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Review

The role of NrCAM in neural development and disorders—Beyond a simple glue in the brain

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ABSTRACT

NrCAM is a neuronal cell adhesion molecule of the L1 family of immunoglobulin super family. It plays a wide variety of roles in neural development, including cell proliferation and differentiation, axon growth and guidance, synapse formation, and the formation of the myelinated nerve structure. NrCAM functions in cell adhesion and modulates signaling pathways in neural development through multiple molecular interactions with guidance and other factors. Alterations in NrCAM structure/expression are associated with psychiatric disorders such as autism and drug addiction and with tumor progression. The mechanisms of NrCAM participation in development and how these might be perturbed in disorders are reviewed.

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Contents

Abbreviations: Ig, immunoglobulin; Fn, fibronectin; UTR, untranslated region; DRG, dorsal root ganglia; GABA, gamma amino butyric acid; PSD, postsynaptic density; EM, electron microscopy; CNS, central nervous system; PNS, peripheral nervous system; SNPs, single nucleotide polymorphisms; CSF, cerebrospinal fluid; CDR, clinical dementia rating; RT-PCR, reverse transcription-PCR; VEGF, vascular endothelial growth factor.

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NrCAM, an *N*gCAM *r*elated *c*ell *a*dhesion *m*olecule, was identified in 1991, based on the high homology to L1/NgCAM during the course of molecular cloning of chick L1/NgCAM cDNAs (Grumet et al., 1991). It was also identified as the Bravo antigen during the characterization of monoclonal antibodies against chick brain glycoproteins, which showed a topologically restricted expression in developing chick retinotectal system (de la Rosa et al., 1990; Kayyem et al., 1992). NrCAM gene knockout mice were first reported in 2001 (More et al., 2001; Sakurai et al., 2001) and the associations of NrCAM with human disorders began to emerge shortly thereafter (Bonora et al., 2005; Ishiguro et al., 2006). In the last 20 years, NrCAM has not only been shown to play roles in many aspects of nervous system development, including axon growth, guidance, synapse formation, and formation of the myelinated nerve structure, but has also been implicated in the pathogenesis/pathophysiology of a wide variety of human disorders, including psychiatric disorders and cancers, through its interactions with several receptors and signaling systems. I will overview NrCAM, its molecular properties, biological activities and functions, and disorders that NrCAM is involved in, summarizing the knowledge accumulated over the last two decades.

1. Molecular structure, splicing isoforms, processing, and gene structure

NrCAM belongs to the L1 family of cell adhesion molecules (CAMs) whose members show a similar structural organization (Hortsch, 2000). NrCAM contains six Ig like domains and five Fn type III repeats in its extracellular region, followed by a transmembrane region, and an approximately 110 amino acid stretch of a cytoplasmic region lacking any enzymatic activity (Fig. 1). The cytoplasmic region of NrCAM is 100% identical at the amino acid level among chick, rodents, and human (except the RSLE exon, see below). A Cys residue close to the end of the transmembrane region, though not proven, might be a site for a fatty acid modification as in the other L1 family members (Grumet, 1992; Ren and Bennett, 1998).

The gene encoding NrCAM is located on chromosome 12 in mouse and on chromosome 7q31 in human (Burmeister et al., 1996; Lane et al., 1996). In the case of human, 35 exons are spread over more than 300 kb. There are three exons encoding the 5′UTR, and the ATG initiation codon is in the middle of exon 4. The first three exons and introns are spread over 200 kb, which may contain regulatory sequences for the expression of NrCAM, ensuring specific spatial and temporal expression patterns (Williams et al., 2006).

