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Reelin: Diverse roles in central nervous system development, health and disease

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Abstract:

Over the past 20 years the structure and function of Reelin, an extracellular glycoprotein with a role in cell migration and positioning during development has been elucidated. Originally discovered in mice exhibiting a peculiar gait and hypoplastic cerebellar tissue, Reelin is secreted from Cajal-Retzius neurons during embryonic life and has been shown to act as a stop signal, guiding migrating radial neurons in a gradient-dependent manner. Reelin carries out its function by binding to the receptors, very low-density lipoprotein receptor (VLDLR) and apolipoprotein E receptor 2 (ApoER2) resulting in the phosphorylation of the intracellular protein Disabled-1 (Dab-1) which is essential for effective Reelin signaling. Abnormalities in the *RELN* gene can result in multiple unusual structural outcomes including disruption of cortical layers, heterotopia, polymicrogyria and lissencephaly. Recent research has suggested a potential role for Reelin in the pathogenesis of neurological diseases such as schizophrenia, autism and Alzheimer's disease. This short review will address the current understanding of the structure and function of this protein and its emerging role in the development of neurological disorders.

Keywords: Reelin, cortical migration, schizophrenia, lamination, Cajal-Retzius neurons

Introduction:

Over the last 50 years, the reeler mouse has been a major model for studying development in a multitude of structures in the central nervous system (CNS), including the cerebral cortex, cerebellar cortex and spinal cord. Reeler mice were the first animal model in which malformations of cortical laminar organization were described, leading to the discovery of the Reelin molecule. Investigations into the cause of this presentation followed suit and led researchers to begin to unravel the actions of Reelin and its role in radial migration and correct cortical lamination. More recently, Reelin has been implicated as having a potential role in certain neurological diseases. This short review will discuss recent findings and summarize our current understanding of this prominent protein.

In the 1950's researchers were studying mice displaying a staggering gait with poor balance and mobility and named them reeler mice. It is now known that reeler mice are a naturally occurring mutant which lacks Reelin. The mice display hypoplasia of the cerebellum, as well as widespread disruption of lamination throughout the brain, which is likely to be responsible for their impaired motor coordination, tremors and ataxia (D'Arcangelo et al., 1995, Ogawa et al., 1995). A study in which Reelin was conditionally knocked-out in two-month old mice, the cytoarchitecture of the cerebral and cerebellar cortices was normal and they displayed normal motor function. This suggests that the absence of Reelin during development, specifically, is necessary to cause the reeler phenotype (Lane-Donovan et al., 2015). Research accelerated in the 1960s, following the discovery of the dramatically reduced cerebellar size and disrupted laminar organization in the cortex. In 1994, an allele unique to the reeler mouse was identified by means of insertional mutagenesis (Miao et al., 1994), enabling the *RELN* gene to be mapped on chromosome 7q22 (D'Arcangelo et al., 1995; Ogawa et al, 1995). Later CR-50 antibodies, targeting the N-terminal of the Reelin protein were developed (D'Arcangelo et al., 1997).

Utilizing immunohistochemistry, antibodies targeting Reelin revealed that it was the Cajal-Retzius neurons that were responsible for the production and secretion of Reelin during development. The Cajal-Retzius neurons are a heterogeneous population of morphologically distinct Reelin-producing cell types found in the marginal zone of the developing cerebral cortex and in the immature hippocampus (Del Rio et al., 1997). Despite the identification of the Reelin gene more than 20 years ago, there are some aspects of Reelin function in neuronal positioning and differentiation at a cellular and molecular level that remain to be fully elucidated (Lee & D'Arcangelo, 2016).

Role of Reelin in CNS development:

Reelin is best known for its role in the developing mammalian cerebral and cerebellar cortices. In the cerebral cortex it is secreted by Cajal-Retzius neurons in the marginal zone. The marginal zone is the outermost cortical layer where neuronal migration is halted. Reelin is highly expressed in the marginal zone during embryonic life but the Cajal-Retzius neurons disappear following completion of neuronal migration. Younger neurons are sequentially located more superficially than the earlier-born neurons that have migrated from the germinal zone, eventually forming cortical layers II-VI in a process known as lamination (Angevine & Sidman, 1961).

Reelin is an important component controlling the stratification of post-mitotic cortical neurons in this inside-out manner (Di Donato et al., 2018).

In the cerebellum most Reelin producing cells are located near the surface of the developing cerebellar cortex, and include cells of the rhombic lip migratory stream, the nuclear transitory zone, and the external granular layer with other Reelin producing cells located in some of the deep cerebellar nuclei and internal granular layer. An important function of Reelin here appears to be to promote Purkinje cell detachment from radial glia in the mantle zone, thus facilitating the migration of Purkinje cells to their final destinations (Lammert & Howell, 2016).

