Review

The Cell Recognition Molecule L1 and Cognition

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Abstract

Cell adhesion molecules were classically known to be key players in a whole array of biological functions during development through cell-cell and cell-substratum adhesion. Accumulating evidence suggests, however, that the functional significance of adhesion molecules may extend well beyond embryonic development into adult stage. The aim of this article is to review our current knowledge on the implications of adhesion molecules in various cognitive processes. Particular emphasis was placed on the immunoglobulin superfamily of adhesion molecules, which are found to be involved in activity-dependent plasticity of the nervous system, and hence promising candidates in modulating cognitive functions.

Key Words: cell adhesion molecule, cognitive functions, learning and memory, gene knockout, anxiety, long-term potentiation

Introduction

The establishment of a functional nervous system involves highly concerted organization of cell migration, differentiation, and connection between neurons and their appropriate postsynaptic targets during development. To date, we begin to understand that neuronal development is under tight regulations through various forms of molecular interactions between cells and their surroundings. The guidance of a developing axonal growth cone to its target, for instance, was found to be under the control of various cell surface or soluble guidance cues present along the path. Last two decades have witnessed the discovery of molecules that are implicated in this process, like fasciclin, NCAM, L1-CAM, netrins, ephrins, slit, and semaphorins. Interestingly, many of them also double as cell adhesion molecules (CAMs), which are well-known for their primary functions in sticking cells together or sorting cells into different populations through cell-cell or cell-substratum recognition process (25, 26). Many adhesion molecules have in fact been found to subserve not only adhesive but also a wide variety of other physiological functions, ranging from neuron migration, axon guidance, to synaptogenesis. The expression of some CAMs persists even in adult stage, suggesting their involvement not only in building and maintaining the nervous system, but also in neuronal regeneration and plasticity in mature stage. This article reviews our current understanding of the emerging role of CAMs in cognitive functions. Particular emphasis was placed on L1-CAM (L1) of the immunoglobulin superfamily, which was found to be involved in activity-dependent plasticity of the nervous system, and hence a promising candidate in modulating cognitive functions.

Immunoglobulin Superfamily of Cell Adhesion Molecule

Members of the immunoglobulin superfamily (IgSF) of cell adhesion molecules exist in the form of type I or GPI-linked membrane proteins. They are characterized by the presence of one or more immunoglobulin-like (Ig-like) domains (3), followed by fibronectin type III (FNIII) repeats (32) (Fig. 1). Ig-CAMs of the same type on adjacent cell membranes can interact homophilically, as exemplified by the cis interaction by L1-CAM that mediates cell-cell adhesion (41) and neurite outgrowth (28). Heterophilic

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Fig. 1. Structural domains of L1-CAM. L1 is a type I transmembrane glycoprotein carrying six immunoglobulin-like (Ig-like) domains and five fibronectin type III repeats (FNIII) in its extracellular moiety, followed by a transmembrane and a cytoplasmic domain.

binding between different Ig-CAMs is also not uncommon. L1, for instance, has been shown to bind heterophilically to other adhesion and extracellular matrix molecules, like axonin-1/TAG-1 (14, 33), integrins (42, 49), and neural cell adhesion molecule NCAM (18, 23). In fact, it is through these homophilic and heterophilic interactions that give rise to the multifaceted functions of CAMs. Because CAMs mediate various biological functions through their bindings to a whole array of molecules, they are also referred to as cell recognition molecules (CRM).

