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SynCAMs – From axon guidance to neurodevelopmental disorders

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ABSTRACT

Many cell adhesion molecules are located at synapses but only few of them can be considered synaptic cell adhesion molecules in the strict sense. Besides the Neurexins and Neuroligins, the LRRTMs (leucine rich repeat transmembrane proteins) and the SynCAMs/CADMs can induce synapse formation when expressed in non-neuronal cells and therefore are true synaptic cell adhesion molecules. SynCAMs (synaptic cell adhesion molecules) are a subfamily of the immunoglobulin superfamily of cell adhesion molecules. As suggested by their name, they were first identified as cell adhesion molecules at the synapse which were sufficient to trigger synapse formation. They also contribute to myelination by mediating axon-glia cell contacts. More recently, their role in earlier stages of neural circuit formation was demonstrated, as they also guide axons both in the peripheral and in the central nervous system. Mutations in SynCAM genes were found in patients diagnosed with autism spectrum disorders. The diverse functions of SynCAMs during development suggest that neurodevelopmental disorders are not only due to defects in synaptic plasticity. Rather, early steps of neural circuit formation are likely to contribute.

Contents

1. Introduction

In the 40 years since their discovery (Brackenbury et al., 1977; Thiery et al., 1977) cell adhesion molecules of the immunoglobulin superfamily (IgSF CAMs) have seen their ups and downs. Initially, they were thought to act mainly as 'glue' holding axons together in fascicles. But it became clear that IgSF CAMs are more than 'sticky' molecules and that they have important signaling properties. Based on the specificity and versatility of their interaction pattern they supported the 'labeled pathway' hypothesis which predicted that during neural circuit formation axons would find the pathway to their target cells via fasciculation mediated by specific surface molecules (Grenningloh and Goodman, 1992). Soon, first links between IgSF CAM dysfunction and neural disorders were found. Based on what was known about IgSF CAMs at the time, the mechanistic focus was clearly on axon guidance and cell migration (Tessier-Lavigne and Goodman, 1996). Then cell adhesion molecules lost their status as axon guidance molecules (Dickson, 2002) but were rediscovered as synapse-inducing molecules (Biederer et al., 2002). In parallel the interest shifted to synapses and synaptic plasticity

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to explain molecular underpinnings of neurodevelopmental disorders (Melom and Littleton, 2011). Now it's time to bring things into perspective.

1.1. IgSF CAMs - from axon guidance to the synapse

At the time when most members of the IgSF CAMs were discovered, the standard functional assay for these molecules was a test for neurite outgrowth promotion. Most of them did well in this assay. However, these were in vitro assays and, therefore, for quite some time, it was only speculation whether these in vitro observations of axonal growth would indicate a role of IgSF CAMs in axon guidance in vivo. The idea how IgSF CAMs would contribute to neural circuit formation was best reflected by the 'labeled pathway hypothesis' which was based on observations in flies. In fly embryos, axons were found to extend toward their target because they followed pioneer axons that had already connected to the target. Each population of axons could identify the correct pioneer tract based on the expression of distinct cell adhesion molecules (Raper et al., 1983; Grenningloh and Goodman, 1992). Experimental ablation of the pioneer tract resulted in axon guidance defects. While this was certainly a solution for follower axons it did not solve the axon guidance problem for pioneer axons. Furthermore, the situation in vertebrates appeared to be different. In zebrafish, the ablation of pioneer tracts did not result in complete failure of axonal connectivity to the target, as follower axons could convert to pioneers and still manage to connect to the target with some delay (Pike et al., 1992). In higher vertebrates, axons did not depend on pioneer tracts to find their target, as experimentally induced defasciculation of axons did not necessarily interfere with axonal navigation (Stoeckli and Landmesser, 1995).

In this context, it is important to distinguish the 'labeled pathway hypothesis' from the so-called 'handshake hypothesis' (Molnar and Blakemore, 1995). The latter describes the need for mutual signals between cortico-thalamic and thalamo-cortical axons during axon pathfinding. At first sight, the 'handshake hypothesis' appears to contradict the finding that in higher vertebrates axons do not need fasciculation for axon guidance. However, as summarized in a recent review by Garel and Lopez-Bendito (2014), the requirement of cortico-thalamic axons for thalamocortical axons to innervate the cortex does not require axon-axon fasciculation. Rather these axonal populations act as guideposts for each other by providing axon guidance cues. Therefore, the handshake hypothesis and the labeled pathway hypothesis refer to different mechanisms of axon guidance.

