● REVIEW

Contactins in the central nervous system: role in health and disease

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Abstract

Contactins are a group of cell adhesion molecules that are mainly expressed in the brain and play pivotal roles in the organization of axonal domains, axonal guidance, neuritogenesis, neuronal development, synapse formation and plasticity, axo-glia interactions and neural regeneration. Contactins comprise a family of six members. Their absence leads to malformed axons and impaired nerve conduction. Contactin mediated protein complex formation is critical for the organization of the axon in early central nervous system development. Mutations and differential expression of contactins have been identified in neuro-developmental or neurological disorders. Taken together, contactins are extensively studied in the context of nervous system development. This review summarizes the physiological roles of all six members of the Contactin family in neurodevelopment as well as their involvement in neurological/neurodevelopmental disorders.

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Introduction

Contactins are a group of six neuronal cell adhesion molecules, contactin-1 to contactin-6. The contactin subfamily comprises six structurally related axon-associated nervous system specific cell adhesion molecules, which belong to the Immunoglobulin (Ig) superfamily (Stoeckli, 2010). Contactins are structurally and functionally rather conserved across species and mainly expressed in neurons (Mohebiany et al., 2014). However, oligodendrocytes and their precursors also express contactins (Colakoglu et al., 2014; Zoupi et al., 2018).

The extracellular components of contactins are structurally very similar, as they all have six Ig-like repeats followed by four fibronectin III-like domains anchored to GPI (glycosylphosphatidylinositol) attached to the outer leaflet of the cell membrane (**Figure 1**). None of them have an intracellular domain and thus need interacting partners for signal transduction within the cell. Contactins can be localized to both pre- and post-synaptic compartments (Dalva et al., 2007). Contactin-1 and contactin-2 are primarily present at the junctions of myelin and axons and facilitate mutual communication among neurons, oligodendrocytes and astrocytes (Pedraza et al., 2001). Furthermore, a specific subset of contactins and their partners (co-receptors), CNTNAPs (contactin associated proteins) additionally regulate the clustering of voltage-gated ion channels involved in saltatory action potential propagation and control of axonal excitability (Peles and Salzer, 2000). The Contactin-associated proteins (Casprs), which belong to the neurexin family (Bellen et al., 1998), generally occur in a cis-complex with a contactin subfamily members (Rios et al., 2000; Fernandez et al., 2004; Labasque and Faivre-Sarrailh, 2010). Moreover, at specific

synapses, contactins and CNTNAPs form complexes within themselves or with each other and take part in establishing synaptic contacts (Rios et al., 2000; Rudenko, 2017), modifying synaptic receptor function and regulating dendritic spine morphology (Stoeckli, 2010). For example, CNTNAP1 forms a complex with Contactin-1, CNTNAP2 with Contactin-2 and CNTNAP4 with Contactin-4 and -5. Contactin-1: CNTNAP1 are involved in the organization of paranodal domains of axons, whereas contactin-2: CNTNAP2 are involved in the organization of juxtaparanodes (Faivre-Sarrailh and Devaux, 2013; Zou et al., 2017). The roles of complexes of contactin 4 and -5 are still to be elucidated.

The most studied members of the contactin family are contactin-1 (F3 or F9 or contactin) and contactin-2 (Transient Axonal Glycoprotein 1, TAG-1) (Shimoda and Watanabe, 2009). The name of the first protein in the group, contactin-1, was coined in 1988 as 'contactin' when it was first characterized as a molecule that interacted with known cell adhesion molecules and found in areas of neuronal contacts (Ranscht, 1988). In comparison, investigations of the other members namely, contactin-3 (BIG-1), contactin-4 (BIG-2), contactin-5 (NB-2) and contactin-6 (NB-3) were performed around ten years later than contactin-1 and -2. Contactins play crucial roles in the organization of axonal domains, axonal guidance, myelination, neuritogenesis, neuronal development, synaptogenesis and axo-glia interactions (Stoeckli et al., 1991; Murai et al., 2002; Poliak and Peles, 2003; Rudenko, 2017). Even though contactin 1-6 have similar roles in the central nervous system (CNS) development process, they are responsible for maintaining separate neuronal circuitries, which is elaborated for each contactin below. Specifically, in

the developmental stages, contactin-1 and -2 act as guidance molecules for axonal pathfinding and fasciculation (Shimoda and Watanabe, 2009). They are highly expressed in the adult human brain as well. We found both contactin-1 (unpublished data) and contactin-2 (Chatterjee et al., 2018) to be expressed in the temporal cortex and hippocampus of adults.

The importance of contactins have been elucidated not only in health as described above but also in disease. Recent studies have revealed the role of improper functioning, incorrect cellular localization or genetic aberrations related to contactins in neurological and neurodevelopmental disorders such as autism (Burbach and van der Zwaag, 2009; Kumar and Christian, 2009; van Daalen et al., 2011) and neuro-developmental delay (Fernandez et al., 2004; Roohi et al., 2009). Here, we focus on the recent progresses in the field of contactins and their roles in CNS development and maintenance of CNS physiology (summary in **Table 1** and **Figure 2**). In this review, we will summarize the expression pattern, physiological functions, and the roles in synapse and myelin formation during neurodevelopment for each of the six contactins as well the implications of dysfunction of contactins in neurological disorders.

