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Assessment of expression of RELN signaling pathway in multiple sclerosis patients

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ABSTRACT

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system. Nearly 85% of MS patients are recognized with relapsing-remitting MS (RRMS), a typical clinical course of disease which is distinguished by several episodes of relapses, separated by remissions of neurological impairment. Failure of repair mechanisms is a main factor in progression of neurological dysfunction in MS. Several lines of evidence suggest that Reelin (RELN) signaling pathway can contribute in the regulation of repair mechanisms in MS patients. In the present study, we assessed expression levels of *RELN* and *Disabled-1* (*DAB1*), two key genes in RELN signaling pathway, in peripheral blood of 50 RRMS patients and 50 matched healthy subjects. *RELN* was significantly down-regulated in total MS patients, and total female patients compared with the matched controls. However, no statistically significant difference was found in *DAB1* mRNA expression between MS patients and controls. Furthermore, considerable correlations were detected between expression levels of *RELN* and *DAB1* in the patients group. There were no significant correlations between expression levels of genes and EDSS, disease duration or age at onset. Our study provides evidences for the role of RELN signaling pathway in the pathogenesis of MS. Further studies are required to clarify the exact clinical significance of this pathway in MS patients.

1. Introduction

Multiple sclerosis (MS) is an autoimmune-neurodegenerative disease that attacks the central nervous system (CNS). MS is characterized by demyelination, inflammation, axonal loss and developing neurologic dysfunction in the CNS (Kuhlmann et al., 2002). It is estimated that MS affects almost 2.3 million people throughout the world and 400,000 people in the United States (Capkun et al., 2015). Increased incidence rate of MS in identical twins and 70% discordance rate in monozygotic twins suggests that both genetic and environmental factors participate in the complex etiology of MS (Sadovnick et al., 1993; Ascherio and Munger, 2016).

Although the exact cause of MS is not clear, changes in dozens of genes are believed to be related to the risk of MS. Several investigations have examined candidate genes in MS. One hopeful category of candidates encodes proteins associated with the relevant neurological and neurodegenerative diseases. Studies on various neurodegenerative disorders including schizophrenia, autism, bipolar disorder, Alzheimer's disease, major depression, and lissencephaly have demonstrated an impaired RELN signaling pathway in the brain (Folsom and Fatemi, 2013).

Furthermore, intrinsic repair mechanisms and damaging immunologic processes are two contradictory factors, that are involved in the determination of the degree of neurological disability and final outcome in MS (Correale et al., 2016). The evidences have provided clues about the role of the Reelin (RELN) signaling pathway in repair mechanisms in MS. RELN, an extracellular matrix protein and its key intracellular adaptor, Disabled 1 (DAB1) are two critical components of this pathway. Both proteins are involved in accurate neuronal positioning during the development of brain. RELN pathway has a pivotal

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role in regulating migration, and cortical lamination (Howell et al., 1999). Furthermore, recent studies in MS have clarified that inflammation induces synaptic dysfunction, especially in the early phases of the disease (Mori et al., 2011). Alteration in the efficacy of synaptic function is reflected in synaptic plasticity. Long-term potentiation (LTP) and long-term depression (LTD) are two principal forms of synaptic plasticity. LTP and LTD correspond to a long-lasting attenuation and a long-lasting strengthening of synaptic efficacy, respectively (Bliss and Cooke, 2011). RELN pathway also has a considerable role in the regulation of synaptic function and plasticity (Weeber et al., 2002; Peineau et al., 2007). Moreover, RELN has the ability to adjust the axonal transport through the suppression of tau (a microtubule-associated protein) hyperphosphorylation and the ability to affect the regulation of remyelination, a key regenerative process for reformation of myelin sheath on demyelinated axons, by interaction with bidirectional EphB/Ephrin-B signaling pathway (Beffert et al., 2002; Sentürk et al., 2011; Bouché et al., 2013). Remyelination and synaptic plasticity are two restorative and compensating mechanisms in MS (Ksiazek-Winiarek et al., 2015).

