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The Amyloidogenic Pathway Meets the Reelin Signaling Cascade: A Cytoskeleton Bridge Between Neurodevelopment and Neurodegeneration

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1. Introduction

Reelin is an extracellular matrix glycoprotein of ~400 kD, expressed in mammals during neurodevelopment by the Cajal-Retzius (CR) neurons, which are located in the marginal zone of the cortex and hippocampus [1], and by the cerebellar granule cells [2]. In adult stages, CR neurons degenerate in both structures [3], limiting Reelin production and secretion to GABAergic interneurons [4]. Meanwhile, the expression in the cerebellum remains being exclusive of granule cells [5]. During development, Reelin synthesis also occurs in structures like the hypothalamus, the olfactory bulb, the basal ganglia and the amygdale. In these last two brain regions, Reelin expression continues into adulthood but at low concentrations [1].

Reelin gene encompasses 450 kb of genomic DNA located on human chromosome 7q22 and in murine chromosome 5. Both genes contain 65 exons that encode a protein sharing a 94,2 (%) of identity [6-7]. The transcription initiation region and the exon 1 of the reelin gene is enriched in CG nucleotides, forming a large CpG island [8], which is associated with a methylation-dependent negative regulation of reelin transcription [9]. In fact, DNA methyltransferases and histone deacetylases inhibitors increase Reelin protein expression, most likely due to decreased reelin promoter methylation [10-11].

In addition to the epigenetic regulation, reelin gene show multiple *cis* elements, which contain binding sites for transcription factors involved in neurodevelopment such as Sp1, Tbr-1 and Pax6, and elements involved in cytoplasm-to-nucleus signal transduction as CREB and NF-κB [7,12]. Tbr-1 deficient mice show a clear disruption of cortical organization, accompa-

nied by decreased Reelin levels [13]. On the other hand, retinoic acid, a known inducer of neuronal growth and differentiation, increase Pax6 and Sp1 levels leading to the activation of the reelin promoter and a subsequent increased Reelin protein synthesis [14].

The full length Reelin protein contains 3461 amino acids, organized from N- to C-terminal by the following domains and motifs: 1.- A signal peptide, 2.- F-spondin-like motif, 3.- 8 repeat domains, composed of a region A and region B spaced by EGF motif, and 4.- A region enriched in basic amino acids [2].

Reelin may undergo proteolytic cleavage at the beginning of the 3rd and 7th A-EGF-B repeat generating many fragments including the N-terminal, the intermediate segment and the C-terminal fragment. Cleavage may be precluded by zinc chelators, known inhibitors of metalloproteinases [15]. Recently a putative protease had been identified as p50 and p70 isoforms of a disintegrin and metalloproteinase with thrombospodin motif 4 (ADAMTS-4). The p50 isoform cleaves at N-terminal only, and p70 cleaves the N- and C-terminal sites [16]. The importance of the proteolytic processing remains unclear, however; several reports showed that the internalization of Reelin at target cells is independent of its cleavage. In turn, only the central region seems to be sufficient for Reelin functions. Reelin cleavage would be required to enable Reelin secretion, allowing the release of a central, active fragment from the extracellular matrix-attached full length protein [17-18]. In contrast to this notion, there are many studies showing that the N-terminal region is important for Reelin secretion (due to the presence of a signal peptide on this region) [19], and to promote the formation of homopolymers, which are essential for proper signal transduction [20]. There is still little evidence about the function of the C-terminal region. The *reeler* Orleans mutation characterized by a deletion of 220 nucleotides at the C-terminal, prevents the secretion of Reelin, suggesting a possible role for this region in normal Reelin functions [21].