An electronic search on Pubmed using search terms- 'CNTN1', 'CNTN2', 'CNTN3', 'CNTN4', 'CNTN5', 'CNTN6', 'Contactin', 'Contactin-1', 'Contactin-2', 'Contactin-3', 'Contactin-4', 'Contactin-5', 'Contactin-6', 'Contactin AND multiple sclerosis', contactin AND Alzheimer's', 'contactin AND diseases' and 'contactin AND biomarker'. Articles were included from year 1985 to 2018. The results were further screened by title and abstract to only present physiological functions and diseases related to the CNS.

Contactin-1

Expression pattern and physiological functions

Contactin-1 is a 130 kDa protein, which is present in a membrane-bound and soluble form (Ranscht, 1988). Its orthologs are named contactin/F11 in chicken and F3 in mouse (Williams and Barclay, 1988). The presence of this GPI-anchored molecule on neuronal membranes has been observed in the retina, spinal cord, cerebral cortex, hippocampus and cerebellum (Ranscht, 1988; Massaro et al., 2012). In the postnatal cerebellum, contactin-1 is highly expressed on migrating granule cells where it shows a primary expression in axonal extensions rather than in cell bodies (Virgintino et al., 1999; Faivre-sarrailh et al., 2000). It is also expressed in axons and cell bodies of mossy fibers and Golgi cells (Faivre-Sarrailh et al., 1992). Normal astrocytes do not express contactin-1 (Williams and Barclay, 1988). However, glioblastomas express this protein, which co-localizes with glial fibrillary acidic protein (Eckerich et al., 2006). In addition, contactin-1 expression has been found in oligodendrocytes (Koch et al., 1997).

Contactin-1 is indispensable for early interactions between axons and glia. It bolsters paranodal junction formation by establishing a complex with the transmembrane protein CNTNAP1 (**Figure 3**). In the axolemma, it interacts with glial neurofascin-155 to establish the axon-glial

contacts (NF-155) (Faivre-sarrailh et al., 2000; Boyle et al., 2001; Sherman et al., 2005; Salzer et al., 2008). The role of contactin-1 in paranodal junction formation was shown by knocking out the CNS *CNTN1* gene in mice. As a result, paranodal junctions were disrupted due to mislocalization of the shaker-type potassium Kv1.2 channels typically delineating juxtaparanodal regions (Boyle et al., 2001). This suggests that contactin-1 is needed to position Kv1.2 and thus to contribute to the paranodal outward current and thereby proper action potential repolarization during action potential conduction. A spontaneous mutation in BALB/c mice that resulted in a null allele of *CNTN1* showed a similar phenotype as the *CNTN1* knock-out mice described above (Davisson et al., 2011). After one week, the homozygous animals were smaller in size than littermates and had abnormal locomotion. These mice died after a few weeks which was similar as in the *CNTN1* knock-out mice.

Besides a role in organization of axonal membranes, contactin-1 also plays an important role in myelination (Colakoglu et al., 2014) and axonal regeneration (Haenisch et al., 2005), where it modulates these processes *via* axo-glia interaction. The maturation and differentiation of oligodendrocytes from oligodendrocyte precursor cells depends on the interaction of contactin-1 with other proteins, one of them being PTPRZ (protein tyrosine phosphatase, receptor-type, Z polypeptide 1). PTPRZ is expressed primarily by oligodendrocyte precursor cells, astrocytes, and mature oligodendrocytes in the developing and adult nervous systems (Canoll et al., 1996; Harroch et al., 2000; Faissner et al., 2006; Lamprianou et al., 2011). In addition, it was found that F3/Contactin aids in oligodendrocyte generation from progenitor cells by acting as ligand of notch (Cui et al., 2004). Binding of contactin to notch leads to the release of the intracellular domain of notch. Intracellular domain of notch then translocates into the nucleus of oligodendrocyte precursor cells and increases notch1 and notch2 expression, which positively regulates oligodendrogliogenesis (Taylor et al., 2007). Furthermore, contactin-1 regulates myelination by participating in a tripartite complex of contactin1-fyn-PTPα promoting the interaction of PTPα (receptor protein tyrosine phosphatase) and fyn, thus controlling dephosphorylation and subsequent activation of Fyn by PTPα (Zeng et al., 1999; Lamprianou et al., 2011). Regulation of fyn is important as it is a Src family kinase, which regulates myelination by oligodendrocytes (Umemori et al., 1994; Zeng et al., 1999; Cui et al., 2004; Kaneko-Goto et al., 2008). These findings suggest that contactin-1 can be a novel major player in the signal transduction mechanism in myelination pathways of CNS due to its interactions with PTPRZ, notch, PTPα and fyn.

Apart from the role in myelination, contactin-1 has a crucial function in the hippocampus, where it augments synaptic plasticity, neurogenesis, and memory in adult mice (Puzzo et al., 2013). In the hippocampus of aged mice, reduced contactin-1 protein and mRNA was observed in the pyramidal neurons of CA1 and in the granule cells of the dentate gyrus, indicating its potential role in age-related loss of memory and cognition (Shimazaki et al., 1998). Moreover, in aged

