Cell, Vol. 88, 745–746, March 21, 1997, Copyright ©1997 by Cell Press

Letter to the Editor

Close Similarity between Drosophila Neurexin IV and Mammalian Caspr Protein Suggests a Conserved Mechanism for Cellular Interactions

A new member of the neurexin family, Neurexin IV (NRX IV), was recently identified in Drosophila (Baumgartner et al., 1996). *neurexins* encode a large family of neuronal cell surface proteins that may be involved in cell–cell interactions and target recognition (Ushkaryov et al., 1992; Garrity and Zipursky, 1995; Ullrich et al., 1995). Three different *neurexin* genes (*I–III*) were identified in mammals, each of which generates two primary transcripts (α and β) through the use of alternative promoters (Ushkaryov et al., 1994). In addition, the *neurexins* are subject to alternative splicing that generates hundreds of isoforms (Ullrich et al., 1995). It has been shown that mutations in the *nrx IV* gene in Drosophila cause paralysis and a breakdown of the blood–brain barrier due to disruption of septate junctions. It was proposed that NRX IV functions as a cell surface receptor linking the extracellular environment with the intracellular components of septate junctions (Baumgartner et al., 1996).

Figure 1 shows that the amino acid sequence of NRX IV is very similar to the amino acid sequence of human and rat Caspr (Peles et al., 1997), suggesting that NRX IV is the Drosophila counterpart of Caspr. Caspr was discovered by virtue of its ability to form a ternary complex with Contactin and the extracellular domain of receptor protein tyrosine phosphatase β (RPTPβ; Peles et al., 1995, 1997). Contactin is a glycosylphosphatidylinositol (GPI)–anchored recognition molecule belonging to the Ig superfamily and is expressed on the cell surface of neurons. We have previously demonstrated that the interaction between the extracellular domain of RPTPβ and Contactin leads to neurite outgrowth and proposed that this interaction may mediate bidirectional cellular signals between neurons and glial cells (Peles et al., 1995). The cytoplasmic domain of Caspr contains a proline-rich sequence capable of binding to a subset of SH3 domains of signaling proteins, suggesting that it may function as a signaling component of Contactin and other GPI-linked cell adhesion molecules (Peles et al., 1997). Because of its similarity to Caspr, Drosophila NRX IV may also function as a signaling component as part of a complex with adhesion molecules. Indeed, the intracellular domain of NRX IV has a binding site for PDZ domain–containing proteins (Saras and Heldin, 1996) and is required for the localization of D4.1-coracle protein, a protein essential for the formation of pleated septate junctions (Baumgartner et al., 1996). The cytoplasmic tails of Caspr and NRX IV proteins may recruit PDZ or SH3 domains containing signaling molecules to specific regions of cell–cell contacts thereby regulating intracellular events in the nervous system and in other tissues.

The structural similarity between Drosophila NRX IV and human Caspr protein implies a conserved mechanism for cell–cell contact mediated by interactions between cell recognition molecules including receptor tyrosine phosphatases.

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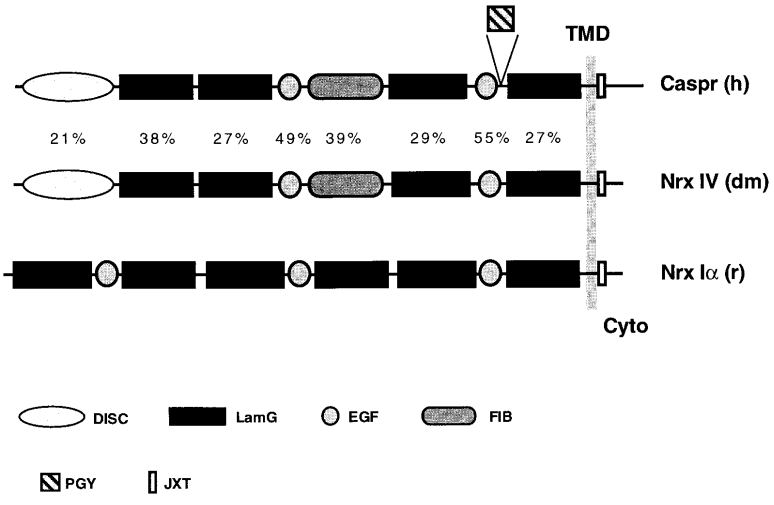

Figure 1. Structural Organization of Human Caspr, Drosophila NRX IV and Rat Neurexin Iα

The percent amino acid sequence identity between the different domains in human Caspr and NRX IV are shown. The discoidin-like domain (DISC) and a region similar to fibrinogen α/β (FIB) are found in NRX IV and Caspr but not in the related mammalian Neurexins. A repeat of proline, glycine, and tyrosine residues (PGY) is only found in Caspr. Other motifs, including laminin G domain (LamG) and EGF repeats, are shared by all members of the Neurexin superfamily. They also share a sequence of 15–20 amino acids in their cytoplasmic juxtamembrane (JXT) region (RxkGsYxtxe) but diverge thereafter. Caspr contains a proline rich region whereas the Neurexins and Drosophila NRX IV contain a carboxy-terminal binding site for PDZ domains. Full alignment of NRX IV and Caspr is available at the *Cell* website (http://www.cell.com). We acknowledge discussions with T. Sakurai.

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