Taken together, we hypothesized that RELN pathway might be involved in MS development and disease course. The aim of our study was to analyze alterations in *RELN* and *DAB1* expression patterns in Relapsing Remitting MS (RRMS) patients in comparison with healthy subjects. The study also attempted to assess the relationship between expression levels of these genes and clinical characteristic of patients such as gender, age of onset, disease duration and Expanded Disability Status Scale of Kurtzke (EDSS) score.

2. Materials and methods

2.1. Study participants

We performed a case–control study of 50 RRMS patients (38 females and 12 males, mean age: 39.6 ± 1.28, age at onset: 30.82 ± 1.39, duration of disease: 8.76 ± 0.89, EDSS: 2.38 ± 0.16) and 50 age and gender matched healthy controls (37 females and 13 males, mean age: 47.06 ± 14.65). Patients were referred to Imam Hussein hospital of Tehran, Tehran, Iran. A neurologist has confirmed the diagnosis of RRMS according to the revised McDonald criteria (Polman et al., 2011). Based on the significant role of HLA- DRB1∗15 in the pathogenesis of MS, in order to have a more pure selection of patients, only HLA-DRB1*15 negative patients were included in the current study. HLA typing had been carried out in a larger cohort of patients previously (Mazdeh et al., 2016). In addition, all of the patients took 20 μg of interferon-beta (IFN-β) three times a week (CinnoVex, Cinagene Company, Iran) and were clinically responders to IFN-β (Sayad et al., 2017; Rahimi et al., 2018). The other exclusion criteria were smoking history and insufficient levels of vitamin D. This study was approved by the local Ethics Committee of Tabriz University of Medical Science. Informed consent was obtained from all participants.

2.2. Blood sampling and RNA extraction

For detection of *RELN* and *DAB1* transcripts, 5 ml of peripheral blood was collected from all participants. Total RNA was isolated using GeneAll HybridR™ blood RNA extraction kit (cat No. 305-101). RNA concentration and quality were assessed by using Nanodrop equipment (Thermo Scientific). DNase I treatment was carried out to remove DNA Contamination, and RNA sample were stored at −80 °C eventually.

2.3. Quantitative real time PCR

RNA was converted to cDNA by using Hyper script first strand synthesis kit (GeneAll, Korea, 601-005). *HPRT1* was selected as the reference gene to normalize the expression level of genes. Specific probes and primers for the *RELN*, *DAB1* and *HPRT1* were designed by Allele ID 7 (Premier Biosoft, Palo Alto, USA). The primers and probes sequences and PCR product length are shown in Table 1. Real-time quantitative polymerase chain reaction was performed by using Applied Biosystems TaqMan® Universal PCR Master Mix (PN: 4304449) in Corbett Rotor gene 6000 instrument (Corbett Life Science).

Table 1
The primers and probes sequences and PCR product length.

Gene name	Primer and probe sequence	Primer and probe length	Product length
HPRT1	F: AGCCTAAGATGAGAGTTC R: CACAGAACTAGAACATTGATA FAM -CATCTGGAGTCCTATTGACATCGC-TAMRA	18 21 24	88
RELN	F: AGTGTCAGCTTGGAATTTTCTACC R: GGTCCAGCACAGATCTCAGG FAM-CGCTCCTGGTCCCTCCTTCACACT-TAMRA	24 20 24	86
DAB1	F: ACGTTTAAGGATTTCCAGATGGC R: GTCAAAGTCATCACAGTCGTCTG FAM -AGCCTCCGCCCGTGCCCTCC-TAMRA	23 23 20	150

2.4. Statistical methods

To compare data acquired from case and control groups, independent *t*-test and analysis of covariance (The one-way ANCOVA) were applied for assessment of differences between the patients and healthy subjects and for controlling the effects of age and sex respectively. In order to identify the correlation between variables, Spearman correlation analysis was applied. P value less than 0.05 was considered as statistically significant. Data were analyzed using the SPSS18 statistical package (Chicago, IL, USA).

