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Review

The immunoglobulin superfamily of neuronal cell adhesion molecules: Lessons from animal models and correlation with human disease

Markella Katidou[1,2], Marina Vidaki[1,2]*, Maura Strigini[2] and Domna Karagogeos[1,2]*

[1] University of Crete, Faculty of Medicine, Vassilika Vouton, Heraklion, Crete, Greece
[2] Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology, Hellas, Vassilika Vouton, Heraklion, Crete, Greece

Neuronal cell adhesion molecules of the immunoglobulin superfamily (IgCAMs) play a crucial role in the formation of neural circuits at different levels: cell migration, axonal and dendritic targeting as well as synapse formation. Furthermore, in perinatal and adult life, neuronal IgCAMs are required for the formation and maintenance of specialized axonal membrane domains, synaptic plasticity and neurogenesis. Mutations in the corresponding human genes have been correlated to several human neurological disorders. Perturbing neuronal IgCAMs in animal models provides a powerful means to understand the molecular and cellular basis of such human disorders. In this review, we concentrate on the NCAM, L1 and contactin subfamilies of neuronal IgCAMs, summarizing recent functional studies from model systems and highlighting their links to disease pathogenesis.

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1 Introduction

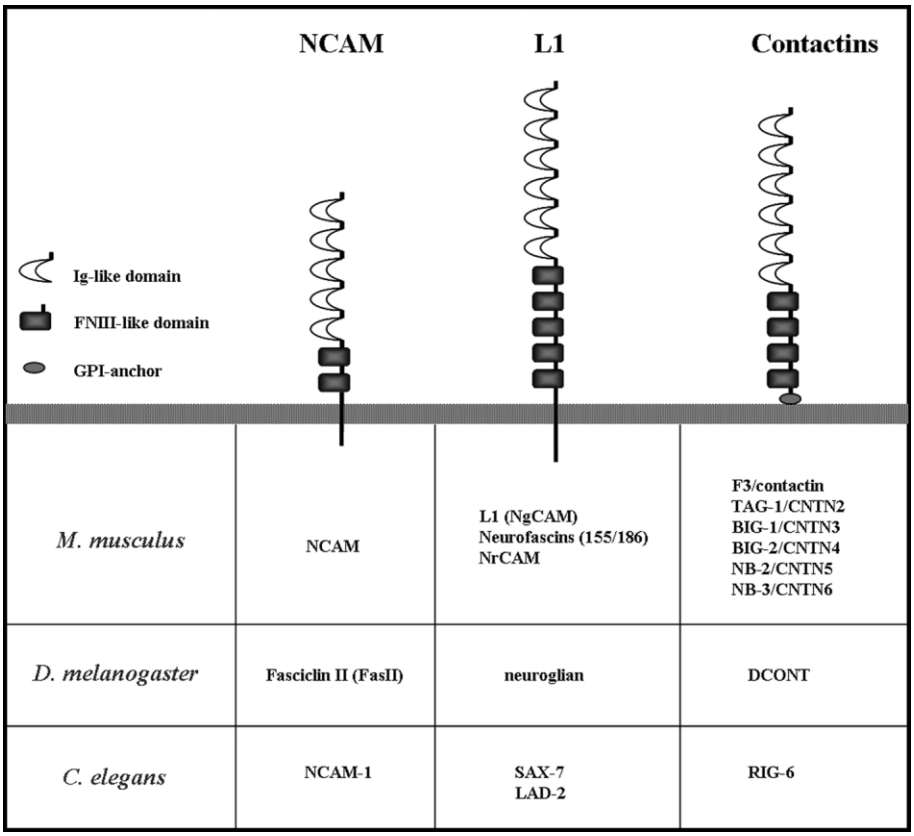
Neural networks are built as a result of regulated cellular interactions. During nervous system development, cells need to adhere to themselves and to their environment and at the same time move to their correct position, extend axons, fasciculate, form and remodel synaptic networks. Adhesion molecules are key players in all of the above processes, and thus are critical for the proper function of the mature nervous system. There are many families of adhesion proteins such as the cadherins, integrins, neurexins and neuroligins, and the immunoglobulin superfamily of cell adhesion molecules (IgCAMs). This review focuses on the functions of three subfamilies of the IgCAMs, notably the NCAM, L1 and contactin subfamilies and their link to pathological conditions.

Structurally, the IgCAMs share modules of N-terminal Ig-like repeats similar to the Ig constant domains, followed by fibronectin type III domains located closer to the plasma membrane (Fig. 1). They span the membrane once and have cytoplasmic regions or are glycosylphosphatidylinositol (GPI) linked. They arose before the beginning of the adaptive immune system and thus, they are one of the most ancient protein motifs. Few structural studies have been conducted but two (on axonin/TAG-1 and L1) that have been published point to a bent conformation allowing individual domains to interact with each other [1, 2]. IgSF proteins are known to interact with themselves (ho-

Correspondence: Professor Domna Karagogeos, IMBB, P.O. Box 1385, Vassilika Vouton, Heraklion, 711 10, Crete, Greece
E-mail: karagoge@imbb.forth.gr
Fax: +30-2810-394530

Abbreviations: AD, Alzheimer's disease; **CSF**, cerebrospinal fluid; **FNIII**, fibronectin type III; **GPI**, glycosylphosphatidylinositol; **IgSF CAMs**, immunoglobulin superfamily cell adhesion molecules; **MS**, multiple sclerosis

* These authors contributed equally to this review.



M. musculus	NCAM	L1 (NgCAM) Neurofascins (155/186) NrCAM	F3/contactin TAG-1/CNTN2 BIG-1/CNTN3 BIG-2/CNTN4 NB-2/CNTN5 NB-3/CNTN6
D. melanogaster	Fasciclin II (FasII)	neuroglian	DCONT
C. elegans	NCAM-1	SAX-7 LAD-2	RIG-6

Figure 1. Structure of the neuronal IgCAM subfamilies reviewed. All subfamilies share common structural characteristics, the Ig-like and the FNIII-like domains. Neuronal IgCAMs can be transmembrane, GPI-linked or secreted. Gene homologies among mice, flies (*D. melanogaster*) and nematodes (*C. elegans*) are also summarized.

mophilic binding) and with other partners (heterophilic partners) either belonging to the same superfamily or not [3, 4].