L1-CAM

Similar to other Ig-CAMs, L1 is a transmembrane glycoprotein featuring six Ig-like domains and five FNIII repeats in its extracellular moiety, followed by a cytoplasmic domain (43) (Fig. 1). It is encoded by a single gene mapped to Xq28, which is highly conserved across species from *Fugu* fish to human (7, 11). The open reading frame of mouse L1 cDNA is 3,783 bp, which translates into a 140 kDa protein (43). It is noteworthy, however, that L1 isolated from mouse brain was found to contain three populations: 200, 140, and 80 kDa. The 200 kDa species was found to be a glycosylated form of the 140 kDa protein backbone (46). The remaining two small populations are proteolytic cleavage products of the 200 kDa species (13). In addition to post-translational modification, several L1 isoforms were found to stem from the same structural gene *via* alternative splicing (40). L1 lacking exon 3, which codes for the amino acids KGHHV in the extracellular domain, is expressed in B lymphocytes (22), whereas isoform lacking exon 3 and 28 (codes for RSLE in intracellular domain) is found in peripheral Schwann cells (51). Interestingly, full-length L1 is predominantly expressed in neurons.

The distribution of L1 is highly restrictive both spatially and temporally. Immunohistochemical analysis showed that it was first detected in postmitotic neurons of the central nervous system (46). In mouse neocortex, for instance, L1 appears as early as embryonic day 10 (E10) in the marginal zone. In mouse hippocampus, L1 is detected throughout all subfields, including strata oriens, radiatum, and lacunosum-moleculare of CA1; stratum molecular and the hilus of dentate gyrus. No expression was found in hippocampus pyramidal layer and dentate granule cell layer (39, 45).

Developmental Significance of L1

L1 was first discovered in mouse CNS by using a monoclonal antibody directed against cerebellar membrane (29), and was soon found to subserve neuron-neuron adhesion *via* homophilic interaction (12, 24). Early studies indicated the extracellular moiety of L1 is sufficient for adhesion functions (56). Nonetheless, the recent findings that L1 cytoplasmic domain (CD) recruits and binds ankyrins (9), which stabilizes L1-mediated homophilic interaction (19), has revealed a new dimension in the regulation of L1 adhesion. Further characterizations of L1 revealed a plethora of physiological functions in the nervous system during development, like the promotion of neurite outgrowth (15, 54), axon pathfinding (5, 6), neurite fasciculation (15), cerebellar granule cell migration (29), and myelination (57).

Human Mutations of the L1 Gene

Considering the multifaceted functions of L1 in the developing nervous system, it is conceivable that mutations of its gene will lead to debilitating disease states. In fact, mutations of the human L1 gene was first implicated in a form of X-linked hydrocephalus known as HASA (hydrocephalus due to stenosis of the aqueduct of sylvius) (48). Together with two other related neurological disorders, these syndromes were collectively re-named as CRASH (acronym for corpus callosum hypoplasia, mental retardation, adducted thumbs, spastic parapelgia, and hydrocephalus) (16). To date, over 100 L1 mutations have been identified in CRASH patients (53). Most of these are "private mutations", which are restricted to members of the afflicted family. Unlike other disease genes, L1 gene shows no hotspot of mutations. Known L1 mutations were found dispersed along the entire gene and in each of the protein domains. Mutations that produce truncations in the extracellular domain of the L1 protein are more likely to produce severe hydrocephalus, mental retardation, and early death than point mutations in the extracellular domain or mutations affecting only the cytoplasmic domain of the protein (58). Interestingly, point mutations in the extracellular domain produce more severe neurologic problems than mutations in the cytoplasmic domain.

Genetic Model of CRASH Syndrome

Two loss-of-function L1 mutants have previ-

ously been generated to understand the molecular basis of human syndromes with L1 mutations (6, 8). Depending on the genetic background, these L1 gene knockout mice phenocopied most if not all symptoms associated with CRASH syndromes. They showed corpus callosum agenesis and failure of callosal axons to cross the midline, brain ventricle dilatation, and hypoplasia of the cerebellar vermis. Reduced corticospinal tract and abnormal pyramidal decussation led to compromised locomotor functions of the lower limbs in the mutant, which resembles spastic parapelgia in human. Mutant hippocampus is smaller in size, with fewer pyramidal and granule cells than their wild-type littermates (10). Detailed analysis also revealed a reduction in axonal association with nonmyelinating Schwann cells in peripheral nerves. These phenotypes are indeed in line with the physiological functions of L1 in brain development. Interestingly, Fransen *et al*. found that L1 nulls are impaired in spatial learning when subjected to water maze test. They showed also defects in exploratory behavior in open-field test (17). The implication of L1 in learning and memory however, should not be over-emphasized based on these findings. Conceivably, developmental abnormalities in the mutant brain will contribute to a certain extent these cognitive impairments.