2. Reelin in neurodevelopment

As outlined in the previous section, Reelin is a glycoprotein, which is expressed in CR neurons starting at embryonic day 11 (E11), mainly in the cortex, hippocampus and cerebellum. It expression remains high until day E18, when CR neurons begin to degenerate [1,3]. The importance of Reelin to neurodevelopment had been elucidated through numerous studies using a mice model exhibiting a spontaneous mutation (partial deletion) in the reelin gene, called the *reeler* mice [22]. These mice had pronounced defects in the correct neuronal positioning in the laminar structures of the brain. At day E11, postmitotic neurons located in the ventricular zone, migrate toward the pial surface to form the preplate. On E13, a new cohort of migrating neurons originated at the proliferative region separate the pre-plate. Pre-plate splitting originates two regions, the marginal zone and the sub-plate, which are positioned adjacent to the pial surface and near the ventricular zone, respectively. The marginal zone is rich in CR neurons, which are the primary source of Reelin during neurodevelopment. Several waves of postmitotic migrating neurons are positioned between the marginal zone and the sub plate, leading to the formation of the cortical plate. During the E14-E18 time lapse,

four successive waves of postmitotic neurons migrate from the ventricular zone, through the sub-plate and neurons already positioned, to reach the marginal zone where the Reelin secreted by the CR neurons acts as a "stop signal" inducing the termination of the neuronal migration. This process is termed as "radial migration", and occurs through an inside-out mechanism, where early migrating neurons are placed at the inner aspects of the cortex [23]. Mechanistically, cortical neurons migrate using two different mechanisms, a glial-dependent process termed locomotion; and a glial-independent one termed nuclear translocation. During migration across the cortical plate, the neurons adopt morphology characterized by the presence of a cytoplasmic extension oriented toward the most outer aspect of the cortex, the leading process. A secondary cytoplasmic extension emerge orthogonally from the leading process and is termed the trailing process. While the leading process will be further developed as the dendritic arbor, the trailing process will become the axon [24].

The *reeler* mutant shows a clear disruption of the cortical layers, characterized by the absence of pre-plate splitting, generating a structure called the superplate [25]. Additionally, migrating neurons fail to establish an inside-out pattern of cortical layers [26]. Thus, in the *reeler* mutant, neurons that migrate earlier during development are placed in the outer aspect of the cortex, leading to an outside-in pattern of cortical layers [23,27-29].

Abnormal neuronal migration is not exclusively for the *reeler* mice cortex. Purkinje neurons in the cerebellum are also aberrantly organized. After birth, the Purkinje cell layer is absent, and a reduction of granule cells number is appreciated, these alterations result in a dramatic reduction of foliation pattern and diminished cerebellar size [30]. At the hippocampal region, the *reeler* mutant is characterized by the presence of non-compacted dentate gyrus and disorganized pyramidal layer [31].

Summarizing, Reeler brain shows smaller size and larger ventricles, the distribution of the dorsal, medial and ventral hippocampus is altered, the cortex display an inverted array of neurons in their layers and the cerebellum shows no foliation and alterations in the organization of its layers [32].

At the molecular level, the Reelin signaling pathway control several processes required for proper neuronal migration. For example, Reelin stabilize the leading process by inducing cofilin phosphorylation at Ser3, which regulates actin dynamics [33]. Furthermore, Reelin can also induce MAP1B phosphorylation through GSK-3β activation. MAP1B function is involved in formation of brain laminated areas, therefore, Reelin can modulate neuronal guidance through post-translational modifications of MAP1B [34]. These two examples show how Reelin can act coordinately to locally regulate the assembly of actin microfilaments and microtubules (Figure 1A).

In addition to its role in neurodevelopment, Reelin controls the formation of neural circuits, promoting the growth and branching of dendrites in hippocampal neurons [35]. Moreover, Reelin can enhance the formation of dendritic spines, supporting a role at the post-synaptic compartment [36].

