Molecular and Cellular Neuroscience 81 (2017) 4–11

Contents lists available at ScienceDirect

Molecular and Cellular Neuroscience

journal homepage: www.elsevier.com/locate/ymcne

The role of cell adhesion molecules in brain wiring and neuropsychiatric disorders

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ARTICLE INFO

Article history:
Received 15 June 2016
Revised 16 August 2016
Accepted 19 August 2016
Available online 22 August 2016

Keywords:
Brain wiring
Cell adhesion
Developmental psychiatric disorders
Synapse

ABSTRACT

Cell adhesion molecules (CAMs) in the nervous system have long been a research focus, but many mice lacking CAMs show very subtle phenotypes, giving an impression that CAMs may not be major players in constructing the nervous system. However, recent human genetic studies suggest CAM involvement in many neuropsychiatric disorders, implicating that they must have significant functions in nervous system development, namely in circuitry formation. As CAMs can provide specificity through their molecular interactions, this review summarizes possible mechanisms on how alterations of CAMs can result in neuropsychiatric disorders through circuitry modification.

Contents

1. Introduction

Cell adhesion molecules (CAMs) in the nervous system have a long history of research and have experienced ups and downs in their appreciation as being important in the nervous system development. The recent explosion of human genetics have once again put CAMs in the spot light in brain development based on their involvement in psychiatric disorders. As a researcher involved in CAM research for many years, I have witnessed much in these arenas and felt compelled to put pen to paper and write down rather personal notes, including some historical aspects and perspectives on CAMs in nervous system development and psychiatric disorders.

2. Structural properties of CAMs

CAMs are membrane bound cell surface molecules and consist of combinations of structural modules (Berezin and Walmod, 2013; Hirayama and Yagi, 2013; Hirabayashi and Yagi, 2014; Basu et al., 2015, Bemben et al., 2015; de Wit and Ghosh, 2016). Extracellular regions support adhesive activities and typically have several structural

Abbreviations: Ig, immunoglobulin; GPI, glycophosphatidylinositol; PSA, polysialic acid; GWAS, genome wide association study.

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http://dx.doi.org/10.1016/j.mcn.2016.08.005
1044-7431/

motifs. Based on their structural signatures, CAMs can be grouped into families, e.g., the Ig superfamily, cadherin family, contactin family, neuroligin/neurexin family, leucin rich repeat molecules, etc (see e.g., de Wit and Ghosh, 2016 for figures). CAMs are either transmembrane proteins or anchored onto cell membrane by a GPI linkage. Many transmembrane CAMs also have intracellular motifs that can bind molecules like cytoskeletal proteins and cytoplasmic adaptors, and/or have enzymatic activities like kinases and phosphatases that could directly or indirectly modulate intracellular events. In some cases such as GPI linked molecules which do not have cytoplasmic region, transmembrane molecules interacting with these molecules would have cytoplasmic regions that modulate intracellular events.

Extracellular interactions have several characteristic molecular features: Extracellular regions can mediate multiple interactions, either homophilically or heterophilically. Furthermore, CAMs can mediate interactions in trans (between opposing cell membranes) as well as in cis (on the same membrane). These increase complexity of molecular binding (Pollerberg et al., 2013; Weiner and Jontes, 2013). Binding affinity of CAMs that can be evaluated by the classical binding affinity constant Kd is usually not extremely high when it is measured for simple 1:1 molecular interactions (Pollerberg et al., 2013). But CAMs can form multimeric complexes that drastically increase binding strength/affinity, implying that during cell–cell adhesion events, through their capability of multimeric interactions, CAMs bring molecules together at the localized region on the cell membrane to make adhesion stronger and restrict movement of molecular complexes at that location (Schwabe et al., 2009). These multimeric interactions can be both homophilic and heterophilic as well as in trans and cis. Binding specificity determined by molecular interactions can be highly unique or promiscuous, depending on the molecules (Berezin and Walmod, 2013; Basu et al., 2015; Bemben et al., 2015; de Wit and Ghosh, 2016).

In addition, CAMs not only support cell adhesion, but also serve as receptors for other molecules, e.g., semaphorins, repulsive molecules that can disrupt adhesion (Castellani et al., 2000). This would further increase complexity of CAM-mediated interactions (e.g., Sakurai, 2012 for NrCAM), making functional characterization of molecular interactions much more complicated (e.g., Demyanenko et al., 2011; Molnar et al., 2012). Furthermore, phenotypes observed in gene knockout (KO) mice for CAMs may not be adhesion phenotypes per se, but phenotypes caused by disruption of other interactions, e.g., serving as semaphorin receptors. In fact, it has taken much effort to figure out which molecular interactions are responsible for the particular phenotypes (e.g., Nakamura et al., 2010 for L1CAM).

