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Journal

Trends in neurosciences, 12(5)

ISSN

0166-2236

Author

Lander, AD

Publication Date

1989-05-01

DOI

10.1016/0166-2236(89)90070-2

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Understanding the molecules of neural cell contacts: emerging patterns of structure and function

Arthur D. Lander

Neural cells make and break many contacts during their lifetime. The processes of neuroblast migration, axon elongation and guidance, synaptogenesis, myelination and synaptic rearrangement all require the selective formation and elimination of cell-cell and cell-substratum associations.

Over the past decade or so, an impressive amount has been learned about cell surface and extracellular matrix molecules that may dictate the associations of neural cells. The success of this effort is attested to by a bewildering variety of names and acronyms – NCAM, NgCAM, L1, N-cadherin, myelin-associated glycoprotein, astrotactin, AMOG, laminin, fibronectin, tenascin, cytostatin, J1, neuroneurin, thrombospondin, hyaluronectin, purpurin, integrin, and others – that have surfaced in the neurobiological literature. Many of these molecules have dramatic effects in assays of cell aggregation, cell attachment, neurite outgrowth and cell migration. The *in vivo* distributions of most of them undergo marked developmental changes. Such results support the increasingly held belief that these molecules play key roles in controlling neural development and regeneration.

Yet, as the list of molecules involved in forming cell-cell and cell-substratum contacts continues to grow, new and puzzling questions have emerged. Why are there so many of these molecules? Why is virtually none of them unique to the nervous system? In what ways are they structurally similar? Are there general principles underlying the functional properties of these molecules?

The emergence of these questions underscores the importance of examining the molecules involved in cell interactions in ways that reveal important structural and functional similarities and differences. To this end, various schemes for classifying these molecules have been introduced in the literature. The earliest classifications reflected *in vitro* functions: a molecule that appeared to mediate cell-cell adhesion was called a 'CAM' (cell adhesion molecule), one that mediated cell-substratum attachment a 'SAM' (substratum adhesion molecule), one that promoted neurite outgrowth a 'neurite outgrowth-promoting factor', one that mediated adhesion but behaved as a multi-molecular particle an 'adheron', and so on¹⁻³. As more has been learned about the molecular identities of these molecules, there has been a tendency to divide

Arthur D. Lander is at the Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA.

them into two groups on the basis of cellular localization: cell surface molecules and extracellular matrix molecules, the former mediating cell-cell adhesion, and the latter mediating cell-substratum interactions⁴.

During the past few years, the cloning and sequencing of cDNAs for many of these molecules has been accomplished, making detailed structural comparisons possible. These observations reveal structural similarities among cell surface 'adhesion' molecules and similar relationships among extracellular matrix molecules, but only a few structural features common to both groups. Such findings suggest that the molecules involved in cell-cell interactions are either unrelated to, or diverged long ago (in evolutionary terms) from those involved in cell-substratum interactions. If this is the case, one might expect the molecular details of the cellular responses to these two classes of molecule to be quite different.

The studies of the past few years have also revealed more detailed information about the expression, cellular localization, and binding properties of molecules involved in cell-cell and cell-substratum interactions. Surprisingly, these data suggest that cell surface and extracellular matrix molecules have a great deal in common, and furthermore, that the distinction between whether a molecule belongs to the cell surface or to the extracellular matrix is not always sharp. This is consistent with the view that the events underlying cellular responses to other cells and to extracellular matrices may not, in fact, be fundamentally different.

The evidence supporting these two divergent views is summarized below. The discussion focuses on eight molecules, four considered to be cell surface 'adhesion molecules' and four considered to be important components of the neural extracellular matrix. One aim of this discussion is to present a framework within which neurobiologists may bring themselves up to date in a field characterized by major upheavals every few years. A second, equally important aim is to point out loose ends and nagging questions that currently preoccupy researchers in this area. Such issues are certain to figure prominently in future upheavals.