The roles of IgCAMs have been investigated mainly during development and more recently in the context of the adult nervous system. Their versatility of regulation/expression and multiplicity of interactions adds complexity and goes beyond the already known functions in adhesion and neuritogenesis. In this review we attempt to detail the phenotypes of mice deficient in NCAM, L1/L1-like and contactins and to provide a correlation between these and human neuronal pathologies.

2 The NCAM subfamily

2.1 NCAM

NCAM (neural cell adhesion molecule) was the first CAM identified in the nervous system, where it was shown to mediate adhesion of cells in the retina [5]. It is a surface glycoprotein widely expressed from the onset of neural tube closure until adulthood, on both neurons and glia. It has been implicated in a variety of processes in the brain, including cell growth and migration. The human *NCAM* is mapped to 1q32.1 region. Alternative splicing of the *NCAM* transcript results in three major isoforms of the protein, termed NCAM180, NCAM140 and NCAM120, based on their molecular weights. All three isoforms share identical extracellular structures, consisting of five Ig-like domains and two fibronectin type III repeats (FNIII). However, NCAM180 and 140 isoforms also contain a transmembrane domain, whereas NCAM120 is anchored to the cell membrane via a GPI linkage. The three isoforms have distinct expression patterns and functions in the nervous system. NCAM180 is predominantly expressed on mature neurons and is particularly enriched at sites of cell contact, NCAM140 is localized on developing neurons, mediating growth cone guidance and neurite outgrowth responses. It is also found on glia. NCAM120 is exclusively expressed by glial cells (reviewed in [6]).

NCAM protein carries chains of α-2, 8-linked sialic acid, called PSA (polysialic acid). This rare carbohydrate has not been found on any other recognition molecule and it modifies the functional properties of NCAM, rendering this protein unique among the rest of the Ig superfamily members [7]. Polysialylation of NCAM is strictly regulated during development, underlying the impor-

tance of this moiety for the regulation of many biological functions of NCAM. In particular, PSA-NCAM is found on growing axons and migrating cells during development. Removal of the PSA increases the adhesive properties of NCAM, and reduces the ability of the protein to stimulate axonal growth, and to enhance migration and axonal pathfinding of neurons (reviewed in [8]). Postnatally, expression of the polysialylated form of NCAM is severely down-regulated. In the adult brain PSA-NCAM is only found in areas where neurogenesis occurs, like on neural stem cells of the dentate gyrus and on newborn olfactory neurons of the rostral migratory stream [9], or in areas of the brain that retain synaptic plasticity, like the piriform and entorhinal cortices, the hypothalamus and the thalamus [10].

2.2 NCAM in disease

Generation of *NCAM*-null mice initially revealed that NCAM is not essential for survival and the most evident defect of these animals is the decreased body weight and reduced size of the olfactory bulb, due to the perturbation of neuronal migration towards the bulb region [11, 12]. These animals also show decreased spatial learning [11], in agreement with later studies revealing that these mice have a reduced number of mossy fibers projecting to the hippocampus [13]. Subsequent studies on several NCAM deficiencies in mice have uncovered behavioral deficits of mutant animals like increased inter-male aggression and anxiety, decreased contextual and cued fear conditioning, decreased pre-pulse inhibition and abnormal circadian cycle. Additional defects include hyperlocomotion and stereotypy as well as depression upon conditional inactivation of NCAM function [14].

How exactly the mouse phenotypes of NCAM loss-of function or dysfunction are reflected in human disease is not yet fully understood, although studies in mouse models have shed light on our understanding of the potential roles of NCAM in several human brain disorders. In particular, NCAM has been linked so far to disorders such as schizophrenia, bipolar disorder [15], depression and Alzheimer's disease (AD) [16, 17].

2.2.1 NCAM in schizophrenia and bipolar disorder

All three isoforms of NCAM are secreted in the cerebrospinal fluid (CSF) and the predominant isoform of NCAM in human CSF is NCAM120 [15]. Additionally, soluble forms of NCAM with a molecular mass of 110 kDa have been detected in blood serum [17]. Patients with schizophrenia show increased levels of NCAM isoforms in CFS [18, 19] and blood serum [20]. Postmortem brain studies on such patients have revealed decreased PSA-NCAM expression in the dentate gyrus of the hippocampus, highlighting reduced neurogenesis [21, 22]. Increased expression of the NCAM120 isoform was also observed in the prefrontal cortex, hippocampus and cingulated area [23]. It is worth mentioning that in monozygotic twins, one of whom was schizophrenic, NCAM was detected in increased levels in the CSF, whereas it was not altered in the healthy twin [24]. This observation implies that the pathology of the disease cannot be explained by an abnormality in the NCAM gene itself. In agreement, comprehensive genetic studies did not uncover any structural alterations in the NCAM gene in schizophrenia [25].

However, NCAM is considered to be the fourth locus among the loci that are most susceptible in schizophrenia [26]. So, what is the role of NCAM in the particular disorder? Schizophrenic patients show abnormally enlarged ventricles [27] and this enlargement over time correlates with altering concentrations of NCAM in the CSF [28]. Several studies have shown that increases in the soluble forms of NCAM found in CSF of schizophrenic patients correspond to cleaved fragments of the protein, resulting from the activity of particular metalloproteases, ADAM10 and ADAM17/TACE (reviewed in [29]). Genes encoding for these enzymes also reside in schizophrenia susceptible loci in the genome [26] and their involvement in the disorder increases the complexity of the system even more. Such observations strongly suggest that NCAM alterations in CSF simply reflect the cellular degeneration process of schizophrenia, rather than explaining its neuropathology.

