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Cell Adhesion Molecules: Implications for Neurological Disease

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Cell adhesion molecules (CAMs) help determine the systems-level structure of the nervous system by controlling the physical interactions between neurons and glia during development and regeneration. Abnormalities in these molecules are becoming associated with a wide range of neurological disorders, including hydrocephalus, fetal alcohol syndrome, schizophrenia, and others, providing new insights into both clinical and basic research.

CAMs comprise a large group of cell surface macromolecules that provide recognition and adhesion between cells that express appropriate CAMs. Binding is primarily homophilic, that is, between like CAMs on adjacent cells, but heterophilic binding between similar molecules is also an important mode of interaction. CAMs are critical for migration and recognition of appropriate cells to form functional assemblies of neurons and for innervation of appropriate targets. They are involved in most of the major developmental processes, including cell migration, neurite initiation, neurite outgrowth, axon pathfinding, axon fasciculation, synaptogenesis, synapse stabilization, and myelination. They perform these functions not only by regulating cell adhesion, but also by activating intracellular signaling cascades that in turn control cytoskeletal dynamics, cell morphology, and neurite outgrowth.

CAMs are divided functionally into calcium-dependent and calcium-independent groups (Fig. 1). The calcium-dependent CAMs include the cadherins, which contain several extracellular calcium-binding domains as well as an intracellular domain that interacts with the actin cytoskeleton and intracellular signaling pathways. Integrins require extracellular calcium for binding, and they are distinguished from the other CAMs by providing cell-to-extracellular matrix (ECM) adhesive contacts. Integrins are heterodimeric proteins that interact with the actin cytoskeleton through several intermediate proteins and signal transduction pathways.

The large family of calcium-independent CAMs do not require extracellular calcium ions for binding, and they include members of the immunoglobulin superfamily of CAMs. These molecules share a similar extracellular structure, consisting of several immunoglobulin (Ig) domains and often fibronectin type III repeats. Various isoforms are known, and many are regulated by phosphorylation and glycosylation. Expression of the various isoforms is highly regulated during development and regeneration.

NCAM

NCAM is the best known member of the Ig superfamily of CAMs. Its function is regulated during development by changes in gene expression, and by posttranslational modification; particularly glycosylation. This involves the addition of polysialic acid (PSA) to NCAM, catalyzed by the enzyme polysialyltransferase (1). Generally, PSA residues reduce the adhesive interaction between NCAM molecules because of steric interference from these large carbohydrate structures (2).

Abnormal levels of different isoforms of NCAM have been associated with some psychiatric disorders. People suffering from bipolar mood disorder type 1, recurrent unipolar major depression (3), and schizophrenia (4) show elevated levels of the 120-kDa isoform of NCAM in their CSF. Medication treatment does not affect CSF NCAM concentrations in these patients. This NCAM may be derived from CNS cells as a secreted soluble NCAM isoform. Patients with bipolar mood disorder type II have normal levels of NCAM 120 in the CSF.

Abnormalities in NCAM in these patients suggests that pathogenesis of schizophrenia and some mood disorders may be related to systems-level neuro-developmental defects. Certain structural abnormalities, including ventriculomegaly (moderately enlarged ventricles) and decreased temporal lobe volume have been reported for both schizophrenia and mood disorders of the type associated with abnormal NCAM levels (3). A corollary of abnormal CAM expression is suggested by experiments showing that skin fibroblasts cultured from schizophrenic patients display decreased cell adhesiveness and abnormal growth and morphology (5).

Recent research has shown that CAMs are involved in activity-dependent plasticity during development and activity-dependent synaptic plasticity in the postnatal nervous system (6). Disturbances in synaptic plasticity and restructuring may be involved in pathogenesis of certain neuropsychiatric diseases. In support of this hypothesis, PSA-NCAM has been implicated in long-term potentiation and learning and memory (7, 8), and postmortem examination of the hippocampal region shows a 20%–95% reduction in the number of PSA-NCAM immunoreactive cells in the hilus region of schizophrenic patients (9).

L1

The cell adhesion molecule L1 (Fig. 1) is expressed on neurons and Schwann cells, where it regulates neurite outgrowth, fasciculation, and Schwann cell-axon association, including myelination (10). The L1 gene is located in the q28 region of the long arm of the X chromosome (11). A number of severe neurological disorders show X-linked inheritance patterns, and in recent years it has become clear that many of these disorders are caused by mutations in the L1 gene. A number of reviews have been recently published on L1 mutations in neurological disease (12–14), including an excellent site on the internet by G. Van Camp, E. Franssen, G. Raes, and P. Willems from the University of Antwerp, Belgium (<http://hgins.uia.ac.be/dnalab/l1>). This resource provides a detailed table of the 79

mutations, gene sequences and structure, references to the literature, and clinical descriptions of disorders associated with L1 mutations, with links to related internet sites.

