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Dysplasia Type Ia, Ib and Hippocampal Sclerosis: Is Reelin the Missing Link?

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Temporal Lobe Epilepsy and Dysplasia Type IIIa

Abnormal radial and/or tangential cortical lamination in the temporal lobe cortex associated to Hippocampal Sclerosis (HS) is now classified as focal cortical dysplasia (FCD) type IIIa in the current ILAE FCD classification. In these cases, the temporal cortex may show architectural abnormalities or hypertrophic neurons outside layer V. Five variants of FCD type IIIa have been recognized: HS with architectural abnormalities in the temporal lobe; HS with Temporal Lobe Sclerosis (TLS), HS with TLS and heterotopic neurons in subcortical white matter, HS with TLS and small "lentiform" heterotopias in subcortical white matter; and HS without TLS but with small "lentiform" subcortical heterotopias [1]. One of these types of histological features is frequently found in specimens of patients with temporal lobe epilepsy.

Temporal lobe epilepsy due to dysplasia type IIIa is a common epileptic disorder and a common cause for refractory seizures [2]. Also, the patients with temporal lobe epilepsy can suffered from depressive, psychotic disorders, visual or verbal memory disturbances leading to poor quality of life [3].

A great majority of patients with TLE due to HS reports an initial precipitating injury before six years of age (called first hit). After that, disabling seizures that evolve to intractability appears months or years letter. For these patients, standard temporal lobectomy has become the most effective treatment [4].

Cerebral specimens obtained throughout this procedure reveal a wide and variable immunohistochemistry features such as: neuronal loss in CA1, CA3, CA4 hippocampal regions, astrogliosis, granular cell dispersion in dentate gyrus and cortical disorganization without cytomegalic or balloon cells [5].

In spite of well-known natural history, clinical presentation and histological features of this epileptic syndrome, little is known about the molecular mechanism that causes this clinic and histopathological disorder. Either, it is understood the relation among the first hit, the second hit, TLE and histopathological features.

The possible role of Reelin

Recently, experimental investigations have reported the roll of the glycoprotein, called Reelin, in the central nervous system development and in cognitive function in mice models. Reelin plays an important role in neuroblast´s migration, cortical lamination, and dendrites orientation. It represents a stop signal for migration. Knockout mice for Reelin gen develop a special phenotype characterized by cortical disorganization and abnormal dendrite orientation. The Reelin role in central nervous system is not limited to the developmental period. Adult knockout mice for Reelin gen have also severe impairment in learning and visuo-spatial memory and it is said that Reelin participated in cortical maintenance [6-10].

Some of the above mentioned pathologic features have been demonstrated in specimens of surgical treated patients who have been suffering from temporal lobe epilepsy. It is interesting that inmuno-histopathology studies in adult patients with temporal lobe epilepsy due to dysplasia type IIIa have showed a low percentage of Reelin positive neurons in temporal neocortex and in the sclerotic hippocampus. Also severe granular cells dispersion in dentate gyrus has been associated with Reelin deficiency [11,12]. Abnormal neurogenesis and neurons' migration in hippocampus have been documented in adult Reelin deficient mice. One study carried out by Haas CA et al., in patients with TLE caused by HS, have demonstrated a similar inverse correlation but between Reelin mRNA expression and granular cells dispersion [13]. These results suggest that Reelin deficits (due to transcription or translational alteration) may explain most of the histopathological features described in dysplasia type IIIa.

How Reelin mediate these changes?

It is thought Reelin plays an important role changing cell morphology. That changes may be observed in migrating neurons, growing axons cones and dendrites process [14]. This suggests that dynamic changes in cell cytoskeleton should be guaranteed to cell achieves this function. It is well known that actin cytosketelon play a notable roll building membrane protrusions. The stability of this cell protrusion is kept by the stabilization of actin protein. The cofilin mediated depolymerization destabilizes the actin skeleton and thus, plasma membrane protrusions. The ability of cofilin to depolymerize F-actin is inhibited by phosphorylation at serine residue 3 of cofilina mediated by LIM kinase-1 activity [LIMK1 (LIMK) and LIM Kinase-2 are actin-binding kinase that phosphorilates members of the $D3/ cofilin family] [15-17]. In mutant mice for Reelin gen, the level of phosphorylated cofilin (p-cofilin) was reduced leading to an increased in the ability to depolymerize actin skeleton and then enhance the ability for reorganization of the actin cytoskeleton. According to that, pyramidal cell dendrites go on ascending uniformly. Supporting that point of view, apical pyramidal cell dendrites lost their characteristic vertical orientation and run to different way in mice Reelin mutants [18].

