Journal of Applied Pharmaceutical Science Vol. 14(02), pp 083-092, February, 2024
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2023.152245
ISSN 2231-3354

Deciphering the molecular mechanism of REST regulation through DEGs and TFs in Alzheimer's disease

Ajmal Nassar[1], Madhavan