L1 and Neural Plasticity

In addition to its significance in the developing nervous system, accumulating evidence suggests the implication of L1 in synaptic plasticity, one of the key components underlying learning and memory. Application of function-blocking anti-L1 antibody or recombinant fragment of L1 Ig-like domains to rat hippocampal slices leads to a reduction in long-term potentiation (LTP) at CA1 (30), an electrical event that may account for memory formation. The lack of effects when these blocking agents were administered after the induction of LTP suggests stage-specific involvement of L1 in the process. Disruption of the formation of L1/NCAM complex, which is important in strengthening homophilic binding of L1 (23), also reduces LTP (30). Interestingly, L1 expression is regulated by specific pattern of neuronal impulse (21). Low frequency electrical pulses delivered to mouse dorsal root ganglion in culture down-regulates the mRNA and protein level of L1. The accompanying reduction in fasciculation of neurites suggests functional significance of L1 in synaptic process.

In fact, several lines of evidence suggested the involvement of L1 in cognitive processes. Intracranial injection of antibody directed against L1 into the brain of day-old chick immediate before, 5.5, or 15-18 hours after passive avoidance training results in amnesia for task recall, whereas injections at other time points impose no effects (52). Continuous infusion of anti-L1 antibody into the brain ventricle of rat also impairs the retention of spatial memory in Morris water maze, though acquisition of spatial tasks is spared (1). In contrast, genetic ablation of L1 in knockout mice results in impairment of both spatial learning and memory retention (17), despite normal LTP manifestation (2). Reduced exploratory behavior in open-field test was also observed in the mutants. More interestingly, ectopic expression of L1 in astrocytes of transgenic mice enhances the flexibility and selectivity of the mutant in spatial learning tasks (55), with a concomitant reduction in LTP (31).

Although these findings apparently point to the implication of L1 in synaptic plasticity and learning, major disparities in the results complicate interpretation of the way L1 may contribute to these processes. For instance, anti-L1 antibodies treatment differs from genetic knockout of L1 in their effects on the acquisition and retention of spatial tasks, as well as on the modulation of synaptic efficacy. These discrepancies could be due to potential specificity uncertainties, clustering effects and triggering of signaling cascades that are associated with antibodies treatments. Severe malformation of brain structures in L1 knockouts due to developmental deficiency of the molecule, as exemplified by the enlarged brain ventricles and cell loss in the hippocampus, may also inevitably contribute to the observed behavioral deficits.

Genetic Model to Understand the Cognitive Functions of L1

To isolate the largely postnatal cognitive functions of L1 from its developmental significance, a novel genetic mutant with restricted ablation of L1 to the postnatal hippocampus was developed (27). It was achieved by harnessing the power of cre-lox recombination system and gene knockout technique (50). Cre-recombinase is a 38kDa enzyme encoded in the genome of bacteriophage P1. It shows high specificity towards a stretch of 34 bp DNA substrate known as loxP, and catalyzes DNA recombination upon recognition of two loxP sites arranged in tandem, resulting in excision of the intervening DNA. This system was adapted in mouse by developing two independent genetic mutants: i) a “L1-floxed” (flanked by lox) mouse in which the L1 gene was flanked by two loxP sites; ii) a “CaMKII-cre mouse” which expressed cre-recombinase transgene in a postnatal forebrain-specific manner, as dictated by the calcium-dependent calmodulin kinase II α-subunit promoter (35, 38). Crossing these two mutants resulted in descendents in which the L1 gene was restrictively disrupted in forebrain structures only after postnatal day 22 and onward.