Cell surface 'adhesion molecules'

The cell surface 'adhesion molecules' of the vertebrate nervous system that have been most extensively studied are NCAM, L1(NgCAM), myelin-associated glycoprotein (MAG) and N-cadherin. Each appears to be capable of mediating neuron-neuron or neuron-glial cell adhesion, as judged from a variety of *in vitro* tests [the details and interpretations of these assays have been reviewed by others (e.g. Refs 1, 4, 5) and will not be discussed here]. Amino acid sequences deduced from cDNAs for these molecules suggest that each consists of a transmembrane polypeptide with a large extracellular domain, a single membrane-spanning region, and a shorter cytoplasmic domain (an exception is the 120 kDa isoform of NCAM, which lacks the transmembrane and cytoplasmic domains and is anchored to the membrane by covalent linkage to a phosphoglycolipid)⁶⁻¹². Three of these four molecules (NCAM, L1 and MAG) possess structural motifs in their extracellular portions that are homologous to immunoglobulin constant region domains (Fig. 1). Interestingly, immunoglobulin-related domains are found in a variety of other

cell surface molecules that have been implicated in cell-cell interactions¹³ as well as in some recently identified vertebrate and invertebrate nervous system proteins suspected to be involved in axonal guidance^{14,15}. The molecule N-cadherin, which mediates cell-cell adhesion in a calcium-dependent manner, lacks immunoglobulin-like domains, but shows marked similarity to other calcium-dependent adhesion molecules (cadherins) that are found in non-neural tissues¹¹.

Extracellular matrix molecules

Although it is generally accepted that the vertebrate CNS contains an extracellular matrix, no method has been developed for isolating it for biochemical studies, and knowledge even of its major components is lacking. Nevertheless, extracellular matrix components that affect the behavior of neural cells *in vitro* have been identified, and they have been localized by immunohistochemistry to various sites within the nervous system. Two of these, laminin and fibronectin, promote neurite outgrowth by several types of neuron and can mediate neuron-substratum attachment (reviewed in Ref. 2). Both are major constituents of peripheral neural and non-neural extracellular matrices; in the CNS, however, they are found only in a small number of restricted areas during embryonic development. Tenascin (also known as cytotactin, and related or identical to J1), is a third extracellular matrix protein that affects neuronal behavior *in vitro*. It also undergoes developmental changes in expression, and appears to be more widely distributed in the developing CNS than either laminin or fibronectin¹⁶⁻¹⁹. Thrombospondin, an extracellular matrix protein released by platelets and smooth muscle cells, has recently been shown to be widely present in mammalian brain, where it is thought to be produced by astroglia^{20,21}. Although nothing is known about the effects of thrombospondin on the behavior of neural cells, if they are similar to its effects on other cells²², thrombospondin is likely to be an important mediator of neural cell-matrix interactions.

Amino acid sequences have recently been deduced from cDNAs for laminin, fibronectin, tenascin and thrombospondin²³⁻²⁸. In agreement with biochemical observations, each consists of two or more large, related or identical polypeptide chains held together by disulfide bonds (Fig. 1). Hydrophobic regions characteristic of membrane proteins are not observed. Although long stretches of sequence similarity are not seen in these four molecules, the subunits of each appear to have been built up from the repetition of various structural motifs, some of which are shared (e.g. cysteine-rich 'EGF-like' repeats, fibronectin 'type III' repeats).

Structural similarities

Despite the clear structural differences between the four cell surface 'adhesion molecules' and the four extracellular matrix molecules described above, a few similarities have been noted. Homologues of one kind of repeated structural motif found in fibronectin and tenascin have been identified in NCAM and L1 (Ref. 8). An unusual carbohydrate moiety, thought itself to play some role in cell interactions, is found not only on NCAM, L1 and MAG, but also on tenascin²⁹. In addition, it is characteristic of NCAM, L1

Fig. 1. Structural features of molecules involved in neural cell contacts. Molecules have been drawn in schematic form to illustrate structural domains that have been established or are suggested by amino acid sequences. Integral membrane proteins are shown inserted into a lipid bilayer, with their extracellular domains drawn above, and intracellular domains below the membrane. The arrangements of polypeptides within extracellular matrix molecules partly reflect the appearance of these molecules by electron microscopy. Disulfide bridges are shown as dotted lines (for tenascin, the location of disulfide bridges, as well as the exact positioning of domains, is speculative since the amino acid sequence of about one-third of the molecule has not yet been determined). Immunoglobulin constant region domains (drawn as loops and indicated by asterisks) may be seen in NCAM, MAG and L1; fibronectin 'type III' repeats (rectangles with diagonal hatching) are found in fibronectin, tenascin, and L1; repeats of cysteine-rich 'EGF-like' sequences (rectangles with horizontal hatching) are found in laminin, tenascin and thrombospondin. Filled arrows indicate positions of known cell-binding domains. Open arrows indicate rough positions of known glycosaminoglycan (heparin) binding sites. Stars have been placed beside NCAM, MAG, and fibronectin to point out sites of molecular variation that are generated by alternative splicing of mRNAs; in the case of NCAM, the largest form ('180 kDa') is shown, and the stars mark the terminations of the '140 kDa' and '120 kDa' forms. (Adapted from drawings and data presented in Refs 5–12, 23–28, 34, 77, 78.)

