Special Focus: Molecular and Cellular Events Controlling Neuronal and Brain Function and Dysfunction

Contactins

Emerging key roles in the development and function of the nervous system

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Abbreviations: Ig, immunoglobulin; GPI, glycosylphosphatidylinositol; RGC, retinal ganglion cell; RPTPβ, receptor-type protein tyrosine phosphatase β; APP, amyloid precursor protein; P, postnatal day; PTPα, protein tyrosine phosphatase α

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Contactins are a subgroup of molecules belonging to the immunoglobulin superfamily that are expressed exclusively in the nervous system. The subgroup consists of six members: contactin, TAG-1, BIG-1, BIG-2, NB-2 and NB-3. Since their identification in the late 1980s, contactin and TAG-1 have been studied extensively. Axonal expression and the neurite extension activity of contactin and TAG-1 attracted researchers to study the function of these molecules in axon guidance during development. After the exciting discovery of the molecular function of contactin and TAG-1 in myelination earlier this decade, these two molecules have come to be known as the principal molecules in the function and maintenance of myelinated neurons. In contrast, the function of the other four members of this subgroup remained unknown until recently. Here, we will give an overview of contactin function, including recent progress on BIG-2, NB-2 and NB-3.

Introduction

It has been well documented that cell adhesion/recognition molecules of the immunoglobulin (Ig) superfamily play a crucial role in the formation and maintenance of the nervous system. They comprise a large number of members and are classified into subfamilies according to numbers of Ig-like and fibronectin III-like domains. Among them, contactin and TAG-1 have been extensively studied for the last two decades and implicated in key developmental events, including neural cell adhesion and migration, neurite outgrowth and fasciculation, axon guidance and myelination (reviewed in refs. 1 and 2). Contactin and TAG-1 show high sequence similarity and share structural features. Based on their homology, BIG-1, BIG-2, NB-2 and NB-3 were identified and classified in a subfamily with contactin and TAG-1. All the members consist of six Ig-like and four fibronectin III-like domains that are anchored to the membrane by glycosylphosphatidylinositol (GPI) (Fig. 1). Then, six members of the contactin subfamily are now referred to as contactin-1 to 6. Over the recent years, further analyses of expression and function of molecules belonging to the contactin subfamily, including BIG-2, NB-2 and NB-3, have been performed using individually gene-deficient mice. Here, we summarize the expression and function of members of the contactin subfamily including recent progress.

Contactin-1 and TAG-1/Contactin-2

Contactin-1 was purified and identified in the late 1980’s by three groups, as contactin or F11 from chicken3,4 and as F3 from mouse.5 Rat TAG-1 and its chick orthologue axonin-1 were identified during the same time period.6,7 Later, a human orthologue of TAG-1 was termed TAX1.8 Now we also refer to TAG-1 as contactin-2.
Expression of contactin-1 and TAG-1/contactin-2 during neural development. TAG-1 expression starts early in development, while expressions of other contactins become apparent after birth. During the embryonic development of the nervous system, TAG-1 expression is regulated in a spatio-temporal pattern in a subpopulation of neurons. TAG-1 is transiently expressed in commissural fibers and subsets of neurons in the spinal cord, the dorsal root ganglia and the retinal ganglion cells (RGCs), as well as in cortical fugal fibers and tangentially migrating neurons that form several precerebellar nuclei. TAG-1 has been implicated in the tangential migration of caudal medulla neurons and cortical interneurons.14,15 In the cortex, GABA-containing interneurons originate primarily in the medial ganglionic eminence of the ventral telencephalon and follow tangential migratory routes to reach the dorsal telencephalon. Migration of these neurons occurs along the TAG-1-expressing axons of the developing corticofugal system. Blocking TAG-1 function with anti-TAG-1 antibodies or soluble TAG-1 protein markedly reduces GABAergic neurons in the cortex, suggesting that TAG-1 is involved in neuronal migration.14 However, migration of GABAergic interneurons is normal in TAG-1-deficient mice.16 These results suggest that TAG-1 may act as a migration cue but is dispensable for cortical interneuron migration, where other molecules may compensate for the absence of TAG-1. In the caudal medulla, neuronal populations destined to form several precerebellar nuclei are generated by the rhombic lip. They gather into the olivary and superficial migratory streams and migrate tangentially around the hindbrain to reach their final position. These migrating cells express TAG-1. Blocking TAG-1 function alters superficial migration.15 Though superficial migration is observed in TAG-1-deficient mice, a significant proportion of the cells in the superficial stream die during migration, which reduces the size of the lateral reticular nuclei.16 Therefore, TAG-1 function is required for survival of neurons in some precerebellar nuclei. In the optic nerve, TAG-1-deficient mice displays anomalies in the axonal caliber of RGCs, associated with an abnormal organization of the astroglial network.17 This result indicates that TAG-1 is essential for the normal structure of RGC axons and their surrounding glial cells.

