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The role of Gpi-anchored axonal glycoproteins in neural development and neurological disorders

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ABSTRACT

This review article focuses on the Contactin (CNTN) subset of the Immunoglobulin supergene family (IgC2/FNIII molecules), whose components share structural properties (the association of Immunoglobulin type C2 with Fibronectin type III domains), as well as a general role in cell contact formation and axonal growth control. IgC2/FNIII molecules include 6 highly related components (CNTN 1–6), associated with the cell membrane via a Glycosyl Phosphatidyl Inositol (GPI)-containing lipid tail. Contactin 1 and Contactin 2 share ~50 (49.38)% identity at the aminoacid level. They are components of the cell surface, from which they may be released in soluble forms. They bind heterophilically to multiple partners in *cis* and in *trans*, including members of the related L1CAM family and of the Neurexin family Contactin-associated proteins (CNTNAPs or Casprs). Such interactions are important for organising the neuronal membrane, as well as for modulating the growth and pathfinding of axon tracts. In addition, they also mediate the functional maturation of axons by promoting their interactions with myelinating cells at the nodal, paranodal and juxtaparanodal regions. Such interactions also mediate differential ionic channels (both Na^+ and K^+) distribution, which is of critical relevance in the generation of the peak-shaped action potential. Indeed, thanks to their interactions with Ankyrin G, Na^+ channels map within the nodal regions, where they drive axonal depolarization. However, no ionic channels are found in the flanking Contactin1-containing paranodal regions, where CNTN1 interactions with Caspr1 and with the Ig superfamily component Neurofascin 155 in *cis* and in *trans*, respectively, build a molecular barrier between the node and the juxtaparanode. In this region K^+ channels are clustered, depending upon molecular interactions with Contactin 2 and with Caspr2.

In addition to these functions, the Contactins appear to have also a role in degenerative and inflammatory disorders: indeed Contactin 2 is involved in neurodegenerative disorders with a special reference to the Alzheimer disease, given its ability to work as a ligand of the Alzheimer Precursor Protein (APP), which results in increased Alzheimer Intracellular Domain (AICD) release in a γ-secretase-dependent manner. On the other hand Contactin 1 drives Notch signalling activation via the Hes pathway, which could be consistent with its ability to modulate neuroinflammation events, and with the possibility that Contactin 1-dependent interactions may participate to the pathogenesis of the Multiple Sclerosis and of other inflammatory disorders.

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1. Adhesion molecules and neural developmental events: the definition of morphoregulatory molecules

The development of the nervous tissue requires the coordination of several processes, including precursor proliferation and migration, neurite growth and fasciculation, axonal pathfinding control and synaptogenesis (see for instance Gerrow and El-Husseini, 2006; Mitsuhashi and Takahashi, 2009; Borodinsky et al., 2015; Missaire and Hindges, 2015). Most of them implicate interactions of neuronal surface glycoproteins with components of the adjacent cell surfaces or of the extracellular matrix (Schmidt and Rathjen, 2010; Giger et al., 2010; Barros et al., 2011; Vitriol and Zheng, 2012; Hirano and Takeichi, 2012; Frei and Stoeckli, 2014; Petrovic and Schmucker, 2015). The molecular players in such events fulfil the operational definition of adhesion molecules since a relevant role for them is to promote and/or stabilize cell interactions. While being of structural relevance, such interactions may also have a more functional meaning, since cell adhesion is also a source of signals known to modulate events involved in nervous tissue development (Ebel et al., 2014; Hildebrandt and Dityatev, 2015), which in turn arise from the physicochemical interactions among such molecules. On this basis, such molecules fulfil the operational definition of morphoregulatory molecules proposed in earlier studies (Edelman, 1992; Edelman and Jones, 1997).

In this review, we consider the properties of a family of adhesion molecules whose expression is tightly regulated during development, consistent with their roles during both early neurogenesis and later stages of neural differentiation, and whose functions extend beyond simple adhesion, encompassing the generation and modulation of morphoregulatory signalling that controls the molecular composition and organisation of the cell surface according to context. We also consider emerging evidence that changes in the expression of these molecules underlie the genesis of specific neurological disorders.