TABLE 1. Binding interactions of molecules involved in neural cell-cell and cell-substratum association^a

Cell interaction molecule	Known ligands
NCAM	NCAM, heparin, heparan sulfate
L1	L1, uncharacterized receptor
MAG	Uncharacterized receptor, heparin, various collagens
N-cadherin	N-cadherin, other cadherins?, Ca ²⁺
Laminin	Laminin, integrin(s), heparin, heparan sulfate proteoglycans, collagen type IV, entactin, glycolipids, other receptors
Fibronectin	Fibronectin, integrins, heparin, heparan sulfate proteoglycans, dermatan sulfate proteoglycan, gelatin, fibrin, collagens, glycolipids
Tenascin (cytotactin)	Chondroitin sulfate proteoglycan, integrin (?), fibronectin
*Thrombospondin	Integrin, heparin, heparan sulfate, sulfated glycolipids, fibronectin, fibrinogen, plasminogen, Ca ²⁺

^aCompiled from Refs 1, 2, 4, 17, 24, 25, 33, 44–48, 56, 57, 79.

and MAG as well as fibronectin, laminin and tenascin to be found in multiple biochemical forms in neural tissue^{2,6,7,10,24,26,30–34}. In several cases, this is known to reflect alternative splicing of mRNA.

Cellular localization: overlapping territories?

Deduced amino acid sequence information supports the conclusion that NCAM, L1, MAG and N-cadherin are integral membrane proteins, whereas laminin, fibronectin, tenascin and thrombospondin occur in the extracellular space. Biochemical and immunochemical studies generally support this view, but not always: for example, significant amounts of L1 and MAG can be isolated from neural tissues in forms that are soluble in the absence of detergent (uncharacteristic of integral membrane proteins)^{31,32,35}. The lipid-linked 120 kDa form of NCAM is also potentially susceptible to release in soluble form from cells as a result of the action of a specific phospholipase³⁶. The existence of 'soluble' forms has been offered as an explanation for the immunohistochemical localization of NCAM, L1 and MAG in what appear to be extracellular matrix locations^{37–39}. Verifying these observations will require electron microscope analysis. In the meantime, their plausibility is strengthened by the existence of binding properties, for NCAM and MAG at least, that could account for retention of soluble forms in extracellular matrices (see below).

Conversely, there are circumstances in which laminin, fibronectin, tenascin and thrombospondin appear to behave as though they were cell surface constituents. In tissue culture, for example, Schwann cells express surface laminin, fibroblasts express surface fibronectin, glial cells express surface tenascin and smooth muscle cells express surface thrombospondin^{40–43}. Such expression undoubtedly reflects association of these molecules with cell surface receptors (see below). What is striking, however, is that not all of the types of cell that can synthesize and bind these molecules normally express them on their surfaces. This observation suggests that maintenance of these molecules on the cell surface is actively controlled by cells, a clue that their localization there may be functionally significant. Indeed, *in vitro* studies of cytotactin (tenascin) indicate that the surface-associated molecule can mediate adhesion of neural cells in suspension¹⁹.

Primary receptors

Crucial to understanding how cell surface and extracellular matrix molecules control the formation of cell contacts is defining the receptor molecules that are involved. Much work has been devoted to identifying the cellular receptors that are primarily responsible for the *in vitro* functions of these molecules.

The cell surface molecules NCAM, L1, MAG and N-cadherin apparently mediate cell-cell adhesion by direct binding to cell surface molecules. In the case of NCAM, binding is homophilic (NCAM on one cell surface binds to NCAM on another), whereas for MAG it is apparently heterophilic, involving an as yet uncharacterized receptor^{44,45}. Investigations of L1-mediated cell adhesion suggest that, depending on the cells involved, either homophilic or heterophilic interactions may occur⁴⁶. Biochemical and functional studies suggest that the calcium-dependent adhesion molecules (cadherins), including N-cadherin, bind homophilically, although some studies suggest that heterophilic interactions between different cadherin molecules can also occur^{47,48}.

