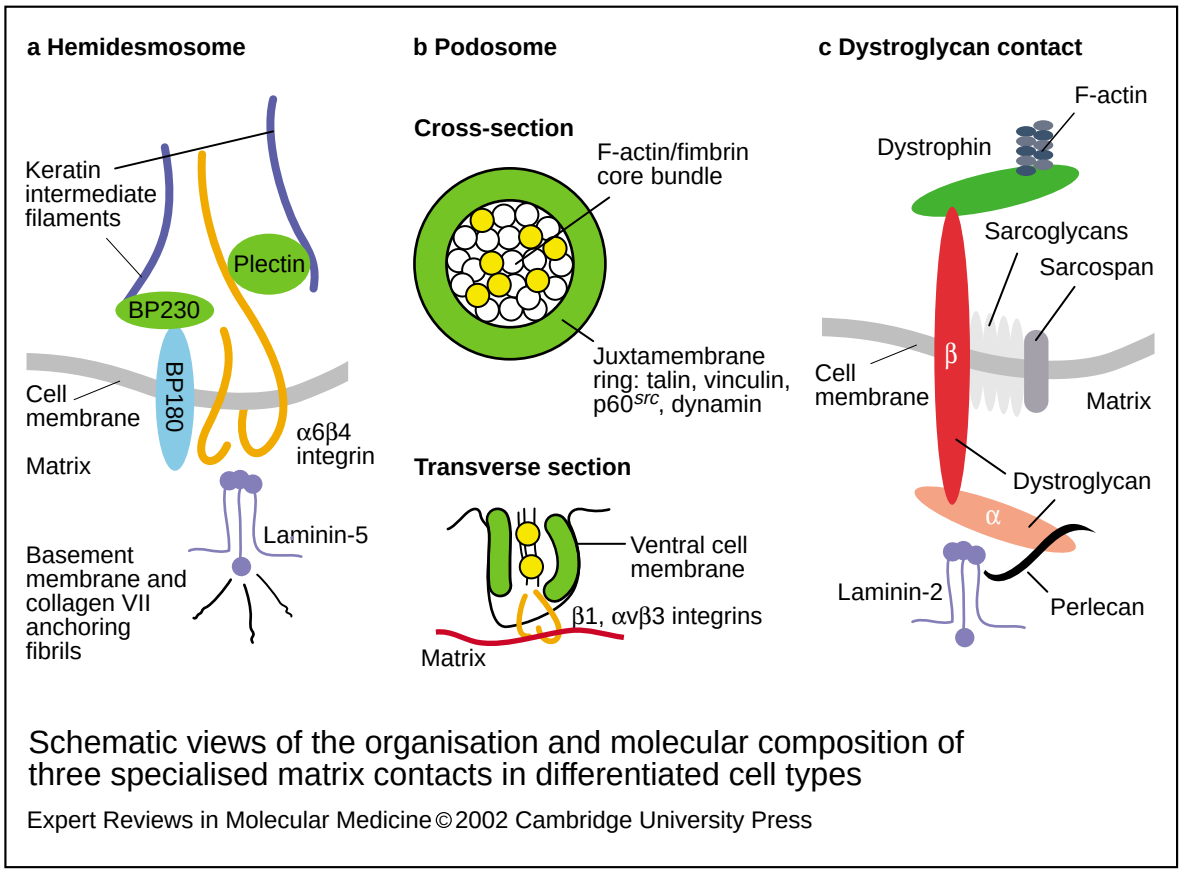

Schematic views of the organisation and molecular composition of three specialised matrix contacts in differentiated cell types

Figure 1. Schematic views of the organisation and molecular composition of three specialised matrix contacts in differentiated cell types. (a) The hemidesmosome of epidermis. The α6β4 integrin stably attaches epithelial cells to laminin-5 in the basement membrane and is linked intracellularly to the non-contractile keratin filament system. (b) The podosome of motile osteoclasts. Migratory osteoclasts attach and move over the bone matrix via the formation of podosomes. These are short cylindrical protrusions of the ventral cell membrane in which a core bundle of actin filaments is connected to the plasma membrane by a circular array of cytoskeletal linker proteins. The αvβ3 integrin on osteoclasts mediates RGD-dependent attachment to osteopontin, bone sialoprotein and collagen within bone matrix, and osteoclast β1 integrins, including α2β1, bind collagen I. (c) The dystroglycan contact of skeletal muscle. α-Dystroglycan binds to specific matrix components and is linked to the plasma membrane through its interaction with β-dystroglycan. The sarcoglycan complex and sarcospan are also present as components of the complex, but it is not known whether these molecules also have matrix ligands. Intracellularly, β-dystroglycan is linked to the actin cytoskeleton by its interaction with dystrophin or utrophin. Not to scale **(fig001jal)**.

the resorptive state – in which they show different types of cell–matrix contacts. Migratory osteoclasts attach and move over the bone matrix via the formation of podosomes. These are short cylindrical protrusions of the ventral cell membrane in which a core bundle of actin filaments is connected to the plasma membrane by a circular array of cytoskeletal linker proteins (Refs 43, 44; Fig. 1b). The αvβ3 integrin on osteoclasts mediates RGD-dependent attachment to osteopontin, bone sialoprotein and collagen within bone matrix, and osteoclast β1 integrins, including α2β1, bind collagen I (Ref. 45). Podosomes form highly transient matrix adhesions and are dynamically turned over within 2–12 min during osteoclast motility. This process might be modulated by the activities of dynamin 2, a GTPase with a known role in endocytosis, which has recently been discovered to be localised in podosomes (Ref. 46). Expression of mutant dynamins known to have dominant-negative effects on endocytosis either disrupted podosome formation or altered the rate of podosome turnover. Thus, dynamin 2 might have