Most of these cellular functions are dependent on a signaling pathway, triggered by the binding of Reelin to its two main receptors, the very-low density lipoprotein receptor

(VLDLR) and the ApolipoproteinE receptor 2 (ApoER2) [37]. The binding of Reelin to its receptor induce the phosphorylation of the adapter protein mDab1 on tyrosine residues [38]. mDab1 phosphorylation lead eventually to the modulation of cytoskeleton effectors molecules such as MAP1B and cofilin [23].
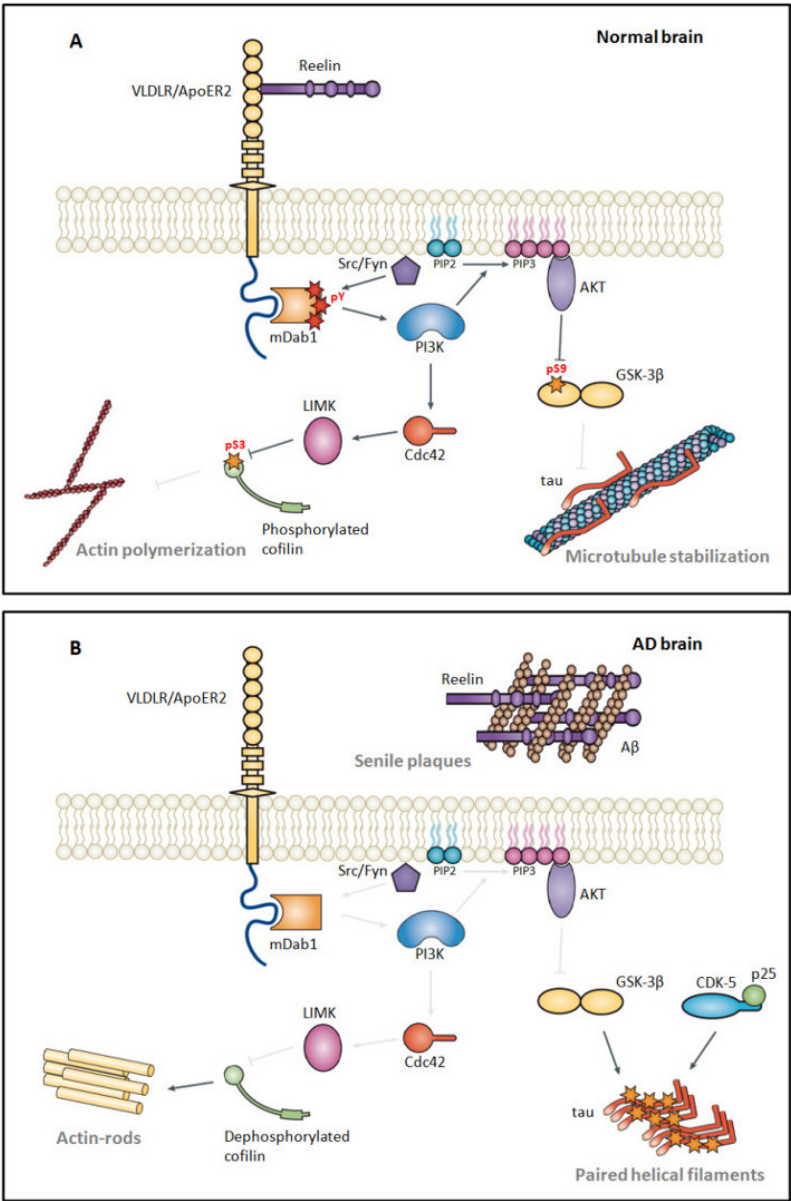

Figure 1. Reelin signaling pathway in normal brain and its impairment in AD brains. The panel A show the intracellular events triggered by the binding of Reelin to its canonical membrane receptors, ApoER2 and VLDLR. mDab1 protein is specifically phosphorylated at tyrosine residues, which concomitantly with the activation of PI3K, regulate actin and microtubule dynamic behavior. LIMK-mediated phosphorylation of cofilin and the Akt inhibitory phosphorylation of GSK-3β are essential to this regulation. On the other hand, in AD brains, diminished Reelin expression and its aggregation in amyloid-like deposits, induce impairment in its signaling pathway (represented by gray lines). Decreased Reelin signaling triggers the dephosphorylation of cofilin, promoting the formation of actin-rods. On the other hand, the activation of GSK-3β and CDK-5, lead to hyperphosphorylation of tau protein inducing its aggregation into PHFs (panel B).

