Reelin: Neurodevelopmental Architect and Homeostatic Regulator of Excitatory Synapses*

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Over half a century ago, D. S. Falconer first reported a mouse with a reeling gate. Four decades later, the Reln gene was isolated and identified as the cause of the reeler phenotype. Initial studies found that loss of Reln, a large, secreted glycoprotein encoded by the Reln gene, results in abnormal neuronal layering throughout several regions of the brain. In the years since, the known functions of Reln signaling in the brain have expanded to include multiple postdevelopmental neuromodulatory roles, revealing an ever increasing body of evidence to suggest that Reln signaling is a critical player in the modulation of synaptic function. In writing this review, we intend to highlight the most fundamental aspects of Reln signaling and integrate how these various neuromodulatory effects shape and protect synapses.

Reelin Signaling during Development

Besides the obvious motor deficits in Reln-deficient mice (1), the most overt reeler phenotype is the abnormal layering of neurons in the brain (2). Reln is essential for normal cortical, hippocampal, and cerebellar neuronal lamination (reviewed in Refs. 3 and 4). While the neocortex is developing, Reln is expressed and secreted by Cajal-Retzius neurons in the outer layers of the developing neocortex, where Reln guides newly born neurons to their correct positions in the cortex in an inside-out fashion (3, 4). Similarly, in the prenatal cerebellum, Reln is expressed in the external granule layer, where it mediates Purkinje cell localization (reviewed in Refs. 3 and 4).

The mechanism of Reln-mediated neuronal guidance was elucidated through the genetic ablation of its downstream signaling partners. Double knock-out of low-density lipoprotein receptor family members, ApoE receptor2 (ApoER2) and very low density lipoprotein receptor (VLDLR),2 or loss of the cytoplasmic adaptor protein Disabled-1 (Dab1) recapitulated the reeler phenotype (reviewed in Ref. 5), suggesting that these molecules are critical for the action of Reln during neuronal migration. Interestingly, singular knock-out of either Reln receptor resulted in a milder migration deficit, indicating divergent roles for the ApoER2 and VLDLR during neuronal migration (reviewed in Ref. 5). These studies ultimately clarified the core components of the Reln signaling pathway whereby Reln binding to ApoER2 and VLDLR results in a Src family tyrosine kinase (SFK)-mediated tyrosine phosphorylation of Dab1 (reviewed in Ref. 5).

Reelin Signaling after Neuronal Migration

Postnatally, Reln is repurposed as a neuromodulator. At this point, inhibitory GABAergic interneurons begin to express and secrete Reln (6) as the Cajal-Retzius cells begin to die out in the cerebral cortex and later in the hippocampus (7). This postnatally secreted Reln acts to modulate axonal and dendritic outgrowth through multiple independent and interconnected pathways by regulating the stability of the cytoskeleton (Fig. 1).

The formation of neuronal connections begins with the outcropping of neuritic filopodia, which develop into axon and dendrites. Acute and chronic Reln application enhances cortical neuritic outgrowth mobility and size (respectively) through an ApoER2/Dab1/Pi3K pathway, which activates the RhoGTPase Cdc42 and stimulates the delivery of membrane and extension of the growth cone (8) (Fig. 1D). Neurons from reeler mice exhibit reduced dendritic branching, and these dendrites produce fewer dendritic spines in vivo and in vitro (9). A similar, more subtle effect is observed in heterozygous reeler mice (HRM), which lack only one allele of the Reln gene and express 50% less Reln. However, neuronal positioning in HRM brains is not affected, indicating that the Reln deficiency is driving the dendritic abnormalities in the reeler mouse and that they are not due to improper neuronal positioning. Acute application of Reln can enhance dendritic outgrowth in both wild-type and reeler neurons in a lipoprotein receptor-dependent fashion that requires the presence and phosphorylation of Dab1 by Src kinases (9). Promotion of the outgrowth and stabilization of dendrites by Reln also requires activation of mTOR through Pi3K and AKT (reviewed in Refs. 5, 10, and 11) (Fig. 1B). Crk family proteins are also important downstream components of the Reln signaling pathway in the regulation of

2 The abbreviations used are: VLDLR, very low density lipoprotein receptor; SFK, Src family tyrosine kinase; HRM, heterozygous reeler mice; mTOR, mammalian target of rapamycin; AMPAR, AMPA receptor; NMDAR, NMDA receptor; LTP, long-term potentiation; LTD, long-term depression; BDNF, brain-derived neurotrophic factor; CREB, cAMP-response element-binding protein; OLS, O-linked sugar; ECD, extracellular domain; ICD, intracellular domain; TLE, temporal lobe epilepsy; KA, kainate; GCD, granule cell dispersion; TrkB, tropomyosin receptor kinase B; AD, Alzheimer’s disease; Aβ, amyloid β; APP, amyloid precursor protein; mGluR, metabotropic glutamate receptor; α7-nACHR, α7-nicotinic acetylcholine receptor; GSK-3β, glycogen synthase kinase-3β; ASD, autism spectrum disorder; Nt, N-terminal; Ct, C-terminal.