Recent evidence suggests that Reelin is expressed as a gradient to differentiate the layers of the cortex and attracts neurons to their appropriate destination (Di Donato et al., 2018). Reelin appears to function as the stop signal for radially migrating neurons, signaling their final destination. It is also likely to be involved in lamination in the developing cerebellar cortex and in neuronal migration generally in other CNS regions, such the brainstem and spinal cord. Impairment of Reelin expression during development results in abnormal structural outcomes including disruption of the cerebral, cerebellar and hippocampal cortical layers. Structural outcomes include heterotopia, polymicrogyria, lissencephaly, with some regions displaying a mirror-image inversion of the normal laminar phenotype (Boyle et al., 2011). Disruption in the Reelin-signaling pathway that results in the improper cerebral and cerebellar laminar formation is likely to be responsible for the phenotypic reeler gait.

Investigations have also begun to reveal a better understanding of the consequences of such highly disturbed lamination of cortical function in the reeler mouse model (Guy et al., 2015). Persistence of a functional sensory map in the absence of correct cortical lamination has recently been described and Reeler mice appear to retain a distorted barrel field, a region of the somatosensory cortex. One study analyzed the connectivity of neurons in the distorted barrel field of reeler mice compared to wild type mice and established the presence of a functional, although altered, cortical network among neurons post CNS development in adult reeler mice (Prume et al., 2018).

Production and Processing of Reelin:

Reelin is transcribed and translated in embryonic and adult life and is subject to epigenetic genomic modification such as DNA methylation to control expression levels. The *RELN* gene is transcribed in the nucleus, then translated by ribosomes bound to the endoplasmic reticulum. These newly formed proteins move to the Golgi for post-translational modification (Sato et al., 2015).

Reelin is a secreted modular glycoprotein, and is crucial to normal central nervous system development and function. Reelin is synthesized as a 3460-amino acid precursor protein with a molecular weight of 410 kDa. The protein structure of Reelin consists of eight unique repeats, each centered around an epidermal growth factor (EGF)-like cysteine pattern typical of extracellular proteins. The protein is cleaved by metalloproteases at sites N-t and C-t , generating three fragments an N-terminal fragment, a central fragment and a C-terminal fragment. Mutant

Reelin proteins containing altered amino acids in these locations have shown resistance to cleavage (Sato et al., 2015).

Reelin Signaling:

Canonical Reelin signaling involves Reelin binding to very low-density lipoprotein receptor (VLDLR) and apolipoprotein E receptor 2 (ApoER2) (Figure 2). Calcium is required for receptor-binding and binding is inhibited in the presence of ApoE (Mata-Balaguer et al., 2018) . Reelin binding results in oligomerization of lipoprotein receptors which interact with the phosphotyrosine kinase domain of Disabled-1(an intracellular adaptor protein) (Yasui et al, 2010). The Dab-1 receptor complexes are then phosphorylated by Src kinases (Yasui et al., 2010). Tyrosine phosphorylation of Dab-1 is a key step in Reelin signaling and is mediated by Fyn kinases and initiates activation of further intracellular signaling cascades. (Arnaud et al., 2003). The phosphorylation of Dab-1 appears to be responsible for correct neuronal migration and layer formation of the cerebral cortex (Kim et al., 2015).

Role of Reelin in the Adult CNS:

Reelin expression peaks shortly after birth, and mRNA levels begin to decrease but Reelin expression can still be detected in adult tissue. In the adult brain, Reelin is expressed by some GABAergic interneurons of the cortex and glutamatergic cerebellar neurons, and by the few extant Cajal-Retzius cells. Among the cortical GABAergic interneurons, Reelin has been detected in a subpopulation of these cells which express calretinin, and calbindin, such as bitufted, horizontal and Martinotti cells (Pesold et al., 1999, Pesold et al., 1998). It is also expressed by interneurons in the spinal cord (Figure 1).

Its role in these regions appears to be in neuronal maturation, synaptic formation and plasticity. Reelin signaling is known to affect the dynamics of the actin and microtubular cytoskeleton, as well as membrane trafficking through the regulation of small GTPases including the Rho and Rap families and molecules involved in cell polarity (Santana and Marzolo, 2017).

The role of Reelin in the adult CNS includes regulation of filopodia formation, dendrite growth and spine formation, and synaptogenesis, as well as modulation of synaptic plasticity and neurotransmitter release (Levy et al., 2014). Reelin is expressed by layer I and II GABAergic interneurons, which project to other cortical layers where they secrete Reelin into the ECM. Upon, release Reelin surrounds and adheres to dendritic shafts and spines of cortical pyramidal cells, indicating it may play a role in dendritic spine regulation. Another study found that mice with mutant Reelin protein had reduced levels of synaptic signaling molecules as well as deficits in excitatory postsynaptic responses, and addition of recombinant Reelin to hippocampal slices significantly enhanced hippocampal long-term potentiation (Levy et al., 2014).

Reelin has also been shown to regulate NMDA-type glutamate receptor activity in adult rodent studies through a mechanism that requires Src-family kinases (SFK) and Dab-1 (Chen et al., 2005). Reelin signaling results in activation of the NMDA- receptor, prompting calcium

influx. Adaptor proteins downstream of Dab-1 called Crk and Crk-like (CrkL) appear to be involved in carrying out Reelin signaling further downstream (Kim et al., 2015). Downstream effects of NMDA-mediated Reelin signaling have been proven to be essential for normal inter-neuronal communication.

