THE ROLE OF GPI-ANCHORED AXONAL GLYCOPROTEINS IN NEURAL DEVELOPMENT AND NEUROLOGICAL DISORDERS

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Abstract:

This review article focuses on the Contactin subset of the Immunoglobulin supergene family (IgC2/FNIII molecules), whose components share structural properties (the association of Immunoglobulin type C2 with fibronectin type III domains), as well as a general role in cell contact formation and axonal growth control. IgC2/FNIII molecules include 6 highly related components (Contactin 1 to Contactin 6), associated with the cell membrane via a Glycosyl Phosphatidyl Inositol (GPI)-containing lipid tail. Contactin 1 and Contactin 2 bear an about 50 (49.38)% similarity at the aminoacid level. They are components of the cell surface, from which they may be released in soluble forms. They undergo homotypic interactions, but bind also heterophilically with multiple partners in cis and trans, including members of the related L1CAM family and Contactin-associated proteins (CNTNAPs or CASPRs). Such interactions are important for organising the neuronal membrane, as well as for modulating the growth and pathfinding of axon tracts. In addition, they also mediate the functional maturation of axons by promoting their interactions with myelinating cells at the nodal, paranodal and juxtaparanodal regions. Such interactions also mediate differential ionic channels (both Na^+ and K^+) distribution, which is of critical relevance in the generation of the peak-shaped action potential. Indeed, thanks to their interactions with Ankyrin G, Na^+ channels map within the nodal regions, where they drive axonal depolarization. On the other hand, no ionic channels map in the flanking Contactin-1-containing paranodal regions, which, thanks to interactions with the Neurexin family CASPR-1 protein and with the Ig superfamily component Neurofascin 155, build a molecular sieve towards the juxtaparanode, where K^+ channels are rather clustered, depending upon molecular interactions with Contactin 2 and the associated neurexin family components CASPR2. Besides in functional organization of axonal domains, nodal, paranodal and juxtaparanodal regions are also of relevance in inflammatory and degenerative disorders, which still imply interactions of the Contactin

molecules. Indeed, Contactin-1 drives Notch signalling activation via the Hes pathway, which is related to its ability to modulate neuroinflammation besides neurodevelopmental events. This is in turn consistent with the possibility that Contactin 1-dependent intreractions participate to the pathogenesis of the Multiple Sclerosis and of other inflammatory disorders. On the other hand Contactin 2 is rather involved in neurodegenerative disorders with a special reference to the Alzheimer disease, given its ability to work as a ligand of the Alzheimer Precursor Protein (APP), which results in increased AICD release in a γ-secretase-dependent manner.

Introduction

The development of the nervous tissue requires the coordination of several processes, including precursor proliferation and migration, neurite growth and fasciculation, axonal pathfinding control and synaptogenesis (see for instance Borodinski et al., 2015; Missaire and Hindges, 2015; Mitsuhashi and Takahashi, 2009). Most of them implicate interactions of neuronal surface glycoproteins with components of the adjacent cell surfaces or of the extracellular matrix (Schmidt and Rathjen, 2010; Giger et al., 2010; Barros et al., 2011; Vitriol and Zheng, 2012; Hirano and Takeichi, 2012; Frei and Stoeckli, 2014; Petrovic and Shumker, 2015). The molecular players in such events fulfil the operational definition of adhesion molecules since a relevant role for them is to promote and/or stabilize cell interactions. While being of structural relevance, such interactions may also have a more functional meaning, since cell adhesion is also a source of signals known to modulate events involved in nervous tissue development (Ebel et al., 2014; Hildebrandt and Dityatev, 2015). On this basis, such molecules fulfil the operational definition of morphoregulatory molecules proposed in earlier studies (Edelman, 1992; Edelman and Jones, 1997).

In this review, we consider the properties of a family of adhesion molecules whose expression is tightly regulated during development, consistent with roles during both early neurogenesis and the later stages of neural differentiation, and whose functions extend beyond simple adhesion, encompassing the generation and modulation of morphoregulatory signalling that controls the molecular composition and organisation of the cell surface according to context. We also consider emerging evidence that changes in the expression of these molecules underlie the genesis of specific neurological disorders.

Morphoregulatory molecules may belong to distinct families of adhesion receptors, the main

grouping being the Cadherins (Basu et al., 2015; Friedman et al., 2015; Gartner et al., 2015), the Integrins (Gardiner, 2011) and the Immunoglobulin superfamily (IgCAM, Maness and Schachner, 2007). Based on their interactions, these molecules may be differentially involved in distinct aspects of neural developmental control (Yogev and Shen, 2014). Broadly speaking, adhesion mediated by Cadherins is strong, overcoming that of other adhesion molecules (Thiery et al., 2012). Classically, cadherins are thought to mediate cell-cell interactions, while integrins mediate those between cell and matrix, though this simple classification is confounded by complex interplay among the molecules (Weber et al 2011; Mui et al., 2016). In any case, the critical developmental role for such molecules depends upon their ability to mediate homo-or heterophilic interactions. For example, in the earliest developmental stages, strong homophilic calcium-dependent cell interactions involving the function of Cadherin family components contribute to the control of events of key ontogenetic relevance such as germ layer separation (Stepniak et al., 2009; Hirano and Takeichi, 2012; McKeown et al, 2013; Barriga and Mayor, 2015; Hayashi and Takeichi, 2015; Duband et al., 2015). However, it is also worth mentioning that members of the same family may mediate the control of later developmental events as neurite growth (Gartner et al., 2012; 2015; Hayashi et al., 2014; Stoeckli, 2014). The functional complexity of these events and their articulated role in neural development is further supported by the evidence that components of distinct gene families may contribute to such events, which may involve either adhesive as the Immunoglobulin (Ig) supergene (Maness and Schachner, 2007) or repellent as the Semaphorin (Pasterkamp et al., 2012; Jongbloets and Pasterkamp 2014) families components. As far as axonal growth is concerned, such a molecular and functional complexity suggests that regulating the expression of the genes encoding such molecules represents an aspect of critical functional relevance (Yogev and Shen, 2014).

This review article will focus on those members of the Immunoglobulin supergene family (IgSF), which are composed of Ig C2-type (IgC2) domains at their N-terminus and Fibronectin type III (FNIII) domains grouped in tandem in the membrane-proximal region. Because of this overall organization, those adhesive glycoproteins may be collectively denominated IgC2/FNIII molecules,

and represent a typical model for adhesive/morphoregulatory molecules expressed at the axonal level. The IgC2 and FNIII domains have similar structural cores (Cota et al., 2001) and likely share a common evolutionary origin. This family undergoes complex interactions with members of the same and different families (Ozkan et al., 2013) and the genomic complexity of family members reflects organismal complexity (Vogel and Chothia, 2006), suggesting roles in elaborating developmental complexity. Like many cell surface molecules, members of the IgC2/FNIII family can be found anchored to the membrane via a typical transmembrane domain, or via a Glycosyl Phosphatidyl Inositol (GPI)-containing lipid tail. We will focus on the latter, specifically the Contactins.

The Contactin family of cell adhesion molecules

Contactins were named to reflect their preferential location at sites of cell to cell contact (Ranscht, 1988). This subfamily comprises six different members (CNTN1-CNTN6; Shimoda and Watanabe 2009), which share the same overall organization, including 6 N-terminal IgC2 domains, associated with 4 C-terminal FNIII repeats, followed by a hydrophobic C-terminal aminoacid sequence, characteristic of most GPI-linked proteins, the processing of which results in their lipid anchorage (Low, 1989). Where it has been studied, the contactins are secreted from cells as well as being found at the cell surface (Ruegg et al., 1989; Furley et al., 1990; Gennarini et al., 1991), apparently the result of specific secretion processing rather than cleavage from the cell surface (Ruegg et al., 1989).

Contactins share in the order of 45-65% protein sequence identity (Yoshihara et al, 1995; Ogawa et al., 1996). The preservation of a clear overall topology of domain organisation suggests that this family arose as the result of a gene duplication event, which occurred after divergence of the ancestral gene from its nearest relatives, the transmembrane-bearing L1 family components, DsCAMs and SideKicks (Yamagata and Sanes, 2012), reflected in the presence of just one member of each of these families in Drosophila (Faivre-Sarrailh et al., 2004; Yamagata, et al., 2002;

Schmucker et al., 2000; Bieber, A. J. et al., 1989).

Since the role of CNTNs 3-6 are considered elsewhere in this issue, here we focus specifically on CNTNs 1 and 2, the first discovered and consequently most widely studied. However, we begin with a brief overview reflecting on the general properties of the subfamily.

The Contactins: developmental role

The Contactins, notably CNTN1 and 2, were identified initially as axonal glycoproteins expressed during neural development that had the property of stimulating or inhibiting axonal growth according to context (Furley et al., 1990; Gennarini et al., 1991; Durbec et al., 1992; Buttiglione et al., 1996; 1998). The other striking feature of such molecules is in their differential developmental profile. Indeed CNTN2 was initially named TAG-1 (Transient Axonal Glycoprotein), being expressed relatively early in neuronal maturation (Dodd et al 1988), when it appears to be engaged in neuronal polarisation (Namba et al 2014), while CNTN1was found associated with more mature stages (Gennarini et al 1989; Perrin et al 2001; Stoeckli, 2010). Subsequently, it has become clear that while some members are expressed in most neurons at some stage (for example, late stage expression of CNTN1 is common to most if not all neurons), others are restricted to subsets of neurons (CNTN5, for instance, is preferentially expressed in central auditory pathways and its loss leads to auditory deficits; Li et al 2003). The differential expression of these related proteins, gives exquisite control of the construction of neuronal circuits, as is beautifully shown in the case of the developing retina, where the family, together with its close relatives (Sidekicks and Dscams), is found to play a critical role in the definition of laminar specificity, dictating both the location of cell bodies and the development of axons tracts in specific sublaminae (Yamagata et al., 2002; 2008; Yamagata and Sanes 2012).

Mechanistically, laminar specificity in the retina is thought to be mediated in part by homophilic interactions among the contactins (and among Sidekicks and Dscams), which are expressed by largely non-overlapping subsets of distinct retinal subpopulations and project to the same sublaminae. Thus, differential expression of the genes encoding these homophilically binding

surface proteins allows the sorting of neurites expressing the same proteins, effectively consituting an IgSF code for layer-specific neurite targeting (Yamagata and Sanes, 2012). Whether this sorting is the result of selective fasciculation or selective synapse formation, or some combination of these is unclear, as contactins are known to be involved in both processes (Sittaramane et al., 2009; Walsh & Doherty 1997; Takeda et al., 2003; Murai et al., 2002)

However, although CNTN2 and CNTN4 bind homophilically (Furley et al 1990; Rader et al., 1993), CNTN1, 3 and 5 do not (Yamagata & Sanes 2012). Nonetheless, neurites expressing the latter still project together with other neurites expressing the same contactin, implying that these may promote laminar specificity via heterophilic interactions. Indeed, many heterophilic partners of contactins have been identified, varying according to family member, but in some cases these partners fall into families themselves. Notable among these are the related L1 family, comprising 4 members (L1/NgCAM, NrCAM, Neurofascin and CHL1; Maness & Schachner 2007), Amyloid Precursor Proteins (APP, APLP1, APLP2; Ma et al 2008; Osterfield et al 2008) and the contactin-associated proteins (CNTNAP/CASPR1-5; Gollan et al., 2002; 2003; Horresh et al., 2008; 2010; Arroyo et al., 2001; Traut et al., 2006). These interactions can occur in trans or in cis (in some cases both) and provide the means by which the GPI-anchored proteins can interact with the cytoskeleton. The significance of these will be discussed in detail in relation to CNTN1 and 2 below.

Overall, the above data indicate an important role for the coordinated expression of Contactins and their associated molecules in the organisation of neuronal perikaria, in the modulation of axonal growth and in synapse formation, dependent upon homo- and heterophilic interactions. It is clear, however, that contactins continue to play a role at later stages, not only in neurons but also in myelinating cells and other glia. Most significantly, the contactins, in molecular complex with L1 family members and CASPRs, play a critical role in the organisation of interactions between neurons and myelinating cells at the level of the nodal, paranodal and juxtaparanodal regions, critically governing the positioning of both Na^+ and K^+ channels to the node and juxtaparanode respectively (Falk et al., 2002; Labasque and Faivre-Sarrailh, 2010; Buttermore

et al., 2013; Salzer et al. 2015), a separation which is vital to the mechanisms leading to action potential generation and conduction.

Much of the focus of the above has been on the role of contactins in post-mitotic events, but increasing evidence indicates they have roles in the modulation of proliferating precursor behaviour. This appears to take the form either of contactins being markers on mature cells that are detected by precursors as feedback signals to trigger or inhibit differentiation (Bizzoca et al 2003; Xenaki et al 2011), or that the contactins are themselves present in the proliferating precursors and part of the apparatus modulating precursor behaviour (Ma et al 2008; Bizzoca et al 2012; Okamoto et al 2013).

Since much of the work on the early roles of contactins, and their roles in dictating the distribution of ion channels in myelinated axons, relates to Contactins 1 and Contactin 2, this review article will focus on these proteins, while the functional roles of Contactins 3 to 6 have recently been explored (Mohebiany et al., 2014; Zuko 2011), and will be part of a different review article in this same Special Issue.

The Contactin 1-2 glycoproteins:

Contactin-1 is the name given to an axonal adhesive glycoprotein originally denominated Contactin or F11 in chick (Ranscht, 1988; Brummendorf et al., 1989) and F3 in rodents (Gennarini et al., 1989 a,b), while Contactin-2 was formerly denominated Transient Axonal Glycoprotein (TAG-1) in rodents (Yamamoto et al 1986; Dodd et al., 1988; Furley et al., 1990), Axonin1 in chick (Ruegg et al 1989; Zuellig et al, 1992) and TAX-1 in humans (Tsiotra et al., 1993; Hasler et al 1993).

Contactins 1 and 2 are closely related to each other in structural terms sharing nearly 50% identity at the aminoacid level (Figure 1) and a similar overall organization (Figure 2A). Classically, both molecules have been shown to stimulate the outgrowth of neurites when presented as substrates (Rathjen et al 1987; Furley et al 1990; Stoeckli et al., 1991; Gennarini et al., 1991) or as soluble molecules (Durbec et al., 1992) and antibodies to them cause defasciculation (e.g. Chang et al.,

1987). As noted above, CNTN2 can bind homophilically to cause cell and bead aggregation (Felsenfeld et al 1994; Rader et al., 1996; Yamagata & Sanes 2012), which is not true of CNTN1 which instead binds heterophilically (See figure 2). However, it is unclear whether homophilic binding occurs in cis or trans (Rader et al 1996; Mortl et al., 2007) and several studies indicate that CNTN2 neurite outgrowth stimulation critically involves heterophilic interactions with other CAMs, including ß1 integrins, L1/NgCAM and NrCAM (Kuhn et al., 1991; Felsenfeld et al 1994; Stoeckli et al 1996; Lustig et al 1999). Thus, both CNTN1 and CNTN2 stimulate axon growth using heterophilic interactions.

Importantly, the heterophilic interactions of CNTN1 and CNTN2 are both similar and distinct (Fig 2B), including shared partners such as L1 and NrCAM, but also interactions that are specific to each, such as Notch with CNTN1 (Hu et al., 2003) and CNTN2 wih APP (Ma et al., 2008). In some cases, although not shared, interactions are with sister molecules, for example CNTN1 binds to CASPR1 while CNTN2 binds to CASPR2 [N.B. In this instance, the binding of CNTN1 to CASPR2, and of CNTN2 to CASPR1, has been tested (Poliak et al 2003), although this is not true for all of the interactions shown in Fig 2B; see legend].

The functional consequences of this variety of interactions is by no means fully understood, but it is clear that the combination of interactions involved and the relative disposition of the components can change the functional outcome significantly. For example, while a cis interaction between CNTN1 and NrCAM stimulates the extension of dorsal root ganglion (DRG) sensory axons on an RPTPß substrate (Sakurai et al., 1997), cerebellar granule neuron axon extension is inhibited by a Tenascin-R substrate for which CNTN1 is the neuronal receptor (Pesheva et al 1993), indicating that the role played by Contactins varies according to cellular and molecular context. This is very much reflected in phenotypes arising from both loss of function and gain of function experiments *in vivo* which will be considered below

Altogether, these results indicated that neurite growth control was a relevant consequence of Contactin 1 expression and suggested that this function implied the activation of a signalling

mechanism. An effect on neurite growth was also observed in the case of Contactin 2 (Furley et al., 1990) whose expression, in addition, correlated with positive effects on granule cells precursor migration (Wang et al., 2011).

These data indicated that, although provided with differential expression profiles, these molecules shared the ability to drive axonal elongation of primary neurons, which, in turn, allowed their definition as neurite growth-promoting molecules. To address the significance of the expression profiles of these molecuìes, *in vivo* models were also adopted.

Significance of Contactins expression as deduced by the use of in vivo models

1.Phenotype of Contactin 1 null mutant mice.