Bipolar disorder and schizophrenia, share some common neuroanatomical characteristics such as ventricular enlargement, decreased temporal lobe volume and disrupted synaptic plasticity, and some common susceptibility genes in humans [30]. *NCAM* has been postulated as such a gene and particular small nuclear polymorphisms (SNPs) from different NCAM regions were associated with bipolar disorders in distinct subpopulations [31, 32]. The soluble form of NCAM120 is elevated in the hippocampus, prefrontal cortex and CSF of individuals with bipolar disorder, and several soluble forms of varying molecular mass have been found to be increased in the hippocampus, similarly to the CSF from schizophrenic patients where soluble forms of NCAM are detected. However, soluble forms found in bipolar disorder patients are different from those in schizophrenic CSF, in that they do not seem to be cleaved from the NCAM protein by metalloproteases. Moreover, the elevat-

ed NCAM120 is probably derived from release of GPI-linked NCAM120 from the plasma membrane [15]. The increase of soluble NCAM forms could imply that its subcellular or synaptic functions are abolished, thus contributing to the pathology of the disorder.

2.2.2 NCAM in depression and anxiety disorders

NCAM has been implicated in depression and anxiety disorders, primarily through mouse models exhibiting symptoms that resemble the human situations. Anxiety disorders, which often precede depression, include several situations such as separation anxiety, social phobia, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, *etc*. Anxiety disorders highly overlap with each other and with depression, stressing out the common mechanisms underlying their pathology [33]. Being brain areas of high synaptic plasticity, the prefrontal cortex and the hippocampus are characterized by increased levels of NCAM expression, where the molecule serves a role in serotonergic and neurotrophic functions. Mouse models of chronic stress, used to study depression and anxiety conditions, exhibit reduced levels of the NCAM140 isoform and increased PSA-NCAM expression in the hippocampus and prefrontal cortex [34]. However, it has been postulated that brain-derived neurotrophic factor (BDNF) is reduced in depressive conditions, increasing the pathology of the disorder. Thus, the elevated expression of PSA-NCAM could reflect the system's compensatory mechanism to overcome BDNF reduction in the hippocampus and prefrontal cortex in depression (reviewed in [29]).

Interestingly, studies on anxiety disorders have shown that mice deficient for NCAM function display increased anxiety in light/dark avoidance testing. Moreover, animals that overexpress the soluble forms of NCAM display decreased excitatory and inhibitory synapses in the prefrontal cortex and amygdala, as a result of decreased growth/branching of the axonal and dendritic arbors, suggesting impaired function of both prefrontal cortex and amygdala due to decreased NCAM interactions [29]. These animals are significantly impaired in contextual and cued fear conditioning, and show increased locomotor activity in open field, resembling the human symptoms of anxiety and providing a way to study the human disorder on its molecular basis.

2.2.3 NCAM in Alzheimer's disease

The pathology of AD reflects on the formation of plaques and tangles in the brain, composed of amyloid, and tau proteins, respectively. The dysregulated production of amyloid, and Tau associated with AD also affects NCAM expression and function. In particular, amyloid, has been shown to directly affect NCAM function *via* reduction of HNK-1, a glycosylation moiety on NCAM that has been implicated in synaptic transmission ([35], reviewed in [29]). Detailed analysis of individual cortical regions of brains with AD revealed a significant decrease in the number of NCAM-expressing neurons in the frontal cortex, but not in the hippocampus or other areas of NCAM expression [36]. While there are conflicting reports on NCAM expression in AD plaques, suggesting a variability of NCAM alterations among individuals with AD, soluble forms of NCAM protein are known to be increased in the CSF of AD patients [17, 37].

Medical treatments used for the disease to date target several molecular pathways. Interestingly, treatment with cholinesterase inhibitors increases PSA-NCAM expression in the hippocampus [38]. Several studies have shown that NCAM cleavage to generate NCAM soluble forms, which are increased in the CSF of AD patients, inhibits the protein's functions on growth and branching of axons and dendrites. There is evidence, however, that surviving neurons in AD reorganize their axons and dendrites, in an attempt to compensate for the loss of neighboring neurons and synapses [39]. Therefore, the increased levels of PSA-NCAM upon treatment might underlie the attempt of surviving neurons to reform lost connections in the brain, balancing the increased levels of soluble NCAM that inhibit growth and synaptogenesis.

Interestingly, peptide derivatives of NCAM are being used in clinical trials as a potential treatment for AD, since NCAM may also serve a neuroprotective role. It has been shown that NCAM can activate a signaling cascade *via* FGFR activation, leading to the phosphorylation of the Tau kinase, GSK3, inhibiting its ability to phosphorylate Tau [40]. The fact that hyperphosphorylation of Tau might be required for the neurotoxic effects in AD exposes the importance of this particular function of NCAM (reviewed in [41]).

3 The L1 IgCAMs subfamily

The L1 family of neuronal adhesion IgCAMs comprises of mouse L1, CHL1 (close homolog of L1, also known as CALL), NrCAM and neurofascins, and their homologs in other species. The proteins consist of six Ig-like domains and four to five FNIII repeats, followed by a cytoplasmic domain that links them to ankyrin and the cytoskeleton (Fig. 1). They are primarily (some of them exclusively) expressed

in the developing and adult nervous system. Work based on interference with protein function in cultured neurons and brain slices, as well as on analysis of knockout mice, showed that L1-CAMs play important roles in axon outgrowth and fasciculation, dendrite guidance, neuronal migration and survival, synaptic plasticity, and regeneration (reviewed in [6, 42]). We limit ourselves here to the most recent loss-of-function studies in animal models, and summarize the literature that relates the disruption in L1 family genes to human pathologies.