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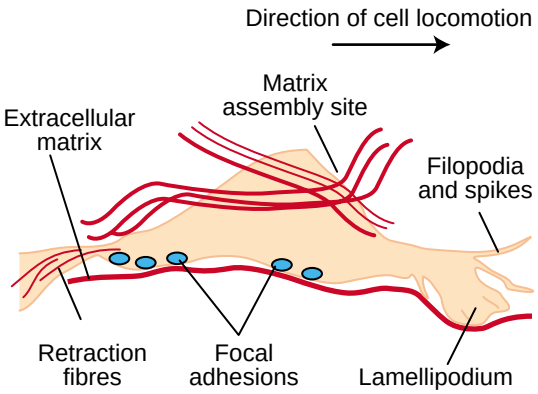
a role in podosome dynamics, perhaps by altering membrane–cytoskeleton linkages (Ref. 46).

In response to cues to remain stationary at particular sites on bone matrix, osteoclasts reversibly switch to the resorptive state. This involves the reorganisation of individual podosomes into a strong and tight adhesive contact, termed the sealing zone, at the ventral periphery of the osteoclast. This enables a contained environment to be formed under the cells for bone degradation. The central region of the ventral plasma membrane forms an elaborate ruffled membrane that maximises the surface area available for secretion of acid and cathepsin K for bone demineralisation and degradation of bone components, and for uptake and transcytosis of degraded matrix material (Ref. 44; see Movie 1, HTML version only). Although the αvβ3 integrin does not localise to the sealing ring, this integrin is critical for the assembly and function of this structure. Mice lacking the β3 integrin subunit have increased skeletal mass (osteopetrosis) and their osteoclasts do not form sealing rings, show poor formation of ruffled membranes and are ineffective in bone resorption assays (Ref. 47). The intracellular face of the sealing zone contains a large circumferential band of F-actin, which is associated with multiple linker and signalling molecules (Table 1). Organisation of the sealing ring correlates with tyrosine phosphorylation of p130^{cas} and PYK2 (proline-rich tyrosine kinase 2), and is inhibited by tyrosine kinase inhibitors (Refs 48, 49, 50). Several lines of evidence demonstrate a critical role for c-Src in osteoclast function: c-*src*$^{-/-}$ mice develop osteopetrosis, and osteoclasts from these mice show poor formation of the ruffled membrane, and deficiencies in p130^{cas} phosphorylation and actin ring formation in culture (Ref. 51). Furthermore, ligation of the αvβ3 integrin activates a complex containing gelsolin, c-Src and phosphatidylinositol 3-kinase (PI 3-kinase), in which gelsolin has a required role in podosome assembly (Ref. 52). Thus, integrin-mediated signalling might be important in regulating the phenotypic switch between the elaboration of podosomes in the motile phase and their agglomeration to form sealing zones in the absorptive phase.



Schematic view of the matrix contacts formed by fibroblasts and other mesenchymal cells when migrating through extracellular matrix

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Figure 2. Schematic view of the matrix contacts formed by fibroblasts and other mesenchymal cells when migrating through extracellular matrix. At the leading edge, filopodia and spikes protrude, relay cues in the adjacent environment into the cell body, and form transient adhesions that become enlarged and stabilised as lamellipodia. (In some cell types, initial protrusions are formed chiefly as lamellipodia.) Behind these structures, focal adhesions firmly anchor the cell body to matrix and and provide the mechanical resistance to the intracellular contractility of the actin cytoskeleton that is needed to maintain cell locomotion. In situations where there is strong attachment between cell and extracellular matrix, retraction fibres form at the cell rear as a result of resistance of the trailing cell margin to detachment from extracellular matrix. The cell is also anchored to matrix by matrix assembly sites, and the nature and density of the surrounding matrix fibrils affect the rate and directionality of cell locomotion **(fig002jal)**.

Focal adhesions and endothelial cell function

Vascular endothelial cells form the inner lining of blood vessels and are exposed throughout life to shear and distension forces due to the pulsating flow of circulating blood (Fig. 3). Experimental comparisons of endothelial cells in static or flowing medium have shown clearly that the application of shear force has major effects on the functional properties of endothelial cells (Refs 53, 54, 55). These include effects on gene expression, the activities of signalling networks and the organisation of the actin cytoskeleton and matrix adhesions. Under conditions of low shear, vinculin adhesion plaques and associated