3. Results

3.1. Demographic and clinical characteristics of study participants

Clinical and demographic characteristics of all study participants are displayed in Table 2.

3.2. Expression analysis of RELN in MS patients compared with healthy subjects

RELN expression was significantly reduced in MS female patients compared with healthy controls (Relative Expression = −0.64, P-value = 0.029). The detailed information of *RELN* expression in distinct sex-based subgroups is displayed in Table 3.

Quantile regression analysis illustrated that after adjustment of the effects of age and sex, there was a notable difference in *RELN* relative expression between patients and controls (P = 0.006) (Table 4).

Table 2
Clinical and demographic characteristics of all study participants (EDSS: Expanded Disability Status Scale, SE: Standard Error).

Variables	MS patients	Healthy subjects
Female/male [no. (%)]	38(76%)/12(24%)	37(74%)/13(26%)
Age (mean ± SE, years)	39.6 ± 1.28	47.06 ± 2.07
Age range (years)	20-62	25-70
Age of onset (mean ± SE, years)	30.82 ± 1.39	–
Duration (mean ± SE, years)	8.76 ± 0.89	–
EDSS (mean ± SE)	2.38 ± 0.16	–
Progression index	3.58 ± 0.56	–

Table 3
Relative expression of *RELN* in distinct sex-based subgroups of MS patients and healthy subjects.

Study groups	Controls Number	Patients Number	Relative Expression [a]	SE	P-value	95% CrI[b]
Total	50	50	−0.64	0.24	0.008	[−1.11, −0.17]
Males	13	12	−0.37	0.64	0.22	[−1.62, 0.95]
Females	37	38	−0.64	0.27	0.029	[−1.19, −0.12]

[a] Relative Expression: $(LN(Efficiency\text{-}(deltaCt))_{case}\text{-}(LN(Efficiency\text{-}(deltaCt))_{control}$.
[b] 95% credible intervals.

Table 4
Quantile regression results of *RELN* expression with controlling the effects of the age and sex.

Variable	Beta	SE	t	P-value	95% CI
Group	−0.82	0.29	−2.83	0.006	[−1.39, −0.24]
Sex	−0.18	0.23	−0.78	0.435	[−0.65, 0.28]
Age	0.01	0.01	0.96	0.341	[−0.01, 0.04]
Sex*group	−0.98	0.49	−1.99	0.049	[−1.95, −0.004]

3.3. Correlation analysis between expression of RELN gene and other variables

Afterward, we evaluated the correlations between expression level of *RELN* in total study participants as well as distinct subgroups of cases and controls. In addition, we assessed the correlations between transcript level of *RELN* gene and age in patient subgroups. The Spearman correlation analysis results are displayed in Table 5. *RELN* expression was correlated with age in male subjects. Moreeover, expression of *RELN* was correlated with expression of *DAB1* in both cases and controls and in female subjects but not male subjects.

3.4. Expression analysis of DAB1 in MS patients compared with healthy subjects

There was no statistically significant difference in *DAB1* expression level between MS patients and healthy controls (P value = 0.96, 95% CI = −1.1 to 0.32) (Table 6). Besides, *Dab1* expression levels were not correlated with sex and age ($P > 0.05$).

3.5. Correlation between expression levels of genes and clinical characteristics of patients

There was no correlation between *RELN* or *DAB1* expressions and age of patients (r = 0.18, P = 0.074 and r = 0.101, P = 0.316 respectively) (Figs. 1 and 2 respectively).

Moreover, expressions of genes were not correlated with age at disease onset, disease duration, or EDSS either in total patients (Fig. 3) or in sex-based subgroups (Table 7). No significant correlation was found between expression of genes and progression index (r = −0.11, P = 0.433 and r = −0.0.42 and P = 0.772 for *RELN* and *DAB1* genes respectively).

