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Relationship Between Epigenetic Factors and Retrotransposons and the Etiopathogenesis of Neurodegenerative Diseases

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ABSTRACT

The pathogenesis of neurodegenerative diseases is associated with proteopathy and the abnormal aggregation of specific proteins, including amyloid-β and tau protein in Alzheimer's disease, α-synuclein in Parikinson disease, and TDP-43 and FUS in amyotrophic lateral sclerosis. Etiological factors may include viral infections because of the protective functions of the above proteins in relation to specific viruses. In turn, the latter may enhance the expression of retroelements. Another cause of neurodegenerative diseases is physiological aging, as it activates retroelements and is associated with proteopathy of antiviral proteins, which normally suppresses the expression of retroelements. It is assumed that the etiological factors of amyotrophic lateral sclerosis, Alzheimer disease, and Parkinson disease include the associated genetic polymorphisms, most of which localize within intronic and intergenic regions where retroelement genes are located. Thus, the etiological factors of neurodegenerative diseases include genetic predisposition to the excessive activation of retroelements, aging, and viral infections, thus causing pathogenic proteopathy and the aggregation of amyloid-β, tau protein, α-synuclein, TDP-43, and FUS. As a result, these proteins lose their ability to inhibit retroelements by causing their excessive activation and an inflammatory immune response to their transcripts. In turn, the expression products of polymorphic retroelements enhance the production of antiviral proteins and their proteopathy and aggregation. A vicious circle develops that promotes the progression of the condition; this circle may be broken by inhibitors of retroelements and specific microRNAs that may become the basis for targeted therapy for neurodegenerative diseases. As such, these processes do not induce nucleotide DNA sequence damage; rather, they indicate the epigenetic mechanisms of these diseases.

Keywords: α-synuclein; amyloid-β; viruses; microRNA; neurodegenerative diseases; retroelements; tau; TDP-43.

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Взаимосвязь эпигенетических факторов с ретротранспозонами в этиопатогенезе нейродегенеративных болезней

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АННОТАЦИЯ

Патогенез нейродегенеративных болезней связан с протеинопатией и патологической агрегацией специфических белков: при болезни Альцгеймера β-амилоида и тау-белка, при болезни Паркинсона — α-синуклеина, при боковом амиотрофическом склерозе — TDP-43 и FUS. Этиологическими факторами могут служить вирусные инфекции, что обусловлено защитной функцией описанных белков в отношении специфических вирусов. Последние, в свою очередь, способны усиливать экспрессию ретроэлементов. Физиологическое старение также является одной из причин нейродегенеративных болезней, поскольку характеризуется активацией ретроэлементов и протеинопатией перечисленных противовирусных белков, которые в норме подавляют экспрессию ретроэлементов. Этиологическими факторами бокового амиотрофического склероза, болезни Альцгеймера и Паркинсона считаются ассоциированные с ними полиморфизмы в геноме, большинство из которых локализованы в интронных и межгенных областях, где расположены гены ретроэлементов. Таким образом, к этиологическим факторам нейродегенеративных заболеваний относятся генетическая предрасположенность способности ретроэлементов к гиперактивации, старение и вирусные инфекции, под влиянием которых в патогенезе развивается протеинопатия и агрегация β-амилоида, тау-белка, α-синуклеина, TDP-43 и FUS. В результате эти белки утрачивают способность ингибировать ретроэлементы, вызывая их гиперактивацию и воспалительный иммунный ответ на их транскрипты. В свою очередь, продукты экспрессии изменённых вследствие полиморфизма ретроэлементов усиливают продукцию противовирусных белков, их протеинопатию и агрегацию. Развивается способствующий прогрессированию патологии порочный круг, воздействие на который с помощью ингибиторов ретроэлементов и специфических микроРНК может стать основой для таргетной терапии нейродегенеративных заболеваний. Поскольку описанные процессы происходят без повреждений нуклеотидных последовательностей ДНК, это свидетельствует об эпигенетических механизмах данных заболеваний.