Contactin 1 null mutant mice (Cntn1ko; Berglund et al., 1999) exhibited a cerebellar phenotype in which cerebellar volume was reduced by ~25% and the parallel fibres of granule cell neurons were misoriented, indicating an effect on axon guidance, but not growth. There was no evidence of gross parallel fibre defasciculation, but axons within bundles were slightly less compact, and mutant granule neurons in culture grew completely defasciculated. Dendritic elaboration from both granule cells and from Golgi neurons were also severely affected, although that of Purkinje neurons was not. However, The cerebellar size was reduced and the parallel fibres were misoriented. In addition, an axonal defasciculation occurred in mutant mice and Purkinje neuron axons exhibited aberrant morphologies. Therefore the cerebellar circuitry was heavily perturbed in Contactin 1 null mice and functionally this morphological phenotype resulted in severe ataxia and postnatal lethality (Berglund et al., 1999).

It seems unlikely that Cntn1ko lethality is due simply to cerebellar dysfunction and indeed further analysis revealed myelination defects in the peripheral (Boyle et al., 2001) nervous system. specifically, changes in the organisation of nodal and paranodal regions of the node of Ranvier. Normally, CNTN1 is located in the PNS in the paranode, the septate-like junction that separates the node, where the Na channels required to propagate the action potential are located, from the juxtaparanode where the Shaker-type voltage-gated K channels (Kv1.1/1.2) required for re-

polarisation reside (Fig 3). Loss of CNTN1 widens the gap between the axolemma and the myelin loop at the paranode and disrupts the junction resulting in the mislocalisation of the Kv1.1/1.2 channels into the node and a concomitant reduction in conduction velocity. Within the paranode, CNTN1 loss leads also to loss of its cis binding partner CASPR1 on the axolemma and of their trans, L1-like binding partner, Neurofascin 155 (NF-155) from the myelin loops. This is mirrored in CASPR1 null mice, which also have defects in conduction velocity, mislocalised Kv1.1/1.2 channels and, importantly, an absence of CNTN1 on the axolemma (Bhat et al., 2001), consistent with CNTN1 and CASPR1 being mutually dependent for trafficking to the cell surface (Peles et al 1997). CASPR1 mutants also display ataxia and have similar swellings in their Purkinje cell axons, which appears to be due to the aberrant accumulation of mitochondria and smooth endoplasmic reticulum at the nascent paranodes, but exhibit no defects in parallel fibre orientation (Pillai et al 2007). Together this indicates that although CNTN1 and CASPR co-operate in the organisation of the paranode, CNTN1 functions without CASPR to establish parallel fibre orientation and, moreover, that the latter defect is unlikely to contribute to the lethality seen in these mutants.

Contactin 2 expression and developmental role

Contactin 2 expression was first characterised by antibody staining of developing rodents, where it is seen transiently on subsets of neurons in the developing spinal cord and brain associated with the early stages of neuronal differentiation and axonogenesis (Yamamoto et al., 1986; Dodd et al., 1988). Most famously it is expressed by commissural spinal relay neurons as they extend to the floor plate, but is turned off after these axons turn orthogonally to ascend to the brain after crossing the midline, after which they instead express L1/NgCAM (Dodd et al., 1988; Karagogeos et al., 1991) and CNTN1 (Perrin et al., 2001). However, CNTN2 is also seen transiently on a number of other developing axon types, including spinal motor and sensory axons, retinal ganglion cell axons, axons in the olfactory nerve, the cortex, midbrain and cranial nerves (Yamamoto et al., 1986; Dodd et al., 1988). It is not on all axons, for instance it is never seen in sympathetic neurons, on Purkinje cells or in ipsilaterally projecting spinal relay neurons, and in some tracts, the corpus callosum for

example, only subsets of axons are labelled (Dodd et al., 1988; Yamamoto 1986; Stottmann and Rivas, 1998). In some regions, notably the cerebellum, it is also found on the cell bodies of migrating granule neuron precursors (Pickford et al., 1989; Furley et al., 1990; Yamamoto et al., 1990), including on cells which label with cell cycle markers (Xenaki et al., 2011), indicating that it can be found on proliferating precursors.

Knockout of Cntn2 (Cntn2ko) in mice has not revealed evidence a critical role in some of the key systems in which it has been implicated from its expression profile. Two independent Cntn2ko mutants are each homozygous viable and display no gross phenotypes in the brain or spinal cord (Fukamauchi et al 2001; Poliak et al., 2003), although a predisposition to seizures (Fukamauchi et al., 2001) and failure to gain weight in response to high fat diet (Buchner et al. 2012) have been reported. Extensive axon tracing analysis of commissural axon trajectories revealed no evidence (Yeomans, Kiernan and Furley, unpublished) of the dramatic pathfinding defects found using a variety of acute function blocking methodologies in chick (Stoeckli & Landmesser, 1995), where CNTN2 has been implicated in interactions with midline-expressed NrCAM in the switching of C axon sensitivities to floor plate-derived repellants (Stoeckli et al., 1997; Pekarik et al., 2003), one of which has been identified to be Semaphorin3B (Nawabi et al., 2010). Similarly, antisense RNA and antibody blocking techniques have suggested a role for CNTN2 in parallel fibre alignment or extension in cerebellar granule neurons (Baeriswyl & Stoeckli, 2008; Wang et al., 2011), yet Cntn2ko animals display only subtle effects on granule neuron progenitor migration (Xenaki et al., 2011). While some of these differences may be due to the species used for investigation (chick vs rodent), more likely is that compensatory mechanisms operate in germline nulls that are not able to function in acute knockdown experiments, as has recently been demonstrated in zebrafish (Rossi et al., 2015).

Nonetheless, Cntn2ko animals do exhibit subtle phenotypes that have given important insight into CNTN2 function. Consistent with earlier work in chick that used function blocking antibodies to disrupt CNTN2 function in ovo (Shiga et al., 1997; Perrin et al., 2001), Law et al

(2008) demonstrated that nociceptive sensory fibres from the DRG enter the dorsal horn of the spinal cord prematurely in Cntn2ko mice. Although Perrin et al. (2001) had interpreted this to represent premature defasciculation of nociceptive fibres from the dorsal root entry zone, in vitro analysis of DRG from Cntn2ko animals revealed these fibres to be insensitive to repellants in the spinal cord that normally repel wild type sensory axons, including Semaphorin3A to which Cntn2ko growth cones showed reduced sensitivity (Law et al., 2008), as had been previously shown for growth cones lacking L1 (Castellani et al., 2000).

Subsequent studies revealed that like L1 (Castellani et al., 2002, 2004), CNTN2 forms a complex with neuropilin1 (NRP1) on the cell surface (Dang et al., 2012); together with PlexinA4, NRP1 is a core component of the Sema3A receptor. However, unlike L1, CNTN2 was not required for NRP1 endocytosis upon Sema3A binding, but instead facilitated the intracellular trafficking of NRP1 and PlexinA4 into lipid raft-enriched vesicles away from co-endocytosed L1, which instead is trafficked into Rab11+ recycling endosomes (Dang et al., 2012; Dang & Furley, unpublished). In the absence of CNTN2, Sema3A-induced CRMP2 phosphorylation, a key signalling readout of PlexinA4 activation (Uchida et al 2005) does not occur.

There remains some uncertainty about which semaphorins are critical to the guidance of spinal sensory axons in vivo: whereas similar defects are seen in Sema3A mutants in the central branches of nociceptive axons in NRP1 knockouts animals (Gu et al 2003), loss of NRP1 or of Sema3A also affects the peripheral branches, whereas loss of CNTN2 does not (Law et al., 2008; Liu & Halloran 2005), suggesting that the in vivo effects of CNTN2 loss may reflect sensitivities to other Semas, for example Sema5B (Liu et al., 2014).

The fact that CNTN2 loss in sensory axons affects just one branch of their bipolar projection, suggests the intriguing possibility that it may play a role in the establishment or maintenance of axonal polarity. This is coherent with observations that antibodies to CNTN2 block the emergence of parallel fibres from granule neuron progenitors and inhibit radial migration, leading to an accumulation of immature cells in the external granular layer (EGL; Wang et al.,

2014), consistent with the delayed maturation of GNPs seen in Cntn2ko mice (Xenaki et al., 2011). Similar observations have been made in the pioneering of the medial longitudinal fascicle of zebrafish (Wolman et al 2008). Moreover, recent data reveals that CNTN2 shRNA knockdown during cortical neurogenesis affects both interkinetic nuclear migration of neural precursors (Okamoto et al., 2013) and the polarisation of newly born neurons (Namba et al 2014), depending on the timing of the knockdown. In early corticogenesis, CNTN2 is found restricted to the basal process of radial neural progenitors and shRNA knockdown results in the accumulation of undifferentiated progenitors near the apical (ventricular) surface due to a failure of knockdown cells to extend a basalward process after apparently symmetric divison at the ventricle (Okamoto et al 2013). At later times, when such divisions become asymmetric and give rise to neuronal progenitors, the nascent neurons fail to polarise to generate an axon (Namba et al., 2014). In both situations, it appears that CNTN2 is required to establish a polarised, basally-projecting process.

Given that CNTN2 is continuely endocytosed and can affect the trafficking of heterologous surface molecules, including L1s, NRPs and Plexins, (Dang et al., 2012) in addition to CASPRs, this suggests that homophilic contact with $CNTN2^{+}$ early-born neurons, stabilises CNTN2 at the surface and begins the process of recruiting the components required to establish polarity by trapping of molecules being co-trafficked with CNTN2. Given that CNTN2/L1-mediated contacts might also negate or reverse responses to Semaphorin3A (Castellani et al 2000; Dang et al., 2012), it is interesting to note that Sema3A also has a role in establishing neuronal polarity (Shelly et al., 2011).

Finally, CNTN2 has a role in myelination, in many respects mirroring that of CNTN1. CNTN2 also associates with a CASPR, CASPR2, and is localised to a subregion of the nodal structure, though in this case the juxtaparanode, where it is found complexed with Kv1.1/1.2 channels (Fig 3). Loss of CNTN2 does not lead to a breakdown of the paranode, but instead localisation of the K channels to the juxtaparanode is disrupted (Poliak et al., 2003), which is is mirrored in the CASPR2 knockout (Poliak et al 2003; Traka et al 2003). As for CNTN1 and

CASPR1 at the paranode, CNTN2 and CASPR2 localisation at the juxtaparanode is also co-dependent (Poliak et al., 2003; Traka et al., 2003). A significant difference, however, is that in this instance an L1-like ligand for CNTN2 is not involved. Instead, CNTN2 expression on the enveloping glia is sufficient to localise CASPR2 and the Kv1.1/1.2 channels (Savvaki et al 2010), although CNTN2 is also expressed on the enveloped axon. Loss of Kv1.1/1.2 channel localisation has no apparent effect on nerve conduction (Poliak et al., 2003; Traka et al., 2003), however Cntn2ko animals exhibit behavioural deficits and defects in sensori-motor gating and motor co-ordination (Savvaki et al., 2008).

Together these experiments show that contactins (and the related L1-like CAMs) have important roles to play in the trafficking and positioning of interacting membrane components into specific domains of the cell surface and also in the modulation of responses to heterologous signals

Contactins expression in non-neuronal cells and the generation of action potentials

The studies reviewed above point to important roles for Contactins 1 and 2 in the generation of neuronal action potentials in the peripheral nervous system, though, as noted, CNTN2 expression is only required in the myelinating glia, not the axolemma (Savvaki et al 2010). In fact, glial expression of contactins was first described for CNTN1 (Koch et al., 1997) where it was found in oligodendrocyte-lineage cells, suggesting there may be differences between the PNS and CNS. Indeed, while bearing some features in common, in the central nervous system, Contactin-1 was found to be expressed not only at the paranode, but also in the juxtaparanode and in the node itself (Peles and Salzer, 2000; Boyle et al., 2001; Savvaki et al., 2010). This is especially relevant for ion channel distribution: in the central nodes, CNTN1 was found associated with Neurofascin 186 (Nfasc186) and NrCAM, in a complex that includes the Na channel β□ subunit, an interaction that is required for functional activity and expression of the latter (Kaplan et al., 2001; Rios et al., 2003; McEwen and Isom, 2004 *a b*). However, this interaction also required submembrane interactions with Ankyrin G (AnkG; Berghs et al., 2000) and β–IV spectrin (Bennett and Lambert, 1999; Ogawa et al., 2006; Chang et al., 2014; Boiko et al., 2001; Komada and Soriano, 2002; Salzer,

2003; McEwen et al., 2004), which in turn are stabilized by Tenascin R (Weber et al., 1999, Figure 3). By contrast in the peripheral nervous tissue, where CNTN1 is not found in the node, Gliomedin was proposed to play a role in ionic channels clustering, in particular through interactions with NrCAM (Feinberg et al., 2010, Figure 3). As we have seen above, in the periphery instead CNTN1 plays a role in the integrity of the paranode, which separates the nodal Na channels from the flanking juxtaparanodal region where the delayed rectifier potassium channels Kv1.1 and 1.2 are located (Rhodes et al., 1997; Wang et al., 1993; Poliak et al., 2003; Traka et al., 2003; Chatzopoulou et al., 2008) (see Figure 3).

These interactions are then of critical relevance in the generation of functional myelin, and therefore of action potentials (Zhou et al., 1998; Tait et al., 2000; Buttermore et al., 2013; Gordon et al., 2014), indicating a critical role for the regulated expression of Contactin family components in these processes (Boyle et al., 2001; Kazarinova-Noyes et al., 2002; Freeman et al., 2016; Buttermore et al., 2013; Salzer et al., 2015). In addition, a comparable organization is shared by the axonal initial segment (AIS), in which action potentials are generated based on the overall input reaching this region from the perikarya. This region extends about 40 μm from the axon hillock (Hedstrom and Rasband, 2006) and it includes both Na channels, which span the whole region, and K channels, which are rather clustered in the distal juxtaparanodal region. As in the node, the location of Na Channels ($Na_v1.2$ and $Na_v1.6$) in the AIS involves AnkG (Hedstrom et al., 2007; Zhou et al., 1998; Gasser et al., 2012; Buttermore et al., 2013), and also Neurofascin 186 (Zonta et al 2011). Contactin 1 is not present at all in the AIS, but CNTN2 is present in the AIS juxtaparanode, along with CASPR2 (Ogawa et al., 2008). However, unlike in the node of Ranvier, in the AIS, loss of CNTN2 (and therefore CASPR2) does not appear to affect the distribution of the Kv1 channels with which they normally cluster (Duflocq et al., 2011). Together these data indicate that the axon initial segment bears several features in common with the node of Ranvier, including the involvement of one of the contactins (CNTN2), although in this instance their function is not

critical, perhaps reflecting some redundancy with other contactins known to be expressed in glia (Cui et al 2004; Hu et al 2006).

Potential significance of regulated expression of Contactins 1 & 2

As noted above, although CNTN1 and CNTN2 have distinct molecular interactions, they also share a number of partners and properties. This suggests that their differential expression may be a critical feature of their distinct function in development. Contactins 1 and 2 are encoded by different genes, *CNTN1* and *CNTN2*, mapping to human chromosomes 12q12 (Berglund and Ranscht, 1994) and 1q32 (Tsiotra et al.,1993; Kozlov et al 1995), respectively (15E3 and 1E4 in mouse). As we have seen, CNTN1 is associated with later stages of neuronal differentiation and is more generally expressed than CNTN2. This is especially evident as GNPs of the cerebellar cortex mature: CNTN2 expression begins earliest, on premigratory precursors in the external granular layer in developing cerebellar cortex, a subset of which, located at the boundary between the outer and inner EGL (iEGL), are proliferating (Xenaki et al., 2011, see also figures 4A-D).. By contrast, CNTN1 expression overlaps only with the innermost CNTN2-expressing cells (Fig 4Ab) in the iEGL which do not express cell cycle markers.

As an alternative approach to understanding the role of these proteins in this differentiation process, gain of function experiments were conducted using elements of the *Cntn2* regulatory apparatus to drive *Cntn1* gene expression (Bizzoca et al 2003). The *Cntn*2 gene, comprising 23 exons, spans more than 40 Kbp of human chromosome 1 (1q32.1), where it lies 'head to head' with the gene encoding Neurofascin, its L1-like relative (Hadas et al., 2013). The basal promoter region of the human gene maps upstream of the first non-coding exon which, together with the 11kb first intron, is sufficient to largely recapitulate the profile of the endogenous mouse *Cntn2* gene in neural cell lines and transgenic animals (Kozlov et al., 1995; Bizzoca et al., 2003).

In the cerebellum, ectopic expression of CNTN1 using this promoter element, in so-called 'TAG/F3' transgenic mice, had a transient, but dramatic effect on cerebellar growth (Fig. 5), delaying its expansion by 25% due to an inhibition of GNP proliferation in the first postnatal week

(Bizzoca et al., 2003, 2009). Subsequent analysis of wild type GNP proliferation in culture demonstrated that a soluble form of CNTN1 was able to suppress proliferation induced by the mitogen Sonic Hedgehog (SHH; Xenaki et al 2011), which normally is produced by Purkinje cells in vivo to support granule neuron expansion in the early postnatal period (Wallace 1999; Wechsler-Reya & Scott 1999; Dahmane & Ruiz I Altaba, 1999). Suppression of SHH-induced GNP proliferation by soluble CNTN1 was shown to be due to its binding to NrCAM (Xenaki et al., 2011). The suppressive effect of premature CNTN1 expression in the cerebellum was interpreted to reflect that CNTN1, which is normally expressed on maturing post-mitotic granule neurons, may provide a feedback signal to proliferating GNPs to co-ordinate cell cycle exit and orderly differentiation (Bizzoca et al., 2003).