Table 5
Spearman correlation between *RELN* and other variables by sex and group.

		Age	*DAB1*
Group	Case	0.038	0.501**
	Control	0.212	0.329*
Gender	Male	0.399*	0.336
	Female	0.108	0.403**

** Correlation is significant at the 0.01 level.
* Correlation is significant at the 0.05 level.

4. Discussion and conclusion

New researches on the pathophysiological study of neurodegenerative diseases have changed from studying disease-causing proteins to identify pathways and protein complexes that may be related to the pathogenesis of the disease. In this pilot study, we measured the *RELN* and *DAB1* expression in peripheral blood of MS patients and healthy controls. We discovered a total *RELN* down-regulation and a significant correlation between *RELN* and *DAB1* in peripheral blood of RRMS patients. There was no statistically difference between the expression of its downstream target i.e. *DAB1* in MS patient and healthy controls. Furthermore, no significant correlation has been detected between expression levels of genes and demographic and clinical characteristics of MS patient including sex, age at onset, duration of disease, EDSS score and progression index.

Due to unaccessibility of brain tissues for expression analysis, we used peripheral blood as an available source in this regard. Based on the mentioned limitation and the results of a previous study regarding high level similarity between transcriptomes of peripheral blood and brain (Liew et al., 2006), perpheral blood can be used as a source of biomarker discovery for CNS diseases.

Some similar phenotypic traits and also coexistence of a number of neurodegenerative diseases and MS, propose that there are probable overlaps in the pathogenic mechanisms of these disorders. Abnormal expressions of *RELN* and *DAB1* have been observed in autism (Fatemi et al., 2005). In addition, changes in blood levels of RELN have been observed in patients suffering from schizophrenia, major depression, and bipolar disorder (Fatemi et al., 2000). Furthermore, as an initial symptom, a reduction in the level of RELN expression has been reported in patients with Alzheimer's disease (Herring et al., 2012). Activation of RELN signaling pathway alters the synaptic efficacy and synaptic plasticity. Regulation of axonal transport by changing the dynamics of microtubules can be considered as another important function of the RELN signaling pathway. Moreover, there seems to be a correlation between RELN and the Bidirectional EphB/Ephrin-B pathway (Sentürk et al., 2011; Lane-Donovan and Herz, 2017). Thus, based on these pieces of evidences, one may hypothesize that changes in the expression of RELN and its primary adapter, DAB1, can contribute to the pathogenesis of MS.

Various studies conducted on animal models have suggested a correlation between a decrease in the level of RELN expression and possible defects in LTP. RELN overexpression causes a significant increase in the level of LTP responses (Pujadas et al., 2010). In addition, previous studies have indicated that RELN induces Src family kinases (SFKs) and DAB1 (Bock and May, 2016). The active SFKs prevent NMDA-induced endocytosis by the phosphorylation of NMDA Receptors (NMDARs), thereby increasing the flow of $Ca2+$ into the cell, which consequently strengthens the LTP (Chen et al., 2005). Evidences suggest that LTP is preserved in RRMS patients while being ineffective in progressive MS patients. Given the crucial role of LTP and LTD in the recovery or relapse phases of MS by neuronal excitability regulation and the critical role of RELN signaling pathway in the regulation of these two mechanisms (Liu et al., 2018), there seems to be a correlation between the changes in the level of RELN expression in MS patients and the regulation of recovery process and overcoming the neurological

Table 6
Relative expression of Dab1 in distinct sex and age subgroups of MS patients and healthy subjects.

Study groups	Control Numbers	Patient Numbers	Relative Expression[a]	SE	P-value	95% CrI[b]
Total	50	50	−0.39	0.36	0.961	[−1.1, 0.32]
Male	13	12	0.96	1.02	0.489	[−1.05, 2.98]
Female	37	38	−0.74	0.42	0.586	[−1.54, 0.06]

[a] Relative Expression: $(LN(Efficiency\text{-}(deltaCt))_{case}\text{-}(LN(Efficiency\text{-}(deltaCt))_{control}$.
[b] 95% credible intervals.

