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Review

A decade from discovery to therapy: Lingo-1, the dark horse in neurological and psychiatric disorders

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ABSTRACT

Leucine-rich repeat and immunoglobulin domain-containing protein (Lingo-1) is a potent negative regulator of neuron and oligodendrocyte survival, neurite extension, axon regeneration, oligodendrocyte differentiation, axonal myelination and functional recovery; all processes highly implicated in numerous brain-related functions. Although playing a major role in developmental brain functions, the potential application of Lingo-1 as a therapeutic target for the treatment of neurological disorders has so far been under-estimated. A number of preclinical studies have shown that various methods of antagonizing Lingo-1 results in neuronal and oligodendroglial survival, axonal growth and remyelination; however to date literature has only detailed applications of Lingo-1 targeted therapeutics with a focus primarily on myelination disorders such as multiple sclerosis and spinal cord injury; omitting important information regarding Lingo-1 signaling co-factors. Here, we provide for the first time a complete and thorough review of the implications of Lingo-1 signaling in a wide range of neurological and psychiatric disorders, and critically examine its potential as a novel therapeutic target for these disorders.

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1. Introduction

Myelination is a fundamental progressive process occurring throughout the brain from embryonic stages of development through to adolescence. During the last decade, novel signaling pathways, largely involving myelin associated inhibitory proteins including: myelin associated glycoprotein (MAG), oligodendrocyte-myelin glycoprotein (OMgp) and neurite outgrowth inhibitor (Nogo) were found to inhibit the growth of neurons and myelination. Mechanisms involved in these processes largely implicate a receptor complex comprised of the p75 neurotrophin receptor and the (then) newly discovered Nogo Receptor (NgR) (Caroni and Schwab, 1988; Chen et al., 2000; Domeniconi et al., 2002; Fournier et al., 2001; GrandPré et al., 2000; Liu et al., 2002; Wang et al., 2002a, 2002b). The mechanism by which NgR regulates axonal growth is initiated by the high affinity binding of Nogo to the NgR, however the NgR itself does not contain a transmembrane domain and as such requires a transmembrane co-receptor in order to elicit intracellular signals. While p75 has been shown to elicit the transduction of inhibitory NgR signals (Wang et al., 2002a), certain NgR containing cell types not expressing p75, were still found to be able to transduce inhibitory NgR signals (Wang et al., 2002a), leading to the discovery of TNF receptor orphan Y (TROY) as a functional homolog of p75 within the signaling complex (Shao et al., 2005). The functional ternary receptor complex was suggested to be complete when a third co-receptor was discovered in the form of Lingo-1 (Leucine-rich repeat and Ig domain-containing, Nogo receptor-interacting protein) (Mi et al., 2004) and the Lingo-1/NgR/p75 or TROY complex was born.

Lingo-1 was first identified as LERN1 (leucine-rich repeat neuronal protein 1), a transmembrane leucine-rich protein coded for by the novel gene *LRRN6A* discovered by Carim-Todd et al. (2003) on human chromosome 15q24-26 just over a decade ago. It was suggested that due to the developmental expression profile of *LRRN6A*, the predicted protein structure of LERN1 and its similarity to proteins already identified as having a vital role in nervous system development and maintenance, that the *LRRN6A* gene and LERN1 protein would be highly relevant for further study in neurobiology. While a number of previously uncharacterized central nervous system-specific proteins were being assessed for their ability to bind to NgR, Lingo-1 was discovered as we know it today, Leucine-rich repeat and Ig domain-containing, Nogo receptor-interacting protein (Mi et al., 2004). Lingo-1 has been widely studied in relation to multiple sclerosis and spinal cord injury due to its prominent role in myelination and myelin related processes, however there has always been lack of information in relation to psychiatric disorders. Considering the ever growing evidence that the essential developmental functions of neurite outgrowth and myelination are disrupted in psychiatric disorders like schizophrenia, it seems timely and topical to consider the role of Lingo-1 in neuropsychiatric disorders. Here we provide a comprehensive review on Lingo-1, a relatively new candidate that since discovery has been studied across a wide range of neurological disorders, and why it is a promising candidate for future research in neuropsychiatric disorders and their therapeutic approaches.

Note: For the purpose of this review, the terms *LRRN6A* and LERN1 will no longer be used and the gene and protein will be referred to as *Lingo-1* and Lingo-1, respectively.