However, this phenotype is not obviously consistent with the reduced cerebellar size of Cntn1ko mutants (Berglund et al., 1999), although the reason for the latter reduction has not been explored in detail. The knockout is a complete null, affecting expression in all cell types, not just neurons, and so the phenotype may also be due to earlier effects on glia or progenitor cells, as indeed may be the case for the TAG/F3 phenotype. As we have seen, CNTN1 is expressed in mature glia and we shall see below that its ectopic expression in other neurogenic areas affects the behaviour of neural progenitors. It is also likely that CNTN1 has different effects according to context and the binding partners (*cis* and *trans*) that are present. Moreover, it is clear that CNTN1 can both elicit signals in a cell to which it binds and generate signals in the cell in which it is expressed (Revest et al., 1999), making it possible that ectopic expression in novel molecular environments cannot directly be equated to loss of function.

Since the promoter element used in the TAG/F3 mice recapitulates a substantial part of normal CNTN2 expression, ectopic expression of CNTN1 is not limited to the cerebellum (Bizzoca et al 2003; Bizzoca et al., 2012; Puzzo et al., 2013). In contrast to results from the cerebellum, in the early developing cerebral cortex, ectopic CNTN1 expression from the *Cntn2* regulatory region – known to be expressed in cortical neural progenitors (see above) - was found to promote neural

precursor proliferation in the subventricular zone and reduce cell cycle exit (Bizzoca et al., 2012). Upon closer inspection, however, it was also clear that this was accompanied by a suppression of neurogenesis, in a manner reminiscent of the effect of activating Notch in this region (Gaiano et al., 2000; reviewed in Imayoshi et al., 2013; Tiberi et al 2012; Pierfelice et al 2011; Cau and Blader 2009), which is discussed in detail below. Importantly, these studies highlighted that CNTN1 itself, often assumed to be a post-mitotic marker, in fact is normally expressed in proliferating cells of the cortical ventricular zone, though the precise identity and state of these cells has not been determined. Thus, these transgenic experiments demonstrate that the precise regulation of contactin expression at all stages of neurogenesis is critical.

Similar effects were seen in the developing hippocampus, where CNTN1 expression is normally observed in the neurogenic region and on both granule and pyramidal neurons and their axonal extensions (Virgintino et al., 1999). Ectopic expression of CNTN1 in development causes a similar suppression of neurogenesis to that seen in the cortex (Puzzo et al., 2013). However, in the adult, where neurogenesis is known to continue (Kemperman et al 2015) the opposite was seen, where neurogenesis was sharply increased as a consequence of the presence of the TAG/F3 transgene, resulting in increased hippocampal size and, in older mice, evidence of enhanced learning and memory: including elevated long term potentiation in CA1, increased pCREB levels and enhanced performance in spatial and object recognition tests (Puzzo et al., 2013).

Seemingly at odds with the suppression of neurogenesis in early development, these results suggest either that the mode of CNTN1 action changes with time just as the potential of the neural stem/progenitor cells is known to vary, for example, in the layering of the developing cortex. Alternatively, because the TAG/F3 transgene is expressed throughout development, it is also possible that early expression, through its inhibition of early neurogenesis, has ‘set aside’ larger numbers of long-lived neural stem cells that survive into the adult.

In any event, together these observations strongly support the view that the mechanisms which drive regulated expression of the contactins is a critical component of their precise function

in vivo. In the next section we briefly review what is known about the transcriptional regulation of the genes encoding the contactins.

Mechanisms which drive differential Contactin genes activation.

The regulatory regions of the mouse *Cntn1* and *Cntn2* genes have both been characterized. These regions display a different level of complexity: compared to the *Cntn2* gene (described above) the mouse *Cntn1* promoter was found to span a very large genomic region, overcoming 100 Kbp in size and including four alternative non-coding exons, three of which associated with distinct alternative 5' neuro-specific promoters, provided with a differential activation profile and undergoing a complex splicing mechanism (De Benedictis et al., 2001; Cangiano et al., 1997; Figure 6 A-C). The activity of the most 5' A1 exon-associated promoter was found to undergo only minor developmental changes, suggesting that it contributed to the basal *Cntn1* gene expression; on the other hand, the exon C1- and exon 0-associated promoters were significantly and transiently upregulated at the end of the first postnatal week (Figure 6D). The demonstration of multiple, alternative and developmentally-regulated promoter elements suggests that regulated developmental activations of the *Cntn1* gene implies both transcriptional and posttranscriptional mechanisms. In turn, such an organization was found to be of critical relevance in the definition of the Contactin 1 gene expression profile for which it carried all necessary molecular features. This was demonstrated by combining these elements into a single *Cntn1* promoter/EGFP reporter-construct which essentially recapitulated endogenous *Cntn1* gene expression (Figure 7, see De Benedictis et al., 2006). These data demonstrate that the *Cntn1* does indeed breakdown into components that are differentially regulated during development, but it remains to be seen whether different elements control expresssion in different cell types (e.g. neurons vs glia, astrocytes vs oligodendrocytes), or whether this is achieved by differential expression of common transcription factors.

A surprising result of this regulatory element characterisation was that mice carrying the condensed EGFP reporter construct exhibited a behavioural circling defect typical of basal ganglion dysfunction, which correlated with a downregulation of the endogenous CNTN1 protein in cells in

which the transgene was expressed at high level, which led to a significant downregulation of the protein particularly in the basal ganglia of adult animals and concomitant increase in the generation of dopaminergic neurons (Massaro et al., 2012). Exactly how this downregulation occurred is not understood, and whether this phenotype is directly due to CNTN1 downregulation awaits the generation of a conditional *Cntn1* mutant that can be directed to the basal ganglia, but such a phenotype at face value remains consistent with the general hypothesis that CNTN1 exerts an inhibitory effect on developmental neurogenesis.

Signalling mechanisms involved in axonal adhesive glycoproteins developmental function.

As noted above, (Bizzoca et al. 2012) the inhibition of neurogenesis observed as a consequence of Contactin 1 overexpression was strongly suggestive of, and demonstrated to correlate with Notch pathway activation, known for its ability to counteract neurogenesis (Imayoshi et al., 2013; Tiberi et al., 2012; Pierfelice et al., 2011; Cau and Blader, 2009). Indeed, the Contactin 1 effects on the neuronal lineage in the cerebral cortex typically reflected activation of the canonical Notch pathway through the Hes transcription factor (Bizzoca et al., 2012). In fact, a relevant indication of Contactin 1 ability to activate the Notch pathway was already available, thanks to the studies from the Zhicheng Xiao (Hu et al., 2003, 2006) laboratory, who demonstrated the Contactin 1 ability to promote oligodendrocyte differentiation, depending upon direct interactions of the molecule with the Notch receptor. This was in contrast, however, with the evidence that activation of Notch by its canonical ligands Delta or Serrate rather results in inhibitory effects on oligodendrocyte differentiation and therefore on myelination, still implying the Hes-dependent pathway activation (Wang et al., 1998; Jessen and Mirski, 2008; Woodhoo et al., 2009), thus sharing the same effects and mechanism activated on the neuronal lineage. However, at the same time the evidence was achieved that Contactin-1 interactions with oligodendrocyte Notch receptors resulted in the activation of the alternate Deltex1-dependent pathway which, in turn, promotes oligodendrocyte commitment and differentiation (Hu et al., 2003; 2006), thus resulting in positive

effects on myelination. This indicated that Notch pathway activation was a general consequence of Contactin 1 expression, and that this resulted in specific and opposite effects on the neuronal and, respectively, on the oligodendrocyte lineages, depending upon the activation of different signalling pathways.

Therefore, both Hes-1 and Deltex-1 dependent pathways were found to be activated by CNTN1 interactions, the former being responsible for early Contactin 1 inhibitory effects on the neuronal lineage (Bizzoca et al., 2012) and the latter for its effects in promoting oligodendrocyte differentiation (Hu et al., 2003). This strongly indicated that Contactin 1 interactions with the Notch receptors represents a pleiotropic effect, which, in fact, differentially contributes to the modulation of neural developmental events.

How these differential responses are elicited in these different scenarios is not understood. The work of Hu et al (2003) is interpreted to reflect interactions of CNTN1 on the axolemma with Notch on oligodendrocyte precursors, i.e. in a *trans* interaction. However, oligodendrocytes themselves express CNTN1 (Haenisch et al., 2005; Çolakoğlu et al., 2014) making it possible that *cis* interactions are involved, which may affect how Notch is trafficked; the trafficking pathways taken by Notch during signalling affects both the level and type of signal generated (Yap & Winckler 2015). This is pertinent to the TAG/F3 experiments in the cortex since ectopic expression of CNTN1 is induced in cells that may already express both CNTN1 and CNTN2 (it is not clear whether this is in the same or different cells), which suggests that it may be the levels, or the subcellular localisations of these proteins that is critical to the signalling outcome. Of particular interest, therefore, is the suggestion that CNTN1 and CNTN2 may compete for common receptors (Xenaki et al., 2011) and that the intracellular trafficking pathways subsequently taken by those proteins may be altered dependent on their association with contactins (Dang et al., 2012). It will be of interest in future to determine whether Notch trafficking is affected by its association with CNTN1.

Overall significance of Contactin 1 regulated expression

The overall idea therefore is that the *Cntn1* gene represents a typical exemple of a developmentally regulated component of the Immunoglobulin superfamily, whose expression regulates neurogenesis in different regions of the nervous tissue and that, in doing so, distinct signalling pathways are in turn activated. The most likely interpretation of the Contactin developmental role is therefore that the function of this molecule mostly results from its ability to promote signalling rather than driving adhesion *per se*. In turn, this supports the idea that the molecule fulfils the definition of morphoregulatory besides of adhesive molecule (Edelman GM, 1992; Edelman and Jones, 1997)..

Potential significance of Contactins expression in neurological disorders.

The use of transgenic mice models indicated that changes in the expression of Contactin family components may affect neural developmental events. In turn, such changes may reproduce the phenotype of specific neurological disorders, either inflammatory or degenerative in nature, consistent with the existence of a behavioural phenotype, indicative of changes in the cerebellar function, in TAG/F3 mice (Coluccia et al., 2004). These disorders may correlate with signalling pathways activation, which, in the case of Contactin 1, may concern either Notch or pCREB factors-associated pathways (Hu et al., 2003; 2006; Bizzoca et al., 2012; Puzzo et al., 2013), known to affect neural precursor proliferation/differentiation events and to be involved in either neurodegenerative or neuroinflammatory (Dragunow M, 2004; Shen J, 2014; Pozueta et al., 2013; Wei et al., 2011) disorders.

As for the latter, the most relevant one in which Contactins appear to be involved is Multiple Sclerosis (MS), in which cell- and antibody-mediated immunity against Contactin 2 have been demontrated (Derfuss et al., 2009; Boronat et al., 2012). As far as Contactin-1, its interaction with Notch receptors was similarly proposed to be involved in the evolution of such disorder, given its ability to promote the remyelination events in the damaged nervous tissue (Aparicio et al., 2013).

As a general rule, the potential role of Contactin family components in demyelinating

disorders was suggested by the demonstration of antibodies to Contactin 1, Contactin 2 and to further components of the nodal complex as Neurofascins, Caspr1 and Caspr2 in chronic inflammatory demyelinating polyneuropaties (Stathopoulos et al., 2015; Miura et al., 2015, Labasque et al., 2014, Querol et al., 2013; Lancaster and Dalmau, 2012), which supports the hypothesis that, in such disorders, these molecules may work as autoantigens. The corresponding autoantibodies were found to belong to either the IgG1 or IgG4 subclasses (Manso et al., 2016) and to affect the integrity of the paranodal region (Kuwabara et al., 2015; Doppler et al., 2015), which could contribute to specific effects observed on the conduction velocity. Besides in demyelinating neuropathies, changes in the expression of the *Cntn1* gene were also demonstrated in some forms of familial and congenital myopathies (Compton et al, 2008).

A relevant aspect concerns the involvement of Contactins in neurodegeneration with a special focus on Alzheimer disease. Indeed, in such disorder, reduced Contactin 2 levels were demonstrated (Mattson and Praag, 2008), suggested to depend upon increased activity of the APP cleaving enzyme BACE1 (Gautam et al., 2014). Indeed, this enzyme was found to recognize Contactin 2 among its potential substrates, which, as a consequence of enzymatic cleavage, resulted in its reduced levels at the cell surface and increased release in soluble form. Indeed, BACE1 activity in Alzheimer neurodegeneration correlated with increased Contactin 2 delivery in soluble form and therefore with decreased tissue levels. In turn, this could suggest that Contactin 2 levels represent a reliable indicator of neurodegeneration (Zoupi et al., 2013). As far as the tissue counterpart of these biological effects, it may be expected that reduced levels of membrane Contactin 2 may result in reduced effects of the molecule on nervous tissue differentiation, thus leading to defects in neurogenesis (Denaxa et al., 2005; Ma et al., 2008) and in neuronal function (Savvaki et al., 2008). As for the underlying molecular pathway, Contactin 2 has been identified as a functional ligand of APP and this interaction was found to result in increased AICD release in a γ-secretase dependent manner and, in the ventricular zone, in the activation of the Fe65 pathway in

the neural stem cells niche (Ma et al., 2008). Altogether, these data seem to confirm the involvement of Contactin 2-associated signalling in the mechanisms leading to neurodegeneration.

Contactins have also been widely implicated in a variety of neural and other tumours (for review see Katidou et al 2008). CNTN1 in particular has been said to have oncogene-like properties (Wu et al 2012) and plays a role in tumour metastasis in a variety of tumours, notably in lung and prostate cancer (Su et al., 2006; Yan et al., 2016). In the former, its expression appears to upregulate AKT, which in turn suppresses E-cadherin expression promoting disaggregation. It has also been found in glioblastoma, where it was found to inhibit cell contacts (Eckerich et al., 2006).

However, besides in specific neural pathologies, which recognize their basis in either neuroinflammatory or neurodegenerative events, a role has been also proposed for Contactin family components in neural regeneration in different systems, and, again, this has been specifically shown in the case of Contactin 2 (Soares et al., 2005; Lin et al., 2012; Devaux et al., 2012; Pang et al, 2012). Altogether, these data thus indicate a complex role for these molecules in modulating the tissue and cellular events underlying neural disorders, either neuroinflammatory, neurodegenerative in nature, but also in neurorepair events.

References

Aparicio E, Mathieu P, Pereira Luppi M, Almeira Gubiani MF, Adamo AM. 2013.The Notch signaling pathway: its role in focal CNS demyelination and apotransferrin-induced remyelination. J Neurochem. 127:819-36.

Arroyo EJ, Xu T, Poliak S, Watson M, Peles E, Scherer SS. 2001.Internodal specializations of myelinated axons in the central nervous system. Cell Tissue Res. 305:53-66

Baeriswyl T, Stoeckli ET. 2008. Axonin-1/TAG-1 is required for pathfinding of granule cell axons in the developing cerebellum. Neural Dev. 3:7. doi: 10.1186/1749-8104-3-7.

Barriga EH, Mayor R.2015. Embryonic cell-cell adhesion: a key player in collective neural crest migration. Curr Top Dev Biol. 112:301-323.

Barros CS, Franco SJ, Müller U. 2011. Extracellular matrix: functions in the nervous system. Cold Spring Harb Perspect Biol. 3:a005108.

Basu R, Taylor MR, Williams ME. 2015. The classic cadherins in synaptic specificity. Cell Adh Migr. 9:193-201.

Battistini C, Tamagnone L. 2016. Transmembrane semaphorins, forward and reverse signaling: have a look both ways. Cell Mol Life Sci. 73:1609-1622.

Bennett V, Lambert S. 1999. Physiological roles of axonal ankyrins in survival of premyelinated axons and localization of voltage-gated sodium channels. J Neurocytol. 28:303-18.

Bhat MA1, Rios JC, Lu Y, Garcia-Fresco GP, Ching W, St Martin M, Li J, Einheber S, Chesler M, Rosenbluth J, Salzer JL, Bellen HJ. 2001. Axon-glia interactions and the domain organization of myelinated axons requires neurexin IV/Caspr/Paranodin. Neuron. 30:369-383.

Berglund EO, Ranscht B. 1994. Molecular cloning and in situ localization of the human contactin gene (CNTN1) on chromosome 12q11-q12. Genomics. 21:571-582.

Berglund EO, Murai KK, Fredette B, Sekerková G, Marturano B, Weber L, Mugnaini E, Ranscht B. 1999. Ataxia and abnormal cerebellar microorganization in mice with ablated contactin

gene expression. Neuron. 24:739-750.

Berghs S1, Aggujaro D, Dirkx R Jr, Maksimova E, Stabach P, Hermel JM, Zhang JP, Philbrick W, Slepnev V, Ort T, Solimena M. 2000. betaIV spectrin, a new spectrin localized at axon initial segments and nodes of ranvier in the central and peripheral nervous system. J Cell Biol. 151:985-1002.

Bhat, M. A., Rios, J. C., Lu, Y., Garcia-Fresco, G. P., Ching, W., St Martin, M., Li, J., Einheber, S., Chesler, M., Rosenbluth, J. et al. 2001. Axon-glia interactions and the domain organization of myelinated axons requires neurexin IV/Caspr/Paranodin. Neuron 30:369-383.