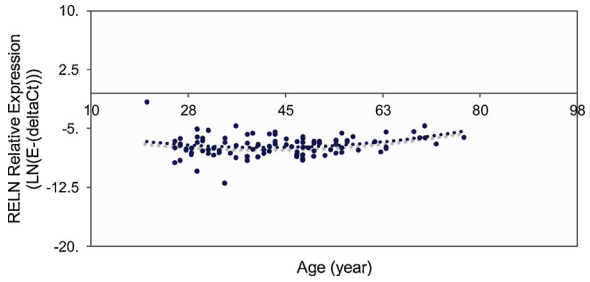

Fig. 1. Correlation between *RELN* and age and age in patients.

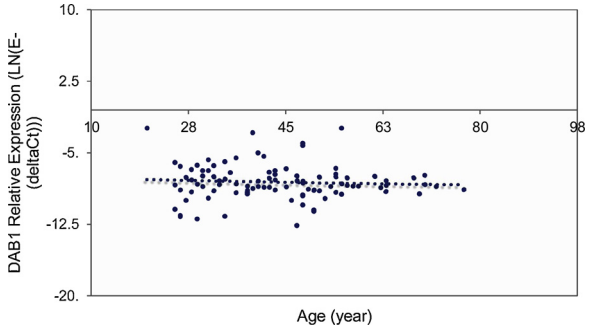

Fig. 2. Correlation between *DAB1* expression and age in patients.

defects.

Additionally, the RELN signaling pathway can play a critical role in regulating the dynamics of microtubules by means of activating the signaling pathway of GSK3β/Akt/PI3K. The RELN signaling prevents the hyperphosphorylation of tau by inhibiting GSK3β. Abnormal tau phosphorylation can be considered as a commonly observed feature of Alzheimer's disease, which may also be present in MS patients (Beffert et al., 2002; Anderson et al., 2008; Kolarova et al., 2012). Therefore, one may reach the conclusion that changes in the level of RELN expression can be associated with the axonal transport disruptions observed in MS patients or other neurodegenerative diseases.

RELN attachment to the extracellular domain of Ephrin Bs is necessary for the phosphorylation of DAB1 (Sentürk et al., 2011). In addition, the attachment of Reelin N-t site to the Eph B receptors can lead to induction of EphB forward signaling pathway (Bouché et al., 2013). Bidirectional EphB/Ephrin-B signaling pathway can play a part in the regulation of remyelination in a way that EphrinB reverse signaling can induce remyelination while EphB forward signaling inhibits myelin sheet formation (Linneberg et al., 2015). Due to a highly possible interaction of Reelin with both Ephrin Bs ligands and EphB receptors, it seems likely that, in addition to affecting the EphB forward signaling pathway, Reelin can also play a role in the EphrinB reverse signaling pathway (Fig. 4).

Since restoration capability is restricted in the CNS injury (Chen and Zheng, 2014), there seems to be a correlation between a decrease in the level of Reelin and the level of disability in patients with RRMS. Although no previous study has assessed expression levels of Reelin and Dab1 in MS patients, a decrease in the expression level of Reelin, and the changes in expression level of Dab1 were reported in other neurologic or psychiatric disorders (Impagnatiello et al., 1998; Fatemi et al., 2005; Torrey et al., 2005).

Studies have revealed that generally the amount of Reelin decreases in adults, however, it may experience an increase in individuals suffering from peripheral nerve injuries (Panteri et al., 2006). In other words, due to a correlation between the Reelin and the restorative and compensatory mechanisms, such as remyelination and synaptic plasticity, it seems that the primary function of Reelin signaling pathway is associated with the regulation of recovery or relapse phases of MS.

Taken together, the observed down-regulation of *RELN* in MS patients might imply a role for it in the pathology of MS. However, it is still not clear whether this disturbance is cause or consequence of MS.