In the postnatal cerebellum, TAG-1/contactin-2 is transiently expressed on premigratory granule cells in the inner part of the external granule cell layer,9 whereas contactin-1 is expressed on migrating granule cells.18-20 During granule cells migration, contactin-1 changes its cellular distribution, as it is downregulated on the cell bodies and remains expressed on axonal extensions within the molecular layer.19 Contactin-1 is also expressed in the axons and cell bodies of Golgi cells and mossy fibers.18 Granule cell axon guidance and dendritic projections from granule and Golgi cells are defective in contactin-1-deficient mice, demonstrating that contactin-1 controls axonal and dendritic interactions between cerebellar interneurons.20 In contrast, no gross morphological abnormalities are detected in the cerebellum of TAG-1-deficient mice.21 On the other hand, transgenic mice in which contactin-1 expression is driven by TAG-1 gene regulatory sequences, display a drastic phenotype in which the size of the cerebellum is markedly reduced during the first two postnatal weeks but subsequently recovers.22 These observations indicate that proper expression of contactin-1 and TAG-1 is essential for normal cerebellar morphogenesis.

Roles of contactin-1 and TAG-1/contactin-2 in myelinated fibers. Contactin-1 and TAG-1/contactin-2 have been identified as components of specialized domains of myelinated fibers (Fig. 2A).23-27 Myelinated axons can be differentiated into distinct structural, molecular and functional domains. These domains include the nodes of Ranvier, the paranodes, the juxtaparanodes and the internodal regions.

The nodes of Ranvier are short, regular interruptions in the myelin sheath. The voltage-gated sodium channels that are responsible for action potentials during saltatory conduction are concentrated at these nodes. Voltage-gated sodium channels are heterooligomers consisting of a pore-forming α-subunit and at least one auxiliary β-subunit. The β-subunits of sodium channels increase functional expression and modulate gating of the α-subunit, and also act as cell adhesion molecules.28 The extracellular domains of these β-subunits contain a single Ig-like domain. The β2-subunit shows homology with contactin-1,29 and the β1-subunit binds to contactin-1.30 Association with contactin-1 enhances cell surface expression of Na+ channels.30-32 The expression of Na+ channels is markedly reduced in the optic nerve of contactin-1-deficient mice.33 The nodes of Ranvier are flanked by the paranodes, which regulate junctional attachment between axonal and glial membranes. Contactin-1 is found on the axolemma at the paranode where it interacts with contactin-associated protein (Caspr, also known as paranodin)34-37 and neurofascin-155 (NF-155), a glial isoform of neurofascin.38,39 Caspr is a member of the Caspr family, a subgroup of the neurexin family, that consists of five molecules (Caspr, Caspr2, Caspr3, Caspr4 and Caspr5).34,40,41 Contactin-1 binds to Caspr in cis34 and their interaction is essential for Caspr sorting from the endoplasmic reticulum to the plasma membrane.42 Association of contactin-1 and Caspr during biosynthesis results in cell surface expression of low molecular weight, high-mannose glycoforms of contactin-1 and Caspr.33,44 A non-conventional Golgi-independent pathway may be implicated in this process. The Pro-Gly-Tyr repeats in the extracellular domain of Caspr, which are responsible for endoplasmic reticulum retention of Caspr, might govern contactin-1 chaperoning of Caspr.39 Moreover, the high-mannose glycoform of contactin-1, which is expressed in association with Caspr, strongly binds NF-155, its glial partner at paranodes.39 Contactin-1, Caspr and NF-155 are all essential for the formation of the paranodal junction. Deficiencies in any of these proteins produces disorganization of the paranodal junctions and reduces nerve conduction velocity.45-47 Intracellular transport and surface expression of Caspr are impeded and Caspr expression at the paranode is abolished in contactin-1-deficient mice.45 Likewise, contactin-1 can not be detected in the paranodes in Caspr-deficient mice.46 Although NF-155 is still detectable at the paranodes in the absence of the contactin-1-Caspr complex,45,46 absence of NF-155 at the paranodes causes the loss of both contactin-1 and Caspr from the paranodal junction.37 The juxtaparanode resides just beyond the innermost paranodal junction next to the internode. At the juxtaparanodal axolemma, Shaker-type K+ channels colocalize with Caspr2, the second member of the Caspr family,40 and TAG-1/contactin-2,48 which is also present in the glial membrane.48,49 TAG-1 can associate in cis with Caspr2 and in trans with itself such that TAG-1 and Caspr2 form a complex consisting of an axonal TAG-1/Caspr2 heterodimer and
Figure 2. The interactions of contactins in a variety of tissues/cells/compartments. Contactins are drawn in blue, and other molecules are in green. (A) The molecular complexes in the myelinated nerves. (B) Interactions of contactins with molecules of the L1 family and NCAM. (C) Interactions of contactins with PTPα. (D) Interactions of contactins with Notch and molecules of the APP family.
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a glial TAG-1. This complex is required for the clustering of Shaker-type K channels at the juxtaparanode. In addition, it was shown that TAG-1 directly interacts with Shaker-type K channels. A TAG-1 or Caspr2 deficiency disrupts enrichment of Shaker-type K channels in this region.

