Extracellular Matrix

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The extracellular matrix is the component of tissue that lies immediately outside and between cells in animals and plants.

Secondary article

Article Contents

Cells, the Extracellular Matrix (ECM), and the Interface Between Them

The tissues of a multicellular organism contain two main components, the cells themselves, on which most biological research has traditionally focused, and the material that lies between the cells. This material is called the extracellular matrix, usually abbreviated to 'ECM'. The ratio of tissue volume occupied by ECM to that occupied by cells varies from less than 1:10 (e.g. in muscles) to more than 10:1 (e.g. in tendons, cartilage and bone). For many years, ECM was dismissed as a relatively inert 'ground substance' whose sole function was packing. However, it has now become clear that the ECM is much more complex than was once supposed and that interaction with the surrounding matrix is one of the major controls of cell behaviour. The main functions of ECM are to fill space between cells, to provide a barrier that isolates tissues from each other, to provide navigational cues for migratory cells, to provide signals that alter cell behaviour, and to sequester biologically active compounds such as growth factors.

ECM of one sort or another is a feature of all multicellular organisms. In plants, ECM appears mainly as cell walls, while in animal tissues it appears in two main forms: basement membranes and stromal matrix (**Figure 1**). Basement membranes are thin layers of ECM gel that underlie epithelial cell sheets, the basement membrane effectively separating the epithelium from underlying connective tissues. Stromal matrix is associated with 'connective tissues' and is frequently fibrous, particularly in load-bearing tissues such as artery walls, tendons, cartilage and skin. Some stromal ECM is also mineralized, to produce bone.

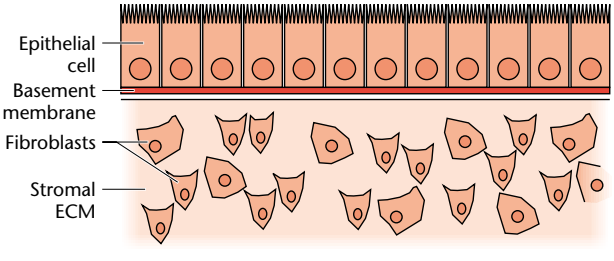

Figure 1 Diagram of an idealized animal tissue showing the two main types of ECM: a basement membrane underlying the epithelial cells of the tissue and a stromal ECM surrounding the cells of the mesenchymal part of the tissue.

The ECM is a mixture of many different molecular components that varies between organisms and also between tissues within one organism, and sometimes also varies with developmental age. The internal structure of the ECM is highly organized, the organization arising partly from the innate properties of its constituent molecules and partly from the activities of the cells that produce it. Cells embedded in the ECM make contact with it mainly through specialized matrix receptor molecules. These allow the cells to adhere to the matrix and may also signal the presence of particular matrix components to the internal machinery of the cell, allowing the matrix to control cell behaviour. The ECM is not a static structure, but is constantly being remodelled by the cells within and around it and by the opposing influences of ECM synthesis and its destruction by proteolytic enzymes.

This article will describe the main components of the ECM in plant and animal tissues, how they are synthesized and organized, and how ECM receptors work. Then it will give an overview of how the ECM is used by cells to allow them to move, to make complex tissue shapes and to differentiate into different types of specialized cells. Finally, it will briefly review the diseases that arise when the formation and maintenance of the ECM and ECM receptors goes awry.

Cellulose: Plant Cell Walls

The cells of plants differ from those of animals in being surrounded by a thick layer of highly specialized ECM called the cell wall. Like most ECMs, plant cell walls derive their strength from binding strong fibres together in a dense matrix – a design reminiscent of the glass-reinforced plastic used in boat hulls and light aircraft. Unlike the ECM of

animal cells, however, plant cell wall ECM is based almost entirely on carbohydrates with only a little protein being involved. The fibres of plant cell walls are composed of a long, unbranched carbohydrate called cellulose. Cellulose, consisting of long chains of linked glucose monomers, is unusual in that it is not made inside cells and secreted, but is rather made within the plasma membrane by cellulose-synthesizing particles embedded in that membrane. Newly made cellulose molecules are able to self-assemble (associate without further help) into fibres, each of which is a bundle of about 100 individual cellulose chains. The precise orientation of each bundle of cellulose chains seems to be organized by a network of microtubules located just below the cell's plasma membrane.