Using in vivo loss-of-function strategies in chicken embryos it was finally possible to demonstrate a role of IgSF CAMs in vertebrate axon guidance (Landmesser et al., 1988; Stoeckli and Landmesser, 1995; Stoeckli et al., 1997). Perturbation of interactions between NCAM and L1CAM interfered with correct muscle innervation of the developing hindlimb (Landmesser et al., 1988). Contactin2 (aka Axonin1 or TAG1) expressed on commissural axons was required for axons to cross the midline of the spinal cord by interacting with NrCAM expressed on floor-plate cells (Stoeckli and Landmesser, 1995; Stoeckli et al., 1997). In mouse, Contactin1 was shown to be required for axonal navigation in the cerebellum (Berglund et al., 1999). L1CAM was shown to be necessary for decussation of the corticospinal tract (Cohen et al., 1998a; Dahme et al., 1997). Most likely due to the promiscuity in IgSF CAM interactions and due to genetic redundancy or compensation mechanisms in knockout versus knockdown approaches it was sometimes difficult to discover axon guidance defects in single knockout animals (see Rossi et al., 2015, for a discussion about pros and cons of the different approaches). However, in specific contexts or in combination, deletion of IgSF CAMs clearly interfered with axon guidance. For instance, mice lacking Contactin2 (Fukamauchi et al., 2001) did not display midline crossing defects in the spinal cord, despite the fact that acute perturbation of Contactin2 function by injection of function-blocking antibodies (Stoeckli and Landmesser, 1995) or knockdown of Contactin2 by in ovo RNAi (Pekarik et al., 2003) did interfere with axon guidance. However, the analysis of sensory neural circuit formation in knockout mice lacking Contactin2 (Law et al., 2008) did reveal similar phenotypes as those observed after acute loss of Contactin2 function in chicken embryos (Perrin et al., 2001) and in zebrafish (Liu and Halloran, 2005). These and many other studies have substantiated the role of IgSF CAMs in axon guidance (reviewed in Tessier-Lavigne and Goodman, 1996; Rougon and Hobert, 2003; Stoeckli, 2004; Katidou et al., 2008).

Over the years many other classes of axon guidance molecules have been discovered, including netrins, slits, semaphorins, ephrins, Ephs, and morphogens (Dickson, 2002; Kolodkin and Tessier-Lavigne, 2011). For many of these axon guidance cues IgSF CAMs serve as receptors: Netrin binds to Dcc (Keino-Masu et al., 1996), Slits bind to Robos (Kidd et al., 1999; Brose et al., 1999; Long et al., 2004), and Boc serves at least as co-receptor for the attractive response of axons to Shh (Okada et al., 2006). Very often it is not possible to clearly make a distinction between ligand and receptor, as molecules can exert both functions depending on the context or where they are expressed. This is particularly true for IgSF CAMs but also for some classes of Semaphorins (Andermatt et al., 2014) and for Eph/ephrins (Klein, 2012). Based on what is known about the expression patterns of IgSF CAMs and the results of in vivo analyses that demonstrated their role in axon guidance there is no doubt that IgSF CAMs contribute to neural circuit formation in the PNS and in the CNS.

The features of IgSF CAMs that make them excellent contributors to axon guidance are of course also ideal for synaptogenesis: a large variety of specific interactions, adhesive strength, and distinct signaling depending on specific binding partners both in cis (in the plane of the same membrane) and in trans (interactions between molecules from two different cells). Thus, not surprisingly, IgSF CAMs were found at synapses and many of them were found to interfere with synaptogenesis when downregulated. For instance, synaptic targeting in the retina was affected in the absence of Contactins, DSCAM, and Sidekicks (Yamagata and Sanes, 2012; reviewed by Missaire and Hindges, 2015). Contactins were also shown to interfere with synapse formation in the cerebellum (reviewed in Stoeckli, 2010).

The best studied IgSF CAM at the synapse is NCAM (reviewed in Bukalo and Dityatev, 2012). Absence of NCAM not only interferes with synaptogenesis but also affects synapse function and plasticity. Due to the many interactions of NCAM with growth factors, FGF receptors, as well as NMDA and AMPA receptors, it is not clear how NCAM affects formation or stabilization of synapses (Dityatev et al., 2004; Senkov et al., 2012; Gascon et al., 2007). However, in contrast to true synaptic cell adhesion molecules (see below), NCAM cannot induce synaptogenesis on its own (Sara et al., 2005). The role of NCAM in vesicle release and synaptic function has also been studied extensively at the neuromuscular junction (Rafuse et al., 2000; Polo-Parada et al. 2001 and 2004). Both in the CNS and in the PNS, the post-translational modification of NCAM with polysialic acid (PSA) has been identified as a crucial determinant for NCAM function (Senkov et al., 2012; Gascon et al., 2007).