A major breakthrough in the understanding of how extracellular matrix proteins interact with cells has been the identification of the family of cell surface receptors known as integrins. Integrins, also known as Arg-Gly-Asp (or RGD) receptors (several recognize Arg-Gly-Asp-containing sequences within their protein ligands), consist of two non-covalently associated transmembrane polypeptides, α and β . Three different β -chains have so far been identified, and for each there exists a distinct set of α -chains in combination with which it may be found⁴⁹. An ability to bind one or more particular extracellular matrix molecule is apparently specified by each different α/β combination. There is strong evidence that integrins are involved in mediating the effects of laminin and fibronectin on neuronal attachment and neurite outgrowth⁵⁰. Integrins also appear to be involved in the binding of cells to thrombospondin and tenascin^{24,51}.

Is there anything in common between the homophilic binding of NCAM or N-cadherin and the binding of extracellular matrix molecules to integrins? The deduced amino acid sequences of several integrin polypeptides fail to reveal any significant relationship to known cell surface 'adhesion molecules'. Nonetheless, there are some interesting biochemical parallels between these two classes of integral membrane protein. In both groups one observes cytoplasmic extensions that appear to interact with the cytoskeleton^{52–54}. This suggests that the cytoskeleton may play a primary role in informing cells of their external contacts, whether they are cell-to-cell or cell-to-substratum. It is also noteworthy that the techniques that have been necessary to demonstrate binding of integrins to extracellular matrix molecules imply that such binding is of relatively low affinity, suggesting that strong cell-matrix associations require multi-point attachment along the cell surface. The techniques that have been required to demonstrate binding of cell surface adhesion molecules to cells (such as in liposome-binding studies) also suggest that multi-valent attachment may be important. Finally, it should be noted that in the immune system, there is direct evidence of an integrin being involved in cell-cell, rather than cell-substratum, adhesion. The receptor specified by this particular α/β

combination associates with an endothelial and lymphocyte cell surface molecule known as ICAM-1 (Ref. 55). Interestingly, ICAM-1, like NCAM, L1 and MAG, is a transmembrane protein that contains multiple extracellular immunoglobulin-related domains. This observation indicates that integrins can act as heterophilic receptors for cell surface 'adhesion molecules', and raises the possibility that integrins could be receptors for L1 or MAG.

Other 'receptors'

The binding interactions discussed above, complex as they are, may represent only a small part of the functionally relevant binding behaviors exhibited by the molecules that mediate cell-cell and cell-matrix interactions. Indeed, multifunctionality of binding (i.e. the presence on a molecule of distinct binding sites for more than one type of ligand) has now been observed for NCAM, L1, MAG, laminin, fibronectin, tenascin and thrombospondin. Some of the ligands identified for these molecules are listed in Table I.

The high incidence of multifunctionality among the molecules presented in Table I suggests that the ability to bind multiple ligands, possibly at the same time, is somehow important for the function of these molecules. Interestingly, the frequency with which proteoglycans (or polysaccharides derived from them, such as heparin, heparan sulfate, chondroitin sulfate and dermatan sulfate) are mentioned suggests that proteoglycans play some special role in influencing the functions of molecules involved in neural cell-cell and cell-substratum interactions. What that role might be remains difficult to assess, given that proteoglycans are a large class of glycoproteins that are widely distributed among cell surfaces and extracellular matrices, and that little is known about the number and types of proteoglycans that are present in the nervous system. However, a few clues as to what proteoglycans may be doing have been provided by *in vitro* studies. One series of studies in which retinal cell adhesion was examined suggested that NCAM must interact with a neuronal cell surface heparan sulfate proteoglycan in order for cell adhesion to occur^{56,57}. An interpretation that was offered was that binding to heparan sulfate might induce a conformational change in NCAM that enhances its ability to bind homophilically to another NCAM molecule. An example of a molecule in which heparan sulfate (or the related heparin) induces a large conformational change is fibronectin⁵⁸. A role for neuronal heparan sulfate in the response of neurons to fibronectin is consistent with the results of several experiments⁵⁹⁻⁶¹, but is far from established. For one type of epithelial cell, however, there is strong evidence that a particular cell surface proteoglycan acts, in addition to integrins, as a major receptor for fibronectin⁶². Recent observations also suggest that a major neuronal receptor for tenascin is a large chondroitin sulfate proteoglycan¹⁷.