3.1 L1

Recent studies investigated the relationship of L1 with two axon guidance systems. A knock-in mouse harboring a novel L1 point mutant, where interaction between L1 and ankyrin is disrupted, shows for the first time a role of L1 in topographic mapping of retinal axons. In this context, L1 appears to interact with the ephrinB/EphB targeting system [43]. L1 functionally and physically interacts with the receptors of the repellent Semaphorin3A, Neuropilin 1 and PlexinA1. Castellani and colleagues [44] showed that FAK-MAPK-dependent signaling downstream of L1 is required for the disassembly of adherent points in growth cones and thus for their collapse in response to Sema3A.

The *Drosophila* homologue of L1, Neuroglian (Nrg), is important for axon guidance and fasciculation [45–47]. Its non-neuronal isoform, also expressed in epithelial and glial cells, is important for the formation of septate junctions, which are functionally, structurally and molecularly related to mammalian paranodal junctions [48]. The analysis of a novel mutant of neuronal Nrg revealed synaptic defects in identified neuromuscular junctions, with a dramatic microtubule reduction, likely to cause the disruption of active zones [49]. Behavioral defects in L1 mutant mice and human patients (see below) could similarly derive from a disruption in synapse formation rather than in axon pathfinding. This seems supported by recent studies on the pre- and post-synaptic role of L1 at the mouse central nervous system (CNS) and neuromuscular junctions [50].

In the nematode *Caenorhabditis elegans*, two L1-related IgCAMs exist: LAD-1/SAX-7 and LAD-2. SAX-7 is required for correct neuronal and axonal positions, *via* interaction with ankyrin, while Lad-2 controls axon pathfinding, *via* interaction with the Sema/Plexin system [51–53]. SAX-7 is also expressed outside the nervous system where it maintains tissue attachment [54, 55]. The worm offers a great opportunity for thorough and fast genetic analysis of L1 interaction partners, both at the level of cytoskeletal elements and signaling pathway.

3.1.1 L1 in disease

3.1.1.1 L1 in the CRASH syndrome

The human homologue of L1 localizes to the telomere of the long arm of the X chromosome in Xq28, where several X-linked mental retardation syndromes have been mapped. Since the first report of mutations in L1 in patients with X-linked hydrocephalus [56], L1 has been clearly related to the so-called CRASH syndrome, a broad-spectrum X-linked neurological syndrome. The acronym stands for corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraplegia and hydrocephalus [57, 58], and it replaces older nomenclatures for L1-associated disorders such as X-linked hydrocephalus/HSAS (hydrocephalus as a result of stenosis of the aqueduct of Sylvius), MASA (mental retardation, aphasia, shuffling gait, and adducted thumbs) syndrome, X-linked complicated spastic paraplegia type I (SPG1) and X-linked agenesis of the corpus callosum (ACC).

Comparison of the defects in CRASH patients to those observed in knock-out L1 mice [59–61] showed similar defects in the development of the corticospinal tract and cerebellar structures, hydrocephalus, and impaired learning [62, 63].

3.1.1.2 L1 in Hirschsprung's disease and the CIIP syndrome

A few patients carrying novel mutations in L1 show X-linked hydrocephalus and Hirschsprung's disease, caused by absence of neural crest-derived ganglion cells in the distal gut, which in turn impairs the neural control of intestinal peristalsis and causes chronic constipation [64–66]. Some, but not all, cases of Hirschsprung's disease correlate with mutations in the RET receptor, implicated in the migration of ganglion cell precursors [67–69]. L1-mediated cell adhesion could be important for the ability of ganglion cell precursors to populate the gut, possibly by modifying the effects of a Hirschsprung's disease-associated gene.

L1 is expressed by migrating ganglion cell precursors in the mouse. Interfering with L1 activity delays neural crest migration *in vitro* and increases the number of neural crest cells excluded from the intestinal ganglion network. L1 knockout mice show a reduction in neural crest cell migration early in development, but the gastrointestinal tract is completely colonized [70]. This supports the hypothesis that the migration of neural crest cells through the developing gut relies on L1 and that mutations in L1 may contribute to the appearance

of Hirschsprung's disease. Mutations of L1 may cause congenital idiopathic intestinal pseudo-obstruction (CIIP), another type of intestinal pseudo-obstruction distension with defects in differentiated Cajal cells in the anterior part of the gut [71]. L1 may thus play a role in the developmental regulation of multiple systems.

3.1.1.3 L1 in the fetal alcohol syndrome

Mental retardation, hydrocephalus, and agenesis of the corpus callosum are observed not only in children with L1 mutations, but also in those affected by fetal alcohol syndrome (FAS). Ethanol inhibits L1-mediated adhesion, but not NCAM140-mediated adhesion, in cultured fibroblasts. Ethanol also inhibits the adhesion of cerebellar granule cells to a monolayer of L1-transfected fibroblasts, but again not to NCAM140-transfected fibroblasts or control cells [72]. On the other hand, ethanol does not alter axon polarization, L1-dependent axon outgrowth or branching, or L1 recycling in axonal growth cones. Ethanol interference with L1 function appears therefore to be dependent on the neuronal context [73].

Given the role of L1 in axonal outgrowth and fasciculation during nervous system development, could L1 reiterate its developmental role in adults following injury, and could one exploit L1 for repair therapy? The role of L1 during repair of spinal cord injuries is still controversial [74–76]. Nevertheless, mice with excitotoxic lesion of the striatum show a behavioral amelioration, after transplantation of L1-transfected embryonic stem cells [77]. Moreover, again in mice, adeno-associated virus-mediated expression of L1 in the glia and neurons of damaged spinal cord promoted functional recovery of the corticospinal tract, possibly by modifying the local environment and inhibiting astrocyte activity at the site of injury [78].

L1 is also expressed outside the nervous system. Its implication in tumorigenesis, which goes beyond the scope of this review, is discussed in [79].