1.2. SynCAMs go the other way: inducers of synapses

As suggested by their name, SynCAMs (synaptic cell adhesion molecules) were first discovered at synapses in a search for vertebrate cell adhesion molecules with Ig- (immunoglobulin) and PDZ-domains (Biederer et al., 2002; Biederer, 2006). SynCAM genes were discovered in different contexts under different names and were later termed CADMs for Cell ADhesion Molecules (Pietri et al., 2008; Takai et al., 2008). SynCAMs were not only localized at pre- and postsynaptic sites, they were also capable of passing the ultimate test for synaptic cell adhesion molecules, as they were sufficient to induce synaptic specializations even when expressed in cell lines co-cultured with neurons (Biederer et al., 2002). Before, only Neuroligin was shown to be sufficient to induce synapses in an in vitro assay (Scheiffele et al., 2000; Sara et al., 2005; Biederer and Scheiffele, 2007). Cadherins, another class of cell adhesion molecules found at pre- and postsynaptic sites

are not capable of inducing synapses in this in vitro test, despite the fact that they play a role in synapse maintenance and function (Takeichi, 2007).

A recent study provided more insight into the distribution of SynCAM1 at the synapse (Perez de Arce et al., 2015). Using different types of electron microscopy and high-resolution fluorescence microscopy SynCAM1 was localized to the edge of the postsynapse. At the synapse, SynCAMs interact with scaffold molecules, such as protein 4.1 (Hoover and Bryant, 2000) and PDZ type II-domain proteins (Hung and Sheng, 2002). Interactions between SynCAMs and MAGUKs, such as calcium/calmodulin-dependent serine protein kinase (CASK), Pals2 and Dlg3 have been demonstrated (Montgomery et al., 2004; Oliva et al., 2012; Biederer et al., 2002; Shingai et al., 2003; Kakunaga et al., 2005; see below).

Like other IgSF CAMs, SynCAMs undergo a plethora of cis- (in the plane of the same membrane) and trans-interactions (interactions between molecules from two different cells). Initially, it was reported that SynCAMs would preferentially form cis-homodimers which would interact homo-and heterophilically with dimers in trans (Takai et al., 2008; Fogel et al., 2007). It is clear now that the interaction pattern is even more complex and cis-heterodimers are clearly formed (Fogel et al., 2010; Fogel et al., 2011; Frei et al., 2014). Furthermore, the composition of cis-dimers determines the affinities for trans-interactions, similar to what was found previously for other IgSF CAMs (Kunz et al. 1996 and 1998; Kunz et al., 2002). Furthermore, binding preferences and binding strengths of SynCAMs are modulated by differential glycosylation (Fogel et al. 2007 and 2010; Galuska et al., 2010).

The role of SynCAM1 and SynCAM2 in synaptogenesis has been extensively studied, as this feature was the basis for their discovery (Fogel et al., 2007; Stagi et al., 2010; Robbins et al., 2010; Park et al., 2016). Confirmation of the role of SynCAMs in synapse formation came from heterologous co-culture assays (Biederer and Scheiffele, 2007; see above) showing that overexpression of SynCAM1 in non-neuronal cells induced functional presynaptic terminal differentiation in co-cultured hippocampal neurons (Biederer et al., 2002; Sara et al., 2005). The induced synapses were functional as co-expression of SynCAM1 with glutamate receptors triggered spontaneous electrical activity. Overexpression of SynCAM1 in hippocampal neurons increased the frequency of spontaneous miniature excitatory postsynaptic currents (mEPSCs) (Biederer et al., 2002; Sara et al., 2005). In line with these in vitro findings are the effects in transgenic mice overexpressing SynCAM1 in excitatory neurons and mice lacking SynCAM1, showing an increase and decrease in excitatory synapse number and mEPSC frequency, respectively (Robbins et al., 2010). More recently a role of SynCAM1 in the structural organization and function of ribbon synapses in the mouse retina has been discovered (Ribic et al., 2014). Thus, SynCAM1 does not only play a role in classical synapses in the hippocampus but also in ribbon synapses of photoreceptors in the retina.