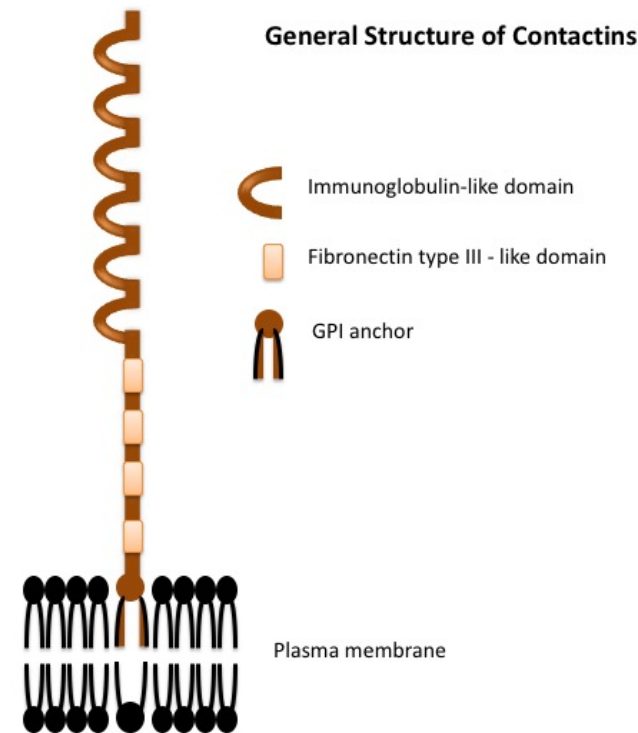**Table 1 Contactins: summary of their main characteristics**

	Expression-pattern[*]	Known key physiological functions	Important interacting partners	Association with neurological disorders	Cause/manifestation of disease (Mutations in the associated gene/auto-antibodies/ differential expression of protein in tissue, CSF or serum)
Contactin-1	Cerebellum (Ranscht, 1988) Hippocampus (Puzzo et al., 2013) Developing and adult retina (Ranscht, 1988) Developing spinal cord (Ranscht, 1988)	Paranodal junction formation (Wang et al., 1993; Faivre-sarrailh et al., 2000; Baumann and Pham-Dinh, 2001; Boyle et al., 2001; Sherman et al., 2005; Salzer et al., 2008) Neurogenesis (Puzzo et al., 2013) Synaptic plasticity (Puzzo et al., 2013) Myelination (Colakoglu et al., 2014)	CNTNAP1 (Faivre-sarrailh et al., 2000) PTPRZ (Lamprianou et al., 2011) Notch (Cui et al., 2004) PTPα (Zeng et al., 1999) Fyn (Zeng et al., 1999) APP (Bai et al., 2007)	Neuro-muscular disorders (Berglund et al., 1999; Compton et al., 2008) CIDP (Querol et al., 2013)	Mutation Autoantibodies in serum/ plasma
Contactin-2	Cerebellum (Wolfer et al., 1994; Yoshihara et al., 1995) Hippocampus (Wolfer et al., 1994; Yoshihara et al., 1995) Olfactory bulb (Wolfer et al., 1994; Yoshihara et al., 1995) Cerebral cortex (Masuda, 2017; Chatterjee et al., 2018)	Juxtaparanodal organization (Traka et al., 2002) Axonal guidance and fasciculation (Traka et al., 2003; Baeriswyl and Stoeckli, 2008; Wolman et al., 2008)	CNTNAP2 (Traka et al., 2002) APP (Ma et al., 2008a; Mattson and Van Praag, 2008; Ramaker et al., 2016) Ng-cell adhesion molecule (Stoeckli et al., 1997) BACE1 (Kuhn et al., 2012; Gautam et al., 2014; Dislich et al., 2015)	Acquired CNS demyelinating syndrome	Increased levels of contactin-2 in CSF
Contactin-3	Cerebellum (rodents) (Yoshihara et al., 1995) Hippocampal dentate gyrus (rodents) (Yoshihara et al., 1995) Outer layer of cerebral cortex (rodents) (Yoshihara et al., 1995)	Extension of neurites from embryonic and neonatal neurons (Yoshihara et al., 1995)	PTPRG (Nikolaienko et al., 2016)	Not known	
Contactin-4	Cerebellum (Kaneko-Goto et al., 2008) Hypothalamic nuclei (Kaneko-Goto et al., 2008) Cerebral cortex (II–IV) (Kaneko-Goto et al., 2008) Amygdala (Kaneko-Goto et al., 2008) Frontal and parietal lobe (Kaneko-Goto et al., 2008) Substantia nigra (Kaneko-Goto et al., 2008)	Axonal guidance (Kaneko-Goto et al., 2008) Olfaction (Kaneko-Goto et al., 2008) Neuroblastoma differentiation (Kaneko-Goto et al., 2008)	CNTNAP4 (Karayannis et al., 2014) APP (Osterfield et al., 2008) APLP (Osterfield et al., 2008) APPsα (Osterfield et al., 2008) PTPRG (Nikolaienko et al., 2016)	3p deletion syndrome (Fernandez et al., 2004) Autism spectrum disorder (Roohi et al., 2009) Spino-cerebellar ataxia type 16 (Miura et al., 2006)	Mutation Mutation Mutation
Contactin-5	Amygdala (Kamei et al., 2000) Occipital lobe (Kamei et al., 2000) Central auditory pathway (rodents) (Ogawa et al., 2001; Li et al., 2003)	Suggested role in synaptogenesis	CNTNAP4 (Ashrafi et al., 2014) APLP1 (Shimoda et al., 2012) PTPRG (Mercati et al., 2013)	Autism spectrum disorder (van Daalen et al., 2011; Zuko et al., 2013)	Mutation
Contactin-6	Cerebellum (Kamei et al., 1998) Thalamus (Kamei et al., 1998) Subthalamic nucleus (Kamei et al., 1998) Corpus callosum (Kamei et al., 1998) Caudate nucleus (Kamei et al., 1998) Spinal cord (Kamei et al., 1998) Accessory olfactory bulb and cerebral cortex II/III,V (rodents) (Lee et al., 2000)	Direct growth of apical dendrites (Huang et al., 2012) Projection and branching of axons (Huang et al., 2012) Synaptogenesis (Sakurai et al., 2009)	CHL1 (Chen et al., 2005) PTPα (Ye et al., 2008) PTPRG (Mercati et al., 2013) Notch receptor (Cui et al., 2004)	Autism spectrum disorder (Zuko et al., 2013) La Tourette Syndrome (Huang et al., 2017)	Mutation Mutation