3. Reelin in the adult brain

Although Reelin function is mainly related to neurodevelopment, several recently studies assign roles in the adult brain, such as the development of dendrites and dendritic spines [36], modulation of synaptogenesis [39], modulation of synaptic plasticity [40-43] and neurotransmitter release [44]. The mechanism by which Reelin can modulate the synaptic transmission is not fully elucidated. Currently it is strongly suggested that Reelin acting through its canonical signaling pathway facilitates the phosphorylation of NR2A and NR2B subunits of the NMDA receptor, favoring the calcium influx into the postsynaptic neuron.

This intracellular calcium increase causes the insertion of the GluR1 subunit of AMPA receptors, allowing the phosphorylation and nuclear translocation of CREB [45]. CREB phosphorylation is required to elicit the formation of dendritic spines. In addition, Reelin reduces the number of silent synapses, facilitating the exchange of subunit NR2B by NR2A of NMDA receptor [46]. Therefore, Reelin modulates synaptic plasticity events involved in learning and memory processes in adults. Consistently with a role for Reelin in the control of neurotransmission, *reeler* mice show diminished expression of presynaptic (SNARE, SNAP-25) [44] and postsynaptic (PSD-95, PTEN) markers [43]. These defects cause failures in the release of neurotransmitters, impairing synaptic transmission.

4. Animals models for neuropsychiatric diseases

Owing to the importance that Reelin have in the correct structuration and lamination of the brain during development and in neuronal connectivity and synaptogenesis in the adult brain, its dysfunction has been directly related to the generation or susceptibility to acquire neuropsychiatric conditions such as depression and schizophrenia, or neurodegenerative diseases such as Alzheimer's disease (AD) [45].

The most tangible evidence supporting these putative relationships was obtained through studies of human brains derived from neuropsychiatric and neurodegenerative conditions. Decreased levels of Reelin are shown in postmortem samples from prefrontal cortex of patients with schizophrenia and bipolar disorders [47]. This decrease may be explained in schizophrenic patients by an abnormal hypermethylation of the *reelin* promoter, an epigenetic modification involved in gene silencing [48]. Furthermore, immunohistochemistry experiments in depressive and schizophrenic patients show decreased Reelin expression at the hippocampus [49]. On the other hand, diminished Reelin levels in the hippocampus of patients with AD had been reported, suggesting a direct correlation between the severity of the disease and the extent of decreased Reelin expression [50]. All of these antecedents provide evidence enough to feature a molecular link between decreased Reelin levels and neurodegenerative/psychiatric diseases.

In order to understand the etiology of neurodegenerative/psychiatric diseases, different animal models had been developed. A widely paradigm is the "two hit" model, which suggests

that genetic and environmental factors may affect the development of central nervous system, acting as "the first hit". These early disorders are linked to long-term vulnerability, which after a "second hit" could cause the symptoms for a disease [51-52]. For diseases such as depression, autism and schizophrenia, the heterozygous *reeler* mice had been used as the genetic "first hit", while stress events after the birth or in adulthood are used as the environmental "second hit". The results indicate that heterozygous *reeler* mice, after a stressful event, such as maternal deprivation or corticosterone injection, exhibit significantly increased depressive or schizophrenic behaviors as compared with wild type littermates [53-54]. Indeed, *reeler* heterozygous animals in the absence of a stressful event, display a phenotype indistinguishable from control animals [55].