SynCAMs team up for synaptogenesis: SynCAM1 and SynCAM2 assemble into a trans-synaptic adhesive complex. By recruiting scaffold molecules and thus indirectly other synaptic molecules, they organize functional synapses and promote transmission (Fogel et al., 2007). Prior to trans-synaptic adhesion SynCAM1 clusters into multimeric complexes and recruits intracellular effector molecules, such as Farp1 (Fogel et al., 2011; Cheadle and Biederer, 2012) (Fig. 1). The SynCAM1-Farp1 complex triggers anterograde and retrograde signals, induces polymerization of actin in spines and organizes presynaptic active zones (Cheadle and Biederer, 2012). Another intracellular binding partner of SynCAM1 is the MAGUK family member CASK (Biederer et al., 2002; Kakunaga et al., 2005). CASK interacts with components of the presynaptic terminal, including Neurexins, Mint1 and Veli, two molecules involved in exocytosis of synaptic vesicles, as well as voltage-gated Ca^{2+}-channels (Biederer et al., 2002; Butz et al., 1998; Cohen et al., 1998b; Hata et al., 1996; Hoover and Bryant, 2000; Samuels et al., 2007) (Fig. 1). CASK also interacts with SynCAMs at the postsynapse and mediates insertion of NMDARs into the synaptic membrane

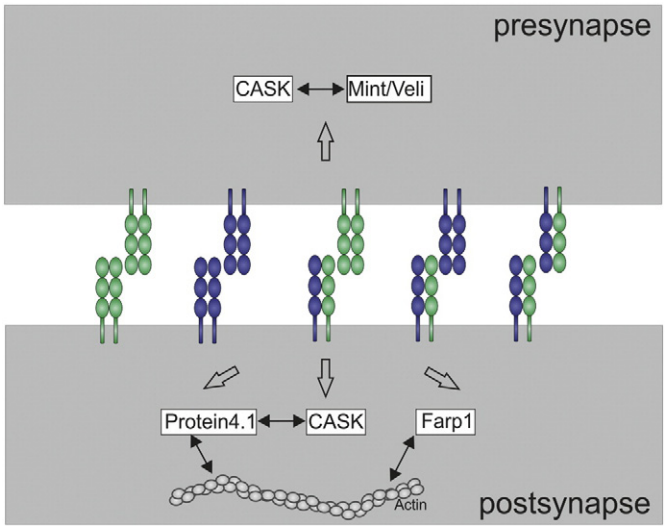

Fig. 1. The composition of cis-dimers regulates trans-interactions of SynCAMs. SynCAM1 (green) and SynCAM2 (blue) interact in cis in homo- or heterophilic manner. The affinity of the cis-dimers for trans-interaction partners depends on their composition. In the presynapse, SynCAMs interact with CASK, which in turn interacts with Neurexins (not shown) but also with Mint and Veli, two proteins involved in the regulation of vesicle exocytosis. At the postsynaptic site SynCAMs not only interact with CASK but also with Farp1 and members of the protein 4.1 family. Through these interactions SynCAMs are linked to the actin cytoskeleton but also affect recruitment and positioning of NMDA- and AMPA receptors (see text for details and references).

(Biederer et al., 2002; Jeyifous et al., 2009). Besides the SynCAM1-Farp1 and SynCAM1-CASK complexes, members of the protein 4.1 family have been identified as postsynaptic effector molecules of SynCAM1 (Hoy et al., 2009) (Fig. 1). SynCAM1 and SynCAM3 interact with protein 4.1B/Dal1 or 4.1N through their FERM-binding domain resulting in the differential recruitment of NMDAR and AMPAR, respectively (Hoy et al., 2009; Zhou et al., 2005).

SynCAM1 not only contributes to synaptogenesis, as it is required later in development for the maintenance of excitatory synapses and for the regulation of synaptic plasticity (Lyckman et al., 2008; Robbins et al., 2010). Overexpression of SynCAM1 abrogates loss of synapses during long-term depression (LTD) whereas loss of SynCAM1 increases LTD (Robbins et al., 2010). The analysis of knockout and transgenic mice demonstrated that SynCAM-dependent decrease or increase in LTD had an effect on cognitive functions, as spatial learning and memory in mice were affected. In contrast to other IgSF CAMs that stabilize LTP (long-term potentiation) and LTD, SynCAM1 prevents LTD without affecting LTP (Bukalo et al., 2004; Murai et al., 2002; Robbins et al., 2010). A role of SynCAM1 in synaptic plasticity was also demonstrated by its increased expression in the visual cortex after monocular deprivation (Lyckman et al., 2008).

In contrast to SynCAM1 and SynCAM2, SynCAM3 has not been found at synaptic contacts but rather at non-junctional sites where axon terminals and astrocyte processes contact to surround pre- and postsynapses (Kakunaga et al., 2005).