Individual cellulose fibres are crosslinked by long branched polysaccharide chains of hemicellulose, which has a somewhat variable composition in terms of sugar chains. The network of thick cellulose fibres crosslinked by thin hemicellulose chains is embedded in a gel-like matrix of complex, negatively charged polysaccharides called pectins. In addition, the wall may contain small quantities of proteins to strengthen it or to give it specialized properties, and the cell walls of secondarily thickened ('woody') plants contain lignin, a polymer of aromatic alcohols that is covalently crosslinked by peroxidases to form the tough, insoluble ECM of wood.

Molecular Composition, Synthesis and Organization of Animal ECM

Animal ECM is composed mainly of glycoproteins and proteoglycans, many of which are able to bind to specific sites on other ECM glycoproteins so that the matrix becomes a highly crosslinked gel. There are approximately 100 known ECM components, more if one includes molecules such as growth factors that are not structurally part of the matrix but which bind to it, but most ECM material is accounted for by a few dominant types of molecule.

The collagens

The collagens are arguably the dominant proteins of the ECM. They constitute a large family of at least 19 related glycoproteins, numbered in a series from collagen I to collagen XIX. All are based on a structure called the triple helix, a tight right-handed helix of three individual collagen chains, each individual chain having the structure of a left-handed helix. The amino acid sequence of those parts of the collagen chain involved in the triple helix is unusual. Because of the way that the triple helix is wound, every third amino acid faces towards the centre of the helix where there is very little space. Only the smallest amino acid, glycine, can fit in this location, so the triple helix-forming sections of collagens all have glycine residues every three amino acids. About a fifth of the other amino acids consist of proline and hydroxyproline, which can make hydrogen bonds that stabilize the helical structure.

Collagens are synthesized by the normal secretory pathway, but are modified in the endoplasmic reticulum and Golgi apparatus so that many prolines are hydroxylated to become hydroxyproline. The collagen chains are further stabilized by disulfide bond formation, and complex carbohydrates are added to the non-triple helix regions of the molecules. Cells do not secrete collagens directly, but rather secrete large precursors called procollagens that have 'extra' domains at each end of the peptides of a mature collagen. These domains are cleaved off outside the cell by specific proteinases, and once free of them most collagen chains can associate with each other to form fibrils, which line up with one another to form larger fibres.

Collagen types I, II and III account for about 90% of all collagen in the body, and form strong fibrils. In life, most individual fibrils are composed of a mixture of these collagens and may also include small amounts of the other fibrillar collagens (e.g. V and XI), with collagen types IX, XII and XIV coating fibrils to alter their sticky or slippery properties. While these fibrillar collagens are common in connective tissue, the basement membranes of epithelia usually contain a quite different collagen, collagen IV, which forms three-dimensional gels rather than fibrils. In contrast to these common collagens, some types are expressed only in a small number of sites in the body.

Elastin

It is important that tissues of the body spring back into shape after deformation; examples of tissues in which this ability is particularly vital include arteries, skin and tendons. Much of the necessary elasticity is achieved by a random network of elastic fibres embedded in the ECM. These fibres depend for their mechanical properties on the protein elastin.

Elastin is synthesized and secreted as a soluble precursor, tropoelastin, which forms elastic fibres in association with other ECM components, chiefly fibrillins 1 and 2 (see below). The fibres are stabilized by an enzyme called lysyl oxidase, which deaminates specific lysine amino acids in the elastin molecule and allows the fibres to be covalently crosslinked. The balance of elastic fibres of elastin and the relatively inelastic fibres of collagen, which varies between different ECMs, is thought to be a key regulator of their mechanical properties.

Fibrillins

Fibrillins 1 and 2 are two very similar proteins that make fine microfibrils in connective tissue. These microfibrils form a scaffold on which elastin is laid down to make elastic

fibres, and may also play other less-well understood roles in stabilizing ECM.

Fibronectins

Fibronectins are a family of proteins produced by alternative splicing of a single gene. Some forms of fibronectin remain soluble and may be found in blood plasma, while others associate into disulfide-bonded fibrils in the ECM. Each fibronectin molecule, itself a dimer of two fibronectin peptides, contains binding sites for a variety of other molecules, such as heparan sulfate proteoglycan, integrins and collagens. Fibronectins therefore serve to bind different components of the ECM together, and to serve as sites on the ECM to which cells can bind (see below).