Localization of contactin-1 and TAG-1/contactin-2 at synapses. Contactin-1 is localized at synaptic sites as investigated at the electron microscopic level. Long-term depression is impaired in the hippocampus of contactin-1-deficient mice. Molecular analyses using the contactin-1-deficient mice indicate that contactin-1 is essential for the synaptic targeting of Caspr and for the proper distribution of receptor-type protein tyrosine phosphatase β (RPTPβ)/phosphacan. On the other hand, deletion of the Caspr gene has no effect on synaptic transmission and plasticity. These results indicate that contactin-1 plays an important role in synaptic plasticity independent of its association with Caspr, on the different molecular mechanism from the paranodal junctions of myelinated nerves. Subcellular fractionation of rat brain homogenate revealed that TAG-1/contactin-2 is also present in the synaptic plasma membrane along with Caspr2, a binding partner of TAG-1 at the juxtaparanodal region of the myelinated axon. In addition, immunohistochemical analyses showed that both NB-2/contactin-5 and NB-3/contactin-6 are colocalized with markers for glutamatergic synapses at the superior olivary complex of the auditory system and the parallel fibers of the cerebellum, respectively (our unpublished results). These observations suggest that contactins might generally play an essential role in synaptic physiology.

BIG-1/Contactin-3 and BIG-2/Contactin-4

BIG-1 and BIG-2 were identified by PCR cloning with degenerate primers based on homologous amino acid sequences in contactin-1 and TAG-1/contactin-2. BIG-1 was also described as plasmacytoma-associated neuronal glycoprotein (PANG). Recently, a chick orthologue of BIG-2 was identified as a binding partner of amyloid precursor protein (APP).

BIG-1/contactin-3 is abundantly expressed in the adult brain. Expression of BIG-1 is uniquely restricted to subsets of neurons, such as Purkinje cells of the cerebellum, granule cells of the hippocampal dentate gyrus, and neurons in the superficial layers of the cerebral cortex. Little more about BIG-1 has been reported so far.

BIG-2/contactin-4 expression in the olfactory system. BIG-2/contactin-4 expression in mice increases after birth and reaches a maximum in adulthood. BIG-2 is expressed in different subsets of neurons in various brain regions, including the olfactory system. Recently, BIG-2 was identified as an axon guidance molecule that mediates proper neuronal wiring in the mouse olfactory system. In the olfactory system, individual olfactory sensory neurons express only one odorant receptor gene. And olfactory sensory neurons expressing the same odorant receptor converge their axons onto a specific set of glomeruli in the olfactory bulb. BIG-2 is expressed in the glomerular array of the olfactory bulb with a mosaic pattern overlapping with but distinct from other axon guidance molecules, such as Kirrel2 and ephrin-A5. In BIG-2-deficient mice, olfactory sensory neurons expressing the same odorant receptor aberrantly project to multiple glomeruli. These results suggest that BIG-2 is crucial for the formation and maintenance of odor map in the olfactory bulb.