Finally, CAMs are subjected to posttranslational modification such as modification by sugar moieties, phosphorylation, etc., together affecting adhesiveness and/or molecular interactions. Sugar modification of CAMs has been well characterized for PSA-NCAM (Bruses and Rutishauser, 2001), and for other CAMs as well (Kleene and Schachner, 2004). However, we do not yet have a complete picture of posttranslational modification and its functional implications in modulating adhesion activities for each CAM.

3. Functions of CAMs

Brain functions require many neuronal circuitries that are made up of sets of neurons, each connected specifically with others. Brain wiring, a process constructing such an intricately wired system as the brain and spinal cord, includes the formation of specific connections among many different neurons whose projections extend long distance. The larger the degree of complexity in the system, the more specificity is required to support the system. CAMs can provide specificity by their expression patterns in time and space, together with their capability of interacting with specific partners (Williams et al., 2010; Missaire and Hindges, 2015). Furthermore, somehow related to specificity, CAMs can exert their functions locally, i.e., adhesion points/events can be modulated individually (Williams et al., 2010; Missaire and Hindges, 2015). This actually endows the system for the enormous freedom/variables (and perhaps at the same time room for error). Through these, CAMs can support specific cell–cell interactions as well as specific cellular localization of molecules, and as a result, CAMs are implicated in 1) axon growth and guidance, 2) fasciculation, 3) target recognition, 4) synapse formation and maintenance, all together contributing to brain wiring (Table 1). Many of these are predicted by numerous biochemical and in vitro/in ovo studies.

CAMs are categorized into short range (contact-mediated) attractive cues in guidance (Tessier-Lavigne and Goodman, 1996). At guidance decision points, CAMs may be differentially expressed, and selective adhesion mediated by CAMs may provide axons with support for their advancement at decision points (specificity). But since axons have to pass decision point and eventually move on, there needs to be tight regulation of adhesive events at these intermediate guidance points (local regulation). Nevertheless, compared to phenotypes such as those observed in mice lacking other guidance factors like netrin, slits, semaphorins, etc. (Kolodkin and Tessier-Lavigne, 2011), many CAM KO mice show only slight guidance phenotypes (though fine detailed analyses have indicated some guidance defects in these mice, e.g., Williams et al., 2006; Kuwajima et al., 2012). Therefore, superficially, CAMs do not appear to be a major determinant in axon guidance (Kolodkin and Tessier-Lavigne, 2011).

CAMs support fasciculation, a process of axon–axon interactions to make axon bundles (Van Vactor, 1998). Selective adhesion with particular axon bundles could be important for axon guidance and target recognition. Using frog and chick systems, it has been predicted that fasciculation mediated by CAMs may be important for axon guidance and target recognition (Milner et al., 1998; Bak and Fraser, 2003). However, only deleting a single gene for CAMs does not induce drastic defasciculation, a phenotype observed in KO mice of inhibitory molecules such as semaphorins (e.g., Taniguchi et al., 1997). Nevertheless, Sakano's group showed that axon sorting via semaphorins to form

Table 1
Examples of function of CAMs.

Function	Molecules	
Axon growth	L1CAMs	Maness and Schachner, 2007
	Contactins	Zuko et al., 2013
	Cadherins/protocadherins	Takeichi, 2007 Hayashi and Takeichi, 2015
Axon guidance	L1CAMs	Cohen et al., 1998; Williams et al., 2006; Kuwajima et al., 2012
Fasciculation	NCAM	Rutishauser, 1984
	L1CAMs	Sonderegger et al., 1998
	Contactins	Redies, 1997
	Cadherins	
Target recognition	Contactins	Yamagata and Sanes, 2008,
	DSCAM	Osterhout et al., 2015
	Cadherins/protocadherins	Yamagata and Sanes, 2012
	Dpr/DIPs (*Drosophila*)	Osterhout et al., 2011 Carrillo et al., 2015, Tan et al., 2015
Synapse formation/maturation	Neuroligins/Neurexins	Bemben et al., 2015
	Ig superfamily CAMs	Biederer et al., 2002
	SynCAM	Ashrafi et al., 2014
	Contactins/CNTNAPs	Takahashi and Craig, 2013
	PTPs	Martin et al., 2015
	Kirrel3	Benson and Huntley, 2012,
	Cadherins	Friedman et al., 2015
	LRR family of CAMs	de Wit and Ghosh, 2014,
	Teneurin	Winther and Walmod, 2014 Mosca, 2015
Formation of myelinated structure	NrCAM/neurofascin	Rasband and Peles, 2016
	Contactins/CNTNAPs	Quarles, 2002
	MAG	
	P0	

This is not to be an exhaustive list, but rather shows that many CAMs are involved in many functions. Most of the examples listed are for mammalian CAMs (indicated otherwise in parenthesis). For details, please refer to citations.