Hydroxyapatite

Perhaps the most obvious example of ECM in the body is provided by the bony skeleton. Bones are composed of a highly specialized ECM that is composed of collagens and other proteins embedded in a mineral matrix of hydroxyapatite. The laying down of this mineral is controlled by a number of proteins, e.g. osteoclacin and osteonectin, made by specialized cells called osteoblasts.

Laminins

Laminins are large ECM proteins, typically the shape of a crucifix, that are composed of three different types of chain, called α, β and γ. The three short arms of the cross represent the N-terminal ends of each chain, while the middle and C-terminal portions of the chains run together down the long arm of the cross. There are several types of α, β and γ chains, and these can associate promiscuously to generate many types of laminin (e.g. laminin-1 has $\alpha1$, $\beta1$ $\gamma1$ chains, laminin-2 has $\alpha2$, $\beta1$, $\gamma1$ chains, etc.).

Laminins contain various sites for binding to receptors on the cell surface (see below), and to other components of the cell matrix such as collagens and proteoglycans.

Matrix metalloproteinases (MMPs)

Matrix metalloproteinases (MMPs) form a large family of proteolytic enzymes, all of which include metal ions (zinc and calcium) for activity, and all of which lyse various ECM proteins such as collagen (each MMP cleaves a different range of ECM components). Secreted MMPs are all produced and secreted from cells in an inactive proenzyme form, which differs from the active form by including an N-terminal 'pro-domain' that blocks the MMP's active site. Pro-MMPs are activated when they are themselves cleaved by other proteases. Some secreted MMPs can activate other MMPs (e.g. MMP-3 can activate pro-MMP-1 and pro-MMP-8), thus beginning a cascade of matrix destruction. Instead of being secreted, MMP-11 is embedded in the plasma membrane; this membrane-bound MMP is believed to be activated by signalling pathways inside a cell, and to be capable of activating other MMPs in the ECM outside. It is therefore an important link in the chain that allows cells to sculpt the matrix in which they are embedded.

The actions of MMPs, which are directed at destroying ECM, are antagonized by tissue inhibitors of metalloproteinases (TIMPs), of which at least three are known. The overall rate of matrix destruction of ECM is determined largely by the balance between the TIMPs and MMPs embedded within it.

Nidogen

Nidogen is a sulfated glycoprotein found in basement membranes. It can bind to both laminin and type IV collagen, and thereby crosslink them into a network that is a major component of the basement membrane gel.

Proteoglycans

Proteoglycans are a diverse set of molecules characterized by having very large and complex carbohydrates attached to a protein core, the mass of the carbohydrate part of the molecule being a large proportion of the mass of the whole. The complex carbohydrates are referred to generically as glycosaminoglycans (GAGs). There are several types of protein core, and many types of GAG. GAGs are classified into various families (e.g. heparan sulfate, chondroitin sulfate, dermatan sulfate, keratan sulfate and hyaluronan; the 'an' is a general suffix for GAGs), but within each of these families there is much detailed variation of precise sequences of sugars. Each protein core can carry a variety of GAGs, and different cores may bear the same type of GAG.

The protein cores of proteoglycans are synthesized by the normal secretory pathway in the endoplasmic reticulum and then pass to the Golgi apparatus, where certain of their serine residues are linked via xylose to long GAG chains that are synthesized *in situ*. In most proteoglycans, these chains are then sulfated by sulfotransferase enzymes, the sulfate groups giving the GAGs a net negative charge.

Proteoglycans have a variety of functions. Many can be bound by receptors on cells, promoting cell–ECM adhesion, and also by ECM molecules such as fibronectin. Most can take up water to form hydrated gels to fill space in the ECM, and some, particularly the proteoglycan heparan sulfate, bind to a variety of growth factors, concentrating them in the ECM and preventing their diffusion to other parts of the body. Examples of matrix proteoglycans include aggrecan, which accounts for 10% of the weight of cartilage and forms a hydrated gel into which collagen

fibres are embedded; lumican, which forms a gel that aids the transparency of the cornea; neurocan, which appears to guide developing nerves to their targets when the nervous system wires itself up in embryonic life; fibromodulin, which appears to inhibit collagen fibril assembly; and perlecan, which forms a filter-like gel in basement membranes.