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both neocortical lamination and postnatal hippocampal dendritogenesis (12, 13) (Fig. 1E). Microtubule and actin stabilities are also promoted by Reelin through the activation of Li-255140 sencephaly 1 (Lis1) through VLDLR (reviewed in Refs. 4, 5, and 11) (Fig. 1A) or by the phosphorylation and inactivation of coflin through LIM kinase 1 (LIMK1) (reviewed in Ref. 3) (Fig. 1C). Each of these actions contributes to the fine-tuning of dendritic outgrowth and helps shape neuronal connectivity.

**Spine Formation and Maturation**

The neuromodulatory effects of Reelin extend beyond the dendrite to the dendritic spine, where presynaptic and postsynaptic contacts form. The major components of excitatory postsynaptic compartments contain ionotropic glutamate receptors, both AMPA and NMDA receptors (AMPAR and NMDAR), which bind presynaptically released glutamate. The number of synaptic connections and the molecular composition of these compartments determine the efficacy of neuronal networks, and Reelin signaling is a critical regulator of both the number and the strength of these connections (14). HRM and reeler hippocampal neurons have fewer dendritic spines along their dendrites when compared with wild-type neurons, and the extent of this effect is proportional to the reduction in Reelin protein abundance (14, 15). Exogenous recombinant Reelin recovers this deficit in cultured hippocampal slices from HRM and reeler mice as well as increases dendritic spine density in wild-type control slices (14). The downstream signaling partners, ApoER2/VLDLR and both Dab1 and SFKs, are essential for this Reelin-mediated spinogenesis (14). Intriguingly, overexpression of the Reelin receptor ApoER2 in dissociated hippocampal neuron cultures can dramatically increase dendritic spine numbers in wild-type neuron cultures, suggesting a critical role of the receptor in promoting synaptogenesis (16).

Reelin signaling also modulates the molecular composition of synapses. During development, the majority of NMDARs at hippocampal synapses are composed of NR2B subunits, which have a higher conductance than NR2A-containing receptors. As synapses mature, the subunit composition of NMDARs shifts from NR2B-containing receptors to the NR2A-containing receptors (reviewed in Ref. 17). This switch is accelerated in hippocampal neuron cultures treated with exogenous Reelin over 24 h, an effect that requires lipoprotein receptors and Src kinase activity (18). Alternately, this switch is prevented by inhibiting Reelin signaling via antisense knockdown of Reelin, perfusion with a Reelin antibody (CR-50), or blocking the GABAergic release of Reelin (18, 19). Chronic Reelin treatment of hippocampal slice cultures (6–8 days) augmented AMPAR currents by increasing GluA1 surface expression while reducing the NMDA-mediated currents by promoting the insertion of NR2A-containing NMDARs and removing NR2B-containing NMDARs (reviewed in Refs. 20–22). This chronic Reelin treatment also facilitates the insertion of AMPARs into synaptic membranes containing only NMDARs (reviewed in Ref. 22); these synapses, containing NMDAR and no AMPAR, are known as “silent synapses” and are unresponsive to glutamate at the resting membrane potential (23). Additionally, Reelin regulates the surface diffusion of NR2B-containing NMDARs without affecting those with NR2A subunits (24). Prolonged treatment with Reelin facilitates the mobility and decreases the synaptic dwell time of NR2B-containing NMDARs, whereas inhibition of Reelin signaling with CR-50 stabilizes these receptors at the synapse (24). Constitutive decreases in Reelin also alter NMDAR composition. The postsynaptic compartments of both homozygous and heterozygous reeler synapses have a drastic and comparable reduction in the NR2A subunit of the NMDAR and PSD-95 in comparison with wild-type synapses (14).