Bieber AJ, Snow PM, Hortsch M, Patel NH, Jacobs JR, Traquina ZR, Schilling J, Goodman CS. 1989. Drosophila neuroglian: a member of the immunoglobulin superfamily with extensive homology to the vertebrate neural adhesion molecule L1.Cell. 59:447-460.

Bizzoca A, Virgintino D, Lorusso L, Buttiglione M, Yoshida L, Polizzi A, Tattoli M, Cagiano R, Rossi F, Kozlov S, Furley A, Gennarini G. 2003. Transgenic mice expressing F3/contactin from the TAG-1 promoter exhibit developmentally regulated changes in the differentiation of cerebellar neurons. Development.130:29-43.

Bizzoca A, Corsi P, Gennarini G. 2009. The mouse F3/contactin glycoprotein: structural features, functional properties and developmental significance of its regulated expression. Cell Adh Migr. 3:53-63.

Bizzoca A, Corsi P, Polizzi A, Pinto MF, Xenaki D, Furley AJ, Gennarini G.2012. F3/Contactin acts as a modulator of neurogenesis during cerebral cortex development. Dev Biol. 365:133-151.

Boiko T, Rasband MN, Levinson SR, Caldwell JH, Mandel G, Trimmer JS, Matthews G. 2001. Compact myelin dictates the differential targeting of two sodium channel isoforms in the same axon. Neuron. 30:91-104.

Boronat A, Sepúlveda M, Llufriu S, Sabater L, Blanco Y, Gabilondo I, Solà N, Villoslada P, Dalmau J, Graus F, Saiz A. 2012. Analysis of antibodies to surface epitopes of contactin-2 in multiple sclerosis. J Neuroimmunol. 244:103-106.

Boyle ME, Berglund EO, Murai KK, Weber L, Peles E, Ranscht B. 2001. Contactin orchestrates assembly of the septate-like junctions at the paranode in myelinated peripheral nerve. Neuron. 30:385-397.

Brümmendorf T, Wolff JM, Frank R, Rathjen FG. 1989. Neural cell recognition molecule F11: homology with fibronectin type III and immunoglobulin type C domains. Neuron. 2:1351-1361.

Buttermore ED, Thaxton CL, Bhat MA. 2013. Organization and maintenance of molecular domains in myelinated axons. J. Neurosci. Res. 91:603-622.

Cangiano G, Ambrosini M, Patruno A, Tino A, Buttiglione M, Gennarini G. 1997. Functional organization of the promoter region of the mouse F3 axonal glycoprotein gene. Brain Res Mol Brain Res. 48:279-290.

Castellani, V., Falk, J. and Rougon, G. 2004. Semaphorin3A-induced receptor endocytosis during axon guidance responses is mediated by L1 CAM. Mol Cell Neurosci 26:89-100.

Castellani, V., De Angelis, E., Kenwrick, S. and Rougon, G. 2002. Cis and trans interactions of L1 with neuropilin-1 control axonal responses to semaphorin 3A. EMBO J 21:6348-6357.

Cau E, Blader P. 2009. Notch activity in the nervous system: to switch or not switch? Neural Dev. 4:36. doi: 10.1186/1749-8104-4-36.

Chang KJ, Zollinger DR, Susuki K, Sherman DL, Makara MA, Brophy PJ, Cooper EC, Bennett V, Mohler PJ, Rasband MN. 2014. Glial ankyrins facilitate paranodal axoglial junction assembly. Nat. Neurosci. 17:1673-1681.

Chang, S., Rathjen, F. G. and Raper, J. A. 1987. Extension of neurites on axons is impaired by antibodies against specific neural cell surface glycoproteins. J Cell Biol 104:355-362.

Chatzopoulou E, Miguez A, Savvaki M, Levasseur G, Muzerelle A, Muriel MP, Goureau O,

Watanabe K, Goutebroze L, Gaspar P, Zalc B, Karagogeos D, Thomas JL. 2008. Structural requirement of TAG-1 for retinal ganglion cell axons and myelin in the mouse optic nerve. J Neurosci. 28:7624-7636.

Charles P, Tait S, Faivre-Sarrailh C, Barbin G, Gunn-Moore F, Denisenko-Nehrbass N, Guennoc AM, Girault JA, Brophy PJ, Lubetzki C. 2002. Neurofascin is a glial receptor for the paranodin/Caspr-contactin axonal complex at the axoglial junction. Curr Biol.12:217-220.

Çolakoğlu G, Bergstrom-Tyrberg U, Berglund EO, Ranscht B. 2014. Contactin-1 regulates myelination and nodal/paranodal domain organization in the central nervous system. Proc Natl Acad Sci U S A. 111:E394-403.

Coluccia A, Tattoli M, Bizzoca A, Arbia S, Lorusso L, De Benedictis L, Buttiglione M, Cuomo V, Furley A, Gennarini G, Cagiano R. 2004. Transgenic mice expressing F3/contactin from the transient axonal glycoprotein promoter undergo developmentally regulated deficits of the cerebellar function. Neuroscience. 123:155-166.

Compton AG, Albrecht DE, Seto JT, Cooper ST, Ilkovski B, Jones KJ, Challis D, Mowat D, Ranscht B, Bahlo M, Froehner SC, North KN. 2008. Mutations in contactin-1, a neural adhesion and neuromuscular junction protein, cause a familial form of lethal congenital myopathy. Am J Hum Genet.83:714-724.

Cota E, Steward A, Fowler SB, Clarke J. 2001. The folding nucleus of a fibronectin type III domain is composed of core residues of the immunoglobulin-like fold. J Mol Biol. 305:1185-1194.

Cui, X. Y., Hu, Q. D., Tekaya, M., Shimoda, Y., Ang, B. T., Nie, D. Y., Sun, L., Hu, W. P., Karsak, M., Duka, T. et al. 2004. NB-3/Notch1 pathway via Deltex1 promotes neural progenitor cell differentiation into oligodendrocytes. J Biol Chem 279:25858-25865.

Dahmane, N. and Ruiz-i-Altaba, A. 1999. Sonic hedgehog regulates the growth and patterning of the cerebellum. Development 126:3089-3100.

Dang, P., Smythe, E. and Furley, A. J. 2012. TAG1 regulates the endocytic trafficking and signaling of the semaphorin3A receptor complex. J Neurosci 32:10370-10382.

De Benedictis L, Polizzi A, Cangiano G, Buttiglione M, Arbia S, Storlazzi CT, Rocchi M, Gennarini G. 2001. Alternative promoters drive the expression of the gene encoding the mouse axonal glycoprotein F3/contactin. Brain Res Mol Brain Res. 95:55-74.

De Benedictis L, Bizzoca A, Corsi P, Albieri I, Consalez GG, Gennarini G. 2006. Activation profile of the F3/Contactin gene in the developing mouse cerebellum. Mol Cell Neurosci.32(4):403-418.

Denaxa M, Pavlou O, Tsiotra P, Papadopoulos GC, Liapaki K, Theodorakis K, Papadaki C, Karagogeos D, Papamatheakis J.2003. The upstream regulatory region of the gene for the human homologue of the adhesion molecule TAG-1 contains elements driving neural specific expression in vivo. Brain Res Mol Brain Res.118:91-101.

Denaxa M, Kyriakopoulou K, Theodorakis K, Trichas G, Vidaki M, Takeda Y, Watanabe K, Karagogeos D. 2005. The adhesion molecule TAG-1 is required for proper migration of the superficial migratory stream in the medulla but not of cortical interneurons. Dev Biol. 288:87-99.

Derfuss T, Parikh K, Velhin S, Braun M, Mathey E, Krumbholz M, Kümpfel T, Moldenhauer A, Rader C, Sonderegger P, Pöllmann W, Tiefenthaller C, Bauer J, Lassmann H, Wekerle H, Karagogeos D, Hohlfeld R, Linington C, Meinl E. 2009. Contactin-2/TAG-1-directed autoimmunity is identified in multiple sclerosis patients and mediates gray matter pathology in animals. Proc Natl Acad Sci U S A. 106:8302-8307.

Devaux JJ, Odaka M, Yuki N. 2012.Nodal proteins are target antigens in Guillain-Barré syndrome. J Peripher Nerv Syst. 17:62-71.

Dodd J, Morton SB, Karagogeos D, Yamamoto M, Jessell TM. 1988. Spatial regulation of axonal glycoprotein expression on subsets of embryonic spinal neurons. Neuron. 1:105-116.

Doppler K, Appeltshauser L, Wilhelmi K, Villmann C, Dib-Hajj SD, Waxman SG, Mäurer M, Weishaupt A, Sommer C. 2015. Destruction of paranodal architecture in inflammatory neuropathy with anti-contactin-1 autoantibodies. J Neurol Neurosurg Psychiatry. 86:720-728.

Dragunow M. 2004. CREB and neurodegeneration. Front Biosci. 9:100-103.

Duband JL, Dady A, Fleury V. 2015. Resolving time and space constraints during neural crest formation and delamination. Curr Top Dev Biol. 111:27-67.

Duflocq, A., Chareyre, F., Giovannini, M., Couraud, F. and Davenne, M. 2011. Characterization of the axon initial segment (AIS) of motor neurons and identification of a para-AIS and a juxtapara-AIS, organized by protein 4.1B. BMC Biol 9:66.

Durbec P, Gennarini G, Goridis C, Rougon G. 1992. A soluble form of the F3 neuronal cell adhesion molecule promotes neurite outgrowth. J Cell Biol.117:877-887.

Ebel J, Beuter S, Wuchter J, Kriebel M, Volkmer H. 2014. Organisation and control of neuronal connectivity and myelination by cell adhesion molecule neurofascin. Adv Neurobiol. 8:231-247.

Eckerich C, Zapf S, Ulbricht U, Müller S, Fillbrandt R, Westphal M, Lamszus K. 2006 Contactin is expressed in human astrocytic gliomas and mediates repulsive effects. Glia. 53:1-12.

Edelman GM. 1992. Morphoregulation. Dev. Dyn.193:2-10.

Edelman GM, Jones FS. 1997. Gene regulation of cell adhesion molecules in neural morphogenesis. Acta Paediatr Suppl. 422:12-19.

Einheber S, Zanazzi G, Ching W, Scherer S, Milner TA, Peles E, Salzer JL. 1997. The axonal membrane protein Caspr, a homologue of neurexin IV, is a component of the septate-like paranodal junctions that assemble during myelination. J Cell Biol. 139:1495-1506.

Faivre-Sarrailh C, Banerjee S, Li J, Hortsch M, Laval M, Bhat MA. 2004. Drosophila contactin, a homolog of vertebrate contactin, is required for septate junction organization and paracellular barrier function. Development. 131:4931-4942.

Falk, J., Julien, F., Bechara, A., Fiore, R., Nawabi, H., Zhou, H., Hoyo-Becerra, C., Bozon, M., Rougon, G., Grumet, M. et al. 2005. Dual functional activity of semaphorin 3B is required for positioning the anterior commissure. Neuron 48, 63-75.

Falk J, Bonnon C, Girault JA, Faivre-Sarrailh C. 2002. F3/contactin, a neuronal cell

adhesion molecule implicated in axogenesis and myelination. Biol Cell. 94:327-334.

Feinberg K1, Eshed-Eisenbach Y, Frechter S, Amor V, Salomon D, Sabanay H, Dupree JL, Grumet M, Brophy PJ, Shrager P, Peles E. 2010. A glial signal consisting of gliomedin and NrCAM clusters axonal Na+ channels during the formation of nodes of Ranvier. Neuron. 65:490-502.

Freeman SA, Desmazières A, Fricker D, Lubetzki C, Sol-Foulon N. 2016. Mechanisms of sodium channel clustering and its influence on axonal impulse conduction.Cell Mol Life Sci. 73:723-35.

Frei JA, Stoeckli ET.2014. SynCAMs extend their functions beyond the synapse. Eur J Neurosci. 39:1752-1760.

Friedman LG, Benson DL, Huntley GW. 2015. Cadherin-based transsynaptic networks in establishing and modifying neural connectivity. Curr Top Dev Biol. 112:415-465.

Fukamauchi F, Aihara O, Wang YJ, Akasaka K, Takeda Y, Horie M, Kawano H, Sudo K, Asano M, Watanabe K, Iwakura Y. 2001. TAG-1-deficient mice have marked elevation of adenosine A1 receptors in the hippocampus. Biochem Biophys Res Commun. 281:220-226.

Furley AJ, Morton SB, Manalo D, Karagogeos D, Dodd J, Jessell TM. 1990. The axonal glycoprotein TAG-1 is an immunoglobulin superfamily member with neurite outgrowth-promoting activity. Cell. 61:157-170.

Gaiano, N., Nye, J. S. and Fishell, G. 2000. Radial glial identity is promoted by Notch1 signaling in the murine forebrain. Neuron 26:395-404.

Gasser A, Ho TS, Cheng X, Chang KJ, Waxman SG, Rasband MN, Dib-Hajj SD.2012. An ankyrinG-binding motif is necessary and sufficient for targeting Nav1.6 sodium channels to axon initial segments and nodes of Ranvier. J Neurosci. 32:7232-7243.

Gardiner NJ. 2011. Integrins and the extracellular matrix: key mediators of development and regeneration of the sensory nervous system. Dev Neurobiol. 71:1054-1072.

Gärtner A, Fornasiero EF, Munck S, Vennekens K, Seuntjens E, Huttner WB, Valtorta F,

Dotti CG. 2012. N-cadherin specifies first asymmetry in developing neurons. EMBO J. 31:1893-1903.

Gärtner A, Fornasiero EF, Dotti CG. 2015. Cadherins as regulators of neuronal polarity. Cell Adh Migr.9:175-182.

Gautam V, D'Avanzo C, Hebisch M, Kovacs DM1, Kim DY. 2014. BACE1 activity regulates cell surface contactin-2 levels. Mol Neurodegener. 9:4. doi: 10.1186/1750-1326-9-4.

Gennarini G, Rougon G, Vitiello F, Corsi P, Di Benedetta C, Goridis C. 1989a. Identification and cDNA cloning of a new member of the L2/HNK-1 family of neural surface glycoproteins. J Neurosci Res. 22:1-12.

Gennarini G, Cibelli G, Rougon G, Mattei MG, Goridis C. J Cell Biol. 1989b. The mouse neuronal cell surface protein F3: a phosphatidylinositol-anchored member of the immunoglobulin superfamily related to chicken contactin. 109:775-788.

Gennarini G, Durbec P, Boned A, Rougon G, Goridis C. 1991. Transfected F3/F11 neuronal cell surface protein mediates intercellular adhesion and promotes neurite outgrowth. Neuron. 6:595-606.

Gerrow K, El-Husseini A. 2006. Cell adhesion molecules at the synapse. Front Biosci.11:2400-2419.

Giger RJ, Hollis ER, Tuszynski MH. 2010. Guidance molecules in axon regeneration. Cold Spring Harb Perspect Biol. 2:a001867.

Gollan L, Sabanay H, Poliak S, Berglund EO, Ranscht B, Peles E. 2002. Retention of a cell adhesion complex at the paranodal junction requires the cytoplasmic region of Caspr. J. Cell Biol.157:1247-1256.

Gollan L, Salomon D, Salzer JL, Peles E. 2003. Caspr regulates the processing of contactin and inhibits its binding to neurofascin. J Cell Biol. 163:1213-1218.

Gordon A, Adamsky K, Vainshtein A, Frechter S, Dupree JL, Rosenbluth J, Peles E.2014. Caspr and caspr2 are required for both radial and longitudinal organization of myelinated axons.

J.Neurosci. 34:14820-14826.

Gu, C., Rodriguez, E. R., Reimert, D. V., Shu, T., Fritzsch, B., Richards, L., Kolodkin, A. and Ginty, D. 2003. Neuropilin-1 conveys semaphorin and VEGF signaling during neural and cardiovascular development. Developmental Cell 5:45-57.

Hadas, Y., Nitzan, N., Furley, A. J., Kozlov, S. V. and Klar, A. 2013. Distinct Cis Regulatory Elements Govern the Expression of TAG1 in Embryonic Sensory Ganglia and Spinal Cord. PLoS ONE 8:e57960.

Haenisch, C., Diekmann, H., Klinger, M., Gennarini, G., Kuwada, J. Y. and Stuermer, C. A. 2005. The neuronal growth and regeneration associated Cntn1 (F3/F11/Contactin) gene is duplicated in fish: expression during development and retinal axon regeneration. Molecular and Cellular Neurosciences 28:361-374.

Hasler, T. H., Rader, C., Stoeckli, E. T., Zuellig, R. A. and Sonderegger, P. 1993. cDNA cloning, structural features, and eucaryotic expression of human TAG-1/axonin-1. Eur J Biochem 211:329-339.

Hayashi S, Inoue Y, Kiyonari H, Abe T, Misaki K, Moriguchi H, Tanaka Y, Takeichi M. 2014. Protocadherin-17 mediates collective axon extension by recruiting actin regulator complexes to interaxonal contacts. Dev Cell. 30:673-687.

Hayashi S, Takeichi M. 2015. Emerging roles of protocadherins: from self-avoidance to enhancement of motility. J Cell Sci. 128:1455-64.

Hedstrom KL, Rasband MN. 2006. Intrinsic and extrinsic determinants of ion channel localization in neurons. J Neurochem. 98:1345-1352.

