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Cell Adhesion Molecules in Plants and Animals

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Introduction: the extracellular matrix

The aim of this review is to describe some of the main cell adhesion molecules in animals and plants in a simple and easy-to-read format and then, where possible, make comparisons to highlight common themes. A recent review by Baluska *et al.* (2003) compared signalling aspects of many of these molecules, while this review will concentrate on cell adhesion processes.

All multicellular organisms have some form of extracellular matrix (ECM). Animal tissues vary enormously in the amount of ECM they contain. Connective tissue is particularly rich in ECM, and the individual cells within connective tissue may not be in close contact. Epithelial tissue, in contrast, has minimal ECM, and the individual cells of epithelial tissue are in very close contact and exhibit strong cell–cell adhesion. All plant tissues are normally associated with an extensive ECM, termed the cell wall. However, the nature of this wall differs between plant species, and within the tissues of an individual plant.

In both plants and animals, the ECM is structurally complex. Its architecture is, however, always remarkably similar, consisting of a rigid framework embedded in a gel-like matrix, a composition not unlike that found in many fibre-composites such as fibre glass. In animals, the ECM is generally composed of glycoaminoglycans

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Abbreviations: AGP, arabinogalactan protein; AJ, adherens junction; bFGF, basic fibroblast growth factor; CAM, cell adhesion molecule; *Cnr*, colourless non-ripening mutant; ECM, extracellular matrix; EF-1α, translation elongation factor-1α; GAG, glycoaminoglycans; HR, hyaluronan receptor; MAPK, mitogen-activated protein kinase; PVN1, plant vitronectin-like 1; RGD, arginine–glycine–aspartic acid integrin binding domain; SLR1, locus glycoprotein-like receptor; *sos5*, salt overly sensitive mutant; VEGF, vascular endothelial growth factor.

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(GAGs), such as hyaluronan, and fibrous proteins, such as collagen. The GAGs are highly charged and hydrated, forming a gel-like matrix within which are embedded the fibrous proteins. Plant cell walls have an analogous structure. In this case, the major components are predominantly polysaccharides with highly charged pectic polymers. Pectins are highly charged, and form a gel within which is embedded a framework of hemicellulose and cellulose fibrils, and an array of proteins, some of which are thought to have a structural role.

The principal function of the ECM is to provide support and strength. The hydrated gel resists compression, and the fibrous components provide tensile strength. The ECM also serves as a substrate for cell adhesion, the regulation of cell migration, and aspects of the control of cellular differentiation and metabolic function. There must be mechanisms within the tissue that serve to both anchor cells within the ECM and also to act as signalling systems between the ECM and the cytoskeleton. These signalling systems also participate in cell–cell communication, and mediate cellular responses to various stimuli, such as mechanical stress. The requirement for specialized cell–cell signalling molecules is likely to differ somewhat in plant and animal cells, since the former are extensively connected via the cell–cell cytoplasmic channels, or plasmodesmata. These structures are not found in animal tissues, although cell–cell connections do exist.

Cell–cell adhesion molecules in animal systems

In animal cell monolayers, whether epithelial (for example, in gut) or endothelial (for example, in blood vessels), there are essentially three types of intercellular junctions: adherens junctions, tight junctions, and gap junctions. Whilst the first two are involved in determining monolayer integrity and barrier function, the latter allows communication between cells. The structure, molecular composition, adhesive strength, and extent of paracellular cleft occupied by tight and adherens junctions vary somewhat with tissue type, microanatomical position, and phenotypic plasticity (Furuse *et al.*, 1993; Dejana, 1996; Leach *et al.*, 2000; Firth 2002; Leach, 2002). Similarly, the frequency of gap junctions, existence of different isoforms of connexins, and composition of connexon channels are dependent on the speed and extent of cell–cell communication required by various tissue types (Dhein, 1998).

ADHERENS JUNCTIONS

Adherens junctions (AJs) are formed by transmembrane adhesive proteins belonging to the cadherin family that are anchored via a complex network of catenins to the actin cytoskeleton of the cell. This complex organization of cadherin–catenin and the cytoskeleton is not only necessary to strengthen cell–cell adhesion, but also to transfer signals between cells (Dejana, 1996).

