Adhesion molecule families: a brief review

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LIST OF ABBREVIATIONS

ECD - Extracellular domain
E-cadherin - Endothelial cadherin
EGF - Epidermal growth factor
E-selectin - Endothelial selectin
ICAM - Intercellular cell adhesion molecule
IgC1/2 - Immunoglobulin constant like domain type 1/2
IgSF - Immunoglobulin super family
IgV - Immunoglobulin variable like domain
LFA-1 - Leukocyte function associated molecule 1
L-selectin - Leucocyte selectin
MAdCAM - Mucosal Adressin cell adhesion molecule
MAG - Myelin associated glycprotein
NCA - Non-specific crossreactive antigen
N-Cadherin - Neural-cadherin
NCAM - neural cell adhesion molecule
P-cadherin - Platelet cadherin
PECAM-1 - Platelet endothelial cell adhesion molecule
P-selectin - Platelet selectin
SCR - Short consensus repeats
T-cadherin - Truncated cadherin
VCAM - vascular cell adhesion molecule
VLA - Very Late Antigen

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ABSTRACT

This paper is a brief review of the main adhesion molecule families, the integrin, the cadherin, the selectin and the immunoglobulin super family. It reviews their structure, tissue distribution and function.

Introduction

Most adhesion molecules belong to one of the four major adhesion molecule families. These comprise the integrins, the cadherins, the selectins and the immunoglobulin super family. Adhesion interactions can be sub-divided into four different types: homophilic when an adhesion molecule is able to bind to a similar molecule on the surface of an opposing cell; heterophilic adhesion when two different molecules are able to bind to each other; homotypic adhesion when cells of the same type are able to form aggregates which may involve either homophilic or heterophilic interactions between the adhesion molecules mediating the aggregation process; heterotypic adhesion when different cell types are able to aggregate in a process that could also be mediated either by homophilic or heterophilic interactions.

The integrin family.

The integrins are a family of

heterodimeric membrane glycoproteins expressed on diverse cell types (reviewed by Hynes, 1987) which function as receptors for extracellular matrix components and as cell-cell adhesion molecules. Structurally they consist of two non-convalently associated subunits, α and β. They were originally classified into three subfamilies (β1 integrins or very late antigen proteins VLA; β2 integrins or leucams and β3 integrins or cyto-adhesins) in which a common β subunit was thought to associate with a number of different a subunits. Since now, at least 15 different a chains and 9 different β chains have been identified and individual a subunits have been shown to associate with more than one type of β subunit functional classifications have become more appropriate.

The molecular weight of integrin β subunits ranges from 90 to 110 kD with the exception of β4 which is 210kD. They all show strong homology at the amino acid level (35-55%). They all contain 56 conserved cysteines (except β4 which has 48) arranged in four repeating units. Comparison of the extracellular regions of β1-β7 revealed a highly conserved region at the N-terminal half of the protein. The cytoplasmic domains are 40-50 residues long, except for β4 which has an unusually long (1018 amino acids) cytoplasmic tail containing four fibronectin type III repeats (Hogervost et al, 1990; Suzuki and Naitoh, 1990). The β subunits also contain five cysteine rich repeats close to the transmembrane region. Consensus tyrosine phosphorylation sequences appear in the cytoplasmic tails of β1, β3, β5, β6 and β7. Although β2 (Hibbs et al, 1991) and β4 (Sacchi et al, 1989) lack such a sequence they are also phosphorylated on seri-ne/tyrosine residues. Further structural diversity of the b subunits is provided by the existence of variant forms which contain alternative cytoplasmic domains or lack four cysteine rich repeats.

The integrin α subunits have a molecular weight that ranges from 150 to 200 kD with an amino acid sequence homology of 20-60%. All contain seven homologous domains of approximately 60 residues. These contain either 4 or 3 divalent cation binding sites. Subunits α1, α2, αL, αM and αX all contain an extra 200 amino acids inserted between repeats 2 and 3 known as the I domain. The other α subunits undergo proteolytic cleavage into heavy and light fragments which are disulphide linked except for the α4 subunit. Additional structural diversity within the integrin α subunits can arise by alternative splicing. A schematic representation of the domain organisation of the α and β integrin subunits is shown in Fig.1.