Cortical structure and lamination are also achieved by a curious mechanism called, somatic translocation. During this process, neurons have to migrate by somatic translocation past their predecessor. Due to Reelin deficiency, the destabilization of actin skeleton the neurons are

unable to migrate by this mechanism resulting in an abnormal layering of the cerebral cortex [19]. This role has been confirmed in vitro where neurons showed a different organization and orientation of their superficial process, depending on the concentration of Reelin molecule in the environment [17]. Thus, the neurons prolongations become stable over time where neurons process encounter Reelin substrate, if not their process changes the position, increased motility and cones and lamellipodia appear. The motility increased of neuronal process that grew-up in environment without Reelin, is accompanied by decreased immunoreactivity for p-cofilin [17].

Are there some effects on the structural organization of some cortical structures in Reelin deficiency neurons during adulthood?

Neurons in dentate gyrus are a well model to answer this question. In molecular layer (ML) of dentate gyrus there is a Reelin gradient. This gradient acts on the granule cells keeping them as a densely packed layer. Reelin prevents proteolysis of NICD (Notch intracellular domain) via Dab1 (disabled-1) signaling. Notch signaling, like cofilin phosphorylation, leads to stopping of process growth and stabilizing of the neuronal network. Then, Notch inhibition may results in migration defects mirroring the phenotype induced by Reelin deficiency. It is know that this functional pathway is inhibited by Dab1 degradation, a process mediated by E3 ubiquitin ligase component Cullin 5 (Cul5). Ubiquitination occurs only if Dab1 has been phosphorilated. Again Reelin seem to be important to inhibit overgrown and cortical disorganization [20].

When Reelin activity is lacking, there is increased motility of the DG granule cells, which then move to the ML causing granule cell dispersion. Reelin deficiency/Notch inhibition lead to dendrites of granular cells become not stabilized or not anchored to the marginal zone and show growth cones and lamellipodia [20].

One question arises from this evidence. Have Reelin some role in adult neurons?

Experiments using Bromo-deoxyuridine (BrdU) (a thymidine analog that is used in cell proliferation studies because it is incorporated into the DNA during DNA synthesis making possible to differentiate newborn from adult cell), has demonstrated that the granule cells, invading the ML, in animal models with Reelin deficiency were not, newborn cells but well diferentiated adult neurons [21]. These findings support the role of Reelin deficiency in the destabilization of cortical architecture and pathological plasticity in the mature brain.

Other important aspect of cortical organization, it is the normal detachment of migrating neurons from the radial glial fiber during cortical lamination. It has been also showed that Reelin induces detachment of the migrating neuron from the radial glial fiber. This function is mediated by integrins (α 3 β 1- integrins). In the Reelin deficiency mice neurons, it continues migrating because the detachment fails [22].

All of the above explained phenomenons could account in patients with temporal lobe epilepsy due to dysplasia type IIIa, and those facts arise the following questions what are yet unsolved: is Reelin deficiency one of the causes of dysplasia type IIIa? Can dysplasia type IIIa be resulted of cross talking of Reelin and Notch signaling in patients who are not deficient for Reelin molecule? What are the signaling cascades that control the maintenance of brain architecture keeping a balance between plasticity and stability? Could have Reelin such a stabilizing function in the human brain?

It remains also to be shown to what extent decreased Reelin expression and aberrant neuronal plasticity contribute to mechanisms underlying cortical disorganization predisposing to epileptogenesis. We need to investigate the conditions under which Reelin expression is altered, whether such secondary network changes take place in patients with TLE in response to decreased Reelin signaling and how they can contribute to disease progression and outcomes. All of the above mentioned aspects could be target of studies aiming to looking for antiepileptogenic drugs or medications that blockages´ disease progression.

Should we study Reelin molecule or it fragments? Is Reelin proteolysis, other target, to investigate?