Hedstrom KL, Xu X, Ogawa Y, Frischknecht R, Seidenbecher CI, Shrager P, Rasband MN. 2007. Neurofascin assembles a specialized extracellular matrix at the axon initial segment. J Cell Biol. 178:875-886.

Hildebrandt H, Dityatev A. 2015. Polysialic Acid in Brain Development and Synaptic Plasticity. Top Curr Chem. 366:55-96.

Hirano S, Takeichi M. 2012. Cadherins in brain morphogenesis and wiring. Physiol. Rev. 92:597-634.

Hivert B, Pinatel D, Labasque M, Tricaud N, Goutebroze L, Faivre-Sarrailh C. 2016. Assembly of juxtaparanodes in myelinating DRG culture: Differential clustering of the Kv1/Caspr2 complex and scaffolding protein 4.1B. Glia. 64:840-852.

Horresh I, Poliak S, Grant S, Bredt D, Rasband MN, Peles E. 2008. Multiple molecular interactions determine the clustering of Caspr2 and Kv1 channels in myelinated axons. J Neurosci. 28:14213-14222.

Horresh I, Bar V, Kissil JL, Peles E. 2010. Organization of myelinated axons by Caspr and Caspr2 requires the cytoskeletal adapter protein 4.1B. J Neurosci.30:2480-2489.

Hu QD, Ang BT, Karsak M, Hu WP, Cui XY, Duka T, Takeda Y, Chia W, Sankar N, Ng YK, Ling EA, Maciag T, Small D, Trifonova R, Kopan R, Okano H, Nakafuku M, Chiba S, Hirai H, Aster JC, Schachner M, Pallen CJ, Watanabe K, Xiao ZC.2003. F3/contactin acts as a functional ligand for Notch during oligodendrocyte maturation.Cell.115:163-175.

Hu QD, Ma QH, Gennarini G, Xiao ZC. 2006. Cross-talk between F3/contactin and Notch at axoglial interface: a role in oligodendrocyte development. Dev Neurosci. 28:25-33.

Imayoshi I, Shimojo H, Sakamoto M, Ohtsuka T, Kageyama R. 2013. Genetic visualization of notch signaling in mammalian neurogenesis. Cell Mol Life Sci. 70:2045-2057.

Irintchev A, Schachner M. 2012. The injured and regenerating nervous system: immunoglobulin superfamily members as key players. Neuroscientist. 18:452-66.

Ivanovic A1, Horresh I, Golan N, Spiegel I, Sabanay H, Frechter S, Ohno S, Terada N, Möbius W, Rosenbluth J, Brose N, Peles E. 2012. The cytoskeletal adapter protein 4.1G organizes the internodes in peripheral myelinated nerves. J Cell Biol. 196:337-344.

Jessen KR, Mirsky R. 2008. Negative regulation of myelination: relevance for development, injury, and demyelinating disease. Glia.56:1552-1565.

Kania A, Klein R. 2016. Mechanisms of ephrin-Eph signalling in development, physiology

and disease. Nat. Rev. Mol. Cell. Biol.17:240-256.

Kaplan MR, Cho MH, Ullian EM, Isom LL, Levinson SR, Barres BA. 2001. Differential control of clustering of the sodium channels Na(v)1.2 and Na(v)1.6 at developing CNS nodes of Ranvier. Neuron. 30:105-119.

Karagogeos D, Morton SB, Casano F, Dodd J, Jessell TM.1991.Developmental expression of the axonal glycoprotein TAG-1: differential regulation by central and peripheral neurons in vitro. Development. 112:51-67.

Katidou, M., Vidaki, M., Strigini, M. and Karagogeos, D. 2008. The immunoglobulin superfamily of neuronal cell adhesion molecules: Lessons from animal models and correlation with human disease. Biotechnol J 3:1564-1580.

Kazarinova-Noyes K, Malhotra JD, McEwen DP, Mattei LN, Berglund EO, Ranscht B, Levinson SR, Schachner M, Shrager P, Isom LL, Xiao ZC. 2001. Contactin associates with Na+ channels and increases their functional expression. J Neurosci. 21:7517-7525.

Kazarinova-Noyes K, Shrager P. 2002 . Molecular constituents of the node of Ranvier. Mol Neurobiol. 26:167-182.

Kemperman G, Song H, Gage FH. 2015. Neurogenesis in the Adult Hippocampus. Cold Spring Harb Perspect Biol. Sept 1:7(9):a018812. doi: 10.1101/cshperspect.a018812.

Koch T, Brugger T, Bach A, Gennarini G, Trotter J. 1997. Expression of the immunoglobulin superfamily cell adhesion molecule F3 by oligodendrocyte-lineage cells. Glia. 19:199-212.

Komada M, Soriano P. 2002. [Beta]IV-spectrin regulates sodium channel clustering through ankyrin-G at axon initial segments and nodes of Ranvier. J Cell Biol. 156:337-348.

Kozlov SV, Giger RJ, Hasler T, Korvatska E, Schorderet DF, Sonderegger P. 1995. The human TAX1 gene encoding the axon-associated cell adhesion molecule TAG-1/axonin-1: genomic structure and basic promoter. Genomics 30:141-148.

Kuhar SG, Feng L, Vidan S., Ross ME, Hatten ME, Heintz N. 1993. Changing patterns of

gene expression define four stages of cerebellar granule neurons differentiation. Development. 117: 97-104.

Kuwabara S, Misawa S, Mori M. 2015. Paranodal destruction and axo-glial dysjunction in a subtype of CIDP with anticontaction-1 antibodies. J Neurol Neurosurg Psychiatry. 86:707. doi: 10.1136/jnnp-2015-310448.

Labasque M, Faivre-Sarrailh C.2010. GPI-anchored proteins at the node of Ranvier. FEBS Lett. 584:1787-92.

Labasque M, Hivert B, Nogales-Gadea G, Querol L, Illa I, Faivre-Sarrailh C. 2014. Specific contactin N-glycans are implicated in neurofascin binding and autoimmune targeting in peripheral neuropathies. J Biol Chem. 289:7907-7918.

Lancaster E, Dalmau J. 2012.Neuronal autoantigens--pathogenesis, associated disorders and antibody testing. Nat Rev Neurol. 8:380-390.

Law CO, Kirby RJ, Aghamohammadzadeh S, Furley AJ. 2008. The neural adhesion molecule TAG-1 modulates responses of sensory axons to diffusible guidance signals. Development. 135:2361-2371.

Li, H., Takeda, Y., Niki, H., Ogawa, J., Kobayashi, S., Kai, N., Akasaka, K., Asano, M., Sudo, K., Iwakura, Y. et al. 2003. Aberrant responses to acoustic stimuli in mice deficient for neural recognition molecule NB-2. Eur J Neurosci 17:929-936.

Lin JF, Pan HC, Ma LP, Shen YQ, Schachner M. 2012. The cell neural adhesion molecule contactin-2 (TAG-1) is beneficial for functional recovery after spinal cord injury in adult zebrafish. PLoS One. 7(12):e52376.

Liu, Y. and Halloran, M. 2005. Central and peripheral axon branches from one neuron are guided differentially by Semaphorin3D and transient axonal glycoprotein-1. J Neurosci 25:10556-10563.

Liu RQ, Wang W, Legg A, Abramyan J, O'Connor TP 2014. Semaphorin 5B is a repellent cue for sensory afferents projecting into the developing spinal cord. Development.141:1940-1949.

Lonze BE, Ginty DD. 2002. Function and regulation of CREB family transcription factors in the nervous system. Neuron 35: 605-623.

Low MG. 1989. Glycosyl-phosphatidyl inositol: a versatile anchor for cell surface proteins. FASEB J. 3:1600-1608.

Lustig, M., Sakurai, T. and Grumet, M. 1999. Nr-CAM promotes neurite outgrowth from peripheral ganglia by a mechanism involving axonin-1 as a neuronal receptor. Dev Biol 209:340-351.

Ma QH, Futagawa T, Yang WL, Jiang XD, Zeng L, Takeda Y, Xu RX, Bagnard D, Schachner M, Furley AJ, Karagogeos D, Watanabe K, Dawe GS, Xiao ZC. 2008. A TAG1-APP signalling pathway through Fe65 negatively modulates neurogenesis. Nat Cell Biol. 10:283-94.

Maness PF, Schachner M. 2007. Neural recognition molecules of the immunoglobulin superfamily: signaling transducers of axon guidance and neuronal migration. Nat. Neurosci. 10:19-26.

Manso C, Querol L, Mekaouche M, Illa I, Devaux JJ. 2016 Contactin-1 IgG4 antibodies cause paranode dismantling and conduction defects. Brain. Mar 26. pii: aww062.

Massaro A, Bizzoca A, Corsi P, Pinto MF, Carratù MR, Gennarini G. 2012. Significance of F3/Contactin gene expression in cerebral cortex and nigrostriatal development. Mol Cell Neurosci. 50:221-223.

Mattson MP, van Praag H. 2008. TAGing APP constrains neurogenesis. Nat Cell Biol.10:249-50.

McEwen DP, Isom LL. 2004. Heterophilic interactions of sodium channel beta1 subunits with axonal and glial cell adhesion molecules. J Biol Chem.279:52744-52752.

McEwen DP, Meadows LS, Chen C, Thyagarajan V, Isom LL. 2004. Sodium channel β1 subunit-mediated modulation of Nav1.2 currents and cell surface density is dependent on interactions with contactin and ankyrin. J Biol Chem. 279:16044-16049.

McKeown SJ, Wallace AS, Anderson RB. 2013. Expression and function of cell adhesion

molecules during neural crest migration. Dev Biol. 373:244-257.

Menezes JR, Luskin MB. 1994. Expression of neuron-specific tubulin defines a novel population in the proliferative layers of the developing telencephalon. J Neurosci.14:5399-5416.

Milev, P., Maurel, P., Häring, M., Margolis, R. K. and Margolis, R. U. 1996. TAG-1/axonin-1 is a high-affinity ligand of neurocan, phosphacan/protein-tyrosine phosphatase-zeta/beta, and N-CAM. J Biol Chem 271, 15716-15723.

Missaire M, Hindges R. 2015. The role of cell adhesion molecules in visual circuit formation: from neurite outgrowth to maps and synaptic specificity. Dev Neurobiol. 75:569-83.

Miura Y, Devaux JJ, Fukami Y, Manso C, Belghazi M, Wong AH, Yuki N; CNTN1-CIDP Study Group. 2015. Contactin 1 IgG4 associates to chronic inflammatory demyelinating polyneuropathy with sensory ataxia. Brain. 138:1484-1491.

Mitsuhashi T, Takahashi T. 2009. Genetic regulation of proliferation/differentiation characteristics of neural progenitor cells in the developing neocortex. Brain Dev. 31:553-557

Mohebiany AN, Harroch S, Bouyain S. 2014. New insights into the roles of the contactin cell adhesion molecules in neural development. Adv Neurobiol. 8:165-94.

Mortl, M., Sonderegger, P., Diederichs, K. and Welte, W. 2007. The crystal structure of the ligand-binding module of human TAG-1 suggests a new mode of homophilic interaction. Protein Sci 16:2174-2183.

Mui, K. L., Chen, C. S. and Assoian, R. K. 2016. The mechanical regulation of integrin-cadherin crosstalk organizes cells, signaling and forces. J Cell Sci 129:1093-1100.

Murai, K. K., Misner, D. and Ranscht, B. 2002. Contactin supports synaptic plasticity associated with hippocampal long-term depression but not potentiation. Curr Biol 12:181-190.

Namba T, Kibe Y, Funahashi Y, Nakamuta S, Takano T, Ueno T, Shimada A, Kozawa S, Okamoto M, Shimoda Y, Oda K, Wada Y, Masuda T, Sakakibara A, Igarashi M, Miyata T, Faivre-Sarrailh C, Takeuchi K, Kaibuchi K. 2014. Pioneering axons regulate neuronal polarization in the

developing cerebral cortex. Neuron 81:814-829.

Nawabi, H., Briançon-Marjollet, A., Clark, C., Sanyas, I., Takamatsu, H., Okuno, T., Kumanogoh, A., Bozon, M., Takeshima, K., Yoshida, Y. et al. 2010. A midline switch of receptor processing regulates commissural axon guidance in vertebrates. Genes Dev 24:396-410.

Ogawa J1, Kaneko H, Masuda T, Nagata S, Hosoya H, Watanabe K. 1996 Novel neural adhesion molecules in the Contactin/F3 subgroup of the immunoglobulin superfamily: isolation and characterization of cDNAs from rat brain. Neurosci Lett. 218:173-176.

Ogawa Y, Schafer DP, Horresh I, Bar V, Hales K, Yang Y, Susuki K, Peles E, Stankewich MC, Rasband MN. 2006. Spectrins and ankyrinB constitute a specialized paranodal cytoskeleton. J Neurosci. 26:5230-5239

Okamoto M1, Namba T, Shinoda T, Kondo T, Watanabe T, Inoue Y, Takeuchi K, Enomoto Y, Ota K, Oda K, Wada Y, Sagou K, Saito K, Sakakibara A, Kawaguchi A, Nakajima K, Adachi T, Fujimori T, Ueda M, Hayashi S, Kaibuchi K, Miyata T.2013. TAG-1-assisted progenitor elongation streamlines nuclear migration to optimize subapical crowding Nat Neurosci. 16:1556-1566.

Osterfield, M., Egelund, R., Young, L. M. and Flanagan, J. G. 2008. Interaction of amyloid precursor protein with contactins and NgCAM in the retinotectal system. Development 135:1189-1199.

Özkan E, Carrillo RA, Eastman CL, Weiszmann R, Waghray D, Johnson KG, Zinn K, Celniker SE, Garcia KC . 2013. An extracellular interactome of immunoglobulin and LRR proteins reveals receptor-ligand networks.Cell.154:228-239.

Pang SY, Chan KH, Mak WW, Kung MH, Lee CN, Yip EK, Ho SL. 2012. Single-nucleotide polymorphism of transient axonal glycoprotein-1 and its correlation with clinical features and prognosis in chronic inflammatory demyelinating polyneuropathy. J Peripher Nerv Syst. 17:72-75.

Pasterkamp RJ. 2012. Getting neural circuits into shape with semaphorins. Nat Rev

Neurosci. 13:605-618.

Pekarik, V., Bourikas, D., Miglino, N., Joset, P., Preiswerk, S. and Stoeckli, E. T. 2003. Screening for gene function in chicken embryo using RNAi and electroporation. Nat Biotech 21:93-96.

Peles, E., Nativ, M., Lustig, M., Grumet, M., Schilling, J., Martinez, R., Plowman, G. and Schlessinger, J. 1997. Identification of a novel contactin-associated transmembrane receptor with multiple domains implicated in protein-protein interactions. EMBO J 16:978-988.

Peles, E. and Salzer, J. L. 2000. Molecular domains of myelinated axons. Curr Opin Neurobiol 10:558-565.

Perrin, F. E., Rathjen, F. and Stoeckli, E. 2001. Distinct subpopulations of sensory afferents require F11 or axonin-1 for growth to their target layers within the spinal cord of the chick. Neuron 30:707-723.

Pesheva, P., Gennarini, G., Goridis, C. and Schachner, M. 1993. The F3/11 cell adhesion molecule mediates the repulsion of neurons by the extracellular matrix glycoprotein J1-160/180. Neuron 10:69-82.

Petrovic M, Schmucker D. 2015. Axonal wiring in neural development: Target-independent mechanisms help to establish precision and complexity. Bioessays. 37:996-1004.

Pickford LB1, Mayer DN, Bolin LM, Rouse RV. J Neurocytol. 1989. Transiently expressed, neural-specific molecule associated with premigratory granule cells in postnatal mouse cerebellum.18:465-478.

Pierfelice T, Alberi L, Gaiano N. 2011. Notch in the vertebrate nervous system: an old dog with new tricks. Neuron. 69:840-855.

Pierre K, Dupouy B, Allard M, Poulain DA, Theodosis DT. 2001. Mobilization of the cell adhesion glycoprotein F3/contactin to axonal surfaces is activity dependent. Eur J Neurosci. 2001 14:645-56.

Pillai, A. M., Garcia-Fresco, G. P., Sousa, A. D., Dupree, J. L., Philpot, B. D. and Bhat, M.

A. 2007. No effect of genetic deletion of contactin-associated protein (CASPR) on axonal orientation and synaptic plasticity. J. Neurosci. Res. 85:2318-2331.

Pillai AM, Thaxton C, Pribisko AL, Cheng JG, Dupree JL, Bhat MA. 2009. Spatiotemporal ablation of myelinating glia-specific neurofascin (Nfasc NF155) in mice reveals gradual loss of paranodal axoglial junctions and concomitant disorganization of axonal domains. J Neurosci Res. 87:1773-1793.

Poliak S, Salomon D, Elhanany H, Sabanay H, Kiernan B, Pevny L, Stewart CL, Xu X, Chiu SY, Shrager P, Furley AJ, Peles E. 2003. Juxtaparanodal clustering of Shaker-like K+ channels in myelinated axons depends on Caspr2 and TAG-1. J Cell Biol.162:1149-60.

Pozueta J, Lefort R, Shelanski ML. 2013. Synaptic changes in Alzheimer's disease and its models. Neuroscience. 251:51-65.

Puzzo D, Bizzoca A, Privitera L, Furnari D, Giunta S, Girolamo F, Pinto M, Gennarini G, Palmeri A.2013. F3/Contactin promotes hippocampal neurogenesis, synaptic plasticity, and memory in adult mice. Hippocampus. 23:1367-1382.