These studies are consistent with the idea that cell surface proteoglycans participate directly in the establishment of both cell-cell and cell-substratum contacts. Another possibility that has been raised is that proteoglycans act as anchors to immobilize molecules in the extracellular space. This effect could explain the observation, referred to earlier, of NCAM and MAG immunoreactivity in 'matrix' locations, since

both bind heparin/heparan sulfate (MAG also binds other matrix components). That NCAM, in association with matrix proteoglycans, is indeed capable of promoting neuron-substratum attachment is shown by work on the adhesion-promoting properties of retinal 'adherons'^{57,63}.

Mechanisms of action: more than adhesion?

The importance of cellular adhesion as a morphogenetic process has long been appreciated both by developmental biologists and neurobiologists. Models involving specific, graded forms of adhesion can explain sorting out of cells within aggregates, release of mesenchymal cells from epithelial structures (as in the formation of the neural crest), directed migration of cells, selective fasciculation of axons, and guidance of growth cones by cellular or substratum-bound cues. The identification and characterization of a number of molecules capable of mediating such adhesion is a great achievement, and will permit the testing of such models.

As details of the molecular structures of these molecules have become known, however, it has become clear that they are generally more complicated than might have been expected. Why do cell surface 'adhesion molecules' need cytoplasmic domains? Why are the lengths of the cytoplasmic domains of NCAM and MAG under elaborate developmental and tissue-specific control? Why are the molecules in Table I all multifunctional in their binding specificities? One possibility is that these features reflect the way proteins must be engineered to exploit the most subtle intricacies of adhesive interactions, especially when such interactions confront cells in combinations. At least as plausible, however, is an alternative view: that 'adhesion molecules' do *more* than just mediate adhesion. In fact, there are notable examples of *in vitro* effects of some of these molecules that are not easily explained as the result of purely adhesive interactions. NCAM and laminin, for example, both influence levels of cytoplasmic enzymes in a manner consistent with effects on gene expression or intracellular second messengers^{64,65}. Laminin, in addition to promoting neurite outgrowth, apparently also has effects on neuronal survival and on the actions of neurotrophic factors⁶⁶⁻⁶⁹. Obviously, it is possible to envisage indirect mechanisms whereby increased cell-cell or cell-substratum adhesion triggers these phenomena (cf. Ref. 70); such hypotheses are difficult to rule out. However, one recent set of experiments⁷¹ provides strong evidence that laminin-mediated neurite guidance is unlikely to be accounted for by an exclusively adhesion-based mechanism. These experiments showed that, even though growth cones exhibited a marked ability to restrict their growth to laminin-containing regions of their substratum, their actual degree of physical adhesion to such regions was no higher than, and in some cases lower than, their adhesion to laminin-free regions of substratum. Exactly how laminin influences the behavior of growth cones remains to be demonstrated, although the influence appears to involve changes in the dynamics of extension and retraction of growth cone filopodia and lamellipodia, events that have recently been tied to changes in intracellular calcium⁷². It is particularly interesting that these and other effects of laminin on neurons appear to involve integrins, because of growing evidence that integrins, upon binding their

ligands, undergo conformational changes that could potentially transmit a signal to the cell interior⁷³⁻⁷⁶.

An assessment

The investigation of molecules that mediate cell-cell and cell-substratum interactions has had, and will undoubtedly continue to have, an enormous impact on neurobiology. Although it is helpful to categorize these molecules as members of either the cell surface or the extracellular matrix, it is important to remember that their physiological sites of action may not always be clear.

A great deal remains to be learned about the biochemistry of these molecules: all of the molecules they bind to, how they appear in their native configuration, what conformational changes follow the binding of ligands or addition of covalent modifications (phosphorylation, glycosylation). This is a difficult task made even more complex by the number of ways in which the multiple binding domains on these molecules could interact. It is encouraging, at least, that the genetic engineering approaches for protein structure/function studies that have recently become available are ideal for such purposes.

Despite the remarkable successes of the past decade, a great deal also needs to be learned about the possible functions of these molecules in the nervous system. The adhesion they mediate needs to be quantified and the influences of other molecules on it identified. The process by which cell-cell and cell-substratum adhesions develop into more permanent contacts needs to be examined. Moreover, as the preceding paragraphs have argued, if the physiological functions of these molecules are to be understood, it is essential to determine whether, in addition to mediating adhesive interactions, these molecules are sending other, more specific messages to cells. If so, cell contact may be a lot like human contact, in which associations of equal adhesive strength – shaking hands or holding hands, restraining someone or embracing him – convey distinctly different messages.

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