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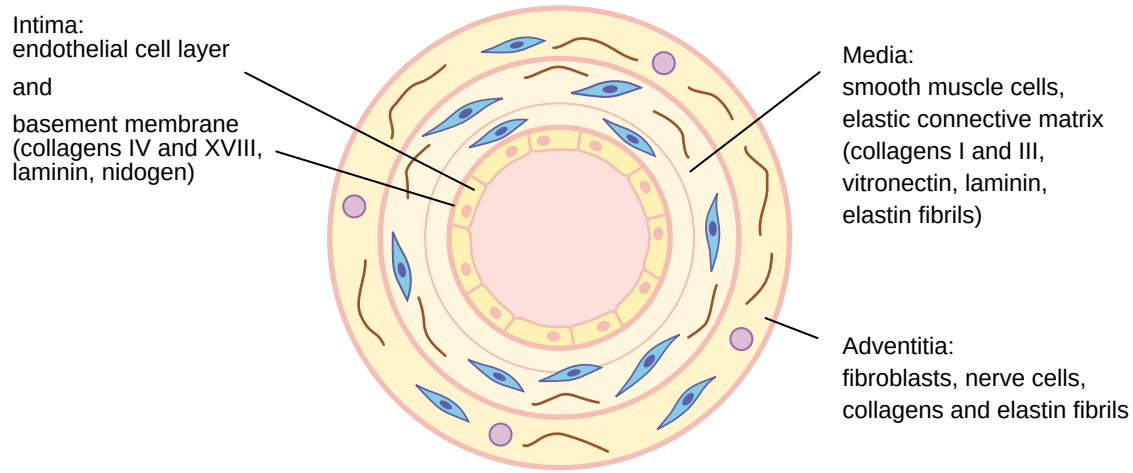

Figure 3. Schematic view of an arterial wall in cross-section. The wall has three layers that can be recognised histologically – the intima, the media and the adventitia – and each layer has a distinctive composition of cells and matrix. The basement membrane of the intima has supportive and barrier functions, and the matrices of the media and adventitia provide elasticity **(fig003jal)**.

microfilaments are most prominent at cell peripheries. When exposed to a directional shear flow, endothelial cells align end-on in the direction of the applied force, and undergo integrin clustering, and enlargement and remodelling of contacts to show prominent focal adhesions and alignment of longitudinal actin microfilament bundles with the direction of flow (Refs 56, 57, 58). The coalignment of microfilaments and microtubules is also quantitatively increased under shear stress (Ref. 59). The alignment of focal adhesions is thought to provide appropriate robustness of adhesion and contractility to the endothelial cell layer and might also be involved in the conversion of extracellular mechanical force provided by blood flow into intracellular biochemical information.

Remodelling of focal adhesions under flow depends upon activation of focal adhesion kinase (FAK) and Src-family tyrosine kinases within the adhesions and upon an intact microtubule network (Refs 58, 60, 61), and is regulated by the Rho–p160ROCK pathway (Ref. 62). Shear stress also induces activation of the receptor tyrosine kinase FLK-1 and the association of activated Shc (Src homology 2 domain-containing transforming protein) with FLK-1, αvβ3 and β1 integrins: these signalling events could affect focal adhesion remodelling (Ref. 63). These alterations in matrix contacts correlate with changes in the localised mechanical stiffness of endothelial cells, as measured by atomic force microscopy. Under static conditions, endothelial cells had most mechanical stiffness at their peripheries. Under shear stress, stiffness increased in correlation with the distribution of stress fibres such that, after six hours, cells were most stiff on the upstream sides (Ref. 64).

During re-endothelialisation of wounds to the blood vessel wall, endothelial cells extend protrusive contacts in order to close gaps in the cell layer. Small gaps in the layer are closed by extension of lamellipodia and pseudopodia between cells. Closure of larger gaps depends on cell migration and involves a decrease in focal adhesions in conjunction with protrusion of lamellae and spikes (Ref. 57). In angiogenesis, the adhesive interactions of endothelial cells are extensively coordinated by several essential morphoregulatory molecules: vascular endothelial-cell-derived growth factor (VEGF), angiopoietin 1, and members of the ephrin family (Ref. 65). These molecules have multifactorial mechanisms of action that include intracellular signalling effects on matrix attachment and matrix-contact structures. For example, VEGF promotes endothelial

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cell migration and tubule formation. These processes involve increased transcription and surface expression of αvβ3 and its ligand osteopontin, and upregulation of the collagen-binding integrins α1β1 and α2β1 (Refs 66, 67).

Angiopoietin 1 has particular regulatory effects on the interactions of endothelial cells with matrix and smooth muscle cells, and promotes capillary sprouting in culture (Refs 68, 69, 70). These activities involve multiple effects on matrix contacts, which include a PI 3-kinase-dependent activation of FAK, the secretion of matrix metalloproteinase 2 (MMP-2) and plasmin, and the suppression of tissue inhibitor of metalloproteinase 2 (TIMP-2). This combination of effects likely favours cell migration by the formation of protrusive matrix contacts (Ref. 71).

Members of the ephrin family are expressed in highly defined patterns within developing vasculature and also contribute to vasculogenesis (Refs 65, 66, 72). Individual ephrins promote tubule formation by endothelial cells from different tissue sources (Ref. 68) and have diverse effects on matrix attachments (Ref. 73). Oligomerisation of ephrin B1 stimulates tubule formation in culture and promotes attachment to fibronectin (Ref. 74). In the context of attachment to RGD peptide or fibrinogen, a certain density of ephrin B1 activates αvβ3 integrin function (Ref. 75). Conversely, activation of ephrin A5 inhibits cell spreading and affects focal adhesion structure through the recruitment of SHP2 protein tyrosine phosphatase and consequent dephosphorylation of FAK and paxillin (Ref. 76). These recent findings all highlight the complex, subtle network of morphoregulatory interactions that appropriately optimises endothelial cell–matrix interactions in the vasculature.