3.2 CHL1

CHL1, or close homolog of L1, is the most recently identified member of the L1-CAM family. Earlier work on the description of CHL1 functions in the nervous system (primarily in axon guidance in the hippocampus and olfactory system, migration and dendritic guidance of cortical neurons, and behavior) is reviewed in [6]. More recent work has highlighted an interaction of CHL1 with the Semaphorin/Neuropilin signaling system [80, 81]. In particular, CHL1 and Neuropilin1 appear to play a role in the guidance of thalamocortical axons in the ventral telencephalon [81]. CHL1, in concert with NB-3 (a GPI-linked IgCAM; see next section), guides apical dendrite orientation in the cortex. The protein tyrosine phosphatase PTP alpha acts downstream of CHL1/NB3 in this process [82]. Finally, CHL1 seems to dictate the synaptic targeting of stellate interneurons onto dendrites of Purkinje cells in the cerebellum: CHL1 is expressed by both stellate cells and the scaffolding glia onto which stellate cells grow towards the dendrites of Purkinje cells [83]. This last function is somewhat reminiscent of that of another L1-CAM, Neurofascin, which guides synaptic formation of another type of interneuron to a different membrane domain of Purkinje cells (see below).

3.2.1 CHL1 in disease

Human CHL1 maps to chromosome 3p26, a region identified as a potential site of susceptibility genes for schizophrenia [84]. Arinami and colleagues [85] reported an association between a missense polymorphism in CHL1 and schizophrenia.

3.2.1.1 CHL1 in the 3p syndrome

Deletion of a terminal segment of the short arm of one chromosome 3 (3p25→pter) results in the 3p syndrome, characterized by multiple congenital anomalies and mental retardation. CHL1 is one of the several deleted genes. Given the known role of its mouse homolog in brain development and function, and given its dosage sensitivity [86, 87], CHL1 has been proposed as one of the genes most likely responsible for the mental retardation of the 3p syndrome [88, 89].

3.3 NrCAM

NrCAM is expressed on growing axons. Consistently, NrCAM-deficient mice show defects in axon guidance, including that of commissural axons in the spinal cord and of retinal axons in the visual system. Mutant mice also display defects in the development of the hippocampus, cerebellum and other brain regions, at the level of survival, neurite growth and neural circuit formation (reviewed in [6]). In these contexts, its functions partially overlap with those of L1 and CHL1 [87, 90]. NrCAM (but not the L1-CAMs) interacts with synaptic proteins SAP90/PSD95 and SAP97, and localizes to the synapse in photoreceptor terminals of the mammalian retina [91]; a synaptic function for NrCAM is reminiscent of that of the L1-CAM homologue Nrg in flies (see above).

In myelinated fibers (both in the CNS and the peripheral nervous system, PNS), the axonal membrane is organized in specialized domains, each

primarily characterized by the type of ion channels present and the type of relationship of the axolemma with the myelinating glial cells (oligodendrocytes in the CNS and Schwann cells in the PNS). Such axonal organization is crucial for the fast saltatory conduction of action potentials (reviewed in [92, 93]). These domains are: the nodes of Ranvier, where sodium channels cluster; the paranodal regions, which are tightly attached to the myelinating glial cells *via* specialized paranodal septate-like junctions; the juxstaparanodal regions, adjacent to the paranodes where potassium channels cluster; and the internodes.

NrCAM localizes to the nodes of Ranvier in myelinated fibers in the PNS but not the CNS [94], where it colocalizes and interacts with ankyrin, sodium channels and Neurofascin [95]. The clustering of sodium channels at the node of Ranvier is delayed upon interference with NrCAM function [96, 97]. Gliomedin is a Schwann cell-specific molecule expressed at the edges of Schwann cells; it binds both NrCAM and Neurofascin and appears to dictate the site of formation of nodes of Ranvier [98].

3.3.1 NrCAM in disease

3.3.1.1 NrCAM in autism

Human NrCAM maps to 7q31.1, a susceptibility region for autism. Indeed, polymorphisms in NrCAM have been recently linked to autism [99–101]. Interestingly, these polymorphisms are detected in the non-coding regions of the NrCAM gene, and could therefore affect its expression (levels, timing or tissue/cell specificity), but not the biochemical properties of its product. Although NrCAM is important for the development and function of the nervous system, it is difficult at the moment to relate the phenotypes observed in autistic patients (most likely carrying hypomorphic mutations in NrCAM) to those of knockout mice. Perhaps the generation of transgenic mice carrying mutations equivalent to those reported in human patients may help in understanding the molecular and cellular bases of the human disorder.

3.3.1.2 NrCAM in addiction vulnerability

The same chromosomal region is associated with substance abuse vulnerabilities (addiction vulnerability). A role for NrCAM in addiction is supported by several lines of evidence: NrCAM is a drug-regulated gene; it is expressed in neurons associated with reward and memory; and NrCAM mutant mice show reduced opiate- and stimulant-conditioned place preferences [102, 103]. Interestingly, protein tyrosine phosphatase receptor type beta (PTPRB), a known interactor of NrCAM, may also be linked to drug abuse [102].