1.3. SynCAMs and neurodevelopmental disorders

In line with a function in synaptogenesis, synaptic organization and plasticity, mutations in synaptic cell adhesion molecules have been identified as causes or risk factors for neurodevelopmental disorders, in particular, intellectual disability and autism spectrum disorders (Dean and Dresbach, 2006; Sudhof, 2008; Bourgeron, 2009). Two missense mutations in SynCAM1 were identified in patients diagnosed with autism spectrum disorders (Zhiling et al., 2008).

These findings were in line with observations in animal models, despite the fact that animal models only reflect isolated traits of these complex human disorders. SynCAM1 knockout mice exhibit deficits in social and emotional behavior, as well as impaired ultrasonic vocalization (Takayanagi et al., 2010; Fujita et al., 2012). Transgenic and knockout mice showed altered spatial learning, as mice overexpressing SynCAM1 in excitatory synapses performed worse, whereas SynCAM1 knockout mice performed better (Robbins et al., 2010). At the anatomical level, neurons expressing mutant SynCAM1 exhibit aberrant dendritic spines and defective synaptic function (Robbins et al., 2010; Fujita et al., 2010). The molecular mechanisms of SynCAM1 dysfunction in these mouse models was not clear, protein trafficking problems or the failure of SynCAM to form cis-interactions and thereby recruit synaptic scaffold molecules were suggested (Fujita et al., 2010; Zhiling et al., 2008; Fogel et al. 2007 and 2011). In line with its collaboration with SynCAM1 at the synapse, also SynCAM2 was identified as a candidate gene for autism spectrum disorders (Casey et al., 2012).

1.4. SynCAMs are axon guidance molecules

SynCAM2 was found in a screen for axon guidance molecules (Niederkofler et al., 2010). At the time, this was unexpected, as SynCAMs had been identified and characterized as synaptic cell adhesion molecules (Biederer et al., 2002). Later, their role in myelination was described both in the CNS and in the PNS. Axonal SynCAM1 and SynCAM3 interact with SynCAM4 on Schwann cells to promote myelination in the PNS (Maurel et al., 2007; Spiegel et al., 2007). In the CNS, SynCAM2 and SynCAM3 have been implicated in myelination, although their detailed expression in axons versus glia is not clear yet (Kakunaga et al., 2005; Park et al., 2008; Pellissier et al., 2007). However, a role in earlier aspects of neural circuit formation had not been considered.

1.5. SynCAMs as axon guidance molecules in the CNS

SynCAM2 was found to be expressed in the floor plate, the intermediate target of commissural axons in the spinal cord (Niederkofler et al., 2010). Expression analyses demonstrated SynCAM1 and SynCAM2 expression also in dI1 commissural axons. The dI1 subpopulation of commissural neurons is the dorsal-most population of interneurons in the spinal cord. They extend their axons ventrally toward the floor plate, their intermediate target (Chedotal, 2011; Nawabi and Castellani, 2011). After crossing the midline, axons turn rostrally into the longitudinal axis to extend toward the brain. Due to their highly stereotypic and simple pathway choices the dI1 neurons have been a favored model for axon guidance studies. Previously, other IgSF CAMs were identified as axon guidance cues for dI1 commissural axons. Contactin2 (aka Axonin1 or TAG1) was shown to bind L1CAM/NgCAM on pre-crossing axons to mediate their fasciculated growth toward the intermediate target. At the floor plate, Contactin2 bound to NrCAM expressed by the floor plate to guide axons across the midline (Stoeckli and Landmesser, 1995; Stoeckli et al., 1997; Fitzli et al., 2000). NgCAM and NrCAM, but not Contactin2, stimulated growth of post-crossing axons along the longitudinal axis of the spinal cord (Fitzli et al., 2000). In addition, a role for another IgSF CAM, MDGA2, in post-crossing commissural axon growth was identified, but it is not known whether MDGA2 binds to either NgCAM or NrCAM (Joset et al., 2011).

In contrast to Contactin2, SynCAMs were not required for floor-plate entry (Niederkofler et al., 2010). Rather, loss of SynCAM2 from the floor plate interfered with dI1 axons' turn into the longitudinal axis. As axonal receptors for floor-plate SynCAM2 both SynCAM1 and SynCAM2 itself were possible. However, SynCAM2-SynCAM2 interactions were found to be extremely weak in comparison to heterophilic SynCAM1-SynCAM2 interactions (Frei et al., 2014; Niederkofler et al., 2010; Fogel et al., 2007). Therefore, it came as a surprise when loss of SynCAM2 function from dI1 neurons also resulted in axon guidance defects at the midline. The interaction between axonal SynCAM1 and floor-plate SynCAM2 was thought to be sufficient for axonal navigation. The most likely explanation why axons required both SynCAM1 and SynCAM2 for their interaction with the floor plate was a heterophilic cis-interaction between SynCAM1 and SynCAM2 (Niederkofler et al., 2010). The existence of such heterophilic cis-interactions was confirmed by in vitro binding studies (Frei et al., 2014). Furthermore, these studies indicated that the nature of the cis-interaction determined the binding partners in trans, as heterophilic cis-interactions changed the binding preferences of trans-binding SynCAMs compared to cis-homodimers (Frei et al., 2014).