Ключевые слова: α-синуклеин; β-амилоид; вирусы; микроРНК; нейродегенеративные болезни; ретроэлементы; тау; TDP-43.

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BACKGROUND

Neurodegenerative diseases (NDDs) are common, chronic, and fatal conditions of the central nervous system. Their risk increases with age, and aging [1–3] and viral infections [4] have been implicated in their etiology. Alzheimer disease (AD) is the most common NDD, affecting 5% of the European population regardless of age and 22.53% of people aged ⩾85 years [1]. The incidence of Parkinson disease (PD) increases from 0.85% in the general population to 1.7% among individuals aged 80–84 years [3]. The average prevalence of amyotrophic lateral sclerosis (ALS) worldwide is 4.42 cases per 100,000 individuals, and this figure increases with age [2]. Among individuals aged 66–90 years, ALS incidence is 22.84 per 100,000 men and 16.05 per 100,000 women [5]. The pathogenesis of these NDDs is associated with the aggregation of specific misfolded proteins into ordered beta-layer-rich and high-molecular-weight fibrils called amyloids. The progression of the pathology is caused by the spread of amyloid fibrils to specific brain regions, which is characteristic of certain diseases [4]. In AD, beta-amyloid (Abeta) fibrils accumulate extracellularly as senile plaques, whereas hyperphosphorylated tau protein accumulates intracellularly as neurofibrillary tangles [1]. In the pathogenesis of PD, dopaminergic neuron degeneration in the substantia nigra of the brain is attributed to alpha-synuclein (alpha-syn) accumulation within these cells, which results in the formation of aggregates known as Lewy bodies [4]. FUS proteinopathy and the formation of TDP-43 protein aggregates in neurons of the central nervous system occur in patients with ALS. This leads to the death of upper and lower motor neurons and skeletal muscle atrophy [6].

During normal aging of the human brain, retroelements (REs), which are deoxyribonucleic acid (DNA) sequences within the human genome, undergo pathological activation. These elements are evolutionarily related to viruses and can move to new loci through the "copy and paste" process [7]. Consequently, RE expression products activate antiviral interferon response and aseptic inflammation in the aging brain [7]. REs occupy almost half of all DNA sequences in the human genome. These include long terminal repeats (LTRs) of REs (9% of the human genome, including human endogenous retrovirus [HERV]). LTR-free REs include long interspersed nuclear elements (LINE) at 21%; short interspersed nuclear elements (SINE), including Alu elements, at 13%; and SINE-variable number tandem repeats-Alu (SVA) at 0.13%, which together comprise a significant portion of the human genome. Moreover, RE genes are primarily found in intronic, regulatory, and intergenic regions [8], where most single-nucleotide polymorphisms (SNPs) associated with multifactorial diseases are located [9]. This pattern is also characteristic of NDDs, as most of the polymorphic loci associated with AD [10], PD [11], and ALS [12], which are etiologic factors of these diseases, are located in intergenic and intronic regions.