Table 1. Comparison of phenotypes between L1 null and conditional knockout mutants

	L1 null mutant	L1-CKO
Morphology		
Gross morphology	Reduced body size, sunken eyes	Normal
Brain ventricle	Dilatation	Normal
Hippocampus	Reduced size, reduced number of neurons	Normal
Cerebellum	Hypoplasia	Normal
Corticospinal tracts	Hypoplasia, abnormal decussation	Normal
Behavior		
Open field-test	Stereotyped circling	Increased locomotion and exploratory behavior
Elevated-plus maze	Not analyzed	Increased exploration of open arms
Water maze	Slower acquisition of spatial tasks, reduced spatial selectivity in transfer trial	Normal acquisition of spatial tasks, altered searching strategies and use of visible cues
Synaptic Properties		
Basal synaptic activity in CA1	Normal	Increased
CA1 LTP	Normal	Normal

Previous studies on L1 null mutants revealed developmental abnormalities in the brain (8). This conditional knockout mutant of L1 (L1-CKO), however, showed no abnormalities in gross morphology (Table 1). The size of brain ventricles, hippocampus, and corticospinal tract were normal. Nissl staining of the mutant hippocampus revealed no overt differences in cytoarchitecture with the control. Neurofilament immunostaining of adult brain sections showed no genotype differences in neuronal cell body. The number and morphology of parvalbumin-positive interneurons in the mutant hippocampus were also normal. Glial fibrillary acidic protein (GFAP) immunoreactivity in mutant brain slice was indistinguishable from that in the control. These findings suggested that L1 might not play indispensable role in the maintenance of forebrain structures after development. In fact, the restricted ablation of L1 gene to postnatal forebrain after the cessation of major developmental events provides an unprecedented genetic model to study cognitive functions mediated by L1.

L1 Is Implicated in Exploratory Behavior and Anxiety

When subjected to open field-test, L1-CKO mutants showed increased locomotion and reduced thigmotaxis as compared to their control counterparts (27). *Post hoc* analysis indicated that the mutant stayed at a higher mean distance to wall throughout the course of study. The percentage time spent by the mutants in the center of arena was about 50% higher than that observed in the control. These findings suggest an increase in exploratory behavior when L1 expression is abrogated in adult mice. This is further supported by the observation that mutants showed an increase in rearing off wall behavior in the test.

In elevated plus-maze test, L1-CKO showed higher number of entries into open arms (relative to the total number of entries into all arms), which normally are avoided by wild-type mice (27). They also spent more time in open arms relative to their total time spent in all four arms. In fact, the mutants displayed less risk assessment behavior towards open arms by spending less time probing into open arms while staying in the center of the plus-maze arena. Further analysis revealed that L1-CKO indeed explored to the very end of open arms in 90% of their visit, as compared to about 30% in control animals. These results point to the involvement of L1 in regulating anxiety in mice.

Surprisingly, these alterations in behaviors in L1-CKO are in sharp contrast to those found in L1 null mutants (Table 1). The hypoactivity and stereotyped peripheral-circling behavior of L1 knockouts in open field-test might be ascribed to brain malformations and cerebellar dysfunctions due to developmental loss of L1 expression (17). Behavioral changes observed in L1-CKO mutants may therefore reflect the specific cognitive functions of L1.

L1 Is Involved in Spatial Learning

The involvement of L1 in learning and memory was assessed by subjecting the L1-CKO mutants to hippocampal-dependent spatial tasks in water maze.

While both mutants and controls performed well in the acquisition phase of extra-maze cued spatial task by showing a gradual improvement in locating the hidden platform upon training, L1-CKO did not show preference towards the trained quadrant in transfer trial, during which the hidden platform was removed (27). These findings suggested that the mutants might not complete the task by encoding spatial relationship between the platform and the extra-maze cues, but relied on alternative search strategies like heading vectors and looping (44). More detailed analysis of L1-CKO mutants supported the notion that a loss of L1 functions led to impairment in the efficient use of spatial information to solve the maze.