1.6. SynCAMs as axon guidance molecules in the PNS

Because of the subpopulation-specific expression of SynCAMs in sensory neurons of the dorsal root ganglia, they were tested for a role in axon guidance in the peripheral nervous system (Frei et al., 2014).

In contrast to other IgSF CAMs, SynCAMs do not have a strong neurite growth-promoting effect (Frei et al., 2014). In an in vitro assay, SynCAMs promoted the adhesion of sensory axons, as growth cones preferentially stayed on SynCAM-expressing cells. Preferential adhesion to SynCAM substrates correlated with a striking change in morphology of sensory axons and growth cones (Fig. 2). Axons appeared flattened and much thicker than those on laminin. Changes in growth cone morphology depending on the interaction between SynCAM1 and FERM domains found in a variety of cytoskeletal linker proteins, e.g. protein 4.1, were also found for hippocampal neurons (Stagi et al., 2010). Growth cone areas were between 3 and 6 times larger when sensory axons grew on SynCAMs compared to Laminin. In analogy to what was shown for Contactin2 before (Buchstaller et al., 1996; Stoeckli et al., 1996), the apical growth cone surfaces were devoid of SynCAM1 and SynCAM2 when axons grew on SynCAM substrates due to a redistribution of SynCAM to the substrate-facing (basal) growth cone surface (Frei et al., 2014). In comparison, SynCAMs were found on the apical growth cone surface on Laminin substrate, where neurite growth is mediated by integrins. These findings strongly suggested that SynCAM-SynCAM interactions were involved in the changes of axonal morphology and changes in growth behavior in vitro which in turn could explain how SynCAM-SynCAM interactions change growth cone behavior during axonal navigation in vivo.

So far, it is unknown how intracellular signals upon SynCAM/SynCAM interactions are transmitted to the cytoskeleton in axons and growth cones. It will have to be tested whether the scaffold molecules identified as intracellular binding partners of SynCAMs in synapse formation and function are also responsible for SynCAM function during axon guidance. Good starting points are interactions between SynCAMs and CASK or FAK (Stagi et al., 2010). FAK (focal adhesion kinase) is well known for its involvement in integrin-mediated neurite growth (Robles and Gomez, 2006). Thus, the differential distribution of SynCAMs on growth cones growing on SynCAM substrates versus Laminin (Frei et al., 2014) may indicate that FAK signaling is a crucial determinant of SynCAM-mediated axon growth.

The most striking differences between SynCAM-mediated and non-SynCAM-mediated axon growth was the exuberant formation of axon-axon contacts. These observations led to the investigation whether SynCAM-SynCAM interactions could be responsible for the specific cell-cell interactions observed during sensory axon entry into the dorsal spinal cord (Frei et al., 2014). Indeed, the formation of dorsal roots by sensory afferents was perturbed after silencing SynCAM2 and SynCAM3 (Fig. 3). Furthermore, the axons failed to form the characteristic homogenous fiber bundle along the longitudinal axis of the spinal cord. This feature had been seen before also after perturbation of Contactin2 function in sensory neurons (Perrin et al., 2001; Law et al., 2008).

Because sensory afferents start to innervate the gray matter of the spinal cord from specific areas, from the medial dorsal funiculus for