The "two hit" model has also been used to study the molecular mechanisms leading to the AD [56]. It is proposed that both oxidative stress and failures in mitotic signaling can independently triggers the onset of the disease; however both are necessary for their progression [57]. In addition, a correspondence had been established between the Reelin expression in the entorhinal cortex of aged rats with their cognitive abilities. A study revealed that aged "cognitively disabled" rats show a significant decreased of Reelin in neurons on layer II of the entorhinal cortex. Such a reduction in Reelin expression was not observed in juvenile or elderly "cognitively able" rats [58].

Since Reelin is expressed from development to adult stages, is conceivable that alterations in Reelin expression, induced by genetic or environmental factors generate a vulnerable stage, and a secondary factor, present in normal aging, may trigger the onset and progression of a pathological condition.

The Reelin-activated signaling pathways, which may be involved in the generation and development of AD are still unclear and will be discussed in next sections. In the last part of this section, we present some of the evidences that correlate altered levels of Reelin and AD. Pyramidal neurons placed in layer II of the entorhinal cortex and the hippocampus derived from AD patients brains exhibit decreased Reelin expression [50]. On the other hand, an increase in the full length and 180 kD proteolytic fragment of Reelin had been observed in the frontal cortex of AD derived samples [59]. The increase of this proteolytic fragment is attributed to problems with the proteolysis of Reelin, associated with decreased Rab11-endocytosis of full length Reelin [60]. In the other hand, an increase of Reelin is also observed in the frontal cortex of AD patients, which may involve a compensatory mechanism in response to the lower expression in disease-related most vulnerable areas like the entorhinal cortex and hippocampus [50].

The CR neurons participation in AD is a controversial issue. While electronic microscopy analysis suggested that CR neurons of the temporal cortex were dramatically reduced in AD patients [61], another study showed no difference between AD patients and normal, healthy subjects [62]. On the other hand, there are some polymorphisms in the Reelin gene which had been associated with AD. Seripa and colleagues reported significant differences in two analyzed polymorphisms in the Reelin gene, in a group of 223 Caucasians AD patients. These differences were exacerbated in female patients [63].

Finally, Reelin had been associated with the pathological hallmarks for AD, the senile plaques and the neurofibrillary tangles (NFT). Reelin can modulate tau phosphorylation, the core protein of NFT [38]. It is also associated with senile plaques, large extracellular aggregates mainly formed for β-amyloid peptide (Aβ). Immunohistochemical studies revealed that Reelin colocalizes with the amyloid precursor protein (APP) in the neuritic component of typical AD plaques, at the hippocampus and cortex of mice expressing a mutant version of APP [64]. Additionally, a reduction of Reelin-producing cells had been observed in older mice and primates. This reduction is accompanied by the presence of Reelin aggregates and memory deficits. Mice harboring APP with AD-associated mutations also showed Reelin aggregates, which co-localized with non-fibrillar amyloid plaques [65]. In addition, Reelin forms oligomeric or protofibrillary deposits during aging, potentially creating a precursor condition for Aβ plaque formation [66].

A direct relationship between decreased Reelin expression and increased levels of Aβ peptide and plaque accumulation was provided by studies using transgenic mice carrying the APP Swedish and *reeler* mutation. The absence of Reelin expression resulted in an age-dependent exacerbation of plaque pathology and increased NFTs in double mutants as compared with the single APPsw mutant [67]. Finally, recent studies demonstrated a feedforward mechanism by which Reelin would favor the formation of senile plaques; and the subsequent Aβ peptide production would increase the Reelin levels by altering its proteolytic processing in the cortex of mice and humans with AD [68].