2. Lingo-1: The gene, structure, expression and function

The identification and characterization of the *Lingo-1* gene (Carim-Todd et al., 2003) was an important first step to uncovering the function of Lingo-1. The *Lingo-1* locus on human chromosome 15q24-26 is a region that has been widely implicated in a number of psychiatric, addictive and anxiety related disorders, and genomic alterations in this chromosomic region are considered to be susceptibility factors for schizophrenia, depression, autism, panic disorders, anxiety and phobic disorders (Gratacòs et al., 2001; McInnes et al., 2010).

The *Lingo-1* gene maintains a very high degree of conservation across a large number of unrelated vertebrate species, including both mouse and rat (Carim-Todd et al., 2003). Furthermore, two additional paralogous genes have been mapped to human chromosomes 9 and 19 which were identified as *LRRN6B* and *LRRN6C*, coding for proteins LERN2 and LERN3 (Carim-Todd et al., 2003) also known as Lingo-3 and Lingo-2, respectively (Chen et al., 2006).

The Lingo-1 structure has been shown to be highly stable in a tetrameric conformation in both its crystal form and in solution, facilitated by its leucine-rich repeat-Ig-composite fold (Mosyak et al., 2006). Due to the tetramer burying such a large surface area into the cell membrane it is thought that this may in fact serve as an efficient and stable scaffold for a binding platform, facilitating the assembly of the Lingo-1/NgR/p75 or TROY complex, localizing signaling functions to the sites of neuronal pathways that terminate axon growth (Mosyak et al., 2006). Accordingly, knowing that Lingo-1 forms tetramers may provide an answer to the still unresolved questions about the stoichiometry of the Lingo-1/NgR/p75 or TROY receptor complex. It has been hypothesized that Lingo-1 may form tetramers relative to the monomers on the cell surface, meaning that each signaling complex may consist of four of each receptor component (4:4:4) rather than one (1:1:1) as previously thought. It is apparent that Lingo-1 is involved in a number of central nervous system processes, in addition to having the ability to bind a number of signaling molecules, thus its functional roles within the central nervous system and its mechanisms of oligomerization may vary depending on where and when it is expressed (Mosyak et al., 2006). Just recently the crystalline tetrameric formation of Lingo-1 has been confirmed by Pepinsky et al. (2014), in addition to showing for the first time that Lingo-1 is also present as a tetramer on cells expressing full-length Lingo-1. This tetrameric formation on transfected cells is indicative of oligomer formation being an intrinsic property of Lingo-1 in the absence of its ligands or co-receptors (Pepinsky et al., 2014).

Proteins containing leucine-rich repeats have been shown to play an important role in protein–protein interactions (Kajava et al., 1995; Kobe and Deisenhofer, 1994; Kobe and Kajava, 2001) in a wide variety of cellular processes (Carim-Todd et al., 2003) including ligand recognition (Brose et al., 1999; Chen et al., 2001; Li et al., 1999; Vourc'h et al., 2003; Wang et al., 2002b). Their implication in important neurodevelopmental functions such as neuronal differentiation and growth (Halegoua et al., 1991) and the regulation of axon guidance, axon branching, cell-migration and regeneration processes (Bormann et al., 1999; Brose and Tessier-Lavigne, 2000; Ishii et al., 1996; Nguyen-Ba-Charvet and Chédotal, 2002), results consequently in their involvement in neurological diseases such as hereditary epilepsy and X-linked stationary night blindness (Bech-Hansen et al., 2000; Kalachikov et al., 2002; Morante-Redolat et al., 2002; Pusch et al., 2000). Since Lingo-1 is a leucine rich repeat protein, and considering its genetic locus is in a chromosomic region associated with a high risk for a number of psychiatric disorders, Lingo-1 makes for an ideal candidate for study in a vast array of neurological disorders.

Within the healthy adult human brain *Lingo-1* RNA expression was found to be abundantly and almost exclusively expressed in the central nervous system (Carim-Todd et al., 2003). A closer look at the distribution of *Lingo-1* across the adult human brain showed that expression was highest in the cerebral cortex (Carim-Todd et al., 2003), a region heavily involved in sensory-motor function, cognition and working memory; the hippocampus (Carim-Todd et al., 2003), responsible for long term memory and the encoding