The acronym “CRASH” has been proposed for the clinical syndrome consisting of **C**orpus callosum hypoplasia, mental **R**etardation, **A**dducted thumbs, **S**pastic paraplegia and **H**ydrocephalus, to encompass a number of X-linked disorders now known to be associated with mutations in the L1 gene (15). The CRASH syndrome therefore encompasses patients with X-linked hydrocephalus (HSAS), X-linked spastic paraplegia (SP1), agenesis of corpus callosum (ACC), and MASA syndrome, an acronym for an X-linked neurological disorder involving **M**ental retardation, **A**phasia, **S**huffling gait, and **A**dducted thumbs.

The fundamental importance of CAMs in nervous system development is evident from the diverse and serious consequences of defects in this one molecule. Agenesis of corpus callosum is an X-linked recessive disorder resulting in partial agenesis of the corpus callosum. These patients exhibit severe intellectual retardation and intractable seizures. An unusual facial appearance, spasticity, or hydrocephalus may be associated with the disease (16-18). X-linked spastic paraplegia, associated with mutation in the L1 gene (19, 20), is designated SPG1 to differentiate it from a similar phenotype resulting from mutation in the proteolipid protein (PLP) gene (designated SPG2). The disease is characterized by spasticity of lower extremities with varying degrees of mental retardation. X-linked hydrocephalus (HASA) is responsible for one-fourth of all male patients with hydrocephalus (21). The severity of the disorder can range from severe mental retardation (IQ 20–50), macrocephaly, and perinatal death, to relatively minimal enlargement of ventricles. Rosenthal et al. (22) showed that mutation in the L1 gene is associated with this phenotype. Hydrocephalus may result from congenital stenosis of the aqueduct of Sylvius. Possible support for this may be provided by experimental studies showing that cleavage of sialic acid by injection of neuraminidase into experimental animals induces ependymal cell death and edema, leading to fusion of the lateral walls of the cerebral aqueduct and hydrocephalus of the third and lateral ventricles (23). However, HASA has also been reported in patients without aqueductal stenosis, suggesting that aqueductal stenosis may be the result rather than the cause of hydrocephalus (24). Adducted thumbs are present in about one-fourth of the cases (25).

Analysis of the functional consequences of mutations in the L1 gene is providing valuable insight into the function of this CAM during human development. The human L1 gene is 16 kilobases long and contains 28 exons. It encodes a protein of 1275 amino acids in length, including the 19-amino acid signal peptide that is cleaved from the mature protein (15). The cytoplasmic domain is highly conserved, sharing 100% homology between human and mouse. Currently, 79 mutations in the L1 gene have been described, consisting of missense point mutations, frame shifts, duplications, deletions, and premature stop codons in the extracellular domain that may result in a secreted form (12). Defects in both the cytoplasmic and extracellular domain of L1 are associated with these neurological disorders. Defects in the short cytoplasmic domain point to the importance of this molecule in interacting with cytoskeletal or intracellular signaling proteins during development because the extracellular domain would retain adhesive properties. Truncations of the L1 molecule can be lethal or result in severe hydrocephalus.

Mental retardation, hydrocephalus, and agenesis of the corpus callosum are also observed in children with fetal alcohol syndrome (FAS). A recent study shows that ethanol interacts with a hydrophobic pocket within L1 to inhibit adhesion in rat cerebellar granule cells in a culture assay (26). Ethanol at a concentration reached in blood and brain after ingesting a single alcoholic beverage inhibits L1-dependent adhesion in mouse fibroblasts transfected with the human L1 gene. Alcohol had no detectable effect on NCAM140-mediated adhesion. These data suggest that disruption of L1-mediated cell-cell interactions could contribute to FAS and possibly other ethanol-associated impairments, such as memory disorders.

CAMs and Myelination

Antibody blockade experiments show that initiation of myelination of sensory neurons in culture is critically dependent on the neural cell adhesion molecule L1 (27). In addition, a number of other CAMs within the Ig superfamily, including myelin protein zero (Po) (28), myelin-associated glycoprotein (MAG), and myelin/oligodendrocyte glycoprotein (MOG) (29) are important components of myelin (30).

