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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.

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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