According to a recent meta-analysis, 23 different SNPs associated with 15 genes are involved in the development of AD. The most significant associations are observed in polymorphisms within genes such as *CD33*, which encodes a protein that activates protein tyrosine phosphatase; *BIN* (bridging integrator), which encodes a nucleocytoplasmic adaptor protein; and *MTHFR*, which encodes an enzyme that catalyzes the conversion of 5,10-methylenetetrahydrofolate into 5-methyltetrahydrofolate. Additionally, peculiarities in the associations of different SNPs have been observed among patients with AD in different populations [10]. Genome-wide association analyses have identified more than 90 independent risk variants for PD. A large-scale meta-analysis of different populations identified 78 independent loci, including 12 potentially novel ones associated with genes such as *PPP6R2*, which encodes regulatory subunit 2 of protein phosphatase 6 involved in vesicle-mediated transport; *EP300*, which encodes the cellular p300 transcriptional coactivator protein associated with the adenovirus E1A and functions as a histone acetyltransferase; *USP8* and *USP25*, which encode ubiquitin-specific peptidases; *MYLK2*, which encodes myosin light chain kinase 2; *FASN*, which encodes fatty acid synthase; *PIGL*, which encodes an enzyme to catalyze the second step of glycosylphosphatidylinositol biosynthesis; *IRS2*, insulin receptor substrate 2; *SYBU* (syntabulin), a part of the motor-adaptor complex of kinesin, which is crucial in antegrade axonal transport; *ADD1* (adducin), a cytoskeleton protein; *PIK3CA* (phosphatidylinositol 3-kinase); and *MTF2*, a protein that activates methylated histone and transcription corepressor binding [11]. ALS is associated with several genes, including *ACSL5*, which encodes a long-chain acyl-CoA synthetase; *ERGIC1*, which encodes a cyclic membrane protein of the intermediate compartment of the endoplasmic reticulum and Golgi apparatus; *FNBP1*, a formin-binding protein; *RAPGEF5*, a member of the RAS proto-oncogene subfamily; *ATXN3* (ataxin-3); *ATXN2* (ataxin-2); *SOD1* (superoxide dismutase-1); *SETX* (senataxin); *SPG11* (spatacsin); *VAPB*, a membrane protein; *ANG* (angiogenin); *FIG4*, a protein with phosphoinositide phosphatase activity; *OPTN* (optineurin); *VCP* (valosin-containing protein); *UBQLN2* (ubiquilin 2); *SIGMAR1* (sigma non-opioid intracellular receptor 1); *CHMP2B*, heteromeric endosomal sorting complex; *PFN1* (profilin-1); *ERBB4*, tyrosine-protein kinase receptor; *hnRNPA1*, encodes ribonucleoprotein; *MATR3* (matrin-3); *TUBA4A* (tubulin alpha-4A); *ANXA11* (annexin A11); *NEK1*, a serine-threonine kinase that regulates the cell cycle; *KIF5A*, a member of the kinesin-5 family; *C9ORF72*, a regulator of endosomal trafficking; *CHCHD10*, a mitochondrial protein that maintains cristae morphology; *SQSTM1* (sequestosome 1); and *TBK1* (TANK-binding kinase) [13]. Although the association of many genes was identified in the described NDDs, the roles of tau and Abeta proteins in AD [1], alpha-syn in PD [4], and FUS and TDP-43 in ALS [6] have been established. Therefore, this review focuses on the relationship between REs and these proteins, which play a significant role in the development of

NDDs. Regarding the genes associated with AD, PD, and ALS, this review considers the importance of REs in the intronic and regulatory regions of these genes. These regions are activated by polymorphisms in their loci, which may elucidate NDD development mechanisms.

The influence of SNPs associated with NDDs and localized in RE regions may be illustrated by the open reading frame 1p (ORF1p)—a LINE1 retrotransposon protein. ORF1p forms cytoplasmic aggregates and is similar to ribonucleic acid (RNA)-binding proteins associated with neurodegeneration [14]. The efficiency of retrotransposition and dynamics of protein aggregation are affected by certain amino acid changes within the ORF1p protein. Key proteins in ALS development co-localize with ORF1p-LINE1 ribonucleoprotein particles in cytoplasmic RNA granules. ALS-associated polymorphisms in intergenic and intronic regions, where REs are located, may show a similar effect, enhancing RE expression products to form TDP-43 aggregates [14]. Therefore, NDD-associated polymorphisms may induce changes in the expression and function of REs, which may interact with Abeta, tau protein [15], alpha-syn [16], and TDP-43 [17]. This demonstrates the role of NDD-associated polymorphisms. Additional contributing factors include aging and viral infections. Furthermore, RE activation may result in an epigenetic imbalance in gene expression regulation in the brain because REs are involved in epigenetic regulation and memory formation [18]. These epigenetic factors include DNA methylation, chromatin remodeling complexes, histone modifications, and noncoding RNAs (ncRNAs). Changes in these factors contribute to the development of AD [19], PD [20], and ALS [21].