Pathological abnormalities of cell–matrix contacts

Given the many different types of cell–matrix contacts that exist and their widespread occurrence in all body tissues, it is not surprising that numerous pathologies have been identified that are caused by alterations or defects in the molecular composition of cell–matrix contacts. These pathologies arise from: inherited genetic defects that cause mutation or lack of expression of individual components of contacts; acquired somatic alterations that affect the expression or organisation of contact components or lead to switches in contact type; and subversion of matrix contacts by pathogens. Major examples of pathological abnormalities are described in Table 4 and three sets of pathologies are highlighted below.

Protrusive contacts and cancer cell motility and invasion

The malignant progression of cancer cells involves downregulation of fibronectin matrix, alterations in the profile and expression levels of integrins and proteoglycans, decreased focal adhesions in culture and a switch to a more migratory phenotype associated with invasive and metastatic behaviour (Refs 77, 78, 79, 80). These changes in adhesion molecules and cell behaviour involve a major alteration in the predominant type of matrix contacts, from contractile focal adhesions and matrix assembly sites to protrusive contacts (Table 1). Alterations in the adhesion receptor profile can directly alter matrix interactions, but in addition the interplay between integrins, proteoglycans and other types of cell-surface receptors also exert potent effects on cancer cell migration.

In general, the secretion of MMPs is associated with protrusion of lamellae and cell motility (Refs 81, 82). There are reports that active MMP-2 binds to αvβ3 integrin on melanoma cells and might also alter the activity state of the integrin (Refs 83, 84). Cell-surface expression of urokinase-type plasminogen activator and its receptor promote αvβ5-dependent cell migration by a molecular process that is separable from cell body adhesion (Ref. 85). Thus, various molecular mechanisms for cooperation with integrins provide fine localisation of matrix protease activity on the cell surface (Refs 86, 87).

Interactions between adhesion receptors and motogenic cytokines are also of importance. For example, interactions between αvβ5 and insulin-like growth factor type 1 receptor promote tumour cell motility through a mechanism that involves redistribution of α-actinin at matrix-contact sites (Ref. 88). Although the relationships between these receptor interactions and the organisation of cell–matrix contacts have not been explicitly demonstrated, it is very likely that the effects on motility are mediated by enhanced formation of protrusive contacts.

Various forms of spikes and filopodia have been reported in different cancer contexts. Fascin-containing spikes are involved in cell

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Table 4. Examples of pathologies associated with abnormalities of cell–matrix contacts (tab004jal)

Contact type	Disease association	Molecular basis
Dystroglycan contact	Muscular dystrophies and inherited dilated cardiomyopathy	Mutations causing perturbation of function in laminin, the cell-surface components, or dystrophin
	Leprosy	*Mycobacterium leprae* binds α-dystroglycan
	Lassa fever	Arenavirus binds α-dystroglycan
	Enteroviral cardiomyopathy	Cleavage of dystrophin by Coxsackievirus protease A2
Fibrillar adhesion	Reduced on cancer cells	Altered integrin expression profiles, decreased fibronectin matrix assembly
Fibrillin microfibril	Marfan's syndrome	Mutations in fibrillin 1 affect fibril assembly
	Cutis laxa, rupture of blood vessels	Mutations in tropoelastin affect elastin assembly
Focal adhesion	von Willebrand's disease	Mutation or absence of vWF blocks platelet attachment
	Bernard Soulier syndrome	Mutation or absence of GPIb blocks platelet attachment
	Glanzmann's thrombasthenia	Mutation or absence of αIIbβ3 integrin blocks platelet adhesion
Hemidesmosome	Epidermolysis bullosas	Mutation or absence of laminin, α6 or β4 integrin subunits, plectin, BPAG1e, or keratins 5 or 14, destabilises contacts
Invadopodium	Invasive cancers (melanoma, breast)	Upregulation of this contact type promotes cell motility, associated with matrix protease activity
Podosome	Wiskott–Aldrich syndrome	Mutation or absence of WASp impairs podosome assembly
Pseudopodium	Invasive cancers	Upregulation of contact associated with cell motility
Spike/microspike	Invasive carcinoma	Upregulation of fascin correlates with carcinoma invasiveness Association of α6β4 integrin with actin-based protrusions Associated with cell motility

Abbreviations: BPAG1e, bullous pemphigoid antigen 1e; FN, fibronectin; GPIb, platelet glycoprotein Ib; LN, laminin; WASp, Wiskott–Aldrich syndrome protein; vWF, von Willebrand factor.

motility in non-transformed cell types (as discussed above). Fascin is upregulated in invasive breast, ovarian and colonic carcinomas and is proposed to contribute to the invasive behaviour of high-grade breast tumour cells (Refs 89, 90). It is likely that the regulatory processes documented for fascin spikes during adhesion and migration in tissue culture have similarities to the mechanisms involved in vivo, and thus the tissue culture situation can be used as a testbed for treatments predicted to alter spike formation and thus adhesive behaviour. It is also likely that such correlations could be made for all other types of matrix contacts. Colonic and breast

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carcinoma cells on laminin matrix do not organise hemidesmosomes, but form actin spikes that mediate motility and concentrate the α6β4 integrin as an adhesion receptor (Ref. 40). The formation of this type of spike depends on signalling by the GTPases Rac and Rho, PI 3-kinase and cAMP-phosphodiesterase (Refs 91, 92).