3.4 Neurofascins

Neurofascins (Nf) are IgCAMs with close resemblance to L1; they are implicated in neurite development (reviewed in [104, 105]) and the organization of specialized axon membrane domains in myelinated fibers. We focus here on the latter function. Neurofascins exist in two isoforms, Nf155 and Nf186, obtained by differential splicing. Both isoforms are expressed on myelinated fibers in the CNS and PNS. Nf155 is produced by glial cells (oligodendrocytes in the CNS and Schwann cells in the PNS) and localizes to the paranodes of myelinated fibers, where it forms part of the tripartite paranodal complex including Caspr/paranodin and the GPI-linked IgCAM Contactin [106, 107]. Nf186 is the neuronal isoform and localizes to the nodes of Ranvier of axons, where it complexes with sodium channels. In a Nf null background (thus lacking both isoforms), two phenotypes are observed in myelinated fibers in the whole nervous system: (i) sodium channels are not clustered in the nodes, and (ii) paranodes are disrupted. $Nf^{-/-}$ mice die at postnatal day (P) 7 [107]. Cell type-specific-rescue experiments have shown that glial Nf155 and neuronal Nf186 contribute to the organization of axon domains, and in particular to the clustering of sodium channels, in different ways in the CNS and PNS [94, 107]. In a Nf null background, expression of Nf186 in neurons can rescue the nodal complex of sodium channels, while the paranodes (lacking any Nf) do not form properly: the Nfasc155/Caspr/Contactin paranodal complex is disrupted due to lack of Nf155. This holds true both for the CNS and PNS. $Nf^{-/-}$ mice with neuronal Nf186 expression survive their $Nf^{-/-}$ littermate and die at P18–19 [94]. In the converse experiment, expression of Nf155 in glial cells of $Nf^{-/-}$ mice does not rescue the nodal phenotype in the PNS; mice die at P7 as with $Nf^{-/-}$ mice [107]. In striking contrast, Nf155 expression is able to rescue the paranodal complex as well as the nodal clustering of sodium channels and other proteins of the nodal complex in the CNS [94]. The discrepancy between PNS and CNS could be attributed to differences in the molecular composition and assembly strategy of nodes in the CNS and PNS: for example, NrCAM is found in PNS nodes, but not in the CNS [94].

In addition, Nf155 (*via* the Nf155/Caspr/Contactin adhesion complex) promotes the migration of oligodendrocyte processes on CNS axons, which is required for effective myelination [94].

Finally, Nf is also expressed in another specialized axon domain, the initial segment. It has been shown that a G-ankyrin-based subcellular gradient of Nf186 directs innervation of GABAergic interneurons (basket cells) onto the initial axon segment of Purkinje cells [108].

3.4.1 Neurofascins in disease

3.4.1.1 Nf in multiple sclerosis

Axoglial contacts, and paranodes in particular, can be severely affected in multiple sclerosis (MS), a de-myelinating inflammatory disease that impairs nerve conduction and causes severe chronic disabilities [109]. Perturbation of Nf function has been linked to MS in a number of recent studies. Disruption of Nf localization is observed in both animal models of MS and in samples from MS patients [110–112]. It seems that Nf defects may precede, and possibly contribute to, the appearance of myelin defects in MS. Autoantibodies against Neurofascin (recognizing both isoforms) have been identified in the sera of patients with MS. It has further been shown, with *in vitro* assays and the use of an animal model of MS, that such autoantibodies can target nodes of Ranvier and trigger an inflammatory response (a complement reaction), causing further axonal injury and worsening the clinical profile. The presence of autoantibodies against Nf in MS patients may contribute to the pathology of the disease [113]. This observation raises the possibility that autoantibody against other axo-glial contact proteins may contribute to MS pathology as well.

4 The Contactin subfamily

The contactin subgroup of the Ig superfamily consists of GPI-anchored proteins that are involved in, among other processes, nervous system patterning. F3/contactin, TAG-1/axonin/CNTN2, BIG-1/ CNTN3, BIG-2/CNTN4 and the more recently identified NB-2/CNTN5 and NB-3/CNTN6 are the vertebrate counterparts of the subfamily. In *Drosophila melanogaster* and *C. elegans* there is one member of the subgroup, named DCONT and RIG-6, respectively. All the members have at least one isoform that is comprised of six Ig-like domains and four FNIII-like domains.

The vertebrate contactins are expressed mainly in the nervous system displaying a distinct and partially overlapping pattern [114]. Among them, TAG-1 starts to be expressed earlier in development, while the rest are highly expressed postnatally. All these molecules, apart from BIG-1 that has not been extensively studied, have been shown to be involved in various developmental processes of the rodent nervous system, and some of them seem to be correlated with known neurological disorders in humans.

4.1 F3/Contactin

Contactin together with TAG-1 are the most well characterized members of the homonymous subgroup. *Contactin* has been mapped to the locus 12.q11-q12, transcribing two alternatively spliced isoforms [115]. Its expression begins towards the end of embryonic life, increases postnatally, and is maintained to adulthood. Contactin is the most widely expressed molecule of the subfamily, and is localized mainly to the cerebellum (during development), hippocampus, neocortex and hypothalamus [114, 116]. *Contactin* mutant mice survive until P18, displaying severe defects in the development of the cerebellum [116].

Several binding partners of contactin have been identified so far, including the IgSF members L1, NrCAM and neurofascin, the receptor protein tyrosine phosphatase RPTPb and its secreted splice variant Phosphacan, as well as the extracellular matrix molecules Tenascin R and β1 integrins. All these interactions have been shown to regulate axon growth or guidance, as shown from *in vitro* studies (reviewed in [117]).

Contactin is implicated in one pathway that leads to oligodendrocyte maturation from oligodendrocyte precursor cells through Notch signaling. Specifically, its *trans* interaction with the EGF repeats of Notch, triggers the γ-secretase dependent translocation of Notch intracellular domain (NICD) and the sequential up-regulation of the myelin-related protein MAG [118]. Moreover, contactin interactions with another series of molecules are fundamental for the organization of myelinated fibers. Initially, biochemical studies have reported the lateral (*cis*) interaction of contactin with the neurexin ortholog Caspr [119] in the paranodal junctions of the peripheral and central myelinated fibers [120]. Furthermore, the study of *contactin*-deficient mice revealed the disrupted formation of the paranodal septate-like axon-glia interactions [121]. Contactin ablation impedes Caspr trafficking to the paranodal axolemma where the former interacts in *trans* with the IgSF molecule Nf155 [122]. In addition, Shaker-type potassium channels Kv1.1 and Kv1.2 are mislocalized. In the CNS, contactin, which is also present in the nodes albeit in lower concentration, interacts with sodium channels that are clustered there [117, 120, 121, 123]. This fact indicates that contactin is involved in both oligodendrocyte development and myelination. It is really

impressive that a conserved type of multimeric complex, essential for septate junction assembly, has been identified in *Drosophila*, where D-contactin interacts in *trans* with the neurofascin and Caspr orthologs, neuroglian and neurexin IV [124].