ROLE OF VIRAL INFECTIONS IN THE ETIOPATHOGENESIS OF NEURODEGENERATIVE DISEASES

The evolutionary relationship between REs and viruses [22] may explain the mechanism of NDD development with respect to the role of viruses as activators of REs and interactions of REs with antiviral proteins. Abeta is an immune system protein that protects against specific viral infections. It accumulates in the brain in response to the spread of herpesviruses by binding to their surface glycoproteins [23]. Moreover, Abeta interacts with the human immunodeficiency virus (HIV). The HIV transactivator of transcription protein binds to Abeta, forming twisted and double-stranded fibrils that aggregate into thick, unstructured filaments and homogeneous amyloid fibrils in the brains of individuals infected with HIV [24]. Human herpes virus 6 increases Abeta and tau expression and the proportion of their phosphorylated forms in human microglial cells [25].

PD is associated with infections caused by herpesviruses, flaviviruses, influenza A viruses [4], and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [26]. Moreover, the influenza A H1N1 virus impairs proteostasis and alpha-syn aggregation [27]. HIV induces alpha-syn accumulation in neurons, elucidating the development of cognitive and motor disorders in HIV-infected patients. The frequency of SNCA/alpha-syn staining is higher in HIV-infected patients than in healthy people of the same age [28]. Similarly, SARS-CoV-2 induces alpha-syn aggregation, contributing to PD development by binding to the S1 protein and activating alpha-syn as part of the immune response to infection [29].

Alpha-syn exhibits biophysical characteristics of antiviral peptides and binds to virus-bearing vesicles. It promotes neuronal resistance to viral infections by signaling the immune system, attracting neutrophils and macrophages, and activating dendritic cells [30]. In response to RNA viral infections, alpha-syn promotes interferon-stimulated gene expression in neurons. Alpha-syn accumulates in the nuclei of interferon-treated human neurons. Alpha-syn expression depends on interferon-mediated phosphorylation of signal transducer and activator of transcription 2, which localizes with alpha-syn after stimulation. Increased alpha-syn serine 129 phosphorylation levels are found in the brain tissues of patients with viral encephalitis caused by the West Nile or Venezuelan equine encephalitis virus [31].

The roles of enteroviruses [32] and SARS-CoV-2 [33] in TDP-43 aggregation and neurotoxicity have been determined. Additionally, the direct antiviral activity of TDP-43 against enteroviruses [34] and HIV [35] has been revealed. In ALS, the antiviral response triggers FUS proteinopathy, which is incorporated into stress granules. FUS aggregates isolate the autophagy receptor optineurin and nucleocytoplasmic transport factors. Virus-activated interferon I promotes FUS accumulation by increasing the stability of its messenger RNA (mRNA). FUS-expressing cells become hypersensitive to double-stranded RNA toxicity [6]. Thus, the above data indicate that Abeta, tau, alpha-syn, TDP-43, and FUS are antiviral brain proteins. The expression of these proteins and their associated proteinopathies and aggregations increase during viral infections (Fig. 1). Figure 1 shows that certain viruses stimulate the expression of proteins (such as tau, Abeta, alpha-syn, and TDP-43) involved in the pathogenesis of NDDs and induce proteinopathy. These proteins are characterized by antiviral inhibitory action against specific viral infections.

ACTIVATION OF RETROELEMENTS BY VIRUSES ASSOCIATED WITH NEURODEGENERATIVE DISEASES

The associations between viral infections and AD, PD, and ALS do not fully explain the complex pathogenesis of these diseases. Viruses may trigger other processes that support the progression of pathology in the brain [24]. These processes were hypothesized to involve REs, whose expression is increased by specific viruses. This increase in expression