Reelin also acts presynaptically (25, 26). Acute application of Reelin increases the spontaneous fusion of vesicle-associated membrane protein 7 (VAMP7)-containing presynaptic vesicles in hippocampal cultures, and this effect is rapid (within 5 min) and robust as early as 6 days in vitro when spontaneous fusion is minimal (25). This increase in VAMP7-containing mobilization of presynaptic vesicles requires release of Ca$^{2+}$ from intracellular compartments, both ApoER2 and VLDLR, and PI3K (25). Taken together, Reelin signaling appears to act as a potent neuromodulator of the structure and function of synapses and their connectivity.

**Modulation of Synaptic Plasticity**

Reelin also enhances long-term potentiation (LTP) of synapses, a proposed cellular correlate to memory (27) (Figs. 2, A and B, and 3, A and B). When Reelin binds postsynaptic lipoprotein receptors, ApoER2 and VLDLR, the receptors cluster and phosphorylate Dab1, leading to an SFK-mediated tyrosine

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**FIGURE 1. Reelin’s role in stabilizing the cytoskeleton.** Reelin signaling participates in axonal and dendritic outgrowth and maturation by stabilizing the cytoskeleton. A and B, microtubule stability is promoted by Reelin through VLDLR-dependent activation of Lis1 (reviewed in Refs. 4, 5, and 11) (A) and inhibition of GSK-3β (reviewed in Ref. 3) (B) through activation of the Dab1/PI3K/Akt pathway, which also activates an mTOR-dependent process that promotes the outgrowth and stabilization of dendrites (reviewed in Refs. 5, 10, and 11) (B). C, Reelin promotes actin stability through the ApoER2/Dab1/PI3K pathway by inducing LIMK1-dependent inactivation of coflin (reviewed in Ref. 3). D, this ApoER2/Dab1/PI3K pathway can also mediate the formation of axons by activating the RhogT1ase Cdc42 (B). E, independent of PI3K, Reelin stabilizes actin by triggering C3G activation of Rap1 through Crk family proteins (Crk), which is essential for normal neocortical lamination and postnatal hippocampal dendritogenesis (12, 13).
Regulating Reelin Signaling

The contextual deficit in fear learning in ApoER2 KOs is recapitulated in mice expressing ApoER2 lacking the alternatively spliced proline-rich domain of ApoER2 (30), indicating that this domain is critical for the downstream action of Reelin in fear memory acquisition. Reelin’s role in fear memory is further supported by the observations that HRM mice have reduced short-term contextual fear learning (32) and deficient long-term association of both forms of fear memory (33). These studies demonstrate a critical modulatory role of Reelin in both spatial and fear memory.

Regulating Reelin Signaling

Many of Reelin’s effects require ApoER2, so an important regulatory factor in Reelin signaling is the alternative splicing of ApoER2. ApoER2 RNA can undergo numerous splicing events; the two most notable for synapses are the cytoplasmic proline-rich region and a highly glycosylated extracellular domain. The ability of Reelin to modulate synaptic strength depends upon the inclusion of the proline-rich cytoplasmic domain of the Reelin receptor, ApoER2 (30). Differential inclusion of the glycosylated region of ApoER2 has a very different role. This juxtamembranous O-linked sugar (OLS) domain regulates the abundance of the receptor by protecting it from proteolytic processing in a glycosylation-dependent manner (34, 35). Loss of ApoER2 cleavage leads to increased ApoER2 expression and a concomitant enhancement of dendritic spine density (34), which is consistent with the published results of ApoER2 overexpression in wild-type neuron cultures (16).

Alternative splicing of ApoER2 can dramatically modify this extracellular proteolytic processing of ApoER2. ApoER2 is sequentially cleaved by extracellular proteases such as ADAM10, resulting in the release of a soluble extracellular domain (ECD), followed by the subsequent γ-secretase-mediated release of the intracellular domain (ICD) (35). Acute application of Reelin can induce this cleavage (36). Both ApoER2 cleavage fragments are negative feedback regulators of the Reelin signal. The ApoER2-ECD acts as a dominant-negative...
receptor for ApoER2 ligands (37), and the ApoER2-ICD can translocate to the nucleus and alter transcription of genes including inhibition of Reelin transcription (38, 39). Alternative splicing of ApoER2 can affect this sequential cleavage. In addition to increased abundance of the receptor, exclusion of the OLS domain, which contains the extracellular cleavage site, imparts a strong resistance to the cleavage of ApoER2 and thus prevents the release of both the extracellular and the intracellular fragments of ApoER2 (34).