[*]The expression pattern of all proteins in the table is mentioned in the context of humans unless stated otherwise. CSF: Cerebrospinal fluid; CNTNAP: contactin associated proteins; PTPRZ: protein tyrosine phosphatase, receptor-type, Z polypeptide 1; PTPα: receptor protein tyrosine phosphatase; APP: amyloid precursor protein; CIDP: chronic inflammatory demyelinating polyradiculoneuropathy; BACE1: beta secretase 1; CNS: central nervous system; PTPRG: protein tyrosine phosphatase, receptor type G; APLP: amyloid beta precursor like protein; CHL1: close homolog of L1.

mice, over-expression of contactin-1 improved hippocampal long-term potentiation and memory compared with wild-type littermates (Puzzo et al., 2015). When F3/contactin-1 was over-expressed within the CA region of hippocampus, it regulated proliferation of neuronal precursors and their commitment towards neuronal fate in a positive manner (Puzzo et al., 2013). Contactin-1 also controls synaptic interactions among cerebellar interneurons. This was found by studying $CNTN^{-/-}$ mice, where granule cell axon guidance and dendritic projections from granule and golgi cells were impaired (Berglund et al., 1999).

Figure 1 General structure of the contactins.
The six members of the contactin sub-family share a common structure in vertebrates. The extracellular component has immunoglobulin-like domains followed by four fibronectin III-like domains. The protein is attached to the plasma membrane with a glycosylphosphatidylinositol (GPI) anchor and there is no intracellular domain.
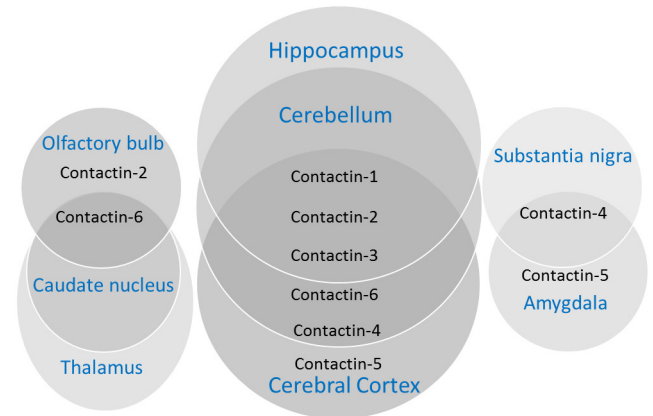
Implications in neuro-muscular disorders

A single mutation in the *CNTN1* gene is known to lead to deficiency of contactin-1 at the neuro-muscular junction (NMJ) in humans (Compton et al., 2008). The mutation is inherited in an autosomal-recessive manner and the deficiency of contactin-1 disrupts the communication between muscles and nerves resulting in lethal myopathy (Compton et al., 2008). This myopathy is related to the clinical spectrum of congenital myopathies and myasthenic syndromes (Puzzo et al., 2013) that fall under the umbrella of neuro-muscular disorders. However, the phenotype of lethal congenital myopathy could not be replicated in *CNTN1* mutant mice. In mice deficient of *CNTN1*, NMJ morphology was totally normal and they did not show the phenotype of human myopathy (Compton et al., 2008). But *CNTN1* knockout mice exhibit myelin detachment in the postnatal paranode which results in a decrease in nerve conduction velocities in CNS and peripheral nervous system (PNS) (Berglund et al., 1999; Virgintino et al., 1999; Boyle et al., 2001; Compton et al., 2008; Sun et al., 2009). These studies suggest that contactin-1 plays an important role in maintaining NMJ function and is thereby indispensable for proper functioning of mature motor neurons.
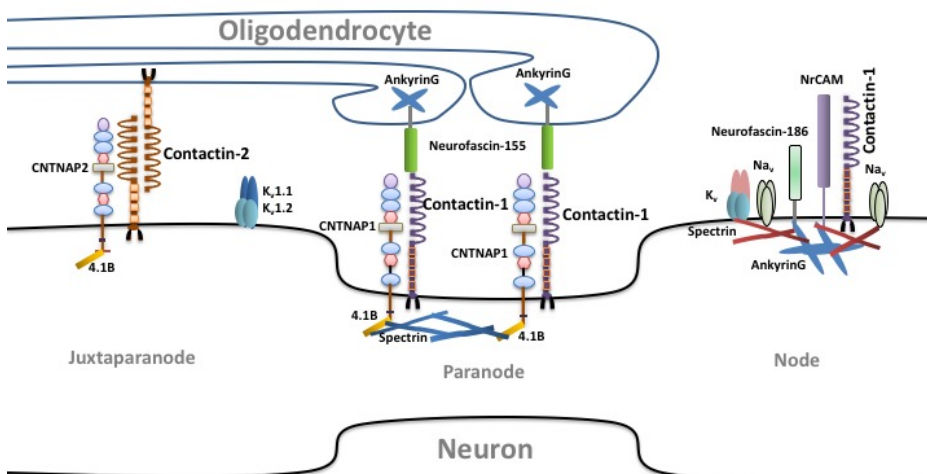

Figure 2 Overlapping and distinct expression patterns of contactins in different areas of brain.