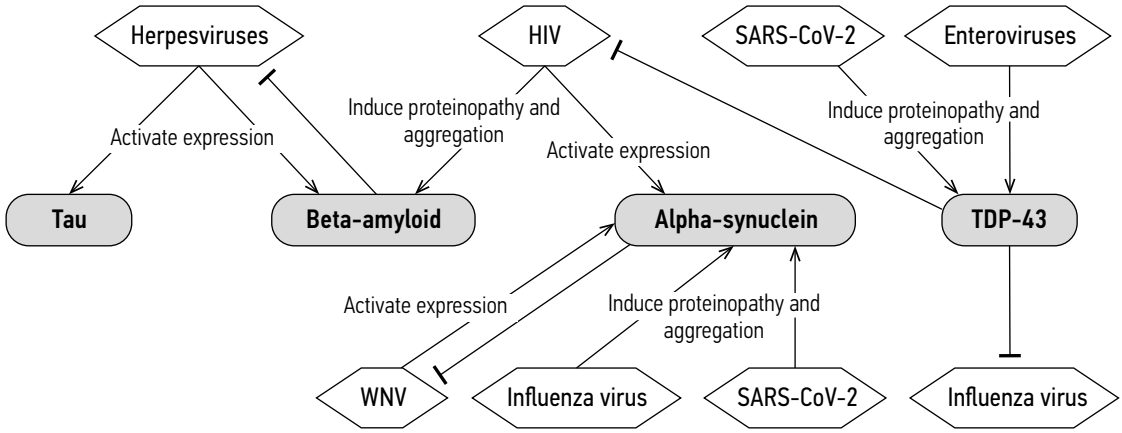

Fig. 1. Relationship diagram of pathogenic proteins in neurodegenerative diseases and viruses (arrows indicate activation, the ⊥ sign indicates inhibition). HIV, human immunodeficiency virus.

causes proteinopathy of Abeta [24], tau protein [25], alpha-syn [27], and TDP-43 [32, 33]. Therefore, in individuals with a hereditary predisposition caused by polymorphisms in RE genes that impair their function and expression [9–11], specific viruses promote proteinopathy and antiviral protein aggregation and activate REs during aging. Aging is characterized by progressive RE derepression or the reactivation of RE expression previously suppressed by epigenetic factors, resulting in interferon activation and inflammation [7]. The latter creates a "vicious circle" as RE expression products activate the production and aggregation of Abeta, tau protein [15, 24], alpha-syn [16], and TDP-43 [37]. These protein aggregates derepress REs, as they are normally involved in RE silencing [15, 16, 36, 37]. Increased RE levels enhance the expression and aggregation of antiviral proteins, thereby contributing to the progression of NDDs (Fig. 2).

Pathologically activated REs promote the expression, proteinopathy, and aggregation of tau, TDP-43, alpha-Syn, and Abeta proteins. These aggregated proteins exhibit inhibitory function loss on REs. NDDs, neurodegenerative diseases; SNPs, single-nucleotide polymorphisms.

Herpesviruses that are involved in the development of AD by interacting with Abeta [23] and tau [25] also activate REs [38]. HIV, which enhances Abeta aggregation, exerts an activating effect on REs [39]. These activated REs then increase tau expression, which contributes to AD progression [15]. The evolutionary relationship between viruses and REs [22] shows that Abeta, in addition to antiviral activity, is capable of inhibiting RE expression, which is associated with the protective effect of the protein against foreign RNA. This is evidenced by the enhanced processing of ncRNAs from SINE B2 transcripts in the hippocampus of mice with pathological amyloid aggregates [40].

Viruses that stimulate alpha-syn expression in PD also activate REs, as observed with HIV [39], influenza viruses [4], and herpesviruses [38]. RE activation during viral infection is associated with evolutionary relationships with viruses [22] and involvement in interferon antiviral pathways [41]. A review of scientific data highlighted the role of SARS-CoV-2 in activating REs that contribute to the neurological complications of coronavirus disease 2019 [42]. TDP-43 is an example of the relationship between antiviral proteins and REs in NDDs. Viruses that interact with this protein also activate REs. This has been observed with HIV [39], influenza A virus [41], SARS-CoV-2 [42], and enteroviruses [43]. RE expression products induce the pathological conformation and aggregation of TDP-43 [17], impairing its ability to inhibit REs [44]. A similar effect occurs with TDP-43 loss [45]. However, normal TDP-43 inhibits REs [46].