Po (Fig. 1) accounts for more than half of the total protein in compact PNS myelin (31), where it functions to stabilize the intraperiod line of compact PNS myelin by homophilic binding (32). Mice lacking Po show severe hypomyelination, abnormal motor coordination, and convulsions (33). Several point mutations in the Po gene in human chromosome 1a22–23 have been found in Charcot-Marie-Tooth disease type 1B (CMT1), and in Dejerine-Sottas (DS) disease and congenital hypomyelination (CH) (13, 34). These diseases are characterized by peripheral nerve demyelination and progressive distal muscle atrophy.

MOG, a CNS myelin component with a single Ig domain, is absent from compact myelin, but it is expressed on the surface of oligodendrocytes and myelin sheath (35), where it presents an important antigen that may be involved in the pathogenesis of autoimmune demyelinating diseases of the CNS, for example, multiple sclerosis (MS) (36–38).

A carbohydrate epitope reacting with the HNK-1 antibody can be expressed on NCAM, L1, Po, MAG, and MOG, where it may function in homophilic and heterophilic binding (30). MAG, which has 5 Ig domains, is abnormally glycosylated in the trembler and quaking mice mutants, which exhibit dysmyelination and pathological symptoms of abnormal impulse conduction (39). Anti-MAG antibodies have been detected in patients with demyelinating neuropathy (40). These antibodies have similarities to the HNK-1 antibody (41), and they cause demyelination in experimental animals (42), with anatomical similarities to MS (41).

CAMs, Neurite Outgrowth and Regeneration, and Synaptic Plasticity

Neurite outgrowth and, therefore, nerve regeneration depend on local cues in the environment provided by ECM and cell adhesion molecules. MAG can bind some ECM components (43) and influence neurite outgrowth (44, 45). MAG has been shown to be a possible factor impeding axon regeneration in the CNS because it induces growth cone collapse and inhibits neurite outgrowth in culture (46), although compensatory mechanisms support axon outgrowth and myelination in MAG-deficient mice (47). Block of cadherin function using a dominant negative N-cadherin mutant results in inhibited axon and dendrite

outgrowth of retinal ganglion cells, as well as other effects indicating an essential role of this CAM in the initiation and extension of axons from retinal ganglion cells in vivo (48). Cadherin expression is also associated with the node of Ranvier (49), postsynaptic densities of central synapses (50-52), and neuromuscular junction, suggesting a role in synapse formation or stabilization (53).

ECM molecules and their integrin receptors regulate neurite outgrowth and synapse stabilization. Abnormalities in ECM and integrins have been associated with a wide range of neurological defects, including defects in cerebellar development (54, 55); experimental allergic encephalomyelitis, an animal model of MS (56, 57); processing and aggregation of beta-amyloid-containing peptides in Alzheimer's disease (58-60); invasion of glioma tumors in rat spinal cord (61); an X-linked form of Kallmann's syndrome resulting in anosmia (62); Hirschprung's disease (congenital absence of ganglion cells in the wall of colon) (63); and congenital muscular dystrophy, an autosomal recessive neurological disorder characterized by muscular dystrophy and brain white matter abnormalities (64). The importance of integrins in synaptic plasticity is suggested by their localization at synapses (65, 66) and blockade of LTP in slices incubated with a peptide inhibiting integrin function (67).

Therapeutic Opportunities

A better understanding of the role of CAMs in neurological disease and nerve regeneration may lead to better therapies. For example, experimental allergic encephalomyelitis is suppressed by monoclonal antibody to alpha 4 integrin (57) or MOG peptide (68), findings that could be useful in the treatment of autoimmune diseases, such as MS. Antibodies neutralizing CNS myelin-associated proteins improve regeneration in the CNS of experimental animals (69), and grafts of genetically modified fibroblasts expressing L1 improve regeneration in transected rat spinal cord (70).

Defective function of neurotransmitter receptors and cytosolic proteins are involved in the causation of many neurological disorders. The important function of CAMs in coordinating the connections between systems of neurons, as well as their association with glia, suggests that future research on this class of molecules will have important implications for congenital neurological defects, neurological trauma, disease, and some psychiatric disorders.

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Fig. 1. Schematic representation of the molecular structure of the three major classes of cell adhesion molecules. The immunoglobulin (Ig) superfamily of calcium-independent cell adhesion molecules do not require extracellular calcium ions for binding. Members of this class of CAMs have one or more Ig domains and often fibronectin type III repeats in the extracellular domain. Cadherins and integrins require calcium ions for binding, and they interact with cytoskeletal proteins and proteins involved in signal transduction pathways. Integrins bind to components of the extracellular matrix, and cadherins bind homophilically to like molecules on adjoining cells.