There are many other components in the matrix that, though they may be minor, rare or uncharacterized, may nevertheless be very important. Interested readers are recommended to see the book by Ayad and coauthors listed in the Further Reading section at the end of this article.

ECM Receptors, Their Specificity and Transmembrane Interactions

Cells are not merely suspended in or resting on the ECM – they bind to specific ECM components using a variety of receptors borne on their plasma membranes. These receptors are of various types; some consist of proteoglycans in which a transmembrane protein core bears GAG chains of the types that can be bound by ECM components, some consist of membrane-bound lectins (proteins that bind to carbohydrate groups in the ECM), but the most important ECM receptors in animal cells are proteins of the integrin family.

Integrins exist as heterodimers of two transmembrane peptides, an α integrin chain and a β integrin chain. There are many different versions of the α and β chains, and the precise binding specificities of an integrin heterodimer are determined by the nature of its α and β chains. For example, $\alpha1\beta1$ integrin acts as a receptor for fibronectin, while $\alpha6\beta1$ is a receptor for laminin.

Integrins that have not bound to any ECM ligand diffuse about freely on the plasma membrane, but once they bind ECM they cluster on the cell surface and induce the formation of a protein plaque on the cytoplasmic face of the integrin. The plaque includes proteins such as talin and paxillin, and these in turn connect to the actin microfilament cytoskeleton of the cell. The complex of integrins and cytoskeleton is called a focal adhesion, or focal contact. (In epithelial cells, $\alpha6\beta4$ integrins bound to laminin-5 connect instead to the cytokeratin intermediate filament system, this type of complex being called a 'hemidesmosome'.) The integrins therefore act as mediators through which the mechanical properties of the cytoskeleton can be connected to those of the extracellular matrix. This integration of cytoskeleton and ECM is important for both – cells use their integrins to 'sense' the arrangement of the matrix and align their internal cytoskeleton appropriately. Reciprocally, tension generated by cells' cytoskeletons and communicated to the matrix via integrins can organize the laying down of new matrix fibres along lines of force. In this way, tissue architecture can adapt to the mechanical demands made of it (see below).

Involvement of the ECM in Cell Motility

The function of many cell types depends critically on their ability to move, either throughout their lives (e.g. macrophages) or during embryonic development (e.g. neural crest cells, which migrate from the neural tube to make neural ganglia in specific sites elsewhere in the body). Cells of higher animals generally move by 'crawling' (sperm are an exception), and crawling depends on the ability of a cell to adhere to its ECM with sufficient strength to allow it to exert traction, but not so strongly that it is glued in one place (the tractive forces themselves come from the cytoskeleton, crosslinked to the matrix via focal contacts). One function of ECM is therefore to provide a suitably adhesive substrate for cell migration.

Much evidence for the critical importance of ECM in migration has come from culture experiments in which cells are plated on substrates with a patterned choice of surface, for example stripes of fibronectin on a background of plastic. Motile cells, or motile parts of cells such as neural growth cones (the tips of extending neurites), migrate well on fibronectin or laminin but much less well on plastic. This is thought to be a reflection of the different adhesiveness of the surfaces, although adhesion between cell and substrate is notoriously difficult to measure directly. The best support for an adhesion model comes from the agreement between a mathematical model of how the speed of cell migration alters with the strength of cell–substrate adhesion and experimental data from cultures set up on various concentrations of laminin. On low concentrations of laminin, the speed of mesenchymal cells is very low, but it rises as the ECM concentration rises to an optimum and then falls away again as the ECM reaches very high concentrations (the cell becomes 'glued' to the spot). The shape of the graph of speed versus laminin concentration matches closely the graph of speed versus adhesion in the mathematical model.

It must be remembered, though, that in living cells, signalling through integrins, as well as adhesion through integrins, might modulate cell motility. The binding of ECM components to integrins can, through the integrin→kinase→rho pathway described below, organize the motile and adhesive machinery of the cell in the first place and the extent to which complex effects like this – as opposed to simple adhesion – dominate the control of cell motility remains unsettled.