In addition to proteolytic processing of ApoER2, the function of Reelin is also influenced by proteolytic processing (reviewed in Refs. 11 and 21). After secretion, Reelin is cleaved as it diffuses through the extracellular space (reviewed in Ref. 21). This processing occurs at two specific sites within the protein, which consists of eight repeated Reelin domains flanked by an F-spondin domain on the N-terminal (Nt) side and a C-terminal (Ct) stretch of acidic residues (reviewed in Refs. 20 and 21). Reelin is cleaved within the third repeat and between the sixth and seventh repeats (Fig. 2A), whereby “completely cleaved” Reelin produces three fragments: the Nt-(N−R2), Ct-(R7−C), and the central-(R3−6) fragments (reviewed in Ref. 11).

The central fragment contains the binding site for ApoER2 and VLDLR (Fig. 2A) and is sufficient to rescue the abnormal neuronal migration in reeler slice cultures (reviewed in Refs. 5, 11, and 20–22). However, the homodimerization of Reelin through disulfide linkage of the N-terminal region of the fragment is required for efficient Dab1 phosphorylation (reviewed in Refs. 5, 11, and 22). Not much is known about the role of the Ct cleavage of Reelin between R6 and R7; however, Reelin-mediated Dab1 phosphorylation is reduced when Reelin lacks the Ct region, so this cleavage would reduce the efficacy of Reelin signaling (reviewed in Refs. 11, 21, and 22). Interestingly, neuronal activity can drive this cleavage by activating tissue plasminogen activator (tPA) (reviewed in Ref. 21), thus diminishing the effect of Reelin after synaptic potentiation.

More is known about the role of the Nt fragment, which has been reported to bind α3β1 integrins, EphB receptors, and the cadherin-related neuronal receptors (CNRs) (Fig. 2A) (reviewed in Refs. 5 and 11). The interaction of Reelin with α3β1 integrins is required for the Reelin-mediated surface diffusion of NR2B-containing NMDARs (24). The interaction of Reelin with EphB receptors may contribute to the proper laminations of the CA3 region of the hippocampus (reviewed in Ref. 11). Recently, EphB receptors were shown to be critical for the development of innate fear in mice, whereby loss of EphB receptors disrupted normal axonal innervation in the amygdala (40). Cleavage of Reelin between R2 and R3 would prevent these known interactions. Additionally, this cleavage is known to reduce the distance Reelin diffuses and the potency of downstream signaling by Reelin (reviewed in Refs. 5, 11, and 20–22).

This cleavage at the N-terminal site plays a potential role in temporal lobe epilepsies (TLEs). The most common risk factor for TLEs is an initial fever-induced seizure. Postmortem studies of TLE patients suggest that in most cases, the seizures are accompanied by dispersion of the dentate gyrus granule cells with a correlated decrease of Reelin-expressing neurons in the hilus (reviewed in Ref. 41). Induction of seizures by intrahippocampal perfusion of kainate (KA), a potent glutamate recep-
MINIREVIEW: Reelin at the Synapse

Alzheimer’s Disease

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder, which first presents as memory loss brought on by synaptic dysfunction. Two pathological hallmarks of AD have been identified: extracellular amyloid β (Aβ) plaques and intracellular neurofibrillary tau tangles. Aβ, the central component in the trademark plaques that build up in the brains of people with AD, is a product of the amyloid precursor protein, APP (reviewed in Refs. 31 and 50). Tau neurofibrillary tangles, the other pathological hallmark of AD, form when the microtubule-associated tau protein is hyperphosphorylated, promoting aggregation and intraneuronal tangle formation (reviewed in Refs. 22 and 31).

Aβ and Tau

Both Aβ and tau are released with normal network activity, so each protein most likely serves a physiological purpose (51, 52). In AD, oligomeric Aβ particles are detectable before tau aggregation and are known to impart toxic effects at the synapse (reviewed in Ref. 53), inducing synaptic dysfunction and likely causing the early manifestation of memory deficits in AD. In a recent study, modification of APP cleavage could prevent Aβ formation and prevent cognitive decline, further supporting this amyloid-induced hypothesis of AD (54). Oligomeric Aβ particles suppress LTP and enhance long-term depression (LTD) through interactions with synaptic proteins (and reviewed in Refs. 31 and 55), such as metabolotropic glutamate receptors (mGluRs) as well as potentially the Ca^2+-permeable α7-nicotinic acetylcholine receptor (α7-nACHR) (reviewed in Refs. 56 and 57). (Fig. 3C). Activation of mGluRs and Ca^2+ release by inhibiting Fyn-mediated phosphorylation of the receptors (59, 60) (Fig. 3D).