The term "integrins" was originally coined to reflect the role of this receptors in integrating the intracellular cytoskeleton with the extracellular matrix (Hynes, 1987). Such integration remains a predominant recognised function of integrins and extracellular matrix proteins (collagen, fibrinogen, fibronectin, laminin, thrombospondin, vitronectin, von Willebrand factor, tenascin and epiligrin) constitute the main category of integrin ligands. Integrins also play an important role in intercellular

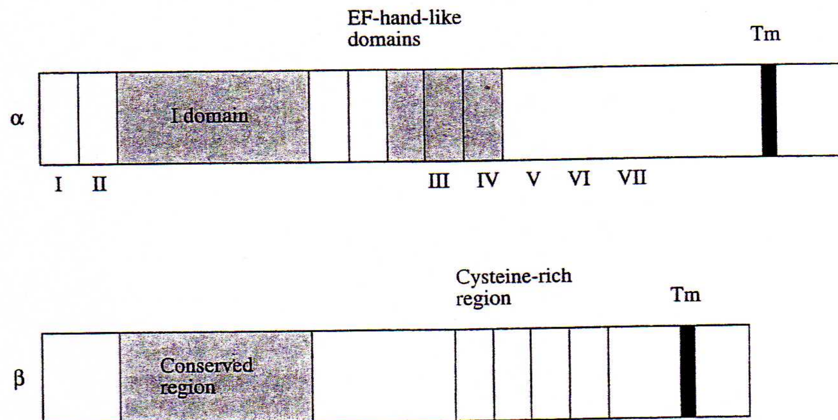

Fig. 1 - Schematic representation of the α and β integrin subunits domain organisation. Domains V-VII in I domain containing integrins (or IV-VII in others) have EF-hand-like cation binding sequences. Tm, transmembrane domain.

adhesion by binding to some of the members of the immunoglobulin super family such as the intercellular adhesion molecules ICAM-1, ICAM-2, ICAM-3 and the vascular cell adhesion molecule VCAM-1. Other ligands include the proteins belonging to the desintegrin family. Originally discovered in snake venom's as potent inhibitors of platelet aggregation mediated by aIIbb3, cellular forms have since been identified (Weskamp and Blobel, 1994). Most integrins are able to bind more than one ligand (e.g.. a1b1 binds laminin or collagen and a3b1 binds collagen, laminin and fibronectin) and some exhibit alternative specificities depending on the cell type in which they are expressed (Elices et al, 1990).

The main recognition site for integrin binding to most of the extracellular matrix proteins is the RGD sequence (arginine, glycine, aspartic acid) found in proteins such as laminin, type I collagen, fibronectin, fibrinogen and vitronectin. The crystal structures of two unrelated RGD containing binding domains (Dickinson et al, 1994; Logan et al, 1993) have shown that these sequences are contained within a highly exposed loop between two β-sheets and that they do not adopt a single static position. Contact of the RGD loop with an integrin is thought to fix its conformation and could be the first step in inducing more global conformational changes in the ligand. However not all integrins bind this ligand sequence as it has been shown for fibrinogen (Farrell and Thiagarajan, 1994) and the leukocyte ligands VCAM-1 (Makarem et al, 1994) and ICAM-1 (Randi and Hogg, 1994). Binding is cation dependent and requires both subunits. It also requires activation of the integrin receptor by

specific signals (e.g. T cell activation by antigen presentation or antibodies) resulting in a conformational change which enables the integrins to bind their ligands. They play a central role in mechanisms such as cell differentiation, leukocyte trafficking, platelet aggregation and T cell activation.

The Cadherin family.