Involvement of the ECM in Embryonic Development

As well as supporting cell motility in general, the ECM can confer direction on cell movement. An example of both effects is provided by gastrulation of the frog embryo, a process in which cells at one point of the surface of the embryo invaginate (sink inwards), and separate into a stream of individual mesodermal cells that migrate along a definite pathway beneath the epithelium. Before this happens, the epithelium secretes a 'track' of fibronectin along which the mesodermal cells will migrate. The role of this fibronectin track in guiding the cells is clearly demonstrated by an experiment in which embryos were injected experimentally with reagents that disrupted the ability of cells to bind fibronectin; the cells still became mesodermal and motile but were unable to migrate along their normal path and just piled up.

A similar requirement is seen in later stages of development when neural crest cells migrate. These cells, which migrate to specific sites of the body to form neural ganglia, pigment cells and most of the face, appear to migrate along fibronectin and laminin tracks both in living embryos and in culture. If antibodies that block interactions between integrins and fibronectin and laminin are injected into the heads of developing chick embryos, neural crest migration is severely disrupted.

As well as acting as a guide for migration, the ECM can act as a barrier. Growing nerves, for example, appear to be repelled by proteoglycans containing chondroitin 6-sulfate; this keeps them out of areas of developing cartilage, which are exceptionally rich in this glycan. Another example in which ECM appears to inhibit development is seen in the dermis of the skin, where large quantities of hyaluronan separate mesenchymal cells. Development of hair follicles, which involves the coming together of mesenchymal cells to form a closely packed aggregate, is accompanied by their expression of the hyaluronan-digesting enzyme CD44. Experimental application of hyaluronan-digesting enzymes from bacteria is sufficient to drive cell aggregation even in areas not expressing CD44, suggesting that the destruction of the hyaluronan is sufficient to drive the early events of follicle development (Underhill, 1993).

ECM plays a role in the folding of epithelial sheets as well as in guiding migratory cells, as can be seen in the developing salivary gland. This organ consists mainly of a highly branched 'tree' of saliva-producing epithelium, which develops by growth and branching of an originally unbranched epithelial tube. Towards its end, each growing tip of the tree expands into a bulbous balloon-like structure. Collagen fibrils produced by the cells that surround the growing epithelium accumulate to form a collagen 'rope' running across the surface of the end of the 'balloon'. As the branch continues to grow, the collagen rope impedes the forward progress of the epithelium immediately underneath it, so that as the free epithelium each side advances, the collagen forces the formation of a deep cleft. This cleft effectively divides the growing epithelium into two tips, creating a new branch point. Each tip grows a new balloon-like expansion as it advances, and the process repeats so that the branches branch anew (Nakanishi and Ishii, 1989).

In one of the best-understood developing organs, the kidney, many different matrix components are required for normal development. The branching of the urinary collecting-duct epithelium (which, like the salivary gland, makes a tree-like pattern) requires sulfated proteoglycans plus integrins containing the $\alpha 3$ chain (Davies *et al.*, 1995; Kreidberg *et al.*, 1996). MMP-9 activity is also possibly needed to allow the growing epithelium to clear space for itself through the ECM that surrounds it. It is not yet known whether collagen plays the same role in kidney that it does in developing salivary gland. The differentiation of kidney mesenchyme into excretory epithelia requires integrin containing the $\alpha 8$ chain and an uninterrupted interaction between integrins containing $\alpha 6$ chains, laminin and nidogen. If any of these molecules is absent, normal kidney development fails.

As well as controlling development by guiding cell migration, aggregation and the folding of tissues, the ECM can also control the process of cell differentiation itself.

Differentiation Driven by Interactions with the ECM

It has long been known that removing animal cells from their normal context and culturing them in a plastic dish usually changes their behaviour. For example, the alveoli of lactating mammary glands consist of an almost spherical cyst of epithelial cells that secrete milk, and this cyst is surrounded by an ECM arranged as a basement membrane. If these cells are removed from their normal context and placed in a plastic culture dish, they form a simple flat monolayer of cells and cease to produce milk, even when all of the appropriate hormones are added to the culture medium. After a while, many die by apoptosis ('cell suicide').