2. Families of morphoregulatory molecules

Morphoregulatory molecules may belong to distinct families of adhesion receptors, the main grouping being the Cadherins (Basu et al., 2015; Friedman et al., 2015; Gärtner et al., 2015), the Integrins (Gardiner, 2011) and the Immunoglobulin superfamily (IgCAM, Maness and Schachner, 2007). Based on their interactions, these molecules may be differentially involved in distinct aspects of neural developmental control (Yogev and Shen, 2014). Broadly speaking, adhesion mediated by Cadherins is strong, overcoming that of other adhesion molecules (Thiery et al., 2012). Classically, Cadherins are thought to mediate cell-cell interactions, while integrins mediate those between cell and matrix, though this simple classification is confounded by complex interplay among the molecules (Weber et al., 2011; Mui et al., 2016). In any case, the critical developmental role for such molecules depends upon their ability to mediate homo-or heterophilic interactions. For example, in the earliest developmental stages, strong homophilic calcium-dependent cell interactions involving the function of Cadherin family components contribute to the control of events of key ontogenetic relevance such as germ layer separation (Stepniak et al., 2009; Hirano and Takeichi, 2012; McKeown et al., 2013; Barriga and Mayor, 2015; Hayashi and Takeichi, 2015; Duband et al., 2015). However, it is also worth mentioning that members of the same family may mediate the control of later developmental events as neurite growth (Gärtner et al., 2012, 2015; Hayashi et al., 2014; Stoeckli, 2014). The functional complexity of these events and their articulated role in neural development is further supported by the evidence that components of distinct gene families may contribute to such events, which may involve either adhesive as the Immunoglobulin (Ig) supergene (Maness and Schachner, 2007) or repellent as the Semaphorin (Pasterkamp, 2012; Jongbloets and Pasterkamp, 2014; Battistini and Tamagnone, 2016) families components. As far as axonal growth is concerned, such a molecular and functional complexity suggests that regulating the expression of the genes encoding such molecules represents an aspect of critical functional relevance (Yogev and Shen, 2014).

3. Axonally expressed adhesive glycoproteins of the immunoglobulin supergene family (Igsf)

This review article focuses on those members of the Immunoglobulin supergene family (IgSF), which are composed of Ig C2-type (IgC2) domains at their N-terminus and Fibronectin type III (FNIII) domains grouped in tandem in the membrane-proximal region. Because of this overall organisation, those adhesive glycoproteins may be collectively denominated IgC2/FNIII molecules, and represent a typical model for adhesive/morphoregulatory molecules expressed at the axonal level. The IgC2 and FNIII domains have similar structural cores (Cota et al., 2001) and likely share a common evolutionary origin. This family undergoes complex interactions with members of the same and different families (Özkan et al., 2013) and the genomic complexity of family members reflects organismal complexity (Vogel and Chothia, 2006), suggesting roles in elaborating developmental complexity.

4. The contactin family of cell adhesion molecules (CNTNs)

Like many cell surface molecules, members of the IgC2/FNIII family can be found anchored to the membrane via a typical transmembrane domain, or via a Glycosyl Phosphatidyl Inositol (GPI)-containing lipid tail. In this review we focus on the latter, specifically the Contactins.

Contactins were named to reflect their preferential location at sites of cell to cell contact (Ranscht, 1988). This subfamily comprises six different members (CNTN1-CNTN6; Shimoda and Watanabe, 2009), which share the same overall organisation, including 6 N-terminal IgC2 domains, associated with 4 C-terminal FNIII repeats, followed by a hydrophobic C-terminal aminoacid sequence, characteristic of most GPI-linked proteins, the processing of which results in their lipid anchorage (Low, 1989). Where it has been studied, the Contactins are secreted from cells as well as being found at the cell surface (Ruegg et al., 1989; Furley et al., 1990; Gennarini et al., 1991), apparently the result of specific secretion processing rather than cleavage from the cell surface (Ruegg et al., 1989).