The phosphorylation of tau inhibits microtubule stability, which is essential for the formation and maintenance of dendritic spines (reviewed in Ref. 61). Cyclin-dependent kinase5 (cdk5) can phosphorylate tau, which is activated by co-factors p35 or p39. Elevated Ca^2+ concentrations activate calpain, which cleaves p35 to p25 (reviewed in Ref. 62). Cdk5 binds p25 longer than p35, which prolongs Cdk5 activity, leading to enhanced tau phosphorylation (Fig. 3E). Both p25 and calpain are elevated in AD brains, and Aβ can induce tau phosphorylation through deregulating Cdk5 activation (reviewed in Ref. 62). At the same time, Reelin signaling through the Dab1/P13K/Akt pathway reduces this phosphorylation by inhibiting glycogen synthase kinase-3β (GSK-3β) (reviewed in Ref. 31) (Figs. 1B and 3F), which would stabilize microtubules and help maintain synaptic stability. VLDLR and ApoER2 KO mice show increased tau phosphorylation in the brain (63), supporting the role of Reelin signaling in the regulation of tau protein hyperphosphorylation and a potential role in AD pathogenesis.

Regulation of Aβ Formation by the Reelin Receptor ApoER2

The production of oligomeric Aβ depends on how APP is processed. The amyloidogenic fate of APP is determined by the initial secretase cleavage step. Non-amyloidogenic cleavage of APP is mediated by extracellular α-secretases, whereas amyloidogenic processing starts primarily in endosomal compartments by β-secretase cleavage (reviewed in Refs. 31 and 50). Thus, subcellular localization plays an important role in whether APP cleavage produces oligomer-prone Aβ.

Multiple intracellular and extracellular adaptor proteins can influence APP localization and processing. Interestingly, the majority of these proteins also interact with ApoER2, which adds an additional layer of regulation to APP localization and processing. Co-expression of ApoER2 with APP promotes APP surface expression and the lipid raft association of APP, both of which reduce Aβ formation (64). The extracellular ligand, F-spondin, binds both ApoER2 and APP, enhances their surface expression, and reduces Aβ formation (65, 66). Intracellularly, APP and ApoER2 bind the adaptor proteins X11α/β (67–70), Fe65 (69, 71, 72), Snx17 (73, 74), Dab1 (75–79), and Dab2 (73, 80), and these interactions regulate their surface expression and processing (Fig. 4).

In addition to protecting against Aβ- and tau-related AD pathology, Reelin signaling is implicated in protecting against pathological effects of the most common genetic risk factor for late-onset AD, the ε4 allele of apolipoprotein E (ApoE4) (reviewed in Refs. 31 and 81). Human carriers of ApoE4 are at increased risk for AD when compared with those carrying the more common ε3 allele (ApoE3), or the protective ε2 allele (ApoE2). ApoE transports cholesterol to cells via lipoprotein receptors through the endosome, where they recycle back to
the membrane or shuttle to the lysosome for degradation. Initial studies in cell lines found that endocytosed particles of lipiddated ApoE4 remained in endosomes longer (reviewed in Ref. 31). The lipidation of ApoE4 is also less efficient than ApoE3. Of note, enhancing ApoE4 lipidation by stimulating the activity of the astrocytic ABCA1 could actually rescue known behavior deficit in ApoE4 knock-in mice (82–84).

In central and peripheral synapses, ApoE is known to bind the low-density lipoprotein receptor-related protein 1 and 4 (Lrp1 and Lrp4) as well as ApoER2 and VLDLR. In a study from our laboratory, we demonstrated that exogenous ApoE4 sequesters neuronal ApoER2 and glutamate receptors in the recycling endosome (85) and endogenous ApoE4 reduced the protective effect of Reelin against Aβ-induced synaptic suppression (86, 87) (Fig. 3G). This ApoE4-mediated ApoER2 sequestration was recapitulated in cells transfected with ApoER2 and APP (67), resulting in enhanced Aβ formation. This increased amyloidogenic processing of APP by ApoE4 required the cytosolic adaptor X11α/β, which binds to the NPXY motif of APP and the alternatively spliced proline-rich insert of ApoER2, leading to enhanced co-endocytosis of the receptors (67). Without X11α/β, ApoER2 actually reduces amyloidogenic processing of APP. Reelin can interrupt this interaction between X11α/β and ApoER2 (68), indicating another protective role of Reelin against Aβ toxicity.