Many tumour cells in culture show extensive formation of pseudopodia that are enriched for β1 integrins, CD44 and the linker protein ezrin (Refs 93, 94, 95, 96; Table 1). These structures are involved in tumour cell motility and their formation is also regulated by motogenic cytokines (Ref. 97). In three-dimensional matrix, tumour cells form protrusive contacts, termed invadopodia, that penetrate into the matrix (Refs 98, 99; Table 1). The role of these contacts in cell motility likely depends on the localised secretion of matrix-degrading proteases (Ref. 100). These proteases are concentrated at invadopodia by matrix-dependent interactions with integrins, and act on many matrix components. Thus, the α3β1 integrin becomes physically associated with the protease seprase at invadopodia upon cell adhesion to collagen (Ref. 101). The formation of invadopodia and increased cell motility depend on the activities of tyrosine kinases and p190RhoGAP and are regulated separately from the matrix adhesion of the cell body (Ref. 102).

In summary, malignant conversion of cells involves alterations to cell–matrix attachment properties and an increased propensity for migration, which both involve an overall decrease in contractile contacts and an increase in protrusive contacts.

Matrix contacts in platelet adhesion and dysfunctional haemostasis

Circulating platelets have critical functions in preventing blood loss from wounds in the vascular system. The normal function of platelets is to plug damaged areas of the vessel wall by their attachment to the exposed subendothelial ECM. Attachment leads to platelet activation, spreading, and release of platelet granule contents, which recruit other platelets and provide additional ECM to form a thrombus to cover the damaged area. This process is termed primary haemostasis. At later times in the healing process, contractility of platelets, in conjunction with remodelling of ECM within the thrombus, acts to bring the wound margins together. Several major pathologies are associated with dysregulation of these processes: inherited bleeding disorders, due to absent or defective platelet–matrix interactions, and thrombosis leading to cardiovascular disease or stroke, due to inappropriate or excessive growth of thrombi (Ref. 103).

Platelet adhesion depends at first on the binding of von Willebrand factor (vWF) in the circulation to exposed subendothelial matrix – in particular to fibrillar collagens (Fig. 3). Under the shear-stress conditions of normal blood flow, platelets become transiently tethered to matrix-bound vWF by the platelet GPIb complex GPIb–IX–V (Refs 104, 105). The shear-force dependency of this attachment might relate to the alteration in shape of vWF, from a globular to an extended linear molecule, that occurs under the application of shear stress (Ref. 106). Subsequent agonist-dependent platelet activation is accompanied by platelet spreading and the formation of firmer, static focal-contact-type adhesions through activation of αIIbβ3 integrin by so-called 'inside-out' signalling (see below) and its subsequent binding to matrix fibronectin, vWF, fibrinogen and vitronectin (Refs 107, 108). Matrix collagen is also bound in a two-step process, involving an initial interaction with collagen bound to vWF by GPIb, and subsequent binding by α2β1 integrin and platelet GPVI (Ref. 109).

The process of platelet spreading has been studied in detail using various forms of microscopy. Circulating platelets have a smooth discoid shape, but initial matrix contact results in the extension of surface spikes and filopodia, and the extension of lamellae between the projections, accompanied by ruffling and a general flattening of the platelet, which results in a fourfold increase in surface area (Refs 110, 111, 112, 113). Spreading involves activation of actin-severing proteins, leading to major changes in the organisation of microfilaments, an increase in platelet F-actin content and the organisation of vinculin-containing focal-adhesion-type structures. Microtubules are also remodelled (Refs 114, 115, 116). During later resolution of the clot, platelet actomyosin-based contractility causes retraction of filopodia and exerts tension on the clot, causing it to shrink.

Inherited bleeding disorders associated with platelet dysfunction arise from abnormalities in several components of these adhesion systems (Table 4). von Willebrand's disease (vWD) is

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the most common form of bleeding disorder. Different forms of vWD result from qualitative, quantitative or complete deficiencies of vWF (Ref. 105). According to the form of vWD, the molecular basis of the disorder stems from a lack of circulating vWF multimers, an increased affinity for GPIb that leads to clearance of circulating complexes of platelets and vWF, or a lack of binding to GPIb and thus a loss of platelet attachment and spreading on matrix under injury conditions (Ref. 117). Failure of platelet attachment and spreading is also seen in Bernard Soulier syndrome, in which GPIb is abnormal or absent (Ref. 118). Absence or dysfunction of αIIbβ3 integrin is associated with Glanzmann's thrombasthenia, a bleeding disorder in which platelets fail to attach, spread or aggregate (Refs 103, 107).

The reverse situation, of an excess of platelet adhesion and thrombus formation, leads to thrombosis and arteriosclerosis. In these pathologies, vessels become occluded by inappropriate, untimely thrombus formation and growth, leading to an iterative situation in which complex interactions between growth factors, matrix, platelets and endothelial and smooth muscle cells participate in the genesis of an atherosclerotic plaque (Ref. 55). Breakage of a thrombus from the walls of a sclerotic vessel might then block smaller vessels and cause a heart attack or stroke. Because the αIIbβ3 integrin mediates platelet adhesion and the final common pathway in platelet aggregation, much effort has gone into the development and clinical testing of antagonists of this integrin. Indeed, several types of inhibitor, including antibodies to integrin αIIbβ3, have been demonstrated to be of benefit in short- and long-term management of coronary artery disease (Ref. 119).