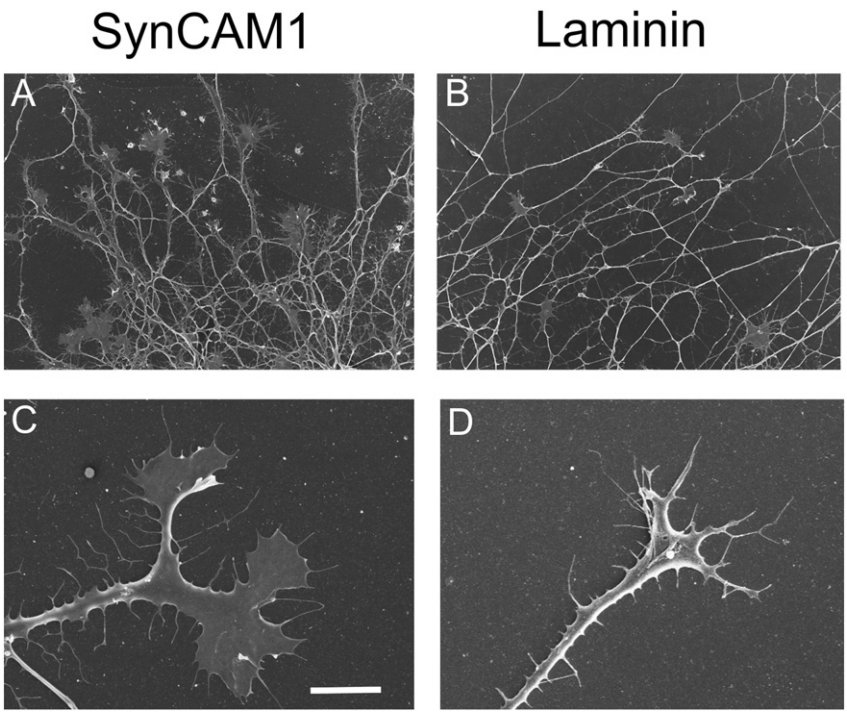

Fig. 2. Axonal morphology on SynCAM1 differs strongly from Laminin substrate. Sensory neurons grown on SynCAM1 substrate exhibit a striking axonal flattening compared to Laminin. The growth cones on SynCAM1 are three times larger than those on Laminin. They were up to six times as large on SynCAM2 (Frei et al., 2014). Bar: 50 μm in A, B; 10 μm in C, D.

proprioceptive fibers versus the dorsolateral areas of the dorsal funiculus for nociceptive fibers, the aberrant entry of sensory axons into the spinal cord was suggested to result in subsequent axon guidance errors. Indeed, this was seen, when older embryos were analyzed. In the absence of SynCAMs sensory afferents aberrantly entered the gray matter of the spinal cord (Fig. 4). Some of these fibers even crossed the ventral midline, a behavior that was never seen in sensory axons of control

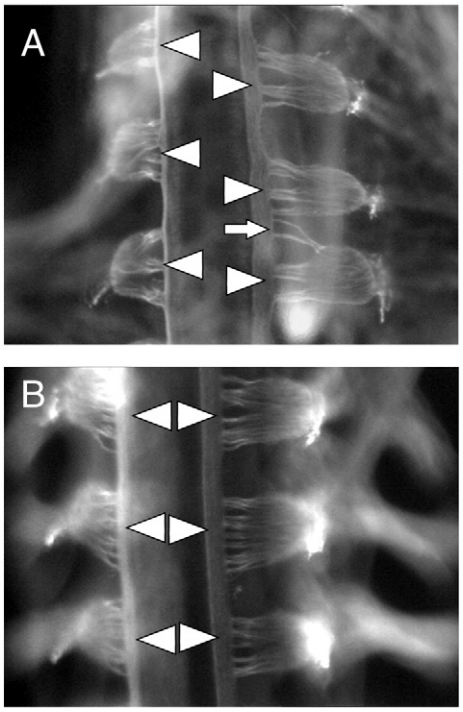

Fig. 3. SynCAMs are required for the proper formation of dorsal root ganglia and dorsal roots. In the example shown here, silencing SynCAM3 in neural crest cells by in ovo RNAi (as described in Frei et al., 2014) resulted in aberrant arrangement of dorsal root ganglia (compare position of arrowheads in the embryo lacking SynCAM3, shown in A, with a control-treated embryo shown in B). Furthermore, fasciculation and extension of dorsal roots to the dorsal root entry zone were highly irregular in the absence of SynCAMs (arrow in (A)).