ACTIVATION OF RETROELEMENTS IN NEURODEGENERATIVE DISEASES AND THEIR RELATIONSHIP WITH ANTIVIRAL PROTEINS

The described mechanisms for RE participation in the pathogenesis of NDDs—including the association of polymorphisms in RE gene sites and RE interaction with viruses that cause proteinopathy and aggregation of antiviral brain proteins—are confirmed by the presence of increased RE expression in NDDs and RE interactions with Abeta, alpha-syn, tau, and TDP-43. HERV transcripts are significantly increased in the brains of patients with tauopathy [47] and AD [48]. Furthermore, tauopathies are associated with increased LINE1 and Alu expression in the brain [15]. Chromatin tags associated with the tau protein have been identified in HERV-Fc1 loci [36]. Thus, normal tau can regulate RE expression in the brain. However, in tau proteinopathy, this function becomes impaired, leading to RE derepression and accumulation of their transcripts and proteins.

In the brains of patients with PD, activation of the immune cytokine network and increased toll-like receptor 3 levels were observed in response to double-stranded RNAs, many

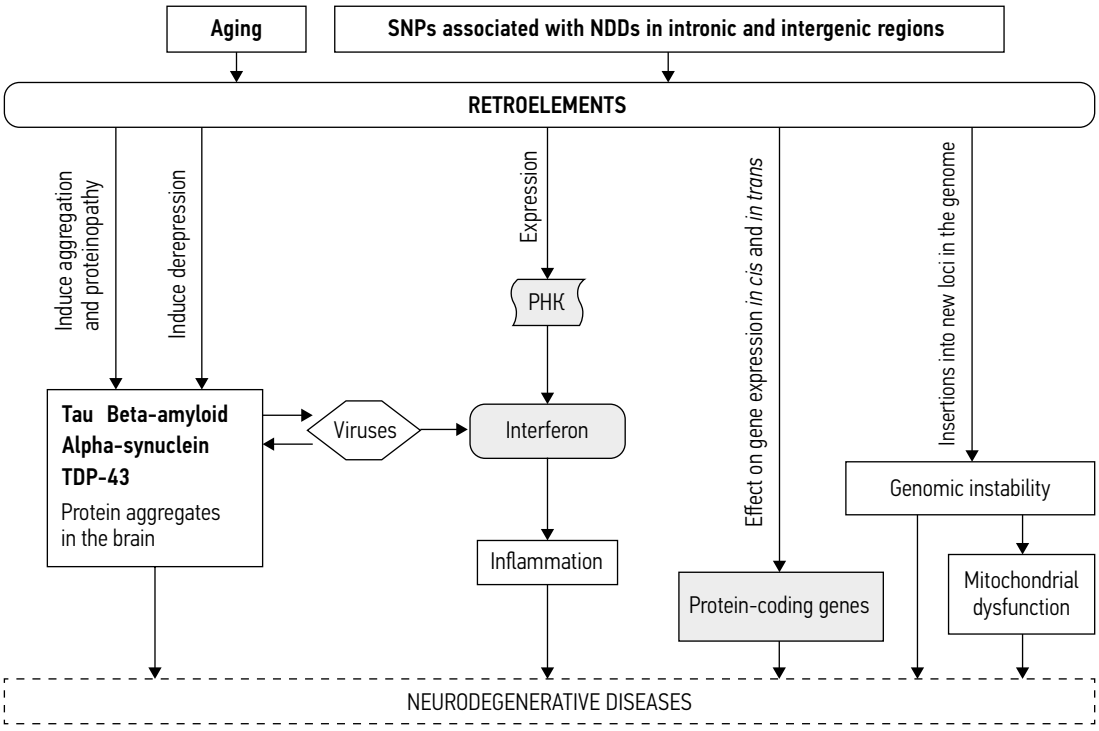

Fig. 2. Diagram of the interactions of pathogenic proteins in neurodegenerative diseases, viruses, and retroelements.