Dystroglycan contacts: roles in muscular dystrophy, cardiomyopathies, leprosy and arenavirus infection

Dystroglycan contacts play a critical, continuous role throughout life in the adhesion of skeletal myotubes and cardiomyocytes to their surrounding basement membranes, and serve to stabilise the sarcolemma throughout muscle contraction and relaxation. At the cell surface, α-dystroglycan binds to specific matrix components and is linked to the plasma membrane through its interaction with β-dystroglycan (Fig. 1c). The sarcoglycan complex and sarcospan are also present as components of the complex, but it is not known whether these molecules also have matrix ligands. Intracellularly, β-dystroglycan is linked to the actin cytoskeleton by its interaction with dystrophin or utrophin. The dystroglycan complex is also present in epithelia, smooth muscle and peripheral nerve and has been found to have important roles in basement membrane assembly. Inherited and acquired pathologies that affect the dystroglycan contact all underscore the importance of the integrity of the whole dystroglycan contact in skeletal muscle and heart, in mediating membrane stabilisation and a mechanically strong functional linkage between matrix and cytoskeleton (Ref. 13).

Mice lacking dystroglycan die at embryonic day 5.5 due to fragmentation of basement membranes, and a major impairment of the development of polymeric laminin matrix is apparent in cultures of embryonic stem cells that lack dystroglycan (Refs 120, 121, 122). In humans, the muscular dystrophies and inherited cardiomyopathies are progressive wasting disorders of skeletal muscle and cardiac tissue that are caused by mutations or deficiencies of any of the components of the dystroglycan complex (Refs 13, 123).

A subset of acquired cardiomyopathies are associated with enteroviral infection of the heart, in particular by Coxsackie B viruses. This pathology arises through the action of Coxsackievirus protease A2, which cleaves dystrophin within its central hinge region and so separates the β-dystroglycan-binding and actin-binding portions of dystrophin (Fig. 1c). This cleavage disrupts the cellular localisation and normal cytoskeletal linkage function of dystrophin in cultured myocytes and in the intact heart (Ref. 124). The disruption of dystrophin also leads to physical dissociation of the sarcoglycan complex from dystrophin, mislocalisation of sarcoglycans and increased permeability of the sarcolemma (Ref. 125).

Other diseases are associated with subversion of the dystroglycan complex by pathogenic organisms. α-Dystroglycan, in association with the G domain of the α2 chain of laminin-2, is bound by *Mycobacterium leprae* and mediates bacterial adherence to Schwann cells. This event might be important for the invasion of Schwann cells by the bacterium in leprosy (Ref. 126). Arenaviruses are pathogens with broad tissue

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trophisms that cause fatal haemorrhagic fevers including Lassa fever in humans. Lymphocytic choriomeningitis virus causes a similar pathology in rodent hosts. These viruses infect host cells by binding to α-dystroglycan; indeed, the presence or absence of α-dystroglycan is sufficient to determine infectivity (Ref. 127). These findings raise the possibility of testing soluble α-dystroglycan extracellular domain as a blocker of viral infectivity of cells.

Future prospects: regulation of matrix contacts

A key aspect of matrix-contact function is that contact formation needs to be appropriately regulated in time and space. For example, epithelial cells have polarised exposure to ECM in the form of the basement membrane (Ref. 8). Circulating leukocytes are non-adherent, but they need to achieve polarised formation of protrusive matrix contacts and podosomes during attachment to endothelium and extravasation and subsequent migration within solid tissue. Immature dendritic cells, which are stably adherent in non-lymphoid tissues, become activated by antigenic challenge to migrate into secondary lymphoid tissues (Ref. 128). These functional processes are not mediated by simple, on–off formation of a single type of contact, but require complex, integrated coordination of multiple matrix-contact types across the entire cell. Recent studies in tissue culture have begun to provide information on the molecular mechanisms involved.

At the cell surface, formation of different types of contacts is regulated according to the molecular composition and organisation of the pericellular matrix, the profile of adhesion receptors expressed, and the ligand-binding affinity states of integrins. These parameters all affect cell attachment and migration speed (Ref. 129). Ligand binding activates and clusters specific integrin adhesion receptors and drives the formation of intracellular linker complexes and their cytoskeletal connections, thereby generating fully functional matrix contacts. This process is termed 'outside-in' signalling Ref. 130) and is best understood for focal adhesions and hemidesmosomes. Several recent reviews discuss the molecular mechanisms of focal adhesion assembly in detail and this will not be covered further here (Refs 131, 132, 133). Integrin activation is also achieved by 'inside-out' signalling, in which integrin–ligand interactions are regulated by the effects of signalling molecules on the assembly and functional status of linker complexes and cytoskeletal filaments. This process has also been most intensively studied with regard to focal adhesions. Multiple pathways that affect this contact have been identified and include the major categories of signalling molecules: FAK, Src-family kinases, PI 3-kinase, protein kinase C and Rho family small GTPases (Ref. 134). I have outlined regulatory mechanisms that act on spikes and podosomes in sections above. Knowledge of other matrix contacts is less developed, and to build a complete understanding of matrix contacts – encompassing their regulation, roles and interactions – a comprehensive view of the molecular organisation and defining features of all forms of contacts is needed.