Querol L, Nogales-Gadea G, Rojas-Garcia R, Martinez-Hernandez E, Diaz-Manera J, Suárez-Calvet X, Navas M, Araque J, Gallardo E, Illa I. 2013. Antibodies to contactin-1 in chronic inflammatory demyelinating polyneuropathy. Ann. Neurol. 73:370-380.

Rader, C., Stoeckli, E., Ziegler, U., Osterwalder, T., Kunz, B. and Sonderegger, P. 1993. Cell-cell adhesion by homophilic interaction of the neuronal recognition molecule axonin-1. Eur J Biochem 215:133-141.

Ranscht B.1988. Sequence of contactin, a 130-kD glycoprotein concentrated in areas of interneuronal contact, defines a new member of the immunoglobulin supergene family in the nervous system. J Cell Biol. 107:1561-1573.

Rathjen, F. G., Wolff, J. M., Frank, R., Bonhoeffer, F. and Rutishauser, U. 1987. Membrane glycoproteins involved in neurite fasciculation. J Cell Biol 104:343-353.

Revest, J. M., Faivre-Sarrailh, C., Schachner, M. and Rougon, G. 1999. Bidirectional signaling between neurons and glial cells via the F3 neuronal adhesion molecule. Adv Exp Med Biol 468:309-318.

Rickman DS, Tyagi R, Zhu XX, Bobek MP, Song S, Blaivas M, Misek DE, Israel MA, Kurnit DM, Ross DA, Kish PE, Hanash SM. 2001. The gene for the axonal cell adhesion molecule TAX-1 is amplified and aberrantly expressed in malignant gliomas. Cancer Res. 61:2162-2168.

Rigato, F., Garwood, J., Calco, V., Heck, N., Faivre-Sarrailh, C. and Faissner, A. 2002. Tenascin-C promotes neurite outgrowth of embryonic hippocampal neurons through the alternatively spliced fibronectin type III BD domains via activation of the cell adhesion molecule F3/contactin. J Neurosci 22: 6596–6609.

Rios JC, Melendez-Vasquez CV, Einheber S, Lustig M, Grumet M, Hemperly J, Peles E, Salzer JL. 2000. Contactin-associated protein (Caspr) and contactin form a complex that is targeted to the paranodal junctions during myelination. J Neurosci. 20:8354-8364.

Rios JC, Rubin M, St Martin M, Downey RT, Einheber S, Rosenbluth J, Levinson SR, Bhat M, Salzer JL.2003. Paranodal interactions regulate expression of sodium channel subtypes and provide a diffusion barrier for the node of Ranvier. J Neurosci. 23:7001-7011.

Rhodes KJ, Strassle BW, Monaghan MM, Bekele-Arcuri Z, Matos MF, Trimmer JS. 1997. Association and colocalization of the Kvbeta1 and Kvbeta2 beta-subunits with Kv1 alpha-subunits in mammalian brain K+ channel complexes. J Neurosci. 17:8246-8258.

Rossi, A., Kontarakis, Z., Gerri, C., Nolte, H., Hölper, S., Krüger, M. and Stainier, D. Y. 2015. Genetic compensation induced by deleterious mutations but not gene knockdowns. Nature 524:230-233.

Ruegg, M. A., Stoeckli, E. T., Kuhn, T. B., Heller, M., Zuellig, R. and Sonderegger, P. 1989. Purification of axonin-1, a protein that is secreted from axons during neurogenesis. EMBO J 8, 55-63.

Sakurai, T., Lustig, M., Nativ, M., Hemperly, J. J., Schlessinger, J., Peles, E. and Grumet, M. 1997. Induction of neurite outgrowth through contactin and Nr-CAM by extracellular regions of glial receptor tyrosine phosphatase beta. The Journal of Cell Biology 136:907-918.

Sakurai T. 2012. The role of NrCAM in neural development and disorders--beyond a simple glue in the brain. Mol Cell Neurosci. 49:351-63.

Salzer JL.2003 Polarized domains of myelinated axons. Neuron. 40:297-318.

Salzer JL. 2015. Schwann cell myelination. Cold Spring Harb Perspect Biol. 7:a020529. doi: 10.1101/cshperspect.a020529

Savvaki M, Panagiotaropoulos T, Stamatakis A, Sargiannidou I, Karatzioula P, Watanabe K, Stylianopoulou F, Karagogeos D, Kleopa KA. 2008. Impairment of learning and memory in TAG-1 deficient mice associated with shorter CNS internodes and disrupted juxtaparanodes. Mol Cell Neurosci.39(3):478-90.

Savvaki, M., Theodorakis, K., Zoupi, L., Stamatakis, A., Tivodar, S., Kyriacou, K., Stylianopoulou, F. and Karagogeos, D. 2010. The expression of TAG-1 in glial cells is sufficient for the formation of the juxtaparanodal complex and the phenotypic rescue of tag-1 homozygous mutants in the CNS. J Neurosci 30:13943-13954.

Schmidt H, Rathjen FG. 2010. Signalling mechanisms regulating axonal branching in vivo. Bioessays. 32:977-985.

Schmucker D, Clemens JC, Shu H, Worby CA, Xiao J, Muda M, Dixon JE, Zipursky SL. 2000. Drosophila Dscam is an axon guidance receptor exhibiting extraordinary molecular diversity. Cell 101:671-684.

Shelly, M., Cancedda, L., Lim, B. K., Popescu, A. T., Cheng, P. L., Gao, H. and Poo, M. M. 2011. Semaphorin3A Regulates Neuronal Polarization by Suppressing Axon Formation and Promoting Dendrite Growth. Neuron 71:433-446.

Shen J. 2014. Function and dysfunction of presenilin. Neurodegener. Dis. 13:61-3.

Schmidt H, Rathjen FG. 2010. Signalling mechanisms regulating axonal branching in vivo.

Bioessays. 32:977-985.

Sherman DL, Tait S, Melrose S, Johnson R, Zonta B, Court FA, Macklin WB, Meek S, Smith AJ, Cottrell DF, Brophy PJ. 2005. Neurofascins are required to establish axonal domains for saltatory conduction. Neuron. 48:737-742.

Shiga, T., Lustig, M., Grumet, M. and Shirai, T. 1997. Cell adhesion molecules regulate guidance of dorsal root ganglion axons in the marginal zone and their invasion into the mantle layer of embryonic spinal cord. Developmental Biology 192:136-148.

Shimoda Y, Watanabe K. 2009. Contactins: emerging key roles in the development and function of the nervous system. Cell Adh Migr. 2009 3:64-70.

Sittaramane, V., Sawant, A., Wolman, M. A., Maves, L., Halloran, M. C. and Chandrasekhar, A. 2009. The cell adhesion molecule Tag1, transmembrane protein Stbm/Vangl2, and Lamininalpha1 exhibit genetic interactions during migration of facial branchiomotor neurons in zebrafish. Developmental Biology 325:363-373.

Scholzen T, Gerdes J. 2000. The Ki-67 protein: from the known and the unknown. J Cell Physiol. 182:311-322.

Soares S, Traka M, von Boxberg Y, Bouquet C, Karagogeos D, Nothias F. 2005. Neuronal and glial expression of the adhesion molecule TAG-1 is regulated after peripheral nerve lesion or central neurodegeneration of adult nervous system. Eur J Neurosci. 21:1169-80.

Stathopoulos P, Alexopoulos H., Dalkas MC. 2015. Autoimmune antigenic targets at the node of Rnier in demyeinating disorders. Nat. Rev. Neurol. 11: 143-156.

Stepniak E, Radice GL, Vasioukhin V. 2009. Adhesive and signaling functions of cadherins and catenins in vertebrate development. Cold Spring Harb Perspect Biol.1, doi:10.1101/cshperspect.a002949.

Stoeckli, E. T. 2010. Neural circuit formation in the cerebellum is controlled by cell adhesion molecules of the Contactin family. Cell Adh Migr 4, 523-526.

Stoeckli ET, Kuhn TB, Duc CO, Ruegg MA, Sonderegger P. 1991. The axonally secreted

protein axonin-1 is a potent substratum for neurite growth.J Cell Biol. 112:449-455.

Stoeckli ET, Landmesser LT. 1995. Axonin-1, Nr-CAM, and Ng-CAM play different roles in the in vivo guidance of chick commissural neurons. Neuron. 14:1165-1179

Stoeckli, E. T., Sonderegger, P., Pollerberg, G. E. and Landmesser, L. T. 1997. Interference with axonin-1 and NrCAM interactions unmasks a floor-plate activity inhibitory for commissural axons. Neuron 18:209-221.

Stoeckli ET. 2014. Protocadherins: not just neuron glue, more too! Dev Cell. 30:643-644.

Stottmann RW, Rivas RJ.1998. Distribution of TAG-1 and synaptophysin in the developing cerebellar cortex: relationship to Purkinje cell dendritic development. J Comp Neurol 395:121-135.

Su, J. L., Yang, P. C., Shih, J. Y., Yang, C. Y., Wei, L. H., Hsieh, C. Y., Chou, C. H., Jeng, Y. M., Wang, M. Y., Chang, K. J. et al. 2006. The VEGF-C/Flt-4 axis promotes invasion and metastasis of cancer cells. Cancer Cell 9:209-223.

Tait S, Gunn-Moore F, Collinson JM, Huang J, Lubetzki C, Pedraza L, Sherman DL, Colman DR, Brophy PJ. 2000. An oligodendrocyte cell adhesion molecule at the site of assembly of the paranodal axo-glial junction. J. Cell Biol.150:657-666.

Takahashi T, Caviness VS.1993. PCNA-binding to DNA at the G1/S transition in proliferating cells of the developing cerebral wall. J Neurocytol. 22:1096-1102.

Takeda, Y., Akasaka, K., Lee, S., Kobayashi, S., Kawano, H., Murayama, S., Takahashi, N., Hashimoto, K., Kano, M., Asano, M. et al. 2003. Impaired motor coordination in mice lacking neural recognition molecule NB-3 of the contactin/F3 subgroup. J Neurobiol 56:252-265.

Thiery JP, Engl W, Viasnoff V, Dufour S. 2012. Biochemical and biophysical origins of cadherin selectivity and adhesion strength. Curr Opin Cell Biol. 24:614-619.

Tiberi L, Vanderhaeghen P, van den Ameele J. 2012. Cortical neurogenesis and morphogens: diversity of cues, sources and functions. Curr Opin Cell Biol. 24:269-276.

Traka M, Goutebroze L, Denisenko N, Bessa M, Nifli A, Havaki S, Iwakura Y, Fukamauchi F, Watanabe K, Soliven B, Girault JA, Karagogeos D. 2003. Association of TAG-1 with Caspr2 is

essential for the molecular organization of juxtaparanodal regions of myelinated fibers. J Cell Biol.162:1161-1172.

Traut W1, Weichenhan D, Himmelbauer H, Winking H. 2006. New members of the neurexin superfamily: multiple rodent homologues of the human CASPR5 gene. Mamm Genome. 17:723-31.

Tsiotra PC, Karagogeos D, Theodorakis K, Michaelidis TM, Modi WS, Furley AJ, Jessell TM, Papamatheakis J.1993.Isolation of the cDNA and chromosomal localization of the gene (TAX1) encoding the human axonal glycoprotein TAG-1. Genomics. 18:562-567.

Tsiotra PC, Theodorakis K, Papamatheakis J, Karagogeos D. 1996. The fibronectin domains of the neural adhesion molecule TAX-1 are necessary and sufficient for homophilic binding. J. Biol. Chem. 271:29216-29222.

Uchida, Y., Ohshima, T., Sasaki, Y., Suzuki, H., Yanai, S., Yamashita, N., Nakamura, F., Takei, K., Ihara, Y., Mikoshiba, K. et al. 2005. Semaphorin3A signalling is mediated via sequential Cdk5 and GSK3beta phosphorylation of CRMP2: implication of common phosphorylating mechanism underlying axon guidance and Alzheimer's disease. Genes Cells 10:165-179.

Virgintino D, Ambrosini M, D'Errico P, Bertossi M, Papadaki C, Karagogeos D, Gennarini G. 1999. Regional distribution and cell type-specific expression of the mouse F3 axonal glycoprotein: a developmental study. J. Comp. Neurol. 413:357-372.

Vitriol EA, Zheng JQ. 2012. Growth cone travel in space and time: the cellular ensemble of cytoskeleton, adhesion, and membrane. Neuron.73:1068-1081.

Wallace, V. A. 1999. Purkinje-cell-derived Sonic hedgehog regulates granule neuron precursor cell proliferation in the developing mouse cerebellum. Curr Biol 9:445-448.

Walsh, F. S. and Doherty, P. 1997. Neural cell adhesion molecules of the immunoglobulin superfamily: role in axon growth and guidance. Annu Rev Cell Dev Biol 13:425-456.

Wang S, Sdrulla AD, diSibio G, Bush G, Nofziger D, Hicks C, Weinmaster G, Barres BA. 1998. Notch receptor activation inhibits oligodendrocyte differentiation. Neuron. 21:63-75.

Wang H, Kunkel DD, Martin TM, Schwartzkroin PA, Tempel BL. 1993. Heteromultimeric K+ channels in terminal and juxtaparanodal regions of neurons. Nature 365:75-79.

Wang W, Karagogeos D, Kilpatrick DL. 2011.The effects of Tag-1 on the maturation of mouse cerebellar granule neurons. Cell Mol Neurobiol. 31:351-356.

Waterhouse, A.M., Procter, J.B., Martin, D.M.A, Clamp, M. and Barton, G. J. 2009. "Jalview Version 2 - a multiple sequence alignment editor and analysis workbench" Bioinformatics 25:1189-1191.

Weber, G. F., Bjerke, M. A. and DeSimone, D. W. 2011. Integrins and cadherins join forces to form adhesive networks. J Cell Sci 124:1183-1193.

Weber P, Bartsch U, Rasband MN, Czaniera R, Lang Y, Bluethmann H, Margolis RU, Levinson SR, Shrager P, Montag D, Schachner M. 1999. Mice deficient for tenascin-R display alterations of the extracellular matrix and decreased axonal conduction velocities in the CNS. J Neurosci.19:4245-4262.

Wechsler-Reya, R. J. and Scott, M. P. 1999. Control of neuronal precursor proliferation in the cerebellum by Sonic Hedgehog. Neuron 22:103-114.

Wei Z, Chigurupati S, Arumugam TV, Jo DG, Li H, Chan SL. 2011. Notch activation enhances the microglia-mediated inflammatory response associated with focal cerebral ischemia. Stroke. 42:2589-2594.

Wolman MA, Sittaramane VK, Essner JJ, Yost HJ, Chandrasekhar A, Halloran MC. 2008. Transient axonal glycoprotein-1 (TAG-1) and laminin-alpha1 regulate dynamic growth cone behaviors and initial axon direction in vivo.Neural Dev. doi: 10.1186/1749-8104-3-6.

Woodhoo A, Alonso MB, Droggiti A, Turmaine M, D'Antonio M, Parkinson DB, Wilton DK, Al-Shawi R, Simons P, Shen J, Guillemot F, Radtke F, Meijer D, Feltri ML, Wrabetz L, Mirsky R, Jessen KR. 2009. Notch controls embryonic Schwann cell differentiation, postnatal myelination and adult plasticity. Nat. Neurosci.12:839-847.

Wu, H. M., Cao, W., Ye, D., Ren, G. X., Wu, Y. N. and Guo, W. 2012. Contactin 1 (CNTN1) expression associates with regional lymph node metastasis and is a novel predictor of prognosis in patients with oral squamous cell carcinoma. Mol Med Rep 6:265-270.

Xenaki D, Martin IB, Yoshida L, Ohyama K, Gennarini G, Grumet M, Sakurai T, Furley AJ 2011. F3/contactin and TAG1 play antagonistic roles in the regulation of sonic hedgehog-induced cerebellar granule neuron progenitor proliferation. Development. 138:519-529

Yamagata M, Weiner JA, Sanes JR. 2002. Sidekicks: synaptic adhesion molecules that promote lamina-specific connectivity in the retina. Cell.110:649-660.

Yamagata M, Sanes JR. 2008. Dscam and Sidekick proteins direct lamina-specific synaptic connections in vertebrate retina. Nature. 451:465-469.

Yamagata M, Sanes JR. 2012. Expanding the Ig superfamily code for laminar specificity in retina: expression and role of contactins. J Neurosci. 32:14402-14414.

Yamamoto, M., Boyer, A. M., Crandall, J. E., Edwards, M. and Tanaka, H. 1986. Distribution of stage-specific neurite-associated proteins in the developing murine nervous system recognized by a monoclonal antibody. J Neurosci 6:3576-3594.

Yan, J., Ojo, D., Kapoor, A., Lin, X., Pinthus, J. H., Aziz, T., Bismar, T. A., Wei, F., Wong, N., De Melo, J. et al. 2016. Neural Cell Adhesion Protein CNTN1 Promotes the Metastatic Progression of Prostate Cancer. Cancer Res 76:1603-1614.

Yap, C. C. and Winckler, B. 2015. Adapting for endocytosis: roles for endocytic sorting adaptors in directing neural development. Front Cell Neurosci 9:119.