Cadherins are a family of single chain transmembranous proteins (more than 15 of the classical type are known) that are responsible for homotypic calcium dependent cell–cell adhesion (Takeichi, 1988; Dejana, 1996). Of these, E-cadherin is the integral membrane protein of epithelial tissue, whereas vascular endothelial (VE)-cadherin is the endothelial equivalent. Intercellular adhesion is mediated via the extracellular domains (Lampugnani *et al.*, 1992; Shapiro *et al.*, 1995) which contain

calcium binding sites. Calcium confers both rigidity of extra-cellular domains and allows homotypic adhesion (Shapiro *et al.*, 1995). The signalling component of cadherins is provided by their association with cytoplasmic catenins (Lampugnani *et al.*, 1995).

All these AJ molecules are rich in tyrosine, serine, and threonine residues, and are therefore vulnerable to phosphorylation and protein kinases. Indeed, phosphorylation of adherens junctional adhesion molecules results in junctional disassembly and decreased barrier function (Esser *et al.*, 1998; Lampugnani *et al.*, 2003; Leach *et al.*, 2004). Moreover, release of β-catenin and plakoglobin to the cytosol results in translocation of these molecules to the nucleus. Here, they can bind to transcription factors, and control gene expression, specifically those involved in cell proliferation and growth (Gottardi and Gumbiner, 2001).

TIGHT JUNCTIONS

Tight junctions are usually the most apical component of the paracellular cleft, and form a circumferential belt-like region of intimate contact between adjacent cells (Anderson and van Itallie, 1995). They provide a regulated barrier against paracellular passage of small molecules. Moreover, they provide segmentation of the phospholipid membrane denoting cell polarity by preserving specific spatial positioning of membrane components, giving rise to unique basolateral and apical divisions in epithelial cells (Citi and Cordenonsi, 1998). Occludin, claudins, and junctional adhesion molecules are the transmembrane components of TJs (Furuse *et al.*, 1993, 1998; Martin-Padura *et al.*, 1998), whereas numerous cytosolic partners, including the zonula occludens 1, 2 and 3, cingulin, 7H6, provide the linkage to the actin cytoskeleton of the cell (see review by Tsukita and Furuse, 1999).

FOCAL ADHESIONS: CELL–ECM ADHESION MOLECULES

In animals, the predominant extracellular matrix glycoproteins are vitronectin, fibronectin, laminin, and collagen. These ECM proteins all contain an arginine–glycine–aspartic acid (RGD) integrin-binding domain, and serve as ligands to these integrins. In fact, the discovery that the binding activity of large insoluble ECM proteins could be reduced to a tripeptide sequence started the search for specific cell receptors, later termed integrins.

Integrins are a diverse family that function as a non-covalently associated αβ heterodimer, both of which contribute to the binding of matrix macromolecules. The binding of integrins to their ligands depends on extracellular divalent cations (Ca^{2+} and Mg^{2+}). To mediate the interaction between the cell cytoskeleton and the extracellular matrix, integrins have to connect with actin filaments, usually via talin and α-actinin. These then bind to vinculin, zyxin, and paxillin, which in turn can bind to tensin (Burridge *et al.*, 1988). These complexes of integrin-linked cytoskeletal proteins in focal adhesions are important for maintaining strong cell–substrate adhesions and promoting cell-spreading. This linkage is important for mechanosensory function. Thus, integrins linking ECM proteins with cell cytoskeleton allow bidirectional signalling in animal cells.

Signalling enzymes and adaptor proteins regulated by integrin engagement control

cell survival, proliferation, motility, and differentiation (for a more extensive review, see Miranti and Brugge, 2002). Attachment to the ECM was found to induce genes involved in differentiated cell functions, including production of cyclin A (Guadagno *et al.*, 1993). Integrins have also been shown to be important in cell survival; detachment from the ECM can result in apoptotic cell death (Aoudjit and Vuori, 2001).