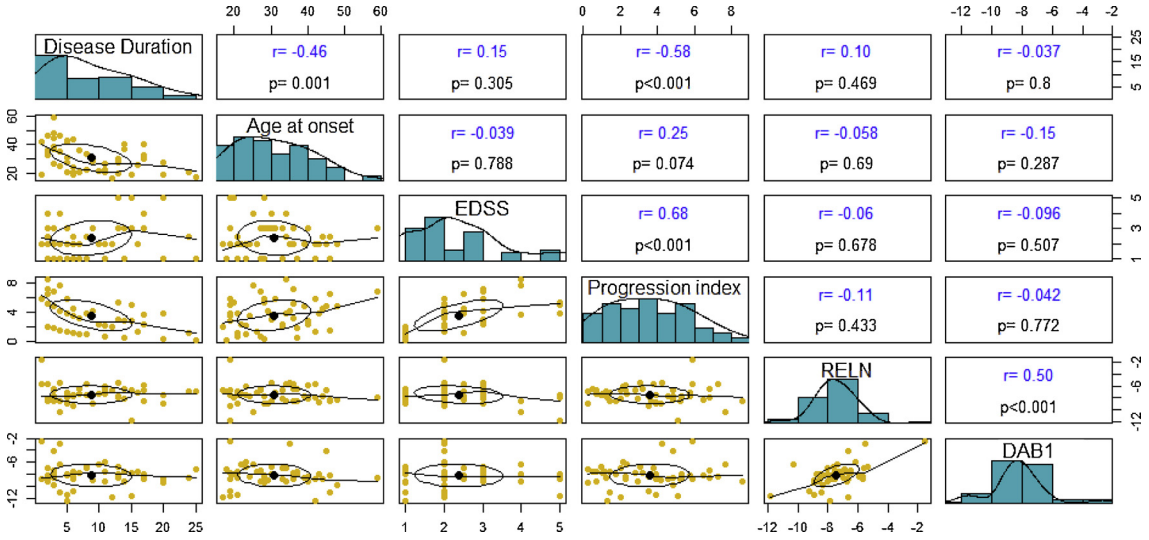

Fig. 3. Correlations between expression levels of genes and patients' data.

Table 7
Correlation between expression of genes and patients' data in sex-based subgroups (Data are presented as r values (P values)).

	RELN expression		*DAB1* expression	
	Male	Female	Male	Female
Disease duration	−0.11 (0.757)	0.19 (0.278)	0.55 (0.066)	0.05 (0.804)
Age at onset	−0.05 (0.88)	−0.07 (0.692)	−0.27 (0.404)	−0.16 (0.342)
EDSS score	−0.47 (0.129)	0.04 (0.842)	−0.28 (0.38)	−0.13 (0.454)