Specifically, in patients with temporal lobe epilepsy due to dysplasia type IIIa, Marucci et al., reported that about 20% of cortical neurons and 13.4 % of hippocampal neurons were positive for Reelin antibody, whereas around 53.3% of cortical neurons and 86.6% of hippocampal neurons were positive for anti-Reelin antibody in patients suffering from hipocampal sclerosis without cortical dysplasia. Although significant statistical differences were found between groups related to the presence of positive anti-Reelin neurons, these features might suggest that Reelin is not the only molecular pathway involved in the pathogenesis of dysplasia type IIIa. It is important to mention that, in this study, the possibility of seizures and drugs may lead to a decreased in expression of Reelin in the hippocampus neurons was rule out, due to, the results were gathered comparing two groups of patients with TLE. Thus, the dysplasia and not the epilepsy phenotype can be related to changes in Reelin. Nevertheless, the pathophysiology of cortical dysplasia induced epilepsy leading changes in Reelin expression cannot be adequately rule out. However, the quantification of Reelin positive neurons in cerebral specimens of two groups of patients (one with cytoarquitectural abnormalities, cortical dyslamination without epilepsy and other with dysplasia type IIIa and epilepsy) may be needed to answer this question equivocally. Nevertheless, with these results the authors concluded that in the cases positive for anti-Reelin antibody, the Reelin pathway was probably normal and they proposed that doublecortin or others molecules, would act to produce cortical and hippocampal alterations typical of dysplasia type IIIa. Taking into account these commentaries we can said that in cases like that, (TLE due to dysplasia type IIIa-Reelin positive neurons), a common pathogenic link could not be demonstrated and we should not use the name of dysplasia type IIIa in these cases [23].

This point of view can be misleading taking into account the new investigations related posttranslational processing of Reelin. In the cited study, Marucci et al., evaluated the whole Reelin molecule but not the specific proteolysis´s fragments that in fact, are the functional part of Reelin molecule [23]. As Marucci et al., stained temporal cortex sections with anti-Reelin (CHEMICON, clone 142, dilution 1:1,000) antisera [23], the specificity of antigen and antibody recognition limited the recognition of others amino-acid sequences in Reelin molecule. Then, they could not rule out both, if positive Reelin neurons were also dysfunctional Reelin molecule, or truncate Reelin molecules where some different fragments did not recognize by the antibody were missed or with some structural modifications. These methodological problems could explain why there were positive Reelin neurons in patient with HS and dispersion of the dentate gyrus.

May be, a severe deficiency in posttranslational processing in Reelin can explain the histopathological association between Reelin and dysplasia type IIIa in this group of patients (about 30% of patients). If this is the case, a common pathogenic link cannot be rule out. To elucidate this hypothesis inmunohitochemistry studies, staining cortical and hippocampus specimens with antibodies that recognized different amino-acid sequences or regions in Reelin molecule should be carried out. If it was demonstrated, the problem would be, why are there different isoform of Reelin and if they would or not functional and what would be the roll of alternative splicing?

How have improved new investigations our knowledge about the possible link in between dysplasia type Ia or Ib and hippocampal sclerosis?

I think that posttranslational processing of Reelin is the principal key in the development of temporal lobe epilepsy caused by dysplasia type IIIa. Many facts support my hypothesis. First; Reelin is regulated by the directed proteolysis of extracellular Reelin. Two sites of cleavage have been shown: 1 between repeats 2–3 (R2–3) and 2.- between repeats 6-7. After proteolysis, five fragments can be found. The role and function of each fragment seems to be different [24]. The N-R2 fragment has been shown to bind to α 3 β 1- integrins during cells migration (this fragment acts during embryogenesis), R3-6 fragment interacts with the very low density lipoprotein receptor (VLDLR) and Apolipoprotein E receptors (ApoER) and it is responsible for downstream canonical signals mediated by (Disabled-1) dab1 adaptor pathway (fragment that acts during embryogenesis and in postnatal life), the C-terminal region (R7-C) has been suggested to be involved in Reelin secretion, tertiary conformation and signaling efficacy [25]. To better understand the signals pathway of Reelin, due to this theme is out the scope of this commentary, we recommend to read the paper entitled "Canonical and Non-canonical Reelin Signaling "published by Hans H. Bock and Petra May in Frontier in cellular Neuroscience [26].