The organisation of a multicellular organism requires the selective association of embryonic cells into specific tissues. One class of cell adhesion molecules playing a crucial role in tissue formation is the cadherin family. The classical cadherins are transmembrane glycoproteins composed of a highly conserved cytoplasmic region and an ectodomain with four structural repeats (referred to as EC1-4) containing calcium binding motifs followed by a cysteine containing region (reviewed by Ranscht, 1994). They are synthesised as a precursor polypeptide which requires a series of post-translational modifications (glycosylation, phosphorylation and proteolytic cleavage) to form a mature protein. A schematic representation is shown in Fig.2. The three-dimensional structures of E (endothelial) and N(Neural)-cadherin N-terminal domains were recently determined by nuclear magnetic resonance spectroscopy (Overduin et al, 1995) and X-ray crystallography (Shapiro et al, 1995), respectively. The data suggests that these domains form a dimer, the strand dimer, in which two monomers are arranged in parallel at the extracellular membrane. The dimer is also able to interact with another strand dimer on a opposite membrane forming an adhesion dimer. It was proposed that the dimers could be arranged like a zipper at the intercellular space, and that this could account for the strong adhesive bonds found in the zonula adherens. The calcium molecules, essential for cadherin function, were found to be involved in linking the successive extracellular domains, conferring a rod-like shape to the cadherin molecules.

The prototypes of the cadherin family are the well characterised E, N and P (platelet) cadherins. The family has however grown to include members with additional extracellular repeats (Sano et al, 1993), no cytoplasmic region (Okazaki et al, 1994) or modified or distinctly different cytoplasmic domains (Berndorff et al, 1994). These include the T (truncated)-cadherin, molecules of the desmosomal, desmocollin and desmoglein subfamily and the ret proto-oncogene (Buxton et al, 1992; Takeichi, 1993).

Cadherins function as calcium dependent adhesion molecules, involved in homophilic interactions. Recent reports of interaction of E-cadherin with the aEb7 integrin (Cepek et al, 1994; Karecla et al, 1995) represent the first evidence of an interaction between a cadherin and a member of a different adhesion family. Classically they are thought to be responsible for the cell sorting necessary to allocate different cell types to their proper positions during development. During embryonic morphogenesis, their expression is spatio-temporally regulated, and correlates with a variety of morpho-

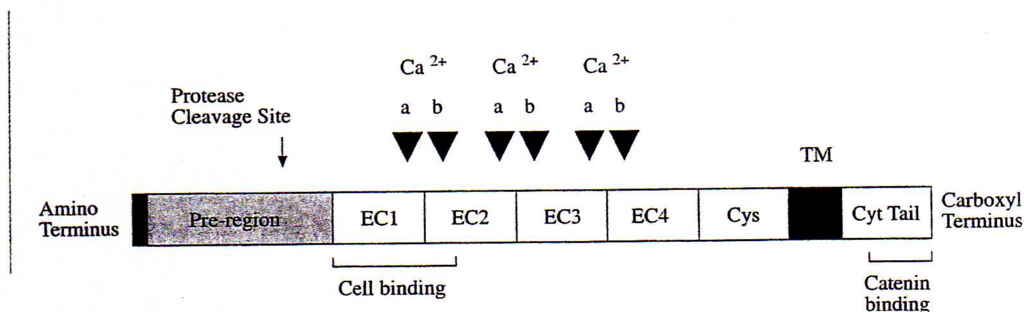

Fig. 2 - Schematic representation of the consensus structure of classical cadherins. Mature cadherins are transmembrane (TM) proteins derived from a precursor by cleavage of the pre-region. The extracellular region is composed of four extracellular repeats (EC1-4) with calcium binding motifs (a and b) and a cysteine containing region (Cys). The cytoplasmic tail (Cyt tail) has a catenin binding region.

genic events that involve cell aggregation and disaggregation (Takeichi, 1991). They are also involved in maintaining the integrity of multicellular structures. E-cadherin and N-cadherin participate in the formation of the zonula adherens, their cytoplasmic domains interacting with α, β, and γ catenins that link the cadherin molecules to the actin based cytoskeleton (Ozawa and Kemler, 1992; Kemler, 1993). Gene products of the src proto-oncogene family have also been found expressed at the zonula adherens (Takeichi et al, 1991) and may be responsible for cadherin phosphorylation raising the possibility that cadherin mediated cell junctions might be used for intercellular signalling (Matsuyoshi et al, 1992; Saffel et al, 1992). Cadherins have also been shown to be expressed during early muscle development and are down regulated but not absent in mature muscle (Moore and Walsh, 1993; Cifuentes-Diaz et al, 1994) with N-cadherin participating in myoblast fusion and being down regulated by nerve activity after the formation of the neuromuscular contacts (Hahn and Covault, 1992; Fredette et al, 1993). Many cadherins are also present in neural tissues (Redies et al, 1993). It has been suggested that they may participate in the segregation of sensory neurons into functional groups (Fredette et al, 1994; Shimamura et al, 1992). However with the exception of N-cadherin, which promotes neurite growth (Rathjen, 1991), little is known about the function of other cadherins in the nervous system.