Reelin expression has also been noted in many extra-neuronal tissues in rat models, including in the chromaffin cells of the adrenal medulla, hepatocytes and pituitary pars intermedia (Smalheiser et al., 2000).

Role of Reelin in Disease:

Reelin abnormalities have been associated with a range of neurological diseases including schizophrenia, autism, and neurodegenerative diseases such as Alzheimer's (Lammert & Howell, 2016; Fikri et al., 2017; Mata-Balaguer et al., 2018). One study found that the post-mortem brain samples of patients with schizophrenia had reduced Reelin protein and mRNA expression compared with unaffected controls; in certain areas by as much as 50%. These areas included the prefrontal cortices (Brodmann's areas 10 and 46), temporal cortices (Brodmann's area 22), hippocampi, caudate nuclei and cerebellar tissue (Impagnatiello et al., 1998). A more recent study determined that, compared to controls, schizophrenic patients had increased levels of *RELN* gene methylation, leading to a subsequent 25-fold decrease in reelin expression in the affected patients (Fikri et al., 2017). Reduced Reelin mRNA expression in the prefrontal cortex in schizophrenia was found to be the most statistically relevant disturbance found in a multicenter study (Knable et al., 2001). These findings indicate that Reelin may be involved in the pathogenesis of schizophrenia, possibly through Reelin-mediated deficits in neuronal migration and connectivity during development. However, further investigation is necessary as it is unclear whether these patients were on medications at the time which could potentially have altered the levels of Reelin.

Schizophrenia is a complex condition which is likely to require a multifaceted approach to therapy. Targeting Reelin and/or its signaling may have a role in such therapies in the future. Schizophrenia is characterised by abnormal neuronal interconnectivity, therefore it is plausible that Reelin may be involved in the disease process as a result of its developmental role in promoting proper neuronal migration and neuronal connectivity. One study has shown mixed results with administering exogenous Reelin to rodent brain slice samples. Exogenous Reelin rescued neuronal migration in certain brain regions such as the intermediate zone. However, in the germinal zones, exogenous Reelin retarded neuronal migration and resulted in abnormal trajectories (Britto et al., 2014). Exogenous Reelin administration may not be a plausible therapy, but it is possible that altering *RELN* gene expression in early development may have beneficial effects.

Autism is another debilitating neurodevelopmental disorder characterized by deficits in cognition, communication, and social interaction. Due to its developmental importance, Reelin has been studied as a potential biomarker for autism. Reduced levels of Reelin have been observed in the plasma of patients with autism compared to healthy controls that were matched for sex and age (Fatemi, et al., 2002).Reelin expression was reduced in locations such as the superior frontal cortex, parietal cortex and cerebellum of subjects with autism when compared to

controls (Lammert & Howell, 2016). Reelin deficiency may contribute to these structural abnormalities as well as contributing to impaired synaptic connectivity. Like schizophrenia, autism is a complex, multifactorial disorder and impaired Reelin function during neuronal maturation, migration and establishment of cell-cell communication may be among the contributory factors.

There is increasing evidence that altered Reelin signaling could contribute to synaptic dysfunction in Alzheimer's disease. Increased concentrations of Reelin fragments have been found in the cerebrospinal fluid of Alzheimer's patients, suggesting altered processing of Reelin in this condition (Chin et al., 2007). Compared with control mice, human amyloid precursor protein (hAPP) transgenic mice showed significantly lower Reelin-expressing pyramidal cells in the entorhinal cortex. This region of the brain has been implicated in Alzheimer's disease, and decreased Reelin expression may play a role in the complex pathophysiology of this disease (Chin et al., 2007). In other brain regions β-amyloid protein has been shown to impair Reelin activity and increase its expression compared to controls through mechanisms yet unknown (Mata-Balaguer et al., 2018).

Reelin is an essential protein in the control of cortical laminar organization during embryonic life and may have additional activity in adulthood. However much further research is required to achieve a fuller understanding of Reelin and its signaling mechanisms and to translate these findings to clinical settings, potentially leading to novel approaches to the treatment of conditions with complex aetiologies such as schizophrenia, autism and, perhaps, even Alzheimer's disease.

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Figure 1.
Reelin expression in the 14 day old rat spinal cord. Reelin is distributed in both white and grey matter and appears localised to populations of interneurons (arrows in insert) and radial astrocytes (arrowhead). (Anderson R.C. 2018 unpublished data.)

Figure 2:
Reelin is secreted from the Cajal-Retzius neurons and interacts with receptors Very Low Density Lipoprotein Receptor (VLDLR) which requires Ca2+ as a cofactor and Apolipoprotein E receptor-2 (ApoER2). This interaction results in the phosphorylation of Disabled-1 (Dab-1) which is an intracellular signalling molecule responsible for carrying out proper cortical layer formation during embryonic development. This occurs via downstream signalling through additional adaptor molecules including Crk and Crk-like and Lis1 and PI3K pathways. Postnatally the Dab1 complex interacts with Serine Family Kinases (SFKs) to phosphorylate N-methyl-D-aspartate receptors (NMDAR) leading to CREB-1 activation.