4.1.1 Contactin in disease

Although the phenotype of *contactin*-deficient mice is the most severe among the mutants of the other members of the subgroup, there is no clear correlation of the gene with a human disorder. Regardless of its essential role in the assembly of axon-glia interactions, contactin has not been directly correlated with impaired myelination in humans. However, it has been shown that in demyelinated centers of brain and spinal cord tissue from patients with long-standing MS, there is absence of Caspr immunoreactivity [125]. Since contactin regulates Caspr trafficking, it could play an intermediate role in the pathogenesis of the disease.

4.2 TAG-1/CNTN2

TAG-1 is expressed mainly developmentally, displaying a dynamic pattern that includes commissural fibers and motor neurons of the spinal cord, the dorsal root ganglia (DRG), cerebellum, hippocampus and corticofugal fibers (reviewed in [3]). *In vitro* and *in vivo* studies have revealed the involvement of TAG-1 in axon outgrowth, fasciculation and neuronal migration [126–132]. TAG-1 and contactin, share many common properties in the context of their binding partners. Specifically, TAG-1 has been shown to interact with L1, NrCAM [133, 134], phosphacan, Tenascin C and RPTPb [135].

Additionally, TAG-1 localizes to the juxtaparanodal regions of the myelinated fibers of the PNS and CNS, where it forms a complex with the neurexin ortholog Caspr2, a critical connection for the clustering of the Shaker-type potassium channels [119, 136–138]. TAG-1 has been recently identified as a ligand of the amyloid precursor protein (APP) that induces a γ-secretase-dependent release of the APP intracellular domain (AICD) and sequentially negatively regulates neurogenesis through the activation of unknown genes [132]. Consistent with these results, the authors have also shown that there is extended neurogenesis in neural precursor cells isolated from double *TAG-1/APP* knockout mice. It is already known that in animal models of AD, impaired neurogenesis and elevated concentration of AICD is observed [139]. Since TAG-1/APP signaling has been shown to influence both processes, it is possible that TAG-1 is involved in AD pathogenesis [140].

4.2.1 TAG-1 in disease

TAX-1, the human ortholog of TAG-1, is mapped to the 1q32.1 locus [141, 142]. Albeit TAG-1 has not been reported to be involved in a human disease, its gene locus has been associated with several disorders. The 1q32 chromosomal region is linked, among others, to Van der Woude syndrome that is characterized by defects in craniofacial development, to Usher syndrome type II, which is related to retinitis pigmentosa and to several malignant gliomas [143–145]. Furthermore, its binding partners Caspr2 and voltage-gated potassium channels (VGKC) have been implicated in severe mental disorders [146–149]. In agreement with these properties, *TAG-1*-deficient mice have impaired learning and memory as well as sensory and motor dysfunction that could be explained by the abnormal juxtaparanodal organization, shortening of internodes and altered VGKC and Caspr2 levels [150].

4.3 BIG-1/CNTN3

BIG-1 is mapped to the 3p26 region and has two alternative variants. Its expression pattern is quite restricted and includes cells of the cerebellum, hippocampus, olfactory bulb and a few nuclei. Apart from the finding that BIG-1 interacts with APP in chick [151] and promotes axon outgrowth *in vitro* [152], no other information is available for this contactin. Although it is mapped in the critical region for the 3p syndrome in humans (see 4.4.1.1), it has not been proposed to contribute to any disorders.

4.4 BIG-2/CNTN4

BIG-2 has two alternative spliced isoforms; the first is widely expressed in many tissues, while the other (*CNTN4A*) is restricted to the brain. Recombinant protein is able to promote neuron outgrowth *in vitro* [114, 153]. A recent study [154] reported that BIG-2 is a crucial adhesion molecule for the olfactory axon convergence to target stimuli. In *BIG-2*-deficient mice, many olfactory neurons that selectively express this gene project to ectopic destinations in the olfactory bulb. Finally, BIG-2, like BIG-1, has been shown to interact with APP and NgCAM, the L1 ortholog in chick, regulating *in vitro* axon outgrowth [151].

4.4.1 BIG-2 in disease

4.4.1.1 BIG-2 in the 3p syndrome

BIG-2 is mapped to chromosome 3p26-p25, in a region that is connected to the rare non-contiguous 3p syndrome. Imbalance of the telomeric sequence of the short arm of the chromosome 3 causes this gene disorder that is characterized by mental and

growth retardation and dysmorphic features. State and colleagues [155] identified a 10-year old child that carried a *de novo* balanced translocation involving chromosomes 3 and 10 (46, XY, t[3;10][p26;q26]). In this study, they showed that the translocation disrupted exclusively the 5′UTR of the mature *CNTN4* mRNA, while other genes of this region that could be implicated in the 3p syndrome, like *CHL1* and *CRBN*, remained intact. In another clinical report [156], loss of both *CNTN4* and *CRBN* has been suggested to cause the 3p syndrome, while loss of CHL1 has been indicated to have an additional effect.

4.4.1.2 BIG-2 in autism spectrum disorder

Interestingly, it has also been proposed that interruption of the *CNTN4* gene in three subjects caused autism spectrum disorder (ASD), a developmental disorder of the nervous system characterized by impaired social interaction, verbal and non-verbal communication and aberrant activities and patterns of behavior [157]. However, these three patients did not present any 3p syndrome symptoms. Furthermore, a polymorphism in the *BIG-2* gene was initially proposed to be responsible for the appearance of spinocerebellar ataxia SCA16 in a Japanese population, although it was shown later from the same group that the disorder was caused by a deletion in the *ITRP1* gene [158]. Nevertheless, *BIG-2* still remains a candidate gene implicated in human mental retardation disorders. Behavioral and detailed histological studies have not been published so far to correlate defects in mutant mice and the implicated syndromes in humans.