5. Cytoskeletal abnormalities in Alzheimer´s disease

5.1. Tau protein and neurofibrillary tangles

Neurofibrillary tangles are amongst the standard characteristics of AD brains. These structures were firstly described by Alois Alzheimer more than a century ago and are composed of a densely packed array of fibers of 20 nm in diameter, called paired helical filaments (PHF), which at the core are mainly composed by the microtubule-associated protein, tau [69-70]. Tau protein stabilizes and enhances microtubule polymerization. It is a heterogeneous protein giving rise to 6 isoforms derived from alternative splicing [71]. It contains 3 or 4 imperfect repeats of 31 or 32 amino acids each in tandem which confers the microtubule-binding properties of the protein. These repeats are enriched in basic aminoacids that interact electrostatically with the mostly acidic C-terminal of β-tubulin subunit [72]. Tau protein is highly phosphorylated in fetal brain [73], but minimally phosphorylated in normal adult brain [74]. The abnormal phosphorylation state of several residues in tau protein plays an important role modulating the affinity to microtubules and promoting its aggregation [75] forming the core of PHFs [69,76-77]. Tau protein can be phosphorylated by many protein kinases such as calcium-calmodulin dependent kinase [78]; PKA [79-81] and PKC [82-83]. Interestingly, many of these residues are hyperphosphorylated in AD brains mainly due to an imbalance in the activity of kinases belongs to the family of proline-directed Ser/Thr protein kinases (PDPKs), such as mitogen-activated

protein kinases (MAPK) [84], the glycogen synthase kinase (GSK)-3β [85], JNK [84], p38 [86] and Cyclin-dependent kinase (Cdk)-5 [87]. The abnormal phosphorylation state of tau protein is not only contributed by protein kinases, but also by deregulated protein phosphatases functions [88]. (Figure 1B)

5.2. Cofilin and actin-rods

NFTs are not the only intraneuronal cytoskeletal protein aggregates found in the brains of patients affected by AD. Hirano´s bodies and actin-rods are two closely related aggregates primarily composed of actin and the actin binding protein, cofilin. Cofilin concertedly with the actin depolymerizing factor (ADF) constitutes the major modulators of actin dynamic assembly.

Hirano's bodies were originally described in 1965 and are defined as paracrystalline structures, eosinophilic intracellular arrangements resembling rod-shaped filaments of 7 nm. The actin-rods differ from Hirano´s bodies by it smaller size, so it is hypothesized that these structures could be precursors of Hirano's bodies.

The formation of actin-rods in neurons seems to be the result of several neurodegenerative insults, such as ATP depletion, excitotoxic levels of glutamate, oxidative stress [89], and $A\beta_{1-42}$ oligomers [90]. A common event to all these stimuli triggers the formation of rods is the dephosphorylation (activation) of cofilin [89]. Cofilin/ADF is inactivated by phosphorylation of a highly conserved serine (Ser3), which precludes its binding to actin filaments and, therefore, its role as promoters of filament severing and actin subunits turnover at the minus end of filaments.

The Ser3 of ADF/cofilin is the only known substrate for the two isoforms of LIM domain kinases (LIM, an acronym for three *Caenorhabditis elegans* genes, *lin-11*, *isl-1* and *mec-3*). LIMKs is activated by phosphorylation at the Thr508, mediated by PAK or ROCK, two kinases that act as effectors for small GTPases Rac1 and RhoA respectively [91]. The regulation of signaling cascades, which target the functions of small GTPases, connect the dynamic control of the actin cytoskeleton with extracellular signals. In AD, different components of the signaling cascade involved in cofilin phosphorylation are altered, including decreased phosphorylation of PAK at Ser141, which is necessary for activation. Although a decrease in phosphorylation and activity of PAK is observed in large areas of cortex and hippocampus of AD brains, neurons located near to amyloid plaques exhibit strong staining for pSer141 PAK, suggesting that while the dephosphorylation is predominant in the brain of patients with AD, the amyloid fibrils present in amyloid plaques increases the activity of PAK [92].

Consistently, hippocampal neurons treated with fibrillar $A\beta_{1-42}$ show increased activity of PAK and its downstream substrate LIMK1 [93-94], most likely through a Rac1 and Cdc42 dependent mechanism [95]. Moreover, the treatment with oligomers of $A\beta_{1-40}$ has the opposite effect, decreasing the phosphorylation of PAK, indicating that oligomeric forms may be responsible for the overall reduction in PAK phosphorylation [92].