NrCAM undergoes extensive splicing events that produce several different isoforms (Ishiguro et al., 2006; Lane et al., 1996; Wang et al., 1998). The most prominent splicing is a 93 amino acid deletion in the fifth Fn type III repeat, resulting in the prevalent form of NrCAM in the brain that has only four, instead of five Fn type III repeats. In addition, several amino acid insertions/deletions can occur in the regions upstream of the Ig domains, between Ig domains, and between the Ig domains and the Fn type III repeats. A four amino acid insertion can also take place in the cytoplasmic region (see below). Although no biochemical/biological differences among isoforms have been demonstrated, it is possible that some of these insertions/deletions may increase the diversity of NrCAM interactions and thereby its biological functions. In the case of L1, splicing isoforms of the cytoplasmic region created by an insertion/deletion of 4 amino acids (the RSLE exon) show different expression patterns, i.e., the RSLE-plus form is a neuronal form, whereas the RSLE-minus form is a glial form. NrCAM also has a similar 4 amino acid insertion in the cytoplasmic region, but the biological implications of the RSLE exon in the cytoplasmic region are not clear for NrCAM. Furthermore, whereas the RSLE exon is identified in NrCAM in chick and human, in the mouse, RSLE is changed to RSFE. It is not known if RSLE affects NrCAM activity or function, and if RSFE behaves similarly to or differently from RSLE. Nonetheless, in light of the possible involvement of changes in splicing patterns of NrCAM in autism spectrum disorders (see below), it is important to clarify whether there is differential expression of splicing isoforms that may be correlated with functional differences.

The full length NrCAM is predicted to be about 200 kDa, but in brain extracts, only a 135–150 kDa protein and a 60 kDa protein are detected, and these presumably derive from the full length form by a cleavage in the middle of the third Fn type III repeat. Supporting this presumption, there is a furin-like cleavage site in this region (Davis et al., 1996; Grumet et al., 1991; Kayyem et al., 1992). Furthermore, there are double Ser-Arg/Lys-Arg sequences at the amino terminal end of the furin site, which provide additional trypsin like proteolytic sites for cleavage (see review by Grumet, 1997). After the cleavage, the 135–150 kDa fragment is either attached to the membrane through interactions with the 60 kDa fragment (Grumet, 1997; Kayyem et al., 1992) or released (Conacci-Sorrell et al., 2005). Recently, Feinberg reported a soluble form of NrCAM that accumulates at the node of Ranvier and is produced by myelinating Schwann cells (Feinberg et al., 2010), but it is not clear if this is a cleaved form of NrCAM or one of its splicing isoforms (without the cytoplasmic region). It is also reported that a ~150 kDa of NrCAM fragment is present in rat brain extracts, which is recognized by anti-phosphotyrosine (presumably a transmembrane form with cytoplasmic tail), but the nature of this form is not clear (Garver et al., 1997).

2. Interacting proteins for extracellular and intracellular regions of the NrCAM molecule

NrCAM interacts with several molecules extracellularly and intracellularly. Through its extracellular region, NrCAM can interact with molecules both on the same membrane (in *cis*) and on apposing membranes (in *trans*). This property of NrCAM, nonetheless, makes

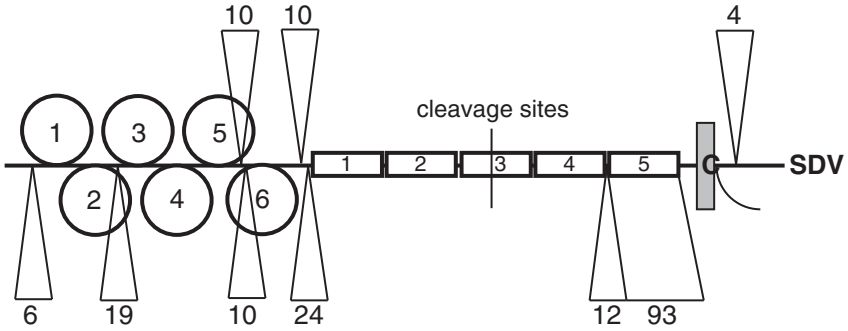

Fig. 1. Schematic view of NrCAM structure. NrCAM has 6 Ig like domains (ovals with number) and 5 Fn type III repeats (squares with number), a transmembrane region, and a cytoplasmic tail. There are several splicing insertions/deletions that are shown by triangles. Numbers of amino acids in these insertions/deletions are shown. There are possible cleavage sites in the middle of the third Fn type III repeat. C in the transmembrane region is Cys, a possible fatty acid modification site. At the C-terminal, there is a PDZ domain binding site shown as SDV.

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