Figure 3 Contactin-1 and contactin-2 in axonal domain organization.
CNTNAP: Contactin associated protein; Na_V: sodium channel, voltage-gated, type II; K_V: Potassium channel, voltage gated; NrCAM: neuronal cell adhesion molecule.

Implications in chronic inflammatory demyelinating polyradiculoneuropathy

Contactin-1 integrity plays a role in another peripheral nervous system disease, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (Querol et al., 2013). Antibodies against the contactin-1/CNTNAP1 complex were present in serum/plasma of a subset of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) patients. CIDP causes predominantly sensory and motor problems such as limb weakness, distal sensory disturbances, and loss of reflexes. These phenotypes are manifested because the autoantibodies impair cell-cell adhesion mediated by Contactin•CNTNAP complex and their interaction with neurofascin-155, thereby disrupting the paranodal junctions (Labasque et al., 2014). Alternatively, contactin-1 is pre-dominantly involved in myelination and the resulting demyelination in CIDP may be caused by the autoantibodies generated against contactin-1 (Querol et al., 2013; Koike et al., 2017). The identification of auto-antibodies to contactin-1 or contactin-1/CNTNAP1 complex even in small subgroups of CIDP patients suggest that these may play a pathogenic role and that they might serve as diagnostic biomarkers in these patients (Querol et al., 2013; Manso et al., 2016). However, further large cohort studies are required to establish antibodies against contactin-1 as a biomarker for CIDP.

Contactin-2

Expression pattern and physiological functions

Human contactin-2, also known as TAX1, was initially discovered as a glycoprotein that is transiently expressed during development in mice (called TAG-1) (Yamamoto et al., 1986; Dodd et al., 1988; Furley et al., 1990). It was also found in chicken where it is known as axonin-1 (Zuellig et al., 1992). The structure of human contactin-2 is very conserved and has a high degree of similarity to rat TAG-1 (91% identity) and chicken axonin-1 (75% identity) (Hasler et al., 1993; Tsiotra et al., 1993). Moreover, expression patterns of contactin-2 are similar across corresponding developmental stages in human and chicken (Hasler et al., 1993; Kozlov et al., 1995). It is regulated in a space- and time-dependent manner in both neurons and glial cells, the expression being highest during early developmental stages (Stoeckli et al., 1997; Pedraza et al., 2001; Kyriakopoulou et al., 2002). In the adult rodent brain contactin-2 is expressed in the hippocampus, olfactory bulb, and cerebellar granule cells (Wolfer et al., 1994; Yoshihara et al., 1995). In adult fish, however, contactin-2 expression is restricted to nasal retinal ganglion cells (Lang et al., 2001). Axonin-1, its chicken homolog, is primarily present in membranes of developing nerve fiber tracts, while a soluble form is secreted from axons and accumulates in the cerebrospinal fluid and the vitreous fluid of the eye of the chicken (Stoeckli et al., 1991).

Although, contactin-2 and contactin-1 have similar functions in the brain, the sub-cellular localizations are different. The primary area of contactin-2 expression on axons is juxtaparanode, where it is needed for the clustered distribution of Shaker-type Kv1.1 potassium channels (**Figure**

3). On the other hand, contactin-1 is primarily expressed on the paranode (Traka et al., 2002; Poliak and Peles, 2003). Contactin-2 is highly expressed on growth cones of extending axons and secreted from the axons into the extracellular matrix and cerebrospinal fluid (Baeriswyl and Stoeckli, 2008; Wolman et al., 2008). Furthermore, contactin-2 is also present on the synaptic plasma membrane in a complex with CNTNAP2 (Lu et al., 2016).

The soluble form of contactin-2 acts as a guiding molecule for the outgrowth of neurites (Stoeckli et al., 1991), and thus plays a role in axon extension initiation, axonal guidance and fasciculation (Baeriswyl and Stoeckli, 2008; Wolman et al., 2008). Evidence for impaired learning and memory as well as for sensory dysfunction was found in *CNTN2*$^{-/-}$ mice (Savvaki et al., 2008). Absence of *CNTN2* led to a reduced number of mitral cells, *i.e.*, the projection neurons of the olfactory bulb. This resulted into decreased odor discrimination and diminished long-term social memory formation (Bastakis et al., 2015). The pivotal role of contactin-2 in learning and memory might explain the role of contactin-2 in dementing disorders such as Alzheimer's disease (AD). Contactin-2 is a ligand of amyloid precursor protein (Ma et al., 2008a, b) and beta secretase 1 (BACE1) (Kuhn et al., 2012). It is well known that amyloid precursor protein processing is at the core of Alzheimer's disease (AD). By binding with amyloid precursor protein, contactin-2 enhances the production of the amyloid precursor protein intracellular domain in a gamma-secretase-dependent manner (Ma et al., 2008a). This suggests that Contactin-2 influences amyloid precursor protein processing and amyloid precursor protein intracellular domain release with concomitant amyloid beta formation, which is an important player in AD pathogenesis (Konietzko, 2012).

Furthermore, contactin-2 has also roles in neural regeneration. Up-regulation of contactin-2 expression was observed in the zebra fish spinal cord caudally to the site where a lesion was set indicating a role in spinal cord regeneration. This was further supported by the fact that during spinal cord injury antisense morpholinos blocking the expression of contactin-2 impeded axon re-growth beyond the lesion site (Lin et al., 2012).