The selectin family.

The selectins are a family of three proteins involved in the inflammatory response (Von Andrian et al, 1993a). They mediate adhesive interactions between leukocytes and the endothelium and between leukocytes and platelets in the blood vascular compartment (Abassi et al, 1993; Von Andrian et al, 1993a). Known as E(endothelial)-, P(platelet)- and L(leukocyte)-selectin, their domain

organisation consists of an amino-terminal C-type lectin domain or carbohydrate-recognition domain (CRD) found in a range of proteins including the serum glycoproteins and proteoglycans of the extracellular matrix (Drickamer, 1989; Drickamer, 1993). This is then followed by an epidermal growth factor (EGF)-like motif succeeded by a varying number of short consensus repeats (SCRs) similar to those found in complement regulatory proteins. Both the EGF-like domains and the SCRs show a high degree of homology between family members. The transmembrane domain is followed by a short cytoplasmic tail. A schematic representation of the selectins domain organisation is depicted in Fig.3. The high degree of homology found between the selectins strongly suggests that they were produced by duplication of an ancestral gene, followed by exon diversification and duplication. This is supported by the fact that the genes for all three proteins are clustered over a short region of human and mouse chromosome 1 (reviewed by Vestweber, 1992; Lasky, 1992).

Because of their C-type lectin N-terminal domain, selectins function as lectin-like receptors with their ligands consisting of specific glycoconjugates (Varki, 1994). Selectins were shown to be able to recognise the sialylated and fucosylated tetrasaccharide antigens sialyl Lewis x (sLex) and sialyl Lewis a (sLea) (Foxall et al, 1992). Although the recognition of sLex/a oligosaccharides is thought to be of significant biological relevance, the additional binding activity of the selectins to various sulphated carbohydrates suggests the possibility of alternative carbohydrate ligands (Green et al, 1992; Nelson et al, 1993). So far, the most potent naturally occurring carbohydrate ligands for both L- and E-selectin are Lex and Lea derivatives, in which the hydroxyl group on carbon 3 of galactose is sulphated rather then sialylated. When immobilised in the form of glycolipids, 3'-sulphated Lex and Lea were shown to support direct binding of all 3 selectins at least as strongly as sLex/a (Green et al, 1992; Yuen et al, 1992; Brandley et al, 1993). A diagram of the sLex molecule is shown in Fig.4. Although these oligosaccharides are often part of the glycosylation patterns of proteins, only a few biological ligands for selectins have been identified. These are GlyCAM-1, a lectin-like receptor glycoprotein, (Imai et al, 1991; Lasky et al, 1992), CD34 (Imai et al, 1991; Baumhueter et al, 1994), the P-selectin glycoprotein ligand 1 (PSGL-1) (Sako et al, 1993; Norgard et al, 1993) and MAdCAM -1, a mucosal vascular adressin (Berg et al, 1993). All have extracellular domains with a mucin organisation, i.e. serine/threonine rich regions that are densely substituted with O-linked carbohydrate chains (Shimizu and Shaw, 1993). A number of other potential ligands, including BGP, have been described (Aruffo et al, 1991; Norgard et al, 1993; Stocks et al, 1993; Walcheck et al, 1993; Lenter et al, 1994;), but for these further studies are necessary to establish whether they serve as biological ligands for the selectins or if they are merely cross-reactive as a result of their fortuitous expression of carbohydrate motifs. The