PROTEOGLYCANS AND GLYCOSAMINOGLYCANS

In addition to integrins in animal cells, other cell surface molecules include proteoglycans and glycosaminoglycans that can interact with the ECM. These show temporal and spatial patterns of expression related to cell type, cellular activation, embryonic development, and cellular differentiation. Glycocalyx coverage of cells represents a substantial barrier to cells, whereas glycan–matrix attachments are important in the maintenance of tissue structure. Moreover, cell surface and ECM glycans can act as local storage sites, a classic example of which are the heparin-binding isoforms of the key angiogenic growth factor, vascular endothelial growth factor (VEGF); these can bind and release other angiogenic growth factors, such as basic fibroblast growth factor (bFGF), which is itself stored on heparan sulfates of the ECM (Jonca *et al.*, 1997). Synergy between these two growth factors is required for new vessel growth or angiogenesis (Asahara *et al.*, 1995). Proteoglycans with trans-membrane core proteins, such as hyaluronan receptors (HR), can interact with the ECM proteins hyaluronan, collagen, laminin, and fibronectin, while interacting with the actin cytoskeleton, thus playing a role in mechanotransduction. Hyaluronan receptors (HR) can bind to actin-linking proteins, such as ankyrin, ezrin, radixin, and moesin. HR can also signal via tyrosine kinases, phosphatidylinositol 3 (PI-3) kinase, protein kinase C, and MAPKs (deAngelis *et al.*, 1993).

The plant cell wall

The majority of plant cells are surrounded by a relatively thick cell wall. This can be several micrometres in thickness. Contact of plasma membranes of adjacent cells within plant tissues is through the plasmadesmata, and the majority of cell–cell adhesion is mediated via the cell wall. The region of the wall immediately adjacent to the plasma membrane is termed the primary wall, and that between adjacent cells is termed the middle lamella. It is the latter region of the wall that is thought to be primarily involved in cell–cell adhesion.

Research into cell–matrix adhesion molecules has revealed sequence similarities between animal, fungal, and plant molecules, although plants are thought to lack true homologues of classical adhesion proteins of animal cells, including integrin, talin, vinculin, filamin, alpha-actinin, and tensin (Baluska *et al.*, 2003). Evidence suggests, however, that to some degree common strategies have been adopted by animals and plants for ECM adhesion and signalling. This includes the observations that: 1) addition of synthetic RGD inhibits gravity-dependent cytoplasmic streaming, several plant growth and development-related responses, including embryogenesis in *Daucus carota* (Staves, 1997); and 2) 'integrin'-like molecules (as well as cadherins) have been immunolocalized in *Arabidopsis* and

Chara, and may well be constituents of the plant plasma membrane (Katembe *et al.*, 1997).

The majority of the plant cell wall is polysaccharide based, although there is a significant structural protein component. There are three major classes of cell wall polysaccharide components, cellulose, hemicelluloses, and pectins. Cellulose is unique amongst these as it is synthesized at the plasmalemma directly into the ECM. It is composed of long linear chains of β(1–4) linked glucosyl residues, which aggregate, via hydrogen bonds, to form microfibrils. These microfibrils are linked together in a framework by interaction with hemicelluloses. This cellulose/hemicellulose framework is recognized to have mainly a support and strengthening role within the wall, and therefore will not be discussed at length in this review. The cellulose microfibrils are found embedded in a gel composed primarily of pectin, but with a contribution from structural proteins. This is the general structure of the primary cell wall. The middle lamella region of the plant cell wall is predominantly composed of pectins, which are the principal polysaccharide molecules involved in cell–cell adhesion.

PECTIN STRUCTURE

Pectins are a very diverse group of plant polysaccharides. A major component of pectin is homogalacturonan, which consists of D-galacturonic acid in an α-(1,4)-linked linear chain in which varying proportions of the acid groups are esterified with methyl groups. This forms the so-called 'smooth regions' of the pectin polymers. Another major component is the rhamnogalacturonan I. In this polymer, the backbone consists of alternating galacturonic acid and rhamnosyl residues, the latter of which are commonly associated with neutral sugar side chains, usually composed of arabinosyl and galactosyl residues (arabinans, galactans, and arabinogalactans). This forms the so-called 'hairy region' of the pectin polymer. Other, less common, structural elements of pectin include rhamnogalacturonan II, xylogalacturonan, and apiogalacturonan (Schols and Voragen, 2002).