of which are products of RE transcription. The antisense C3 complement oligonucleotide, which switches splicing and promotes unproductive C3 mRNA splicing, has been shown to prevent alpha-syn changes [44]. In PD, pathological alpha-syn aggregates (Lewy bodies) fail to inhibit RE expression, leading to their derepression and increased HERV levels in the brain and blood of affected individuals [16]. A study of the cerebral cortex of people who died of ALS revealed that TDP-43 loss results in the overexpression of LINE1 and other REs, as TDP-43 binds directly to retrotransposon mRNA [37]. Studies have shown that polymorphisms in SVA distribution influence, in trans, the expression of *HLA* (human leukocyte antigens) and *MAPT* (microtubule-associated protein tau) in the genomes of patients with ALS, both of which are involved in the pathogenesis of this disease [50].

REs influence the aggregation of TDP-43, which plays a crucial role in ALS progression. HERV activation substantially increases the distribution of prion-like proteins in ALS-modeled cell cultures [17]. Studies on RNA–protein interactions and gene expression profiles have revealed extensive binding of RE transcripts to TDP-43. A significant proportion of REs were derepressed in ALS-model mice, indicating the protective role of TDP-43 against RE activity [44]. Neurons isolated from patients with ALS lacking TDP-43 exhibited increased chromatin accessibility around LINE1, demonstrating the role of TDP-43 in RE silencing at the transcriptional level [45]. TDP-43 functionality loss may explain the decrease in LINE1 retrotransposition-capable methylation detected in the motor cortex of patients with ALS [51].

The role of TDP-43 in LINE1 inhibition has been studied in embryonic stem cells and preimplantation mouse embryos. Functional analysis has revealed that TDP-43 interacts with the LINE1 protein ORF1p, protecting the genome from insertions [46]. In patients with ALS, disease progression was associated with increased antibody titers against various HERV-K envelope glycoproteins and TDP-43 epitope fragments, with a positive correlation observed between them [52]. The expression of HERV-K, whose Env protein promotes neurodegeneration, was examined in cortical and spinal cord neurons of patients with ALS and was not detected in healthy individuals [53]. Experiments on Drosophila demonstrated that ERVs stimulate human TDP-43 aggregation, which promotes increased ERV expression [54].

In addition to interacting with antiviral proteins and forming pathological conformations and aggregates, activated REs contribute to inflammatory processes driven by interferon activation within the vicious cycle of NDD progression [7]. These elements disrupt gene expression in the proximity of introns where they are located. This disruption is particularly significant considering their role as mobile elements in regulating gene expression in the brain [55]. Furthermore, HERV-K envelope RNA binds to and activates human toll-like receptor 8 in neurons and microglia, promoting neurodegeneration [56]. The most abundant stimulators of interferon response and subsequent inflammation in the brain in NDDs are LINE1 [57] and Alu [58]. In PD, Alu integration into mitochondrial genomes destroys these organelle populations in neurons, contributing to neuronal dysfunction progression [59].

PERSPECTIVES ON EXPOSURE TO RETROELEMENTS IN NEURODEGENERATIVE DISEASES

The etiological mechanisms of AD, PD, and ALS share common characteristics, including a vicious cycle involving REs and antiviral proteins. Aging, viruses, and genetic predisposition are the triggers of these diseases. Because REs contribute to increased expression, proteinopathy, and aggregation of Abeta, tau, alpha-syn, FUS, and TDP-43, inhibiting REs may be a promising treatment for NDDs. The role of REs in ALS pathogenesis has been established; therefore, methods to suppress RE activity using reverse transcriptase inhibitors have been proposed for ALS treatment [60]. Antiretroviral therapy yields favorable results in treating ALS in HIV-infected patients [61]. Considering that REs are activated by epigenetic deregulation, the use of drugs that remodel chromatin, such as methotrexate [62] and remodulin (an N-acetyltransferase 10 inhibitor) [63], may be a feasible treatment option for NDDs. Other proposed treatments include antibodies against the Env protein of HERV-K to eliminate neurotoxicity [64] and antiviral drugs that inhibit prion-like protein spreading by targeting HERV proteins [17]. These techniques may be used to treat ALS, AD, and PD. The mechanisms by which REs contribute to the pathogenesis of these diseases are similar, as described in the present review.