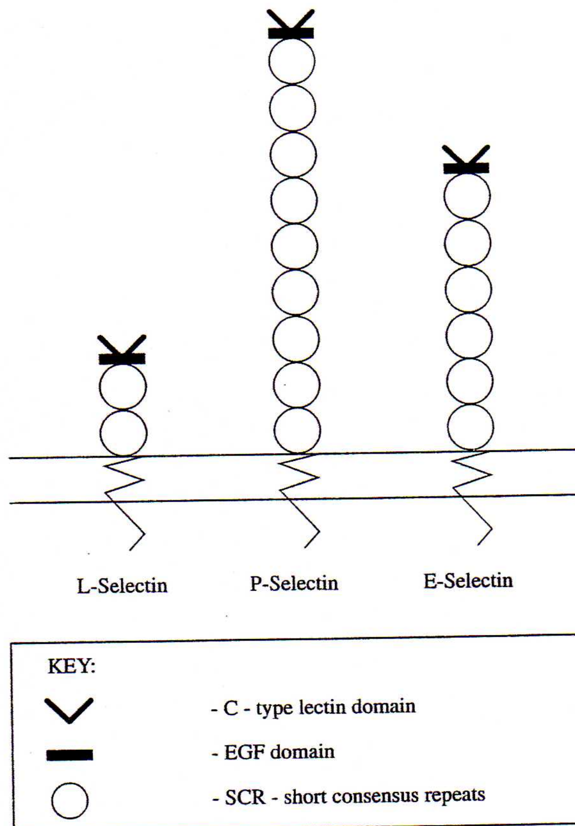

Fig. 3 - Schematic representation of the domain organisation of the selectin molecules.

three-dimensional structure of the lectin and EGF domains of E-selectin has been resolved (Graves et al, 1994), but so far a co-crystal with a bound oligosaccharide is not yet available.

Functionally, the selectins are involved in the earliest phases of a cascade of events leading to leukocyte extravasation. Selectins are able to arrest freely flowing leukocytes and mediate rolling of cells along the endothelium of blood vessels (Springer, 1994). Confirmation of the importance of selectins has come from the description of two patients with leukocyte adhesion deficiency type 2, who lack functional myeloid ligands for E- and P-selectin and are unable to recruit neutrophils to sites of inflammation (von Andrien et al, 1993b). Neutrophils from these patients roll poorly *in vivo* and fail to attach to venules under normal shear-stress conditions.

The enormous potential of carbohydrates for encoding specific information which could be used in cell recognition had long been postulated.

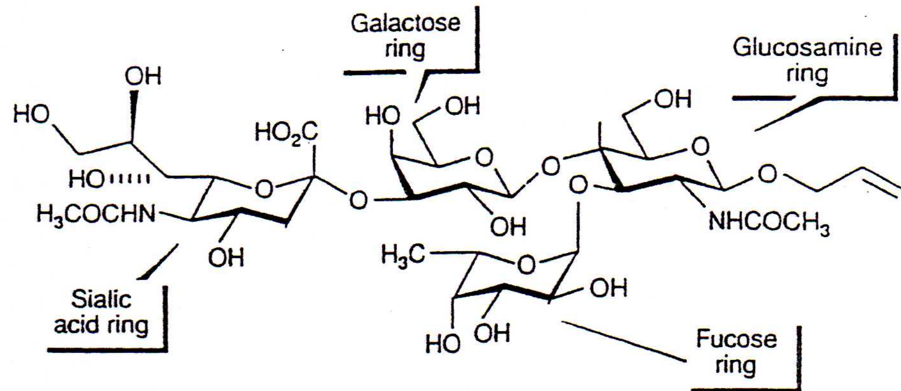

Fig. 4 - Schematic representation of the sLex carbohydrate moiety.

The discovery of the selectin family has played a major role in validating the view that carbohydrates define recognition determinants in specific cell-cell adhesion events (Varki, 1994). Although considerable progress has been made in identifying the minimal structures for ligand recognition, much remains to be learnt about the context in which they are presented to confer specificity and how selectin mediated interactions are interlinked with other adhesion pathways.

The immunoglobulin super family.