Pectins and cell adhesion

It has long been known that, in certain plant tissues, cell separation can be induced by floating tissue sections in calcium-chelators or using pectin-degrading enzymes (Vennigerholz and Walles, 1987; van Buren, 1991). Adjacent pectin chains can be cross-linked by calcium ions (Grant *et al.*, 1973), and this is likely to be a major factor in cell–cell adhesion in plants. Additional factors which may be important in determining the 'adhesive properties' of pectin include the presence of arabinan and galactan side chains (Iwai *et al.*, 2001). Several mutants where pectin levels or composition are affected, have been isolated. In *emb30*, abnormal distribution of pectin leads to loss of cell adhesion (Shevell *et al.*, 2000). The *quartet* mutants of *Arabidopsis* produce tetrad pollen in which microspores fail to separate during pollen development. This is due to the mutations causing a failure of pectin degradation in the pollen mother cell wall as the result of a defect in a developmentally regulated polygalacturonase required for pollen mother cell wall degradation (Rhee and Somerville, 1998; Rhee *et al.*, 2003). In the *colourless non-ripening* (*Cnr*)

mutant of tomato, the fruits show very reduced cell adhesion, and the pericarp tissue has a mealy appearance. The cell walls of *Cnr* have significantly less calcium-binding capacity in comparison with wild type, and this results from a modified homogalacturonan network in the middle lamella. Additionally, the deposition of α-(1–5) arabinans in the cell walls of the mutant is disrupted (Orfila *et al.*, 2001).

Plant cell wall proteins

Although the plant cell wall is composed predominantly of polysaccharides, there are a variety of structural proteins also present (Cassab, 1998). The major classes of proteins are the hydroxyproline-rich glycoproteins, arabinogalactan proteins, glycine-rich proteins, and proline-rich proteins. These, like the polysaccharide components of the wall, have been shown to differ between cell types, and this may reflect specific functions within individual tissues. However, even less is known about the function of these plant cell wall proteins than their polysaccharide counterparts. Perhaps the most intensively studied of these proteins are the extensins. Their structures are variable, but commonly tend to consist of repeating Ser-$(Hyp)_4$ motifs. They are likely to have a predominantly structural role within the plant cell wall. Many other hydroxyproline-rich proteins have been identified in the cell wall, which tend to be chimeric in that they contain extensin-like domains associated with other elements. Several of these, as we shall see, have been implicated in cell–cell adhesion.

POLLEN AND POLLEN–STIGMA INTERACTIONS

Locus glycoprotein-like receptor 1 (SLR1) proteins participate in pollen–stigma adhesion. These are glycoproteins that are made in the stigma and then secreted into the cell walls of the mature stigmatic papillae. Luu *et al.* (1999) used a biomechanical assay to test pollen–stigma adhesion in *Brassica* where SLR1 protein production had been suppressed using an antisense construct. Pollen adhesion force was reduced in those plants with less SLR1. They concluded that these proteins were involved in pollen–stigma adhesion, possibly through interaction with pollen coat proteins.

BASIC CYSTEINE-RICH PROTEINS AND POLLEN TUBE ADHESION

Two fractions from the stigma–style transmitting tract of lily have been shown to be necessary for pollen tube adhesion. The first component was a 9 kDa protein named stigma-style cysteine-rich adhesin. The other fraction contained a pectic polysaccharide. In animals, an analogous case where similar types of components interact together would be in neuron guidance. Here, a large matrix molecule and a small peptide act together to guide neurons via a receptor in the neuron surface (Lord, 2000).