4.5 NB-2/CNTN4

NB-2 has two alternative spliced variants and is expressed in high levels in the amygdala and occipital cortex, resembling mostly the pattern of *BIG-1* in humans [159]. In concordance with other contactins, it can promote axon outgrowth *in vitro* [160]. Generation of *NB-2*-deficient mice revealed that this gene is not essential for the development of the brain architecture, since pathological abnormalities have not been observed. However, mutant mice responded aberrantly to acoustic stimuli [161]. Although there is no clinical study that correlates NB-2 with a disorder, it is interesting that this gene is mapped to 11q21-q22.2, a region that includes several genes responsible for schizophrenia and other neuronal disorders.

4.6 NB-3/CNTN5

The murine *NB-3* gene starts to be expressed clearly after birth, with a peak of expression at P7 [162]. Its expression declines in the cortex later, but it remains in the cerebellum until adulthood. The *NB-3* gene has two alternative isoforms and is mapped to the 3p26-p25 region close to *BIG-2* [163]. All the known information about NB-3 comes from animal models. More specifically, it has been shown that *NB-3*-deficient mice, which appear normal, have impaired motor coordination that is not due to a defect of the cerebellar synaptic transmission [164]. Moreover, the same mice show abnormal apical dendrite projections of deep layer pyramidal neurons of the visual cortex. It seems that the interaction of NB-3 with CHL1 and protein tyrosine phosphatase α (PTPα) potentially regulates this process [82]. In accordance with the Contactin/Notch interaction that promotes oligodendrocyte maturation, it has been shown that NB-3/Notch binding through the EGF repeats of the latter, direct oligodendrocyte differentiation from neural precursor cells and oligodendrocyte precursor cells. *Trans* interaction of the two molecules triggers the γ-secretase-dependent NICD nuclear translocation and the recruitment of Deltex1, resulting in the up-regulation of myelin-related proteins [165, 166].

Despite the fact that this gene is included in the critical region for the 3p syndrome, similarly to *BIG-2* and *BIG-1*, there is no evidence of its implication in any neurological disorders.

It is intriguing that contactins using the same binding partners, or at least same categories of binding partners, cooperate to regulate essential processes of the nervous system. Interactions of contactin resemble those of TAG-1 concerning the extracellular matrix components and IgSF molecules, as well as the complex formation in the paranodes and juxtaparanodes, respectively. Contactin and NB-3 bind to Notch, a procedure that leads to oligodendrocyte maturation. Finally BIG-1, BIG-2 and TAG-1 interact with APP. A speculation could be that, at least in some cases, one contactin could compensate the disruption of another, thus making a straightforward connection of a contactin to a disease difficult to postulate. It is intriguing that in *Drosophila*, when the single contactin is ablated, the flies die. In the latter case the complex that is formed is, once again, evolutionary conserved, resembling that of myelinated fibers in mammals [124].

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Table 1. Summary of the mouse phenotypes due to neuronal IgCAM deficiency/dysfunction and correlation to human disease

IgSF members	Mouse phenotypes	Link to human disease
NCAM subfamily		
NCAM/PSA-NCAM	Decreased body weight / Small olfactory bulb / Decreased spatial learning / Reduced projections of mossy fibers in the hippocampus / Increased anxiety / Increased inter-male aggression / Decreased contextual and cued fear conditioning / Decreased pre-pulse inhibition / Abnormal circadian cycle / Hyperlocomotion / Stereotypy	Schizophrenia Bipolar disease Depression Anxiety disorder Alzheimer's disease
L1 subfamily		
L1-CAM	Corticospinal, thalamocortical and callosal axons defects / Small hippocampus / Abnormal cerebellar development / Defective spatial learning and sensorimotor gating	CRASH syndrome Hirschsprung's disease Fetal alcohol syndrome CIIP syndrome
CHL1	Defects in attention, exploratory behavior and sensory gating / Alterations in stress and anxiety, sociability and aggression / Defective lamination of cortical neurons / Guidance errors of hippocampal mossy fibers and olfactory neurons	3p syndrome Schizophrenia
NrCAM	Guidance defects of spinal commissural, retinal and anterior commissural axons / Abnormal cerebellar development / Lens fiber abnormalities / Defects in sodium channel clustering at the nodes of Ranvier	Addiction vulnerability Autism
Neurofascin	Defective myelination	Multiple sclerosis
Contactins		
F3/contactin	Defective myelination	Not identified
TAG-1/CNTN2	Impaired learning and memory / Sensory and motor dysfunction / Abnormal juxtaparanodal region of myelinated fibers / Shortening of internodes on myelinated fibers / Smaller lateral reticular nuclei	Not identified
BIG-1/CNTN3	No animal model	Not identified
BIG-2/CNTN4	Ectopic projections of olfactory neurons	3p syndrome Autism spectrum disorder (ASD)
NB-2/CNTN5	Aberrant response to acoustic stimuli	Not identified
NB-3/CNTN6	Impaired motor coordination / Abnormal projections of deep layer pyramidal neurons of the visual cortex	Not identified

5 Concluding remarks

Up to now, numerous IgCAMs have been identified and studied in many model systems. We have focused here on the functions of three well-studied subfamilies of the IgCAMs, notably the NCAM, L1 and contactin subfamilies, and we have reviewed studies that link members of these subfamilies to neuronal pathological conditions in animal models and humans. A summary of phenotypes due to neuronal IgCAM deficiency/dysfunction and correlation to human disease is given in Table 1. The challenge now is to identify the exact mechanism by which several IgCAMs contribute to the pathology of neuronal disorders. The elucidation of these pathways will allow the development of therapies for major diseases like schizophrenia, depression, MS, AD disease, autism, etc.

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Domna Karagogeos is Professor at the Medical School, University of Crete and a Researcher of the Institute of Molecular Biology and Biotechnology, IMBB-FORTH, in Iraklio, Crete, Greece. She received her PhD from Harvard University, and did her postdoctoral research at Columbia University, New York in the lab of Tom Jessell. She has run an independent lab in Crete since 1991, working on developmental neurobiology in vertebrate and invertebrate model systems.

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