Posttranslational studies have revolutionized our conception about the function of Reelin and its fragments. Thus, Takao K et al., described the importance of Reelin C-Terminal Region, not only during development, but also in the maintenance of cerebral cortex during postnatal life. They emphasized recently, that the Reelin C-terminal region is critical in postnatal cerebral cortex development but not in embryonic stages. Knockout mice for Reelin C-terminal region (KO–RCT mice) have a grossly normal cortex but cerebral cortex became narrower in postnatal period compared with normal littermates. Furthermore, they found that CA1 pyramidal cell layers were split into two layers in the hippocampus and dentate granule cell layers were more disperse compared with normal littermates. They also observed that KO-RCT mice had the primitive cortical zone disorganized with blurred border among different cortical layers. These results indicate that Reelin CTR is required for correct maintenance of the cerebral cortex organization in postnatal life [24,25,27]. Second: It has described that the deficiency of C-terminal region of Reelin affects dendrite orientation and branching. After morphologic studies in transfected neurons lacking Reelin C terminal region secretion, have been found that apical dendrites were disoriented or poorly branched, the total apical dendrite length and the number of apical dendrite branching points were significantly reduced. The authors concluded that Reelin CTR is required for proper orientation and branching of apical dendrites and for the positioning of neurons in the postnatal cerebral cortex [25,28]. Third, the authors have documented that Reelin CTR binds to neuronal cell membrane yet when the binding to canonical Reelin receptors was excluded. Probably these results suggest the presence of a different receptor that binds only to the Reelin CTR [25]. Fourth, the effect of Reelin requires the existence of long term potentiation, without it, the adequate cleavage in CTR region would not take place [25]. This feature could explain why the hippocampus is where Reelin exerts primary its effects and also, the first hit hypothesis in the hippocampal sclerosis development. According to the two hit hypothesis, in the development of hippocampal sclerosis, fibril convulsion, meningoencefalitis, slight head trauma, slight hypoxia can initializing the epileptogenesis process involved disabling seizures [29]. According to Reelin hypothesis's, the deficiency in the canonical pathway could explain the first hit, lowering the convulsive threshold and them, contributing to epileptogenesis [30].

Studies carried out by Korn et al., support this notion. They found that conditional Dab1 deletion in Mice reduces seizure threshold [30,31]. But what was more interesting is that they also found that Dab1-deficient mice have altered seizure susceptibility and developed an interictal electroencephalogram pattern characterized by frequents spikes and waves. Dab1-deficient mice did not have spontaneous seizures but had reduced latency to pilocarpine-induced status epilepticus. After chemoconvulsant treatment, around 90% of mice deficient for Dab1 developed generalized motor convulsions with tonic-clonic movements, rearing, and falling [30]. Dab1-deficient mice showed a severe neurogenesis alteration, decreased of immature neurons and severe cytoarquitectural changes in dentate gyrus [30]. In the above mentioned paper, the authors thought that this "abnormal neurogenesis" causes a compensatory plasticity within the Dentate Gyrus lacking the inhibition of the pre-existing Dentate Granular Cells. These changes have been demonstrated in animal models of TLE subject to prolonged seizures [32], suggesting that patients with some abnormal signaling in the Reelin pathway may develop chronic epilepsy.

Taking into consideration all the above facts it is plausible that Reelin C-Terminal region plays an important pathogenic roll in the developing of temporal lobe epilepsy cause by dysplasia type IIIa. Thus, new investigations should be directed to test this hypothesis in patients suffering from TLE due to FCD type IIIa. In other hand, proteolysis of Reelin makes it easily to diffuse far away from the sites of secretion through extracellular matrix to different cortical layers. It is important to explore other unknown receptors for small fragments gathering throughout proteolysis mechanism. It important to evaluate if Reelin fragments can be find in the blood or in the cerebrospinal fluid. If its serves as biomarker of abnormal Reelin cleavage, dysplasia type IIIa, disease progression or intractability. Doing that, we can not only improve our knowledge about molecular basis of epilepsy but also, we can find molecular targets needed to develop anti-epileptogenic medications.

Conclusion

If we evaluate Reelin's effects on postnatal cortical layer maintenance, synaptic plasticity, hippocampus and dentate gyrus neurogenesis, we could explain not only the association between hippocampal sclerosis and cortical dysplasia type Ia and Ib (dysplasia type IIIa) but also to know part of the natural history of temporal lobe epilepsy, the subjacent theory of two hit hypothesis, develop new antiepileptogenic drugs and diseases progression biomarkers.

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