Studies exploring the pathology of AD in both human patients and mouse models have unveiled multiple paths that could repress Reelin signaling. The numbers of Reelin-expressing cells are reduced in the entorhinal cortex, where the earliest signs of AD pathogenesis emerge, in both an AD mouse model as well as postmortem human AD brains (88). Altered cleavage of Reelin was also found in AD mice as well as postmortem brain tissue and the cerebrospinal fluid of human AD subjects (89). This altered cleavage may enhance the adsorption of Reelin into Aβ plaques (90), which would further exacerbate the deficit in Reelin signaling. Furthermore, alternative splicing deficits observed in both AD mice and human brains leads to reduced inclusion of the proline-rich cytoplasmic domain of ApoER2 (91), which would reduce the ability of Reelin to modulate synaptic strength.

The likelihood that Reelin signaling is in fact repressed in AD is further solidified by evidence of suppressed activity of pathways downstream of Reelin. mTOR activity, which is increased by Reelin signaling (92), is lower in AD mice (93). Reduced Reelin expression in HRM mice exacerbates the accumulation of both Aβ and phosphorylated tau (94), whose production is inhibited by Reelin signaling (Ref. 76 and reviewed in Ref. 31). Similarly, the learning deficits in an AD mouse model are exacerbated by loss of Reelin expression after development (49), further solidifying the protective role of Reelin in AD. Enhancing Reelin signaling by either exogenous supplementation of Reelin (95) or reversing the ApoER2 splicing deficit with antisense oligonucleotides (91) can improve the cognitive performance of AD mice in a murine model of AD.

Schizophrenia and Autism

Genetic linkage analyses implicate Reelin polymorphisms in the pathophysiology of two complex neurodevelopmental disorders, schizophrenia and autism spectrum disorders (ASDs) (reviewed in Ref. 10). Postmortem studies reveal a decrease in the expression of Reelin in schizophrenia and ASD brains as well as the cerebrospinal fluid of autistic subjects (reviewed in Refs. 10, 22, and 96). Spine density of schizophrenic individuals is reduced, similar to the reduction observed with Reelin deficiency (reviewed in Refs. 10 and 22). Interestingly, expression of downstream signaling partners is also altered in postmortem ASD brains, with reduced Dab1 expression and increased VLDLR (96). The time and place at which Reelin signaling is reduced may prove to be the deciding factor for the extent of cognitive impact that defective Reelin signaling may have (97). Many parallels have been drawn between the pathology of synaptic dysfunction and behavior in the HRM and schizophrenia and ASD phenotypes (reviewed extensively in Ref. 20).

Concluding Remarks

The implication of Reelin in a variety of neurological conditions is intriguing, with the most obvious common thread being reduced Reelin signaling during development and at the synapse. Considering the multitude of modulatory mechanisms by which Reelin alters brain function during development and in the adult CNS, the diversity of pathologies linked to faulty Reelin signaling is not surprising. Because of the vast role of Reelin throughout the brain at all ages, future investigation of suspected deficits in Reelin signaling linked to a disease should pay special attention to the spatial and temporal appearance of these deficits. Clinical application of targeted therapies like the antisense oligonucleotide-mediated reversal of ApoER2 splicing deficits will require understanding not only how disease-associated abnormalities in Reelin or associated downstream effectors contribute to disease but also when and where. A convincing example of the benefit of this approach is a study that focused on Reelin expression in the entorhinal cortex and hippocampus. This focus revealed that Reelin-expressing neurons in the entorhinal cortex are especially vulnerable to Aβ toxicity and die off before obvious signs of Aβ accumulation. As the site of the earliest neuronal loss in AD pathogenesis, loss of Reelin-expressing cells at this time and place in both an AD mouse model as well as postmortem human AD brains clarifies how Aβ might instigate AD pathogenesis by reducing Reelin levels and increasing the vulnerability of synapses to the toxic effects of Aβ (88). As both schizophrenia and autism are believed to arise from early neurodevelopmental deficits, special attention should be given to the effect of genetically associated Reelin mutations during development: a time at which Reelin is critical for neuronal migration and the formation of axons and dendrites as well as the maturation of the synapses formed between them.

Intriguingly, recent studies have thrown a spotlight on novel functions of Reelin expressed in the periphery (98) that are independent of its roles in the CNS, which we have reviewed in depth here. These recent findings have demonstrated that Reelin controls inflammatory responses in the vascular wall or colon, respectively (99, 100). To date, there is no known inflammatory role of Reelin in the CNS, and these newly uncovered peripheral inflammatory actions raise the possibility that Reelin
may also play a role in inflammatory syndromes of the CNS, such as multiple sclerosis.

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