Similarly, cofilin dephosphorylation and the subsequent formation of actin-rods seem to be also a spatial-restricted phenomenon. In example, actin-rods occur in a subpopulation of neurons in organotypic slices treated with Aβ [96]. (Figure 1B)

The mechanisms involved in the Aβ-mediated cofilin dephosphorylation are dependent on changes in the activity of its upstream kinase, LIMK [90], and the activity of two known cofilin phosphatases, chronophin [97] and slingshot [94].

Interestingly, ATP depletion induces chronophin activation in a mechanism involving the dissociation of chronophin-HSP90 complex. This mechanism would be responsible for the formation of actin-rods under energy deprivation conditions [97].

6. Is the AD-associated Reelin reduction a major factor involved in the neuronal cytoskeleton pathology?

6.1. Reelin reduction in AD brains

There is an increasing body of evidence indicating that a deficiency in Reelin signaling may play a major role in the progression of AD. First, decreased Reelin expression is early observed in brains of AD transgenic mice model, even before Aβ deposition. Accordingly, Reelin expression is also decreased in brains of patients at the presymptomatic stages of AD. The progression of the disease causes in both cases, potentiate the Reelin deficiency from the hippocampus to the entorhinal cortex in mice and from the frontal cortex to the hippocampus and entorhinal cortex in humans [50,98]. The decrease in Reelin expression is linked to a reduction in CR cells at the cortical layer I in AD brains [61].

Reelin itself can form amyloid deposits in advanced stages of AD, which can or cannot be associated with Aβ senile plaques [64-66]. However, Aβ pathology seems to be a prerequisite for the formation of Reelin aggregates, as these only occur after formation of senile plaques [98].

On the other hand, the proteolytic fragments of Reelin showing aberrant glycosylation pattern are increased in the cerebrospinal fluid of patients with AD [59,99]. Altogether these antecedents support the hypothesis that the Reelin intracellular signaling is impaired at early stages of AD.

6.2. Cytoskeletal pathologies and Reelin signaling

Reelin signaling is triggered by the binding of Reelin to two members of the lipoprotein receptor family, the very low density lipoprotein receptor (VLDLR) and the ApoE receptor 2 (ApoER2)[100]. The signal is then transduced by a cytoplasmic adapter protein, the mammalian homologue for the *Drosophila* protein *disabled* (mDab)-1, which interacts with the NPXY motifs of the intracellular domain of several members of the LDL receptor family, including VLDLR and ApoER2.

As VLDLR/ApoER2 or mDab1 deficient mice exhibit a phenotype indistinguishable from *reeler* mice, it is suggested that both receptors and the adapter protein can be linearly placed on the same signal transduction pathway [37,101].

The binding of Reelin to its receptors induces mDab1 tyrosine phosphorylation, mediated by non-receptor tyrosine kinases from the Src family [102]. The mutation of these tyrosines residues by phenylalanines in a *knockin* mouse recapitulates several features of the *reeler* mouse, supporting that these phosphorylation events are required for proper Reelin signaling [103].

Several genetic models suggest that canonical Reelin signaling plays an essential role in controlling the phosphorylation state of tau and, therefore, modulating a critical event in the progression of AD (Table 1).

Mice deficient in various components of the Reelin signaling pathway, including Reelin itself, VLDLR, ApoER2 and Dab1 show increased tau phosphorylation in several AD-associated epitopes, such as those recognized by the antibodies AT8 (pSer202/205) and PHF1 (pSer396/404) [38,104-106].

The increase in tau phosphorylation is caused by increased activity of two main kinases, Cdk5 and GSK-3β [105], suggesting that Reelin is playing a negative control over the activities of these kinases.