The concept of the immunoglobulin super family (IgSF) was proposed in 1982 (Williams, 1982) and encompasses a diversity of molecules that share a common structural feature, the immunoglobulin homology domain. Members of the IgSF are important in mediating both the humoral and cell mediated immune reactions, they serve as cell surface receptors responsible for positional cues during embryonic development and can be viral and growth factor receptors. They also function as intercellular adhesion molecules and signal transducing receptors or as both (reviewed by Buck, 1992).

Structurally the immunoglobulin homology unit consists of 70-110 amino acids organised into 7-9 β strands. These contain 5-10 amino acids and are juxtaposed in an anti-parallel manner such that the hydrophobic side chains are facing one another on the interior of the molecule with the hydrophilic side chains exposed to the external side. The β strands form a sandwich stabilised by the interior hydrophobic groups and in most cases by a disulphide bridge formed between specific β strands. A model of the immunoglobulin fold is shown in Fig.1.5. The homology units have been classified as V or C according to their similarity to the homology units found on the variable (V) or constant (C) domains of the immunoglobulin molecule. In the V domain, the β sandwich is formed by two β sheets, one of 3 and the other of

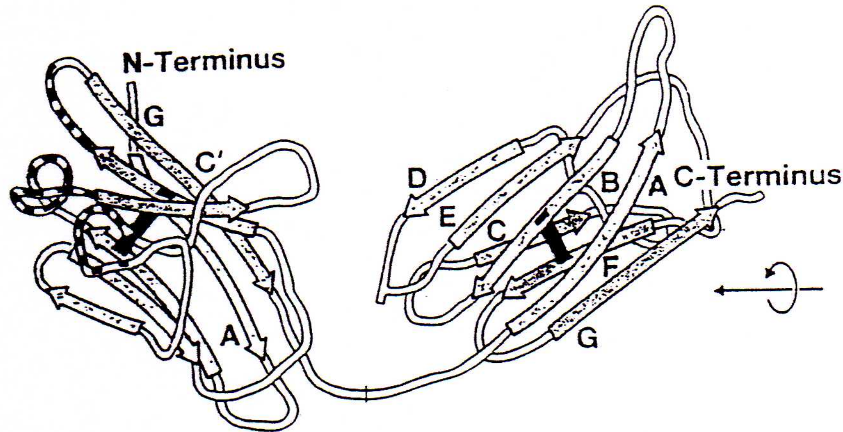

Fig. 5 - Structure of an immunoglobulin light chain variable (VL) and constant (CL) domains (from the X-ray crystallographic studies for a Bence-Jones protein (Schiffler et al, 1973). One face of each domain is composed of four chains (grey arrows) arranged in an antiparallel β-pleated structure stabilized by interchain hydrogen bonds between the CO and NH groups running along the peptide backbone, and the 3 chains (green arrows) in the other face of the domain; the dark bar represents the intra-chain disulphide bond; the stripped loops represent the hypervariable regions which are the light chain contribution to the antibodies binding site.

4 b strands. Sequestered between these two β sheets are an extra two β strands, C' and C", which in antibodies form the second hypervariable loop. In the C domain these two strands are missing. The C domain has further been subclassified into C1 and C2 type. The C2 type domain is mainly found in the IgSF adhesion molecules and is generally more compact than either the V or C1 domains. The genetic organisation of the IgSF molecules suggests a sophisticated mechanism for the evolutionary conservation of structural and functional diversity (Williams and Barclay, 1988). Each Ig homology unit is encoded by a single exon, thus preserving each domain as a functionally important element of any receptor. The exon organisation is such that the 3' end of an exon ends with the first base of the first codon in the immediately following homology unit and the 5' end of each exon begins within the last two bases of the codon of the immediately preceding homology unit. Exceptions to this are all the Ig-like domains of neural cell adhesion molecule (NCAM), and domain 1 of CD4, where each domain is encoded by two exons. This may reflect the possibility that the immunoglobulin fold was itself formed by the duplication of an ancestral domain (Bourgois, 1975).