In considering potential mechanisms by which single cells integrate formation of multiple contact types, the regulatory balance between protrusive and contractile matrix contacts can be envisioned as important to cell function. Without protrusive contacts, cells cannot extend to sample their surrounding environment, make transient adhesions or maintain a leading edge for locomotion. Without contractile contacts, cells cannot assemble matrix or exert the tension on surrounding matrix and cytoskeleton that is also needed for locomotion. These considerations lead to a model in which regulated disassembly of focal adhesions, or other types of contractile contacts, is coordinated with the formation of protrusive contacts. A number of observations from different experimental systems give support for such a model and indicate directions for new areas of research.

Experiments on defined mixed matrices have demonstrated coordination of matrix contacts by cells. Cells adherent on mixed TSP-1–fibronectin matrices show graduated formation of focal adhesions and fascin spikes according to the ratio of the two proteins (Ref. 34). Addition of tenascin-C downmodulates focal adhesions in cells on fibronectin and promotes membrane ruffling (Ref. 36). Inclusion of tenascin-C in mixed fibrin–fibronectin matrix gels also promotes the formation of cell projections (Ref. 135). Mixtures of fibronectin domain fragments promote stable lamellipodia at certain molar ratios (Ref. 136). These experiments indicate that different matrix molecules, or fragments thereof, can determine

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overall coordination of focal adhesions and protrusive contacts by cells.

Of the known signalling regulators of focal adhesions, regulation of Rho GTPase could be a common mechanism for contact coordination. As for all the small GTPase family, the Rho protein cycles between an inactive, GDP-bound state and an active, GTP-bound form. The cycle is regulated by the activities of guanine diphosphate dissociation inhibitors (GDIs), guanine-nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs) (Ref. 137). Several studies have documented that inhibition of Rho activity, either by C3 exotransferase or by overexpression of RhoGAP or RhoGDI, decreases focal contact organisation and promotes the formation of extensive cell-surface projections (Refs 138, 139, 140, 141). This suggests that molecular links involving Rho exist between contractile focal adhesions and protrusive contacts.

In the context of matrix interactions, several molecular pathways have been outlined that lead to inhibition of Rho activity, as assessed by the Rho–GTP content of whole-cell extracts. These include Rac-mediated suppression of Rho activity (Ref. 142), p190GAP-mediated depletion of active Rho in suspended cells treated with monomeric RGD peptide as an integrin ligand (Ref. 143), inhibition mediated by $p120^{ctn}$ (Refs 144, 145, 146), and a tenascin-C-induced inhibition of Rho–GTP content of cells in three-dimensional matrix (Ref. 135). Knowledge of the molecular basis for these effects should be relevant to the question of molecular connections between protrusive and contractile contacts.

Given the large number of structural and signalling molecules associated with the linker complexes of focal adhesions, it is not surprising that other mechanisms that destablise focal adhesions have been described. Microtubule targeting of focal adhesions has been documented as a physical process that correlates with dissolution of focal contacts (Refs 147, 148). Conversely, depolymerisation of microtubules leads to increased formation of focal adhesions, increased cell contractility and decreased lamellipodial protrusion, by molecular processes that depend on Rho and Rac activities (Refs 149, 150, 151, 152). Calpain protease activity contributes to focal adhesion turnover in migratory fibroblasts (Refs 153, 154) and has an important role in inside-out and outside-in signalling through αIIbβ3 integrin in platelets (Ref. 155).

It would be important to know the repertoire of matrix components that engage particular focal adhesion destabilisation mechanisms, and whether these mechanisms also operate on other types of contractile contacts. In all the experiments described above, matrix contacts were formed without cell polarity (i.e. in cells adherent on uniform layers of matrix proteins) and biochemical measurements were made on whole-cell extracts. In reality, spatial compartmentalisation of contact assembly or disassembly mechanisms must be important to maintain polarity and achieve coherent cell organisation and behaviour. New methods for subcellular spatial resolution of protein interactions or activated signalling molecules offer prospects for unravelling this level of regulation (Refs 156, 157).

At the supramolecular level, matrix-contact formation might also be coordinated by membrane microdomains. In migrating cells, the cell membrane is more deformable at the cell rear (Ref. 158). Lipid rafts, which are zones of the lipid bilayer enriched in cholesterol and glycosphingolipids, are proposed to cluster certain proteins and to create specialised protein–lipid complexes within the plasma membrane (Ref. 159). Lipid microdomains or rafts contribute to the polarised recruitment of chemokine receptors in growth-factor-mediated chemotaxis and, although not required for structural assembly of pseudopodia, are needed for the spatial localisation of pseudopodia at the leading edge that contributes to effective cell migration (Ref. 160). It would be interesting to know if rafts are needed for the assembly of other types of protrusive contacts, how the clustering of adhesive receptors relates to lipid microdomains or rafts, and how raft positioning in cells is regulated to build up spatial asymmetries.