Ye, H., Tan, Y. L., Ponniah, S., Takeda, Y., Wang, S. Q., Schachner, M., Watanabe, K., Pallen, C. J. and Xiao, Z. 2008. Neural recognition molecules CHL1 and NB-3 regulate apical dendrite orientation in the neocortex via PTP alpha. EMBO J 27, 188-200.

Yogev S, Shen K. 2014. Cellular and molecular mechanisms of synaptic specificity. Annu Rev Cell Dev Biol. 30:417-437.

Yoshihara, Y., Kawasaki, M., Tamada, A., Nagata, S., Kagamiyama, H. and Mori, K. 1995.

Overlapping and differential expression of BIG-2, BIG-1, TAG-1, and F3: four members of an axon-associated cell adhesion molecule subgroup of the immunoglobulin superfamily. J. Neurobiol. 28:51-69.

Zeng, L., D'Alessandri, L., Kalousek, M. B., Vaughan, L. and Pallen, C. J. 1999. Protein tyrosine phosphatase alpha (PTPalpha) and contactin form a novel neuronal receptor complex linked to the intracellular tyrosine kinase fyn. The Journal of Cell Biology 147, 707-714.

Zhou D, Lambert S, Malen PL, Carpenter S, Boland LM, Bennett V. 1998. AnkyrinG is required for clustering of voltage-gated Na channels at axon initial segments and for normal action potential firing. J. Cell Biol. 143:1295-1304.

Zonta, B., Desmazieres, A., Rinaldi, A., Tait, S., Sherman, D. L., Nolan, M. F. and Brophy, P. J. 2011. A Critical Role for Neurofascin in Regulating Action Potential Initiation through Maintenance of the Axon Initial Segment. Neuron 69:945-956.

Zoupi L, Markoullis K, Kleopa KA, Karagogeos D. 2013. Alterations of juxtaparanodal domains in two rodent models of CNS demyelination. Glia. 61:1236-1249.

Zuellig RA, Rader C, Schroeder A, Kalousek MB, Von Bohlen und Halbach F, Osterwalder T, Inan C, Stoeckli ET, Affolter HU, Fritz A, Hafen H. and Sonderegger P.1992. The axonally secreted cell adhesion molecule, axonin-1. Primary structure, immunoglobulin-like and fibronectin-type-III-like domains and glycosyl-phosphatidylinositol anchorage. Eur J. Biochem. 204:453-463.

Zuko A, Bouyain S, van der Zwaag B, Burbach JP. 2011. Contactins: structural aspects in relation to developmental functions in brain disease. Adv Protein Chem Struct Biol. 2011;84:143-180.

Figure legends

Figure 1:

Alignment of Contactin 1 and Contactin 2 aminoacid sequences by using the CLC sequence viewer 7.6.1, scored by the Jalview 2.9.0b2 software (Waterhouse et al., 2009).

Figure 2:

A: Overall organization of the Contactin 1 and Contactin 2 axonal glycoproteins, showing the Immunoglobulin type C2 domains in the N-terminal, and the Fibronectin type III repeats in the C terminal, premembrane regions as well as the GPI attachment.

B: Schematic summary of the interactions of CNTN1 and CNTN2, illustrating that some of them are held in common while others are distinct. Interacting molecules are grouped into families where relevant, structural similarities are indicated by icon colour and shape. Interactions between some of these and the CNTNs is promiscuous (e.g. with the L1-like family), while others appear to be specific (e.g. with the CASPRs). CNTNs 3-6 are also shown with their known interactions, while the whole CASPR family is also shown to illustrate that further interactions with CNTNs seem likely, but have not been documented. In these cases, molecules with no known interactions with CNTN1 or CNTN2 are shown in lighter colours. Abbreviations (with refs not in main text): NCAM, neural cell adhesion molecule (Milev et al., 1996); NRP, neuropilin (Falk et al., 2005); L1, L1CAM; CHL1, Close Homolog of L1 (Ye et al., 2008); Nf, neurofascin; Nr, NrCAM or NgCAM-related CAM (Falk et al., 2005); APP, Amyloid Precursor Protein; APLP, APP-like protein; RPTP, Receptor-like Protein Tyrosine Phosphatase; Phosphacan, splice variant of RPTPβ (Milev et al., 1996); Tenascin (Rigato et al., 2002); PTPα, Protein Tyrosine Phosphatase (Zeng et al., 1999); Kv1, Shaker-type, Potassium voltage-gated channel.

Figure 3:

Molecular organization of the Nodes of Ranvier, of the paranode and of the juxtapananodal regions in both central and peipheral nervous tissue. In central nodes, contactin-1 (CNTN1) associates *in cis* with Neurofascin186 (NF-186) and with NrCAM as well as with Na channels β1 subunit (Nav). In addition, it undergoes submembrane interaction with Ankyrin G and with βIV spectrin, stabilized by Tenascin R. In peripheral neurons, Contactin-1 is not expressed in the nodal region.

In the paranode, axons and myelinating glia interact via the Contactin1/CASPR1 binary complex with glial Neurofascin 155. This region separates nodal Na channels from K channels, restricted to the juxtaparanode by their interactions with the Contactin2/CASPR2 molecular complex. Delayed rectifier potassium channels Kv1.1 and 1.2 are clustered in the same region based on their interaction with such a complex. In the peripheral nervous tissue Gliomedin is involved in NrCAM clustering with ionic channels.

Figure 4:

A. Immunohistochemical localization of the Contactin 2 (TAG1 red, a) and Contactin 1 (F3, green, b) glycoproteins in postnatal day 5 cerebellar cortex. c shows a merged picture, counterstained with DAPI. IGL, Inner Granular Layer; ML. Molecular layer. EGL, External Germinal Layer; Scale bar in c: 40 μm.

B. Double stain of Contactin 2 (TAG-1) with either Ki67 (a) or PCNA (b) proliferation markers in postnatal day 5 cerebellar cortex. Arrowheads point to elements displaying different levels of double immunostainings.

C,D: primary cerebellar cultures stained with Ki67 (red), Contactin 2 (TAG1) (blue) and Tuj1 (C) (green) or with Contactin 2 (TAG1) and BrdU antibodies (D). Asterisk indicates $Ki67^{+}/TAG1^{-}$, arrowhead $Ki67^{+}/TAG1^{+}$ and arrow Ki67-/TAG1+ granule cells.

Figure 5:

A: Organization of the TAX-1 gene promoter/Contactin 1 cDNA construct. The Contactin 1 regulatory region, incuding the 5' flanking exons A1, 0, B and C1, and the associated alternative promoter elements was replaced for by the human TAX-1 gene regulatory region, which included the 5'flanking region, the first two exons as well as the intervening intron of the TAX-1 gene, fused to the Contactin 1 cDNA.

B. Phenotype of the postnatal day 6 cerebellum from either wild type (WT) and TAG/F3 transgenic mice, demonstrated by Contactin 1 immunostaining. Note the relevant reduction of the cerebellar size. egl, external granular layer; igl, inner granular layer; PCl, Purkinje cells layer; WM, white matter; CP, Choroid Plexus. Scale bar: 200 μm (from Bizzoca et al., 2009).

Figure 6:

A. Exon intron organization of the 5' region from the *Cntn1* gene, including the regions surrounding exons A1, 0, and C1, whose 5' ends correspond to the *Cntn1* gene transcription start sites. Exon 1 includes the translation initiation site (ATG). The size of the first 3 introns is also reported.

B. C. The 5' flanking exons of the Cntn1 gene are shown in B, which undergo the complex splicing events shown in C, resulting in a high level of complexity of the Contactin 1 mRNA.

D. Relative utilization of the Contactin 1 5' exons A1, 0, B and C1 as determined by densitometric scan of RT/PCR amplification profiles obtained by using exon-specific primers (from De Benedictis et al., 2001).

Figure 7:

A. Map of the Cntn1 promoter/EGFP reporter construct and, in B, its expression in developing cerebellar cortex at postnatal days 0 (P0) and 8 (P8). egl, external granular layer; igl, inner granular layer; PCl, Purkinje cells layer; WM, white matter. Scale bars: P0, P8 = 200 μm (insets 20 μm).

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Figure 1

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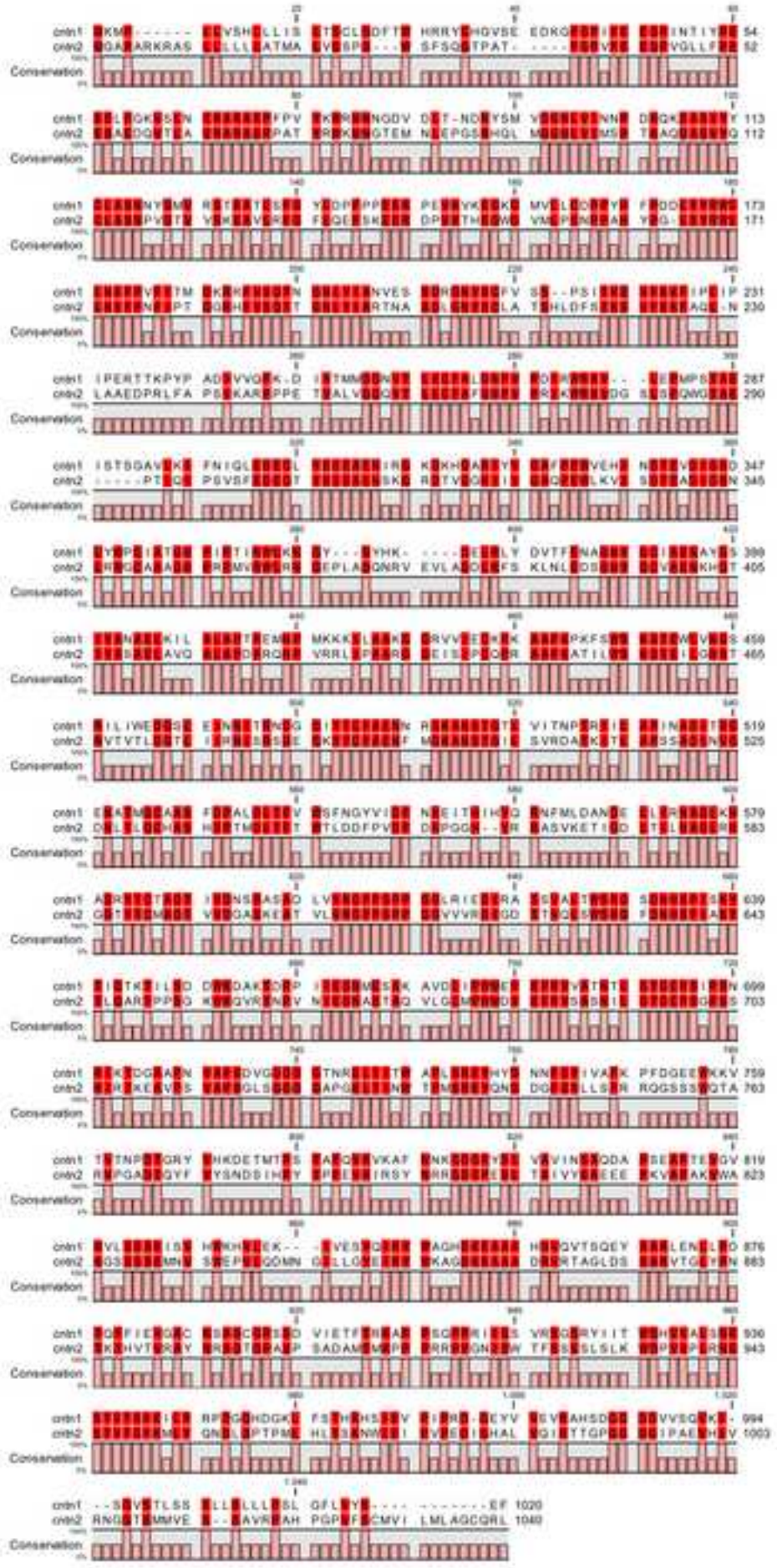

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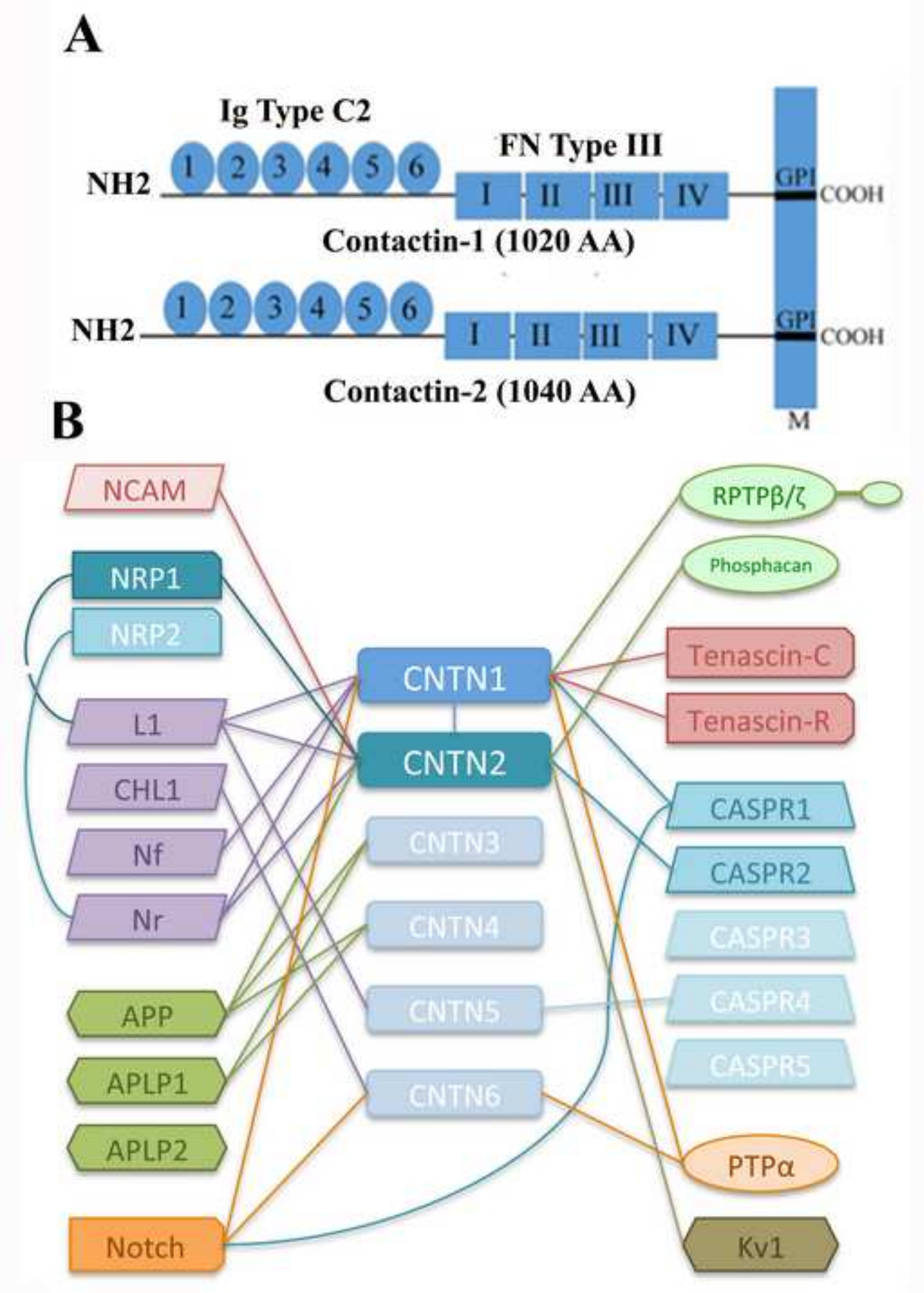