VITRONECTIN-LIKE MOLECULES IN PLANTS

Vitronectin-like proteins have been identified in several species of flowering

plants (Sanders *et al.*, 1991; Zhu *et al.*, 1993a, 1994). These proteins have been identified as immunologically related to the animal substrate-adhesion molecule, vitronectin. The plant proteins can bind to glass and to heparin, and have adhesive activity based on the hamster kidney cell-spreading assay. Also, plant vitronectin-like 1 (PVN1) was shown to be localized in the cell walls of cortical and transmitting tissue cells of pollinated mature styles (Zhu *et al.*, 1994). However, partial amino acid sequences from PVN1 revealed no apparent homology at this level with vitronectin, but the protein was closely related to translational elongation factor-1α. This study indicates that proteins structurally related to EF-1α may function in the cell wall by possibly interacting with membrane receptor proteins. PVN1 most likely performs functions not related to translation. PVN1 contains a motif that may be a functional cell-binding motif, possibly sharing characteristics with fibronectin-like proteins in animals (Zhu *et al.*, 1994). Cells of tobacco adapted to grow in high concentrations of NaCl develop tight zones of adhesion between the plasma membrane and the cell wall, and total levels of vitronectin-like proteins were enriched in the salt-adapted cells, providing evidence that these proteins could be involved in these cell–matrix links (Zhu *et al.*, 1993a). In contrast, arabinogalactan proteins (AGPs) are lost from these salt-adapted cells, and it has been proposed that these proteins have a role in enhancing wall loosening; it is proposed that cell-surface AGPs bind to linked ferulic acids in the cell wall to prevent the formation of diferulic acids, thereby regulating wall extensibility (Zhu *et al.*, 1993b).

PROTEINS WITH FASCICLIN-LIKE DOMAINS

The first plant homologue to an animal cell adhesion molecule (CAM) was identified in the algae, *Volvox* (Huber and Sumper, 1994). This was identified by using antibodies that inhibited aggregation of embryonic cells. This protein seems to contain three domains – the first is an extensin-like domain rich in serine and proline, and the other two are repeats of a domain with homology to fascilin 1 – a CAM involved in neuronal development in *Drosophila*. Fasciclin domains are present in several proteins known to function in cell adhesion in animals (Kawamoto *et al.*, 1998).

The *Arabidopsis salt overly sensitive5* (*sos5*) mutant shows swollen root tips and inhibition of root elongation in response to salt stress. The mutation occurs in a gene encoding a protein with arabinogalactan-like and fasciclin-like domains. The SOS5 sequence shows strong similarity with several cell–cell adhesion proteins from non-plant organisms. The cell walls of the mutant are altered. There was evidence for a loss of middle lamellae, the walls appeared less well organized and less tightly attached to the cell membrane (Shi *et al.*, 2003).

Additional evidence for the role of protein-rich components in cell adhesion comes from studies of texture differences in Cox apples. Electron energy loss spectroscopy has revealed a correlation between the presence of high levels of cell wall nitrogen and firmer texture in apple fruits. This cell wall nitrogen appeared to be associated with high molecular weight compounds, and could reflect higher levels of cell wall structural proteins (Huxham *et al.*, 1999).

Conclusion

In the case of plants, the cell wall is central to determining tissue integrity, in particular the pectin-rich middle lamella serves to maintain cell–cell adhesion. In both plants and animals, an equally important function for adhesion molecules is likely to be anchoring the cell to its ECM. This type of link may also have important consequences for the extent and types of components synthesized during ECM biogenesis. This, in turn, could affect cell–cell adhesion and tissue integrity. In animals, many of the cell adhesion molecules have been clearly demonstrated to have roles in cell signalling. This would be consistent with a role during biogenesis.

There may be common biochemical themes utilized by animal and plant systems to connect cells with their ECM. The adoption of molecules in both plant and animals, which possess serine, glycine residues, as well as the RGD peptide domain, shows an overlap in strategy. Thus, the presence of these domains on plant ECM proteins may provide new clues as to their function. At present, the evidence for a similar array of systems of cell adhesion and signalling in animals and plants is slight, but there are hints of common structural features which could provide important insights into cell adhesion processes in living systems. The challenge is for researchers from the different areas to understand the biology of the two systems. We hope that this, and other recent reviews, will help with that process.

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