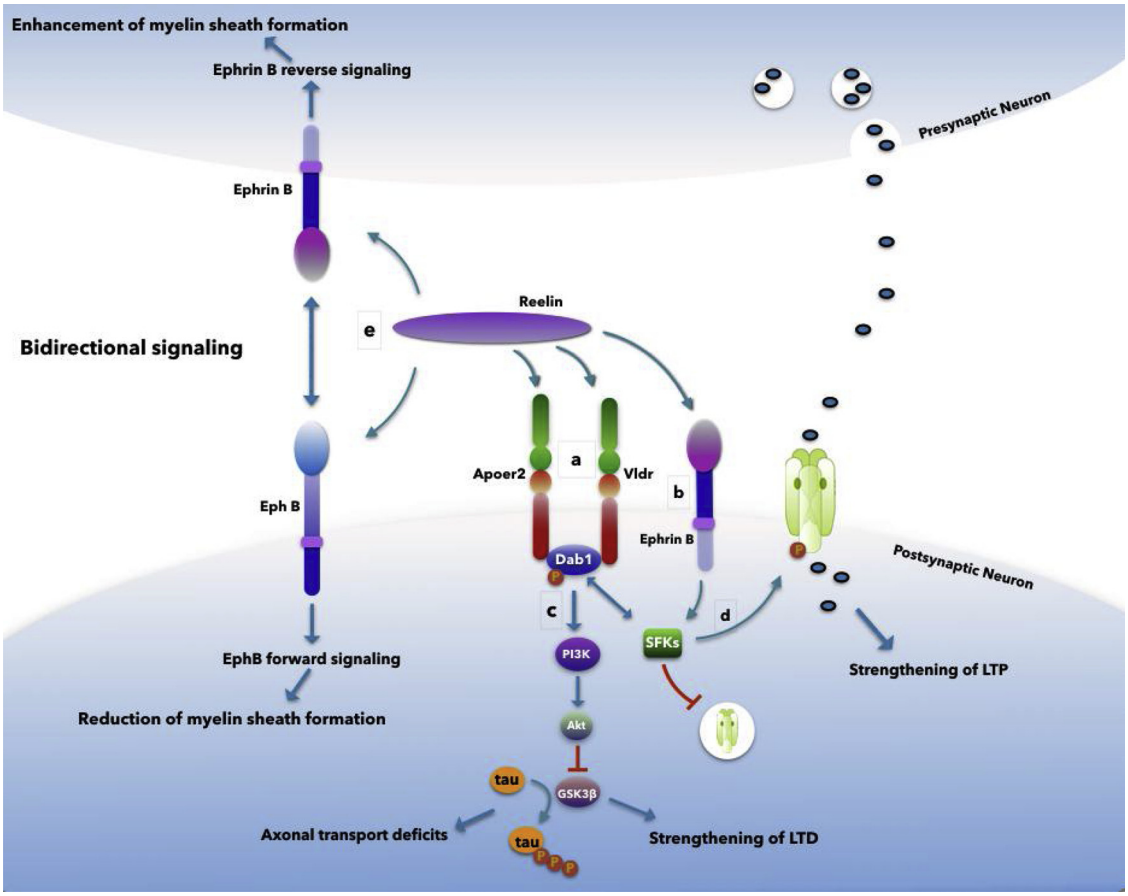

Fig. 4. Important activating signals of RELN signaling pathway related to MS. a. The central fragment of Reelin binds to its two receptors, Vldlr and Apoer2, and induces Dab1 signaling. b. Binding of Reelin to the extracellular domain of ephrin-Bs is required for Dab1 phosphorylation. Ephrin Bs phosphorylate Dab1 by the recruitment and activation of Src Family Kinases (SFKs).c. Dab1 phosphorylation inhibits GSK3β via the NMDA-PI3K-Akt pathway. GSK3β suppression, can inhibit LTD (Long-term depression) and also tau hyper phosphorylation, which in turn prevents the axonal transport defects. d. The active SFKs by NMDA receptor phosphorylation (NMDARs) prevent NMDAR endocytosis, and consequently, increase the flow of Ca + 2 into the neuron and enhance long-term potentiation (LTP). e. Binding of N-terminal region of Reelin to the EphB receptors can induce the EphB forward signaling pathway. The Bidirectional EphB/Ephrin-B pathway plays a role in myelination regulation and it appears that Reelin has a function as an intermediate factor in adjusting the bidirectional EphB/Ephrin-B pathway.

In summary, much more extensive studies are needed in order to shed some light on the precise molecular mechanism of RELN signaling pathway and the associated changes in the expression level of other important genes of this particular pathway in MS patients. Moreover, the small sample size of MS patients, absence of drug-naïve patients as controls and lack of in vitro studies for assessment of the effects of IFN-β on expression of RELN can be regarded as a limitation of this study. Therefore, further studies with a larger sample size should be carried out. Finally, we need further studies at the protein level in order to confirm the results of our study.

Conflict of interest

The authors declare they have no conflict on interest.

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