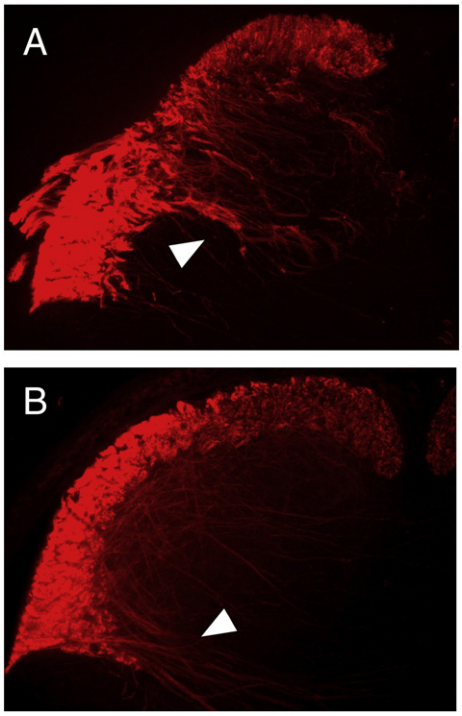

Fig. 4. Sensory afferents enter the dorsal horn of the spinal cord from aberrant positions after perturbation of SynCAM2 function. After downregulation of SynCAMs by in ovo RNAi, collaterals of sensory axons start innervating the gray matter from aberrant positions in the dorsal funiculus (Frei et al., 2014). In the example shown in (A) the population of nociceptive collaterals normally extending horizontally into the dorsal gray matter extends mostly from a more dorsal position. Note also the aberrant shape of the dorsal funiculus in the slice taken from an embryo lacking SynCAM (A) compared to the control (B).

animals. Thus, consistent with results from in vitro assays, loss of SynCAMs does not primarily prevent growth of axons, but interferes with their navigation and, thus, connectivity. Taken together, these in vitro and in vivo observations confirm the hypothesis that SynCAMs are crucial for the selection of axon-axon contacts that are required for neural circuit formation.

1.7. SynCAMs – the 'do-it-all' in neural circuit formation

SynCAMs are involved in axon guidance, synapse formation, and synaptic plasticity. They are linked to neurodevelopmental disorders based on linkage and genome-wide association studies. Individual traits of these neurodevelopmental disorders in humans have been confirmed by observations in animal models.

So what do we learn from the analyses of the roles of SynCAMs in neurodevelopment and function? For one, SynCAMs are very versatile. They affect many steps in the formation of neural circuits. Clearly, their contribution starts much earlier than synaptogenesis. However, this should maybe not be too much of a surprise based on the dynamic expression of SynCAMs during early and late stages of neural development (Frei et al., 2014; Hunter et al., 2011; Niederkofler et al., 2010; Thomas et al., 2008). Furthermore, an involvement in many steps of neural development and function is common to other families of IgSF CAMs as well. The L1 and the Contactin families identified as axon growth and guidance molecules are also linked to neurodevelopmental disorders.

Mutations in L1CAM were identified as the cause of MASA (Mental retardation, Aphasia, Shuffling gait, and Adducted thumbs; Kenwrick et al., 1996) or CRASH syndrome (Corpus callosum hypoplasia, Retardation, Adducted thumbs, Spasticity, and Hydrocephalus; Yamasaki et al., 1997). Mutations in Contactin family members were identified in patients diagnosed with autism spectrum disorders (Zuko et al., 2013). NrCAM was not only linked to autism but also to a changed behavior in tests for addiction in animals (Sakurai, 2012). NCAM, especially elevated levels of the soluble form of NCAM, NCAM-120, was linked to schizophrenia. Based on mouse models lacking NCAM, NCAM was also linked to depression and anxiety disorders (reviewed in Katidou et al., 2008; Giagtzoglou et al., 2009).

So it is clearly not so special for molecules to be involved in many aspects of neural circuit formation. The IgSF CAMs Contactin1 and Contactin2 were not only shown to guide axons (see above) but also to affect neurogenesis in the cerebellum, the cortex, and also the adult hippocampus (Bizzoca et al. 2003 and 2012; Ma et al., 2008; Xenaki et al., 2011; Puzzo et al., 2013). In order to understand the link between neural development and neurodevelopmental disorders, we will need to take a more integrative look at the role of molecules and mechanisms in neural circuit formation. In fact, the molecules involved in neural circuit formation may turn out to have a contribution to neurodegenerative disorders. Clearly, neural circuits that were formed sub-optimally may function satisfactorily throughout decades, but they may be more sensitive for functional disturbances induced by ageing or environmental insults. Along these lines, one could make sense of findings from genetic and genomic studies linking neurodevelopmental molecules, such as IgSF CAMs to neurodegenerative diseases (Antonell et al., 2013). In turn, APP, the amyloid precursor protein, binds to Contactin2 to negatively regulate neurogenesis (Ma et al., 2008).

Thus, the discovery of an axon guidance function of SynCAMs fits well to the overall functional spectrum of IgSF CAMs. They are versatile molecules with the required functional features that can be used to guide axons, make synapses, and keep them plastic, because the complex interaction patterns between cis- and trans-interacting IgSF molecules provides the specificity and variability that is needed in all these processes. But the broad functional spectrum of IgSF CAMs should also be taken as a reminder that neurodevelopmental disorders can be caused by more than just a defect in synaptic plasticity.

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