NB-2/Contactin-5 and NB-3/Contactin-6

NB-2 and NB-3 were isolated by our group using a strategy similar to that described for BIG-1 and BIG-2. A chick orthologue of NB-2 has been described as FAR-2. NB-2 and NB-3 are exclusively expressed in the central nervous system.

NB-2/contactin-5 expression in the developing auditory system. Expression of NB-2/contactin-5 becomes apparent after birth and reaches a maximum around postnatal day (P) 14. NB-2 mRNA is expressed in highly restricted brain regions, the auditory system in particular. Immunohistochemistry using an anti-NB-2 monoclonal antibody revealed that at P7, NB-2 is expressed in all areas of the auditory system. NB-2-deficient mice have no gross abnormalities but they are less sensitive to the audiogenic seizure susceptibility test and express less c-Fos after audiogenic seizure susceptibility induction and pure-tone stimulation than wild-type mice. We measured the auditory brainstem response to examine whether NB-2-deficient mice are hard of hearing. Auditory brainstem response thresholds did not differ significantly between NB-2-deficient and wild-type mice, indicating that NB-2-deficient mice are not hard of hearing. However, auditory brainstem response wave latencies tend to be delayed in NB-2-deficient mice compared to wild-type mice (our unpublished results). The number of fibers and synapses in the auditory region of the brainstem is reduced in NB-2-deficient mice (our unpublished results). Thus, NB-2 may be involved in auditory system development.

NB-3/contactin-6 expression in the developing cerebellum. Expression of NB-3/contactin-6 mRNA in the cerebellum is evident after birth, reaches a maximum around P7 and declines thereafter to low levels. In contrast, NB-3 expression in the cerebellum increases until adulthood. However, NB-3-deficient mice show no gross abnormalities in the brain, including the cerebellum. Based on the strong expression of NB-3 mRNA in the cerebellum, it has been suggested that NB-3 plays a role in cerebellar control of motor coordination in adulthood. Behavioral tests that examine motor function, such as the rotarod test and wire hang test, revealed that motor coordination is impaired in NB-3-deficient mice. We hypothesized that this functional impairment must result from cellular and/or molecular defect(s) in the cerebellum. NB-3 immunofluorescence in neonatal cerebellum revealed that NB-3 localizes to the radially migrating granule cells located underneath the inner edge of TAG-1/contactin-2-positive zone (our unpublished results). NB-3 expression is observed as punctuated signals and overlapped with vGluT1, a presynaptic marker of glutamatergic neurons. The number of vGluT1-positive puncta in NB-3-deficient mice was less than that in the wild-type mice (our unpublished results), suggesting that NB-3 may play an important role in granule cell maturation and/or synaptic formation in the developing cerebellum.

Molecular Interactions of Contactins

As described above, contactins are involved in a variety of molecular and cellular events. The molecular mechanisms underlying these events require complex interactions between contactins and other proteins (Fig. 2). Interactions of contactin-1 or TAG-1/contactin-2 with molecules of the L1 family of the Ig superfamily have been studied extensively. The L1 family is comprised of L1, NrCAM, neurofascin and close homologue of L1 (CHL1). L1 binds to TAG-1.
in cis\textsuperscript{70-74} and to contactin-1 in trans.\textsuperscript{75} NrCAM binds in trans to TAG-1\textsuperscript{176,77} and both in cis and in trans to contactin-1.\textsuperscript{78-81} FAR-2, a chick ortholog of NB-2/contactin-5, binds weakly to L1 but not to NrCAM.\textsuperscript{85} Recently, it was reported that CHL1 associates with NB-3/contactin-6 in cis and enhances cell surface expression of NB-3.\textsuperscript{82} Besides the L1 family, it has been reported that contactins associate with various molecules including transmembrane proteins and extracellular matrix components. Contactin-1 associates with protein tyrosine phosphatase \( \alpha \) (PTP\( \alpha \)) in cis, thereby recruiting intracellular src family tyrosine kinases to receptor complexes.\textsuperscript{83,84} NB-3 also interacts with PTP\( \alpha \) to regulate apical dendrite orientation in the visual cortex.\textsuperscript{85} TAG-1 binds to NCAM, phosphacan and tenasin-C.\textsuperscript{85} Contactin-1 associates with tenasin-C, tenasin-R and RPTP\( \beta \).\textsuperscript{86-91}