Implications in demyelinating diseases

Recently, contactin-2 has been found to be involved in oligodendrocyte maturation (Zoupi et al., 2018). Contactin-2 expression was associated with regulation of genes responsible for myelination and oligodendrocyte proliferation (Zoupi et al., 2018). Apart from regeneration, contactin-2 might also have implications in demyelination and may have use as a biomarker for developmental demyelinating neurological diseases. Even though in the absence of *CNTN2*, demyelination was not observed in mice (Zoupi et al., 2018), it was found to be differentially expressed in the CSF of children suffering from a demyelinating disease, multiple sclerosis (Singh et al., 2015). In addition, a previous proteomic study found that CSF contactin-2 was higher in abundance, among few other neuronal proteins, in children with mul-

tiple sclerosis than in children with monophasic acquired CNS demyelinating syndrome (ADS) (Singh et al., 2015).

Contactin-3

Expression pattern and physiological functions

The cDNA cloning and characterization of contactin-3, also called brain-derived immunoglobulin superfamily protein 1 (BIG-1) or plasmacytoma-associated neuronal glycoprotein (PANG), was first reported in 1994 in rats (Connelly et al., 1994; Yoshihara et al., 1994). Contactin-3 appeared structurally closely related to TAG-1/axonin-1 and F3/Fll. Contactin-3 is highly expressed within the adult rat brain in specific subsets of neurons such as granule cells of the hippocampal dentate gyrus, neurons in the outer layer of cerebral cortex and Purkinje cells of the cerebellum of mice (Yoshihara et al., 1995). Purkinje cell-specific localization of contactin-3 is distinct from the expression patterns of contactin-1 and contactin-2 in the sense that contactin-1 and -2 expression were not seen in Purkinje cells (Yoshihara et al., 1995; Hansford et al., 2003). Another difference is that expression of contactin-3 is highest in the adult mouse brain, very low in embryonic brain and absent in peripheral tissues, which is also in contrast to contactin-1 and -2 (Yoshihara et al., 1995). There are no studies of human contactin-3 yet which would reveal the expression pattern of this protein.

Similar to contactin-1 and contactin-2, contactin-3 exists in two forms, *i.e.*, membrane-bound and secreted. Even though the distinct roles of membrane-bound and soluble forms are not clear, the membrane bound forms might be responsible for intercellular communication, axonal domain organization and axo-glia interaction whereas the soluble form may act a guiding molecule for axonal guidance and fasciculation. The authors of the original study (Yoshihara et al., 1994) also found a unique spliced form of *BIG-1* cDNA in rats that consists of a signal peptide followed by one immunoglobulin like domain. This form was not found among alternatively spliced forms in related TAG-1/axonin-1 and F3/Fll subgroups and is thus unique for contactin-3. This new spliced form may give rise to a unique soluble form of contactin-3 with a possibly different role as a guidance molecule.

The physiological functions of contactin-3 appear to be similar to TAG-1/axonin-1(contactin-2) and F3/Fll (contactin-1) in that it supports the extension of neurites from embryonic and neonatal neurons. It is possible that contactin-3 may have a role in the elongation of axons and the connections between specific types of neurons (Yoshihara et al., 1995). Much is still to be elucidated regarding this protein, especially its role in neurological disorders.

Implication in autism spectrum disorder

CNTN3, the gene encoding contactin-3 is associated with autism spectrum disorder (ASD). A study of families in which parents shared ancestors aimed to identify inherited factors in autism found that a rare loci mapped to *CNTN3* (Morrow et al., 2008). Furthermore, a GWAS study found a large subset of autism-related genes, including *CNTN3* that were involved in the outgrowth and guidance of axons and

dendrites (Hussman et al., 2011). This study highlighted that disruptions in axonal guidance and fasciculation are manifested in autism.

Contactin-4

Expression-pattern and physiological functions

Contactin-4, also known as brain-derived immunoglobulin super-family protein 2 (BIG-2), was first cloned in the rat (Hansford et al., 2003). Contactin-4 expression was found in testis, thyroid, small intestine, uterus and brain (Yoshihara et al., 1995). Unlike contactin-1, -2 and -3, the expression of contactin-4 is not highest in brain (Hansford et al., 2003). It was found that all contactin-4 expressing tissues manifested a transcript of approximately 4.7 kb, whereas testis expressed an extra transcript of approximately 1.8 kb, which was possibly a splice variant of the *CNTN4* gene. Within the brain the highest expression was seen in the paracentral gyrus of the cerebral cortex, amygdala, thalamus, cerebellum, and parietal and frontal lobes. Contactin-4 expression was found in pyramidal neurons of layers Vb and VIa, and all types of interneurons (Oguro-Ando et al., 2017). In addition, contactin-4 was also found to be expressed in retinal ganglion cells (Osterhout et al., 2015). However, its expression in the hippocampus was weak, localized specifically dentate gyrus granule cells whereas it was rather strong in olfactory sensory neurons (Kaneko-Goto et al., 2008). In contrast to the hippocampal expression of contactin-4, contactin-1 expression was found overall in the hippocampus, contactin-2 expression was seen in CA3 pyramidal cells and contactin-5 expression was predominant in CA1 pyramidal cells (Yoshihara et al., 1995).