If, however, the cells are suspended in an artificial ECM, they will survive, form cysts very like those in a real mammary gland, and produce milk, provided that the artificial ECM contains laminin. The cells are now known to bind the laminin via integrins, and this binding triggers a signalling cascade (see below) that results in milk production and cell survival (Pullan *et al.*, 1996). In life, the cessation of milk production (at weaning) is accompanied by destruction of the alveoli, which have to be formed new for the next pregnancy. The death of the alveolar cells at weaning follows the destruction of their matrix by MMPs,

suggesting that the differentiation and survival of milk-producing alveoli is largely under the control of the ECM.

The development of cartilage is normally accompanied by loss of fibronectin from the ECM and by the differentiation of mesenchyme cells into chondrocytes, which produce collagen II, a key component of cartilage, rather than collagen I. If these chondrocytes are placed in an environment rich in fibronectin, they dedifferentiate back into mesenchyme cells that produce collagen I. In these cells, as in others, differentiation is therefore controlled tightly by the ECM in which the cells find themselves.

Adhesion-mediated Signal Transduction

Adhesion to the ECM is 'reported' to the rest of the cell via the ability of integrins to interact with signalling pathways. While integrins tend not to originate signals when they have not bound to ECM ligands, their binding to ECM and their resultant clustering in the cell membrane allows them to form associations with various signal transducing molecules. One of these, which colocates in focal adhesions with integrins and the actin-associated proteins, talin and paxillin, is focal adhesion kinase (FAK; **Figure 2**). Activated FAK can phosphorylate a variety of targets that control cell survival, differentiation and proliferation.

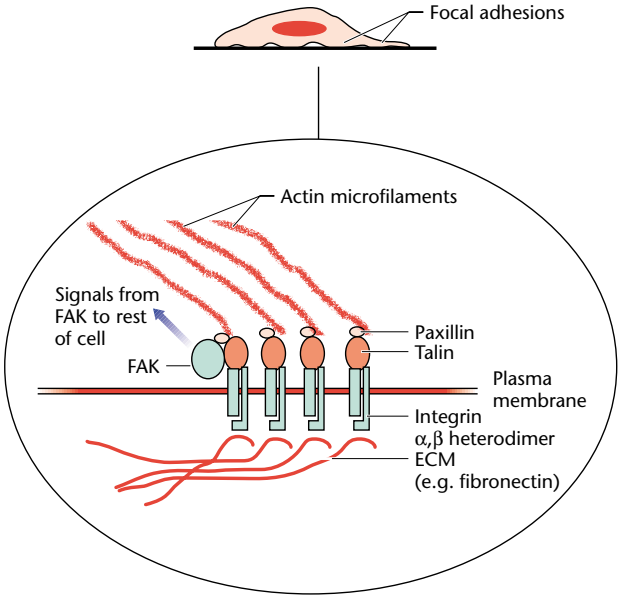

Figure 2 The structure of focal adhesions. The top part of the figure shows a cell migrating on an ECM substrate, while the main figure illustrates the focal adhesions made between the cell and the ECM. FAK, focal adhesion kinase.

Signalling pathways originating with integrins can interact with signals originating in the binding of quite unrelated molecules, producing an integrated response to a number of ligands acting on a cell simultaneously. In many cells there is a pathway triggered by extracellular proteins of the Wnt family, which results in the activation of a protein called β-catenin, which in turn forms a complex with a transcription factor called lymphoid enhancer-binding factor (LEF)-1 and switches on the transcription of a set of genes. But this pathway is inhibited by a protein complex consisting of the proteins adenomatous polyposis coli (APC), GSK-3β and axin, which destroy β-catenin before it can act. The APC–GSK-3β–axin complex can itself be inhibited, however, by an enzyme called integrin-linked kinase (ILK), which is activated by integrins. The interacting molecules therefore perform a function rather like the Boolean AND used in search mechanisms – only when Wnts AND integrin ligands are present can β-catenin activate gene expression.