In conclusion, cell–matrix contacts are dynamically regulated, multiprotein entities that are vital to integrated cell behaviour. Basic research on cell–matrix contacts is entering exciting new areas. An understanding of the molecular makeup and regulation of all forms of matrix contact is likely to reveal new prospects for biomedical applications. Cell adhesion is needed for the survival of normal cells (Refs 161, 162) and thus strategic interventions that alter cell locomotion or guidance behaviour

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without totally blocking cell–matrix attachment could be of value in promoting acute wound healing, tissue replacement or nerve regeneration, or in managing chronic conditions such atherosclerosis or inflammatory disorders. Approaches that specifically target cancer cells and downregulate protrusive contacts could have potential to block metastatic spread of primary tumours, or enforce the stasis of residual cells after surgery or chemotherapy that would otherwise progress to secondary tumours. Understanding how to control particular types of matrix assembly sites, and thus the nature of pericellular matrix, could be a route to achieve localised regulation of cell behaviour and differentiation status and thus to modify phenotype in cancerous or ageing cells. To determine how these complex biological processes could be resolved as therapeutic targets will need a coordinated convergence of cell biology, tissue engineering, and molecular medicine.

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Box 1. Glossary of selected terms used in this article

Angiogenesis: the formation of new capillary blood vessels through stimulation of endothelial cell proliferation and migration and regulation of cell–cell and cell–matrix interactions in endothelial cells and smooth muscle cells

Capillary sprouting: the formation of new capillary blood vessels by growth and migration of endothelial cells from existing blood vessels

C3 exotransferase: an exotoxin produced by the *Clostridium botulinum* bacterium; when introduced into cells, it binds irreversibly to Rho GTPase in the GDP-loaded state and thus irreversibly and specifically blocks Rho activity

GTPase pulldown assay: affinity precipitation method, in which the binding domains of GTPase effector proteins that selectively interact with the GTP-loaded form of small GTPase molecules (typically the binding domains from rhotekin or p21-activated kinase) are expressed as recombinant fusion proteins and mixed with cell lysates; the relative proportion of the total pool of the GTPase that become bound to the fusion protein gives a measure of the activity state of the GTPase

Integrin outside-in signalling: the transduction of a signal initiated by occupancy of an integrin by its ligand, propagated down the integrin molecule to bring about a conformational shift of the integrin α/β cytoplasmic domains and resulting in the altered activities of cell signalling pathways and other cellular activities

Integrin inside-out signalling: the regulation of the extracellular integrin–ligand binding interaction by intracellular factors such as the extent of linkage to the cytoskeleton, activity states of cell signalling pathways or signals provided through the activities of integrin-associated proteins

Isometric tension: the state of mechanical force balance that exists in cells, in which the inward pull from actomyosin-based contractility of the cytoskeleton is opposed by the tethering of cells to extracellular matrix (ECM) in conjunction with the particular physical properties of the ECM (e.g. the ECM of bone is more rigid than that of connective tissue)

Lamellipodia: sheet-like protrusion of the cell margin, formed during initial cell spreading on two-dimensional matrix, in three-dimensional matrix and during cell migration

Linker complex: multiprotein assemblies that couple adhesion receptors and cytoskeletal filaments. These generally have signalling and actin-organisational activities

Membrane retrograde flow: constitutive rearward movement of the plasma membrane over the apical surface of cells

RGD-dependent adhesion: binding of ECM molecules to their specific integrins via the tripeptide motif RGD, first identified as the primary, high-affinity integrin-binding site in fibronectin; these interactions can be competitively inhibited by soluble RGD-containing peptides

Rigid versus deformable extracellular matrix: a rigid ECM (e.g. bone matrix, plastic tissue culture dish) resists the contractile force of the cytoskeleton on adhesive contacts, whereas a deformable matrix (e.g. connective tissue, vascular basement membrane, flexible rubber culture surfaces) becomes flexed or puckered when cell contractility changes

Sarcolemma: the plasma membrane of syncytial myofibrils

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Further reading, resources and contacts

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The WWW Virtual Library of Cell Biology contains links to websites on cell adhesion, the extracellular matrix, the cytoskeleton and cell motility.

http://vlib.org/Science/Cell_Biology/

The Medscape website has information about preclinical and clinical studies related to various fields including cell–matrix research.

http://www.medscape.com/

The Signal Transduction Knowledge Environment website covers all aspects of signal transduction research.

http://stke.sciencemag.org/

The Wound Healing Society website has links to relevant journals and other links to cell–matrix research in wound healing.

http://www.woundheal.org

Features associated with this article

Figures

Figure 1. Schematic views of the organisation and molecular composition of three specialised matrix contacts in differentiated cell types (fig001jal).
Figure 2. Schematic view of the matrix contacts formed by fibroblasts and other mesenchymal cells when migrating through extracellular matrix (fig002jal).
Figure 3. Schematic view of an arterial wall in cross-section (fig003jal).

Tables

Table 1. Characteristics of protrusive cell–matrix contacts (tab001jal).
Table 2. Characteristics of contractile cell–matrix contacts (tab002jal).
Table 3. Characteristics of mechanical support cell–matrix contacts (tab003jal).
Table 4. Examples of pathologies associated with abnormalities of cell–matrix contacts (tab004jal).

Animation

Movie 1. An osteoclast in three dimensions (swf001mhu; http://www-ermm.cbcu.cam.ac.uk/00001678h.htm).
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