GSK-3β is normally inhibited by phosphorylation at its N-terminal region by the protein kinase Akt, mainly at the Ser9. Reelin signaling in turn, activates Akt through its recruitment to membrane domains rich in phosphatidilinositol 3-phosphate (PIP3), whose formation is involved the activity of the phosphatidilinositol 3-kinase (PI3K). Reelin activates PI3K by potentiating the interaction between tyrosine phosphorylated-mDab1 and the p85α subunit of PI3K [107-108].

Moreover, it has been proposed that the increased activity of Cdk5 in Dab1 or Reelin deficient mice may be due to a remarkable increase of the proteolyzed form of a Cdk5 activator, called p25 [105]. This fragment induces a non-physiological activation of Cdk5, which is present mainly in pathological conditions, including brains of patients with AD [109]. Since the proteolysis of the Cdk5 activator is due to the activity of calpain, it may be hypothesized that the Reelin signaling pathway could regulate calpain-dependent proteolysis of p35.

It has been proposed that Cdk5 could not be directly regulated by the Reelin signaling cascade, because cortical neurons treated with Reelin do not exhibit any significant change in the Cdk5 activity [107] or a diminished phosphorylation state of Cdk5-dependent substrates [110]. However, it may not be ruled out that a subset of substrates still not analyzed can be phosphorylated by Cdk5 due to impairment in Reelin signaling.

Protein	Functions in Reelin signaling	Association with Alzheimer´s disease	References
Reelin	Extracellular matrix glycoprotein	Diminished levels in restricted areas of AD brain. Reelin-deficient mice show increased tau phosphorylation	[50, 98]
ApoER2	Reelin receptor	VLDLR and ApoER2 dKO mice present elevated levels of phosphorylated tau	[38]
VLDLR	Reelin receptor	VLDLR and ApoER2 dKO mice present elevated levels of phosphorylated tau	[38]
mDab1	Intracellular adapter for Reelin receptors	mDab1-deficient mice show increased tau phosphorylation and early death.	[106]
PI3K	Lipid kinase essential for membrane recruiting of Akt	Impairment in PI3K-Akt pathway was observed in aged APP-PS1 transgenic mice.	[112]
Akt	Phosphorylates and inhibits GSK-3β	Impairment in PI3K-Akt pathway was observed in aged APP-PS1 transgenic mice.	[112]
GSK-3β	Major tau kinase	Phosphorylates tau at AD-associated epitopes	[85]
tau	Microtubule-associated protein. Promotes microtubule assembly and stabilization	Hyperphosphorylated tau constitutes the core of NFTs	[77]
Cdc42	Small GTPase associated with actin dynamics	A lesser Aβ-induced actin-rod formation is observed in cdc42 null neurons	[96]
LIMK1	Major effector of Rho-family GTPases. Phosphorylates and inactivates cofilin	The expression of constitutively active LIMK1 reduces Aβ-induced actin-rods in hippocampal slices	[90]
Cofilin	Actin binding protein with F-actin depolymerizing activity	Ser3 dephosphorylation triggers its aggregation into actin-rods	[89]

Table 1. Association of Reelin signaling pathway with Alzheimer´s disease

The Reelin signaling pathway can target not only microtubule cytoskeleton, but also the actin microfilament formation. Acting through its canonical signaling pathway that involve receptors VLDLR and ApoER2, the adapter protein Dab1 and activation of PI3K, Reelin is able to activate the small GTPases Rac1 and Cdc42, increasing actin polymerization. These

changes in small Rho GTPases are responsible of increased mobility of growth cones and promote the appearance of filopodia in the axon of cortical neurons in culture [111]. The stabilization of actin filaments is mediated directly by an increase in activation of LIMK and phosphorylation of cofilin Ser3 [33]. LIMK and cofilin phosphorylation are two key events that regulate actin microfilament turnover in a Rac-dependent manner. Currently, there are no studies showing a causal relationship between impaired Reelin signaling and molecular changes affecting cofilin phosphorylation that could regulate the formation of actin-rods. However, it is tempting to speculate that further studies may solve a linkage between the decreased Reelin signaling observed in AD brains and abnormal actin dynamics.

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