The role of the immunoglobulin fold in cell adhesion is thought to have originated by the interaction of single, identical domains on opposing cells (Williams and Barclay, 1988). With the evolving of multidomain molecules, the capacity for homophilic adhesion

has been maintained with interactions between non-identical family members, such as CD2 and LFA-3, being an extension of this mechanism. The three dimensional structure of the first two domains of CD2 has been resolved by X-ray crystallography (Jones et al, 1992) and the presence of crystals involved in homophilic binding in the solution further confirms both the adhesion capacity of the immunoglobulin fold and the fact that homophilic binding may have been the first type of interaction developed by the IgSF.

Ligands for the IgSF now comprise non-IgSF members such as LFA-1 (CD18/CD11a) and Mac-1 (CD18/CD11b) which bind ICAM-1 (Marlin and Springer, 1987; Diamond et al, 1990) VLA-4 (a4/b1) and a4/b7 which bind to the vascular adhesion molecule 1 (VCAM-1) (Elices et al, 1990; Ruegg et al, 1992). All these belong to the integrin family. Components of the extracellular matrix are also among the counter receptors for the IgSF. For example collagen and heparin are recognised by the myelin associated glycoprotein (MAG) and heparin and heparan sulphate are recognised by NCAM (Cole and Glaser, 1986; Reyes et al, 1990) and the platelet endothelial cell adhesion molecule, PECAM-1 (Newman et al, 1990; Albelda et al, 1991). It has been proposed that proteoglycans could modulate the homophilic mediated adhesion of IgSF members. PECAM-1 transfected L cells have been shown to undergo Ca^{2+} dependent PECAM-1 mediated aggregation (Albelda et al, 1991). This could however be inhibited by heparin, heparan sulphate and chondroitan sulphate or simply by proteoglycanase digestion of the cells (Delisser et al, 1993). Also the observation that HIV binding to CD4 can be blocked by dextran sulphate and heparin (Lederman et al, 1991) further points to a role in the modulation of the function of the IgSF molecules by proteoglycans.

Functionally, members of the IgSF are integral participants in several independently regulated adhesive activities that lead to cell activation, receptor expression, cell adhesion or cell invasion. It has become apparent that molecules originally defined as adhesion molecules may have diverse functions and that in some cases the adhesion role may be of secondary importance. Accumulating evidence indicates that an exclusive role in cell adhesion may well be the exception rather than the rule, with the majority of molecules serving both as adhesion receptors and signal transducers. One of the molecules that illustrates multiplicity of function well is NCAM. It was one of the earliest members of the IgSF to be assigned the title of cell adhesion molecule. It has become apparent that in addition to any direct role in cell adhesion, NCAM is also involved in regulating the ability of cells to interact (Rutishauser and Landmesser, 1991) and in signal transduction (Doherty et al, 1991).

IgSF members are also widely used during development and in the regulation of the immune system and are part of a well coordinated cascade of adhesive events involving members of other receptor families (Harlan, 1985; Berg et al, 1989; Makgoba et al, 1989; Albelda and Buck, 1990;

Springer, 1990; Butcher, 1991). For example, their role in the development of the nervous system is particularly evident (Doherty et al, 1991; Edelman, 1992). A group of molecules with multiple Ig domains coupled to a varying number of fibronectin type III repeats, is involved in cell migration, the stimulation and inhibition of neurite outgrowth and the adhesion of neurites (Rathjen and Jessel, 1991). Homologues of this group have been found in species as diverse as insects and man emphasising the fundamental importance of these molecules. Cellular interactions within the immune system are no less complex than those found within the nervous system and here too IgSF members are widely used. Examples are the interactions of resting T cells with antigen presenting cells (involving ICAM-1 binding to LFA-1) (Springer, 1990); adhesion of neutrophils and macrophages to activated endothelial cells and subsequent transmigration through post capillary venules (Springer, 1990; Williams, 1991); macrophage movement into the skin and peritoneum, and for the homing of lymphocytes to specific lymph nodes (Albelda and Buck, 1990; Butcher, 1991; Makgoba et al, 1989; Shimizu et al, 1991).

The structural features of the IgSF molecules have allowed the acquisition of a wide range of functional diversity resulting in the evolution of important molecules for morphoregulatory processes as well as the evolution of a highly sophisticated immune system in which they function as part of a well coordinated series of events involving both cell-cell and cell-matrix adhesion.

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