Increased Basal Synaptic Activity in Hippocampal CA1 of L1-CKO Mutant

In light of the intimate relationship between spatial learning and long-term potentiation (LTP) in the CA1 subfield of rodent hippocampus, it is tempting to speculate that the impairment in spatial learning of L1-CKO may be accompanied by a deficiency in CA1 LTP. Similar to L1 null mutants, however, theta-burst stimulation of Schaffer collateral pathway in L1-CKO resulted in LTP of comparable level to that in control littermates (2). Surprisingly, analysis of stimulus-response curve in CA1 of L1-CKO mice revealed a significantly higher basal synaptic activity as compared to that in control littermates when stimuli of identical strength were applied (27). This phenomenon can be caused by an increase in postsynaptic response, or an increase in the efficiency of Schaffer collaterals firing in mutant hippocampus. The finding of normal pre-spike presynaptic fiber volley at all tested stimulation strengths in mutant slice renders the latter unlikely. To test the hypothesis of an increase in postsynaptic response in mutant, activity-dependent disinhibition of excitatory synaptic transmission was analyzed by measuring multiple population spikes (polyspikes) in response to repetitive stimulation at the Schaffer collateral pathway. No significance differences were found between genotypes. Although the reason behind an increase in CA1 synaptic transmission in L1-CKO remains unclear, it is noteworthy that this phenotype was not observed in L1 null mutants (Table 1). The discrepancy is probably due to ontogenetic compensatory mechanism in the hippocampus of L1 null mutants that made up for the loss of L1 functions during development.

Mechanistic Role of CAMs in Synaptic Plasticity

In contrast to the former view that the nervous system remains stable and rigid after embryonic development, accumulating evidence has demonstrated the plastic nature of neuronal circuitry on both functional and structural levels even at adult stage. Neuronal plasticity is in fact one of the key features of our nervous system that empowers us the capability to learn, to remember, and to develop intelligence. In addition to plastic changes in synaptic efficacy through the modulation of ion channel properties, the remodeling of neural circuitry has become an emerging view to account for the mechanism underlying learning and memory (36). The fact that the expression of L1 and many other Ig-CAMs, which play pivotal role in brain ontogeny, can be regulated in an activity-dependent manner (21, 47) makes these molecules promising candidates in mediating synaptic and structural plasticity that underlies various cognitive processes.

In light of the basic cell-cell adhesion mediated by many Ig-CAM members, a potential model for their regulation of synaptic strength can be the stabilization or weakening of existing synaptic contacts through adhesion or de-adhesion processes respectively. The remodeling of neural circuitry may also involve the formation of new synaptic contacts or regression of existing synapses, which calls for modulation of adhesive force between the opposing synaptic membranes. One possible way of altering CAM-mediated membrane adhesion is through the regulation of their expression on gene transcription level or post-translationally *via* internalization and proteolytic cleavage of the molecule. L1 and NCAM, for instance, have been found localized to synaptic membrane and subjected to modulation by synaptic activities (37, 45). In particular, L1 has recently been shown to serve as a specific substrate to neuropsin, a serine protease activated by LTP. The cleavage of hippocampal L1 at its extracellular membrane-proximal site by neuropsin happens as early as 15 min after chemical induction of LTP by NMDA (37). Although the heterophilic interaction partner of L1 on postsynaptic membrane remains to be identified, the candidate molecule is likely to be part of the NMDA receptor complex, as suggested by a recent proteomic study that shows the presence of L1 in NMDAR immunoprecipitate (20). It is thus not impossible that L1 may indirectly modulate ion channel properties through interactions with NMDAR complex.

Conclusion

Analyses of the L1-CKO mutant demonstrated unequivocally the involvement of L1 in cognition, which is independent of its effects in ontogenetic development. Characterizations of other CAM mutants also revealed their implications in various cognitive events (4, 34). This supports an emerging view that molecules pivotal in molding developing ner-

vous systems may also play significant role in activity-dependent form of neural plasticity. A thorough understanding of the cognitive functions of CAMs and an elucidation of the underlying mechanisms will definitely contribute to the overall picture of how we learn and remember.

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