It has recently been proposed that contactins play a novel role in regulation of neural precursor cell differentiation. Notch signaling pathways are controlled by regulated intramembrane proteolysis in which \( \gamma \)-secretase cleaves type-1 transmembrane proteins to release their intracellular domains. This cleavage is regulated by ligand binding to the receptor protein. Contactin-1 and NB-3/contactin-6 are functional ligands for Notch that are involved in oligodendrocyte differentiation.\textsuperscript{82}\textsuperscript{93} APP is cleaved by \( \gamma \)-secretase in a similar manner. It was reported recently that TAG-1/contactin-2 and BIG-2/contactin-4 interact with APP\textsuperscript{90,94} TAG-1 and APP colocalize in the neural stem cell niche of the mouse fetal ventricular zone, and interaction between these two proteins negatively regulates neurogenesis.\textsuperscript{60} APP and BIG-2 are expressed in locations that permit an interaction in the developing chick retinotectal system, where their interaction is involved in axon outgrowth in vitro.\textsuperscript{94} In addition, in vitro binding assays reveal direct interactions of APP, and its homologue amyloid precursor-like protein 1 (APLP1), with BIG-1/contactin-3 and BIG-2/contactin-4.\textsuperscript{94} NB-2/contactin-5 binds to APLP1, but not to APP.\textsuperscript{94}

Contactins and Neuropsychiatric Disorders

Contactin-1-deficient mice show a weight loss and die by P19,\textsuperscript{20} resembling the anorexia mouse. Contactin-1 is expressed in the hypothalamic neuropil of wild-type mice.\textsuperscript{95,96} and contactin-1-deficient mice show hypothalamic alterations similar to the anorexia mouse.\textsuperscript{96,97} Thus, the contactin-1-deficient mouse may be a good model for studying eating disorders. Human BIG-2/contactin-4, NB-3/contactin-6 and CHL1 genes are contiguously located on chromosome 3p25-p26.\textsuperscript{98-100} The loci are deleted in 3p deletion syndrome, which is characterized by developmental delays, growth retardation and dysmorphic features. Furthermore, the BIG-2 gene is disrupted or deleted in subjects with characteristic features of the 3p deletion syndrome.\textsuperscript{101,102} BIG-2 mutations also have been found in subjects with autistic spectrum disorder,\textsuperscript{103} although none of these subjects demonstrate symptoms of the classical 3p deletion syndrome. In addition, it has been reported recently that human CNTNAP2 gene encoding Caspr2, a binding partner of TAG-1/contactin-2, is associated with a number of neuropsychiatric disorders, including seizures, mental retardation, schizophrenia and autistic spectrum disorder.\textsuperscript{95,104-107} These findings suggest that contactins might play an important role(s) in the normal development and maintenance of central nervous system function.

Concluding Remarks

Each of contactins is expressed in a cell- or tissue-specific manner and distributed almost separately with each other. It is likely that contactins play distinct roles in the development and function of the nervous system. On the other hand, there may be some common features in the molecular mechanisms by which contactins function. Formation of molecular complexes, contactin-1 with Caspr and TAG-1/contactin-2 with Caspr2, on the myelinated axon suggests possibility of other combination between each of contactins and any member of the Caspr family. Because contactins are linked via GPI-anchor to the membrane and therefore lack cytoplasmic domain, if contactins are acting as a receptor, they need to associate in cis with transmembrane proteins in order to transduce extracellular signals across the membrane. Contactins can associate in cis with some of the Caspr family, some of the L1 family, PTP\( \alpha \) and likely unidentified co-receptors. Moreover, a novel role of contactins in intercellular interaction has been raised recently. Contactins were characterized as a functional ligand of Notch or APP. Though there seems to be little common structural feature between Notch and APP, they are cleaved by \( \gamma \)-secretase depending on the binding of contactins. In both cases, we need to understand the mode of ligand-receptor interaction and clarify intracellular signaling pathways activated by contactins. These elucidations of extracellular and intracellular mechanisms will reveal an essential role(s) of contactins in the formation and maintenance of a variety of tissues/cells/ compartments in the nervous system.

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