Another example of how signalling pathways originating in integrins are integrated with other pathways appears in the milk-producing mammary gland epithelium described in the section above. The mammary gland cells require both the hormone prolactin and the extracellular matrix molecule laminin before they will produce milk. Prolactin binds to its own receptor, jak-2, which becomes phosphorylated and goes on to phosphorylate and therefore activate a transcription factor, stat-5, that switches on expression of genes coding for milk proteins. There is, however, a phosphatase enzyme that antagonizes this pathway and dephosphorylates jak-2 so efficiently that the pathway is shut down even when prolactin is present. The binding of laminin to integrins blocks the action of that phosphatase and therefore allows the prolactin pathway to activate milk production (Edwards *et al*., 1998). Again, the ability of the integrin to inhibit an inhibitor of the other pathway has created a Boolean 'AND'.

There is now growing evidence that the clustering of integrins can also activate intracellular pathways involving the small GTPases Rac and Rho, which are famous for their ability to organize the actin cytoskeleton and cell movement. The precise way in which integrins act on the Rac and Rho pathways is not yet clear, but it is clear that a link between integrins, by which the cytoskeleton is linked to the ECM, and the systems that control the formation of the cytoskeleton, would be a very powerful way of organizing cell shape and movement according to the arrangement of the ECM. Even more intriguingly, it appears that placing mechanical stress on an ECM (for example by pulling it in an experimental culture system) can itself cause greater clustering of integrins in the membrane of a cell attaching to it. If this clustering activates integrin-associated signalling pathways, we will have an explanation of how cells respond to the stresses set up in the matrix around them. That they can so respond is beyond doubt, and is perhaps best illustrated by the ability

of cells forming and maintaining bone to orient the fibres and trabeculae of the bone in precisely the best direction to stand up to the applied stress, even when this stress is being applied from an unnatural direction.

Diseases of the ECM

A number of serious human congenital diseases are associated with abnormal extracellular matrix and are caused by mutations in genes coding for various ECM components. Many of these centre on collagen chains, and present themselves primarily as defective skeletal growth. Mutations in genes encoding collagen I, for example, lead to osteogenesis imperfecta ('brittle bone disease'), which is characterized by reduced formation of bone matrix resulting in brittle bones that break repeatedly, and also abnormal dentine in teeth and valves in the heart. Some mutations in collagen II cause Kniest dysplasia, a severely defective growth of the skeletal system; other mutations cause lethal hypochondrogenesis (failure of normal cartilage formation); while other milder mutations are associated with late-onset osteoarthritis. Mutations in collagen V account for some types of Ehlers–Danlos syndrome (another disorder of connective tissue), while some other types of this broadly defined syndrome are associated with deficiencies in lysyl oxidase, an enzyme important in the production of elastin fibres (see above). Mutations in collagen type X cause another skeletal abnormality, Schmid metaphyseal chondrodysplasia.

Congenital abnormalities of the ECM that have their most serious effects on parts of the body other than the skeletal and connective tissue systems include Alport syndrome, in which mutations in collagen IV cause a failure of maturation of the glomerular basement membrane, which is the filter responsible for making urine in the kidneys. The kidneys of Alport syndrome patients are inflamed as a result, causing damage – the patients also frequently have defective sight and hearing. Usher syndrome type II, which also causes defects in the eyes and ears, appears to be caused by mutations in a recently discovered and so far little-characterized ECM protein that includes regions homologous to laminins and to fibronectins.

Mutations in molecules responsible for making cell–matrix adhesions can also cause severe disease. One example is epidermolysis bullosa, a blistering disease in which the upper layers of the skin fail to adhere to the lower and blister out; epidermolysis bullosa is caused by mutations in a molecule normally involved in making hemidesmosomes.

Diseases of the extracellular matrix are by no means all congenital. One of the most well known noncongenital diseases of ECM is scurvy, which is caused by the instability of collagen triple helices and the failure of collagen molecules to become properly crosslinked into fibrils. This causes weakening of connective tissue, resulting in skeletal abnormalities and bleeding of the gums in chronic mild cases and in death through rupturing of arteries in severe cases. The cause of scurvy is dietary deficiency of vitamin C, a reducing agent critical to the hydroxylation of proline and lysine residues in procollagen (see above).

Many other important diseases, such as osteoporosis, arthritis, rheumatism and glomerulonephritis, exert their most destructive effects on ECM, but these diseases arise primarily through problems in other cells or systems, for example the immune system, and will therefore not be discussed here.

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