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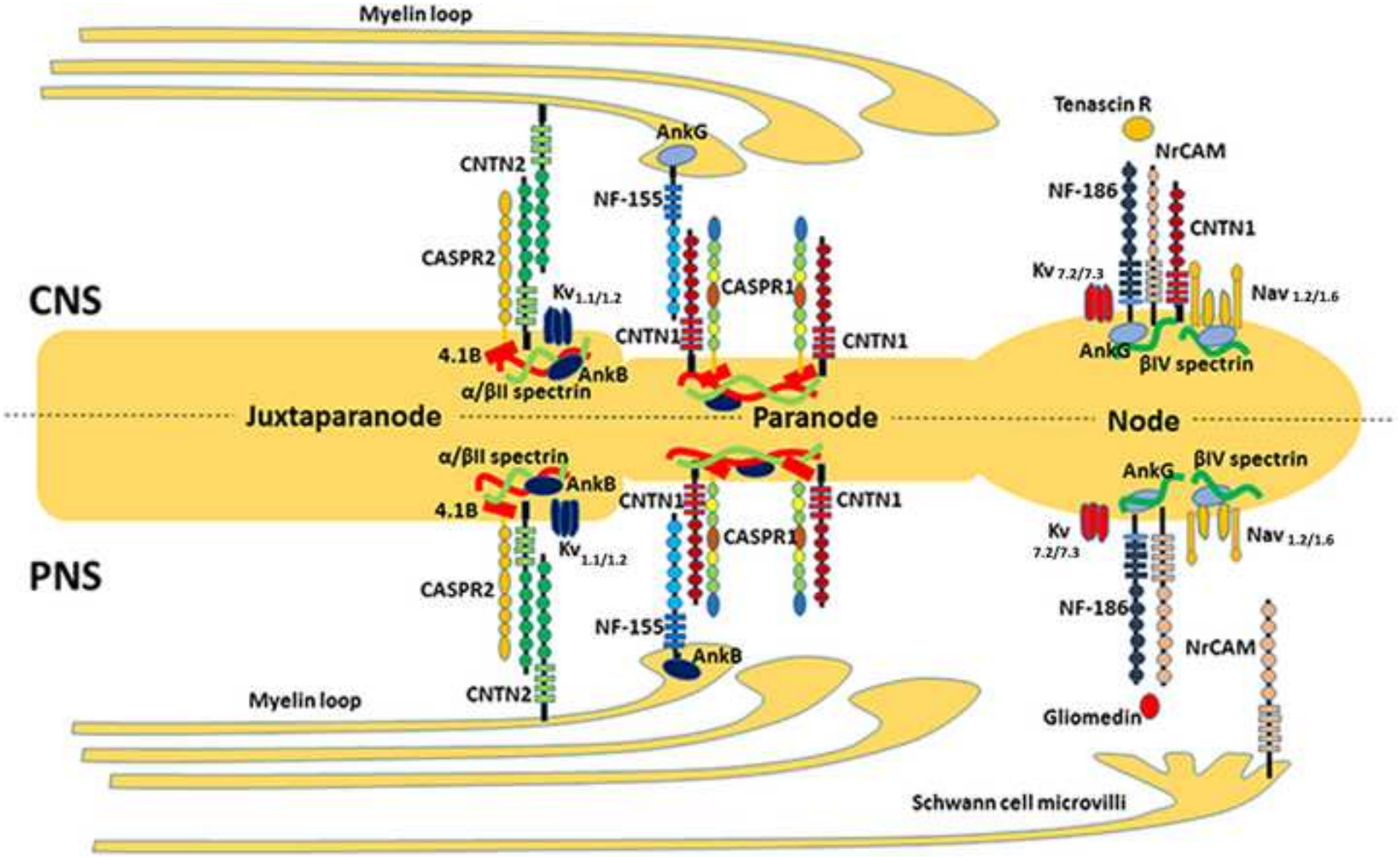

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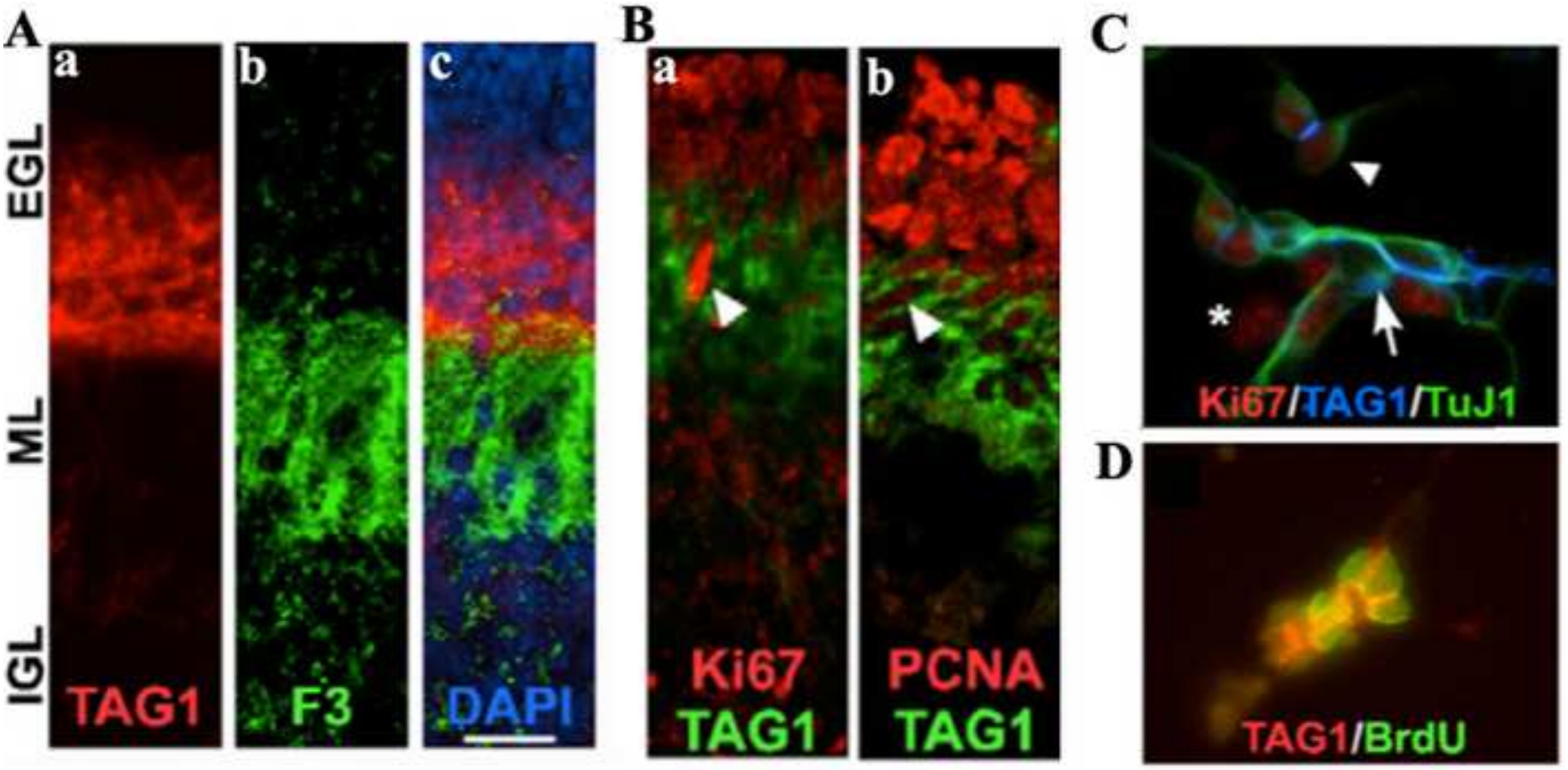

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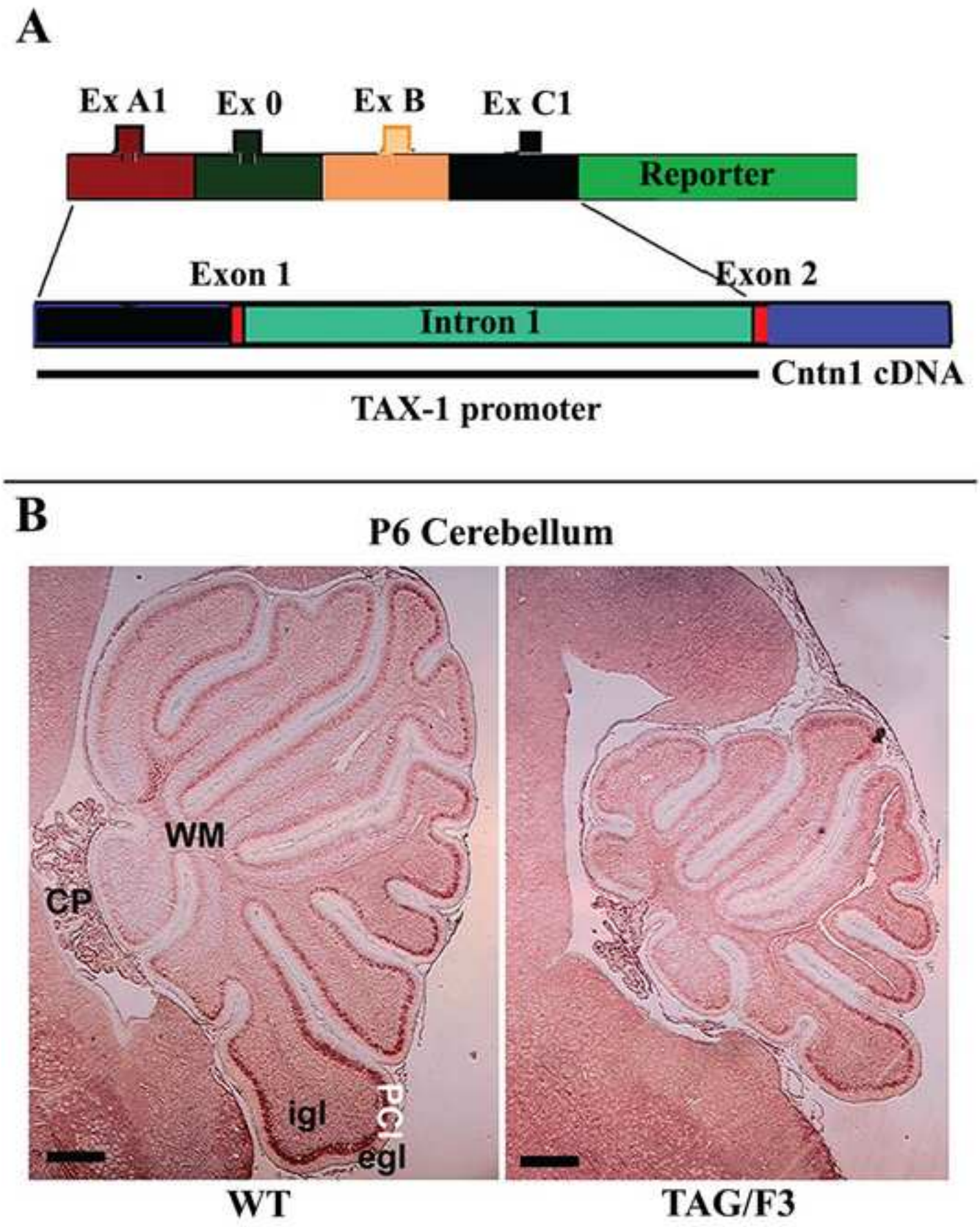

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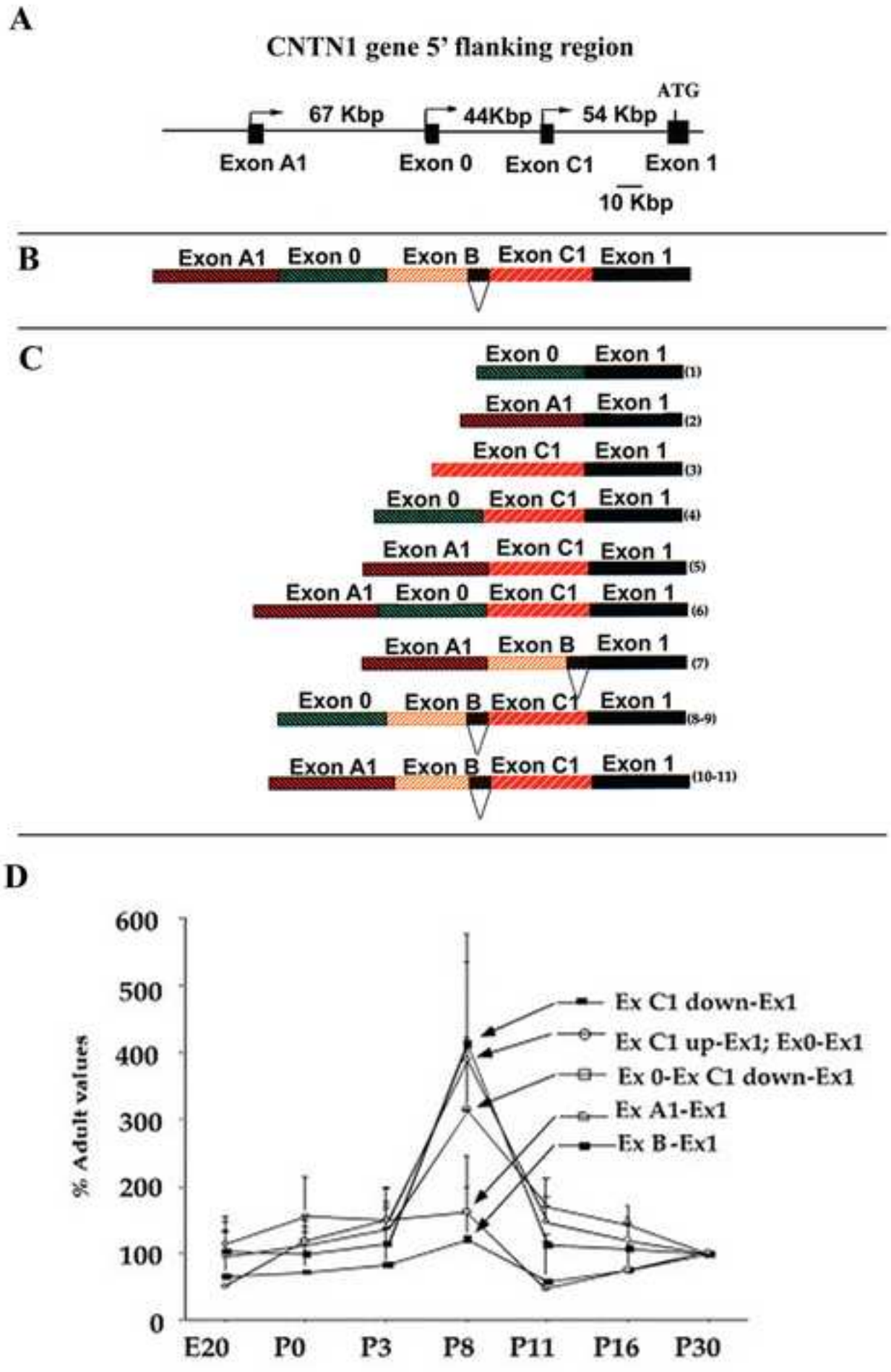

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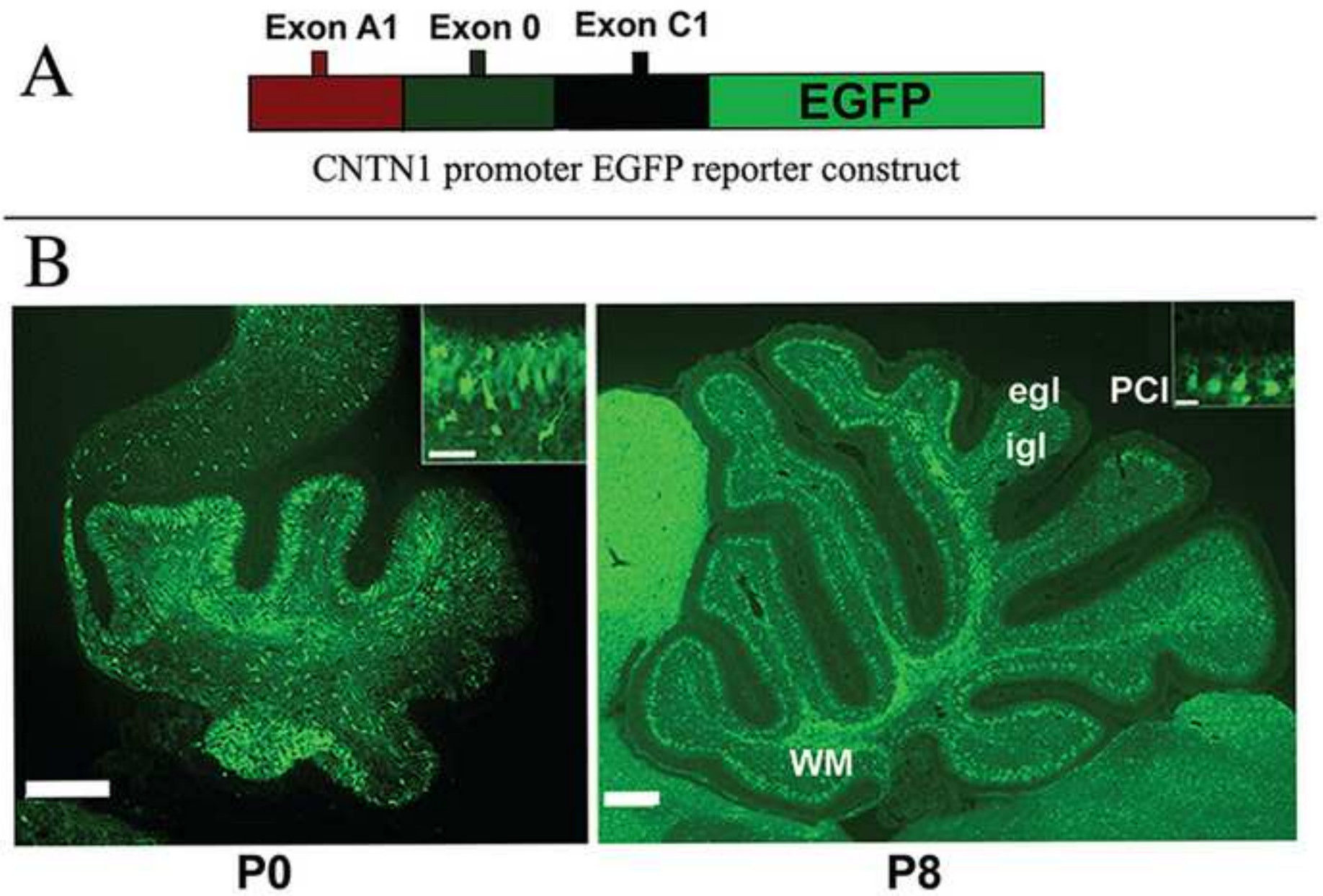

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