However, nonspecific suppression of RE activity may be insufficient, as demonstrated in patients with ALS who are not HIV-positive [61]. Additionally, REs are crucial in the epigenetic regulation of gene expression during normal brain development and function, including memory formation [55, 65]. Therefore, nonspecific inhibition of REs for NDD treatment may be ineffective and dangerous due to the potential development of adverse effects and exacerbation of cognitive and memory impairments. Each NDD may be characterized by the pathological activation of specific REs, as evidenced by genetic studies identifying polymorphic loci associated with NDDs [10–13]. Thus, a more effective approach to treating NDDs may involve targeted therapy using specific microRNAs to inhibit REs implicated in disease pathogenesis. Selecting microRNAs that evolved from REs and are fully complementary to their sequences may be a strategy for suppressing REs in NDDs [66].

CONCLUSION

Patients with AD, PD, and ALS exhibit significantly increased RE expression in the brain, cerebrospinal fluid, and blood. These findings support the hypothesis that a vicious cycle of interactions between antiviral proteins (Abeta, tau, alpha-syn, and TDP-43), which are well-established contributors to disease development, and REs is involved in the progression of pathology. Specifically, a hereditary predisposition associated with NDD polymorphisms in intronic and intergenic regions, where RE genes are located, influences the activation of REs and their interaction with aggregation-prone antiviral proteins. Moreover, the increased incidence of AD, PD, and ALS in older and senile individuals confirms the hypothesis, as aging results in RE hyperactivation, which induces interferon and inflammatory processes. Proteinopathy of Abeta, tau, alpha-syn, and TDP-43, which tends to aggregate, is also observed in physiological aging. Specific viral infections induce NDDs by stimulating the expression of antiviral proteins in the brain and their proteinopathy and aggregation. However, the mechanisms involved in this process are related to the interaction of evolutionarily related RE viruses, which also stimulate the production and aggregation of Abeta, tau, alpha-syn, and TDP-43. The aggregates of these proteins fail to inhibit RE expression, resulting in their derepression, as these proteins normally promote RE silencing. This new perspective on the etiology of NDDs recommends the use of methods to suppress endogenous retrovirus activity to treat AD and PD, as indicated for ALS therapy. Targeted therapy using specific miRNAs that inhibit REs involved in disease pathogenesis, but not in normal cognitive processes and memory formation, may be a promising and safe option.

ADDITIONAL INFORMATION

Author contributions: M.R.N.: investigation, data curation, writing—original draft, writing—review & editing. The author approved the version of the manuscript to be published and agreed to be accountable for all aspects of the work, ensuring that issues related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад автора. М.Р.Н. — проведение исследования, работа с данными, написание черновика, пересмотр и редактирование рукописи. Автор одобрил рукопись (версию для публикации), а также согласился нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой её части.
Этическая экспертиза. Неприменимо.
Источники финансирования. Отсутствуют.
Раскрытие интересов. Автор заявляет об отсутствии отношений, деятельности и интересов за последние три года, связанных с третьими лицами (коммерческими и некоммерческими), интересы которых могут быть затронуты содержанием статьи.

Оригинальность. При создании настоящей работы автор не использовал ранее опубликованные сведения (текст, иллюстрации, данные).
Доступ к данным. Редакционная политика в отношении совместного использования данных к настоящей работе не применима, новые данные не собирали и не создавали.
Генеративный искусственный интеллект. При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.
Рассмотрение и рецензирование. Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали три внешних рецензента, член редакционной коллегии и научный редактор издания.

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