The protein was shown to be responsible for neurite-promoting effects, like other contactins. Given the expression of contactin-4 in retinal ganglion cells s, it has been found to be important for target-specific axon arborization in the visual system of mice in a complex with amyloid precursor protein (Osterhout et al., 2015). It has been identified as an important factor needed by a subset of retinal ganglion cells to connect to the accessory optic system (Osterhout et al., 2015). Contactin-4 acts as an axonal guidance molecule for the formation of the olfactory odor map as well in the olfactory bulb of mice (Kaneko-Goto et al., 2008). This was supported by the fact that mice devoid of contactin-4 showed ectopic innervations of multiple glomeruli by olfactory sensory neurons expressing a particular odorant receptor. Apart from the role of contactin-4 in olfaction and vision, in humans it was found responsible for the differentiation of neuroblastoma cell lines, which are derived from embryonic neural crest cells (Kaneko-Goto et al., 2008).

Processing of APP can be modulated by contactin-4 indicating a potential role in neural development and disease, at least in chicken, although the exact mechanism is unknown. Contactin-4 may be involved in AD in a manner similar to contactin-2.

Implications in neuro-developmental disorders

Though the number of studies focusing on the *CNTN4* gene

and contactin-4 is limited, the available studies indicate that they are associated with neuro-developmental disorders. Human *CNTN4* locus 3p26.2–3p26.3 is involved in 3p deletion syndrome having hallmarks including developmental delay, postnatal growth retardation, and dysmorphic features (Fernandez et al., 2004). *CNTN4* disruption has been observed in a few patients with ASD (Roohi et al., 2009). ASD is a set of complex neurodevelopmental disorders with impairments in learning, verbal and non-verbal abilities and social interactions. A patient with a severe autistic phenotype with a maternally inherited ~535 kb deletion within the 5′ UTR of *CNTN4* has been recently identified using comparative genome hybridization (Cottrell et al., 2011). In addition to deletion, duplications in *CNTN4* in ASD has been identified as well (Glessner et al., 2009; Nava et al., 2013). A point mutation in the 3'UTR of *CNTN4* on chromosome 3p26.2–3p26.3 was also found to be associated with spino-cerebellar ataxia type 16 (SCA16) in patients, which involves cerebellar degeneration (Miura et al., 2006).

It has been postulated that aberrations in the process of local dendritic and synaptic protein synthesis play pivotal roles in autistic-like phenotypes as they lead to improper synapse functions (Kelleher and Bear, 2008; Zuko et al., 2013). Many genes encoding such pre- and post-synaptic proteins are associated with ASD (Zuko et al., 2013). Copy number variations or disruptions in *CNTNs* possibly affect the local synaptic protein synthesis leading to abrupt neuronal transmission, although the exact role of contactins in ASD is not yet clear. Since, there are evident clinical symptoms related to visual (Simmons et al., 2009) and olfactory impairments (Rozenkrantz et al., 2015) in patients with ASD, it can be further speculated that abnormalities in *CNTN4* might be one of the underlying causes, given the role of contactin-4 in the formation of optical and olfactory neuronal circuitry.

Contactin-5/NB-2
Expression pattern and physiological functions
NB-2, the contactin-5 ortholog in rodents, was first identified in rat brain in 1996 along with NB-3 (Ogawa et al., 1996), a contactin-6 ortholog. cDNAs encoding two splicing isoforms of human *CNTN5*, the gene encoding contactin-5, were identified later in 2000 (Kamei et al., 2000). The expression pattern of human contactin-5 was found to be very similar to contactin-3; high expression of contactin-5 was seen in the amygdala and occipital lobe in the human brain, whereas the expression was low in the corpus callosum, caudate nucleus, and spinal cord (Kamei et al., 2000). In rodents, strong expression of contactin-5 was in the thalamus, caudate putamen and weaker expression was seen in the cerebral cortex (Kleijer et al., 2015). Interestingly, in rodents, NB-2/contactin-5 is expressed preferentially in the central auditory pathway including the ventral cochlear nucleus, ventral acoustic stria, lateral and medial superior olivary complex, superior paraolivary nucleus, medial nucleus of the trapezoid body, ventrolateral lemniscus, and central nucleus of the inferior colliculus highlighting its pivotal role in the auditory system (Ogawa et al., 2001; Li et al., 2003; Toyoshima et al., 2009).

Similar to other contactins, contactin-5 is involved in cell adhesion during development but it might be the only contactin sub-family member responsible for maintaining neural circuitry in the auditory system (Ogawa et al., 2001; Li et al., 2003). Furthermore, contactin-5 has been implicated in dendritic morphogenesis (Peng et al., 2017). Complex of contactin-5 with its partner CNTNAP4 acts as a scaffold on inter-neurons where dendrites of direction-selective ganglion cells can fasciculate (Ashrafi et al., 2014; Peng et al., 2017).

Implication in ASD
There are indications of an involvement of *CNTN5* in ASD (Zuko et al., 2013). Copy number variations in *CNTN5* gene in cohorts of multiplex and simplex families suffering from ASD have been reported (Hussman, 2011; van Daalen et al., 2011; Mercati et al., 2013). It is known that many children suffering from ASD manifest pre- and post-stimulus superior temporal gyrus auditory oscillatory abnormalities and delayed auditory responses (Edgar et al., 2015). The involvement of *CNTN5* in ASD may be linked to the primary physiological function of contactin-5 in the maintenance of neuronal circuitry within auditory system.

Contactin-6/NB-3
Expression pattern and physiological functions
The last member of the contactin family, contactin-6, is functionally similar to contactin-4 and contactin-5 as it is involved in brain development like the former two (Mercati et al., 2013, 2017). Evolutionarily, it is close to contactin-3 and located at the same position on chromosome 3 (Kamei et al., 1998). The cDNA of human *CNTN6* was isolated from the cerebellum and the expression of contactin-6 was found to be highest in the cerebellum followed by the thalamus, sub-thalamic nucleus, corpus callosum, caudate nucleus and the spinal cord (Kamei et al., 1998). Contactin-6 expression has also been widely studied in rodents where it is known as NB-3 (Takeda et al., 2003). Pronounced expression of NB-3 has been seen in the developing cerebellum after birth. Here its expression increased until adulthood whereas in the cerebrum, the expression reached its maximum on postnatal day 7 and then declined (Lee et al., 2000). *In situ* hybridization demonstrated that NB-3 mRNA was preferentially expressed in the accessory olfactory bulb, layers II/III and V of the cerebral cortex, piriform cortex, anterior thalamic nuclei, locus coeruleus of the pons and mesencephalic trigeminal nucleus, and in Purkinje cells of the cerebellum (Lee et al., 2000). The expression of NB-3 co-localizes here with the presynaptic vGLUT1 indicating that NB-3 is localized pre-synaptically at glutamatergic synapses between parallel fibers and Purkinje cells (Sakurai et al., 2009, 2010).

Contactin-6 has an important role in guidance of neuronal tracts during development. For example, it was shown to direct the growth of apical dendrites of deep layer cortical pyramidal neurons and to regulate the projection and branching of axons of the corticospinal tract during development (Huang et al., 2012). Very low levels of contactin-6 lead to increased death of granule cells and decreased

synapse density between parallel fibers and Purkinje cells during cerebellum development, suggesting that contactin-6 is important for both survival of granule cells and synapse formation (Sakurai et al., 2009). Contactin-6 interacts with close homolog of L1 (CHL1) and protein tyrosine phosphatase alpha where it is involved in controlling apical dendrite orientation in the visual cortex (Ye et al., 2008). CHL1 is an important neural cell adhesion molecule involved in synaptic remodeling and cell migration (Chen et al., 2005). Protein tyrosine phosphatase alpha is a receptor protein tyrosine phosphatase which plays a principal role in nervous system development (Zeng et al., 1999). Contactin-6 also interacts with protein tyrosine phosphatase receptor-gamma (Peles et al., 1997; Bouyain and Watkins, 2010). This latter finding confirms its importance of this contactin for neural circuit construction. In addition, contactin-6 was recently found to play a major protective role in apoptosis (Zuko et al., 2016). This idea was suggested by the observation that the population of apoptotic cells increased in the cortex of $CNTN6^{-/-}$ mice compared to wild-type controls. Lastly, due to its interaction with the Notch receptor (Hu et al., 2006), contactin-6 can also play a role in oligodendrocyte development in a manner similar to contactin-1 (Cui et al., 2004).

CNTN6 knock-out mice also showed a significant reduction in Cux1$^+$ (marker for upper cortical layer) projection neurons in cortical layers II–IV and increased projection of FoxP2$^+$ (marker for deep cortical layer) projection neurons in layer VI of visual cortex were observed in as compared to wildtype mice (Zuko et al., 2016). Moreover, parvalbumin$^+$ (inhibitory) interneurons were decreased. These findings corroborate the view that contactin-6 is important for developmental functions involving cell survival, migration and fasciculation (Takeda et al., 2003).

Implications in ASD and Tourette syndrome

Like *CNTN3*, *CNTN4* and *CNTN5*, copy number variations have been identified in the *CNTN6* gene in ASD in humans (Saus et al., 2010; van Daalen et al., 2011). Recently, a large scale European genome-wide association study study has identified *CNTN6* duplication as one of the genetic risk factors for Tourette syndrome (Huang et al., 2017). Cerebellum is at the core of motor and coordination functions, which are disturbed in neuro-developmental disorders such as ASD and Tourette syndrome (Tobe et al., 2010; Becker et al., 2012; Caligiore et al., 2017). Since the expression of contactin-6 is highest in the cerebellum, it can be speculated that loss of proper functioning of this protein may have implications in neuronal circuitry dysfunction in the cerebellum thus affecting motor functions in ASD and Tourette syndrome.

Conclusion

Contactins are cell adhesion molecules that are highly expressed in the brain and are involved in the physiology and pathophysiology of the CNS (See **Table 1** for summary). The six members of the Contactin family have some common functions during development but maintain exclusive neuronal circuitries. Almost all members are major players in axonal guidance, fasciculation and synaptic integrity, although the sub-polpulation of neurons where they are expressed may be different. Many non-overlapping roles of contactins have been demonstrated in recent years. For example, contactin-1 and contactin-2 are expressed on paranodes and juxta-paranodes in association with their interaction partners CNTNAP1 and CNTNAP2 respectively, wherein they are involved in axonal domain organization. Given their role in myelination, both contactin-1 and contactin-2 are implicated in demyelinating diseases. However, the cellular and molecular pathways where the next member, contactin-3 is involved are still largely unknown. Contactin-4 is a key guiding molecule in olfactory odour map formation and correct wiring of optic neurons, whereas contactin-5 has been implicated in circuitry of the auditory neurons. Contactin-6 is involved in oligodendrocyte development and synapse formation similar to contactin-1. Given the roles of contactin-4-6 in key CNS developmental processes, mutations in the genes encoding them lead to complex neurodevelopmental disorders such as ASD. In summary, further studies are warranted to completely understand the cellular and molecular mechanisms mediated by contactins which may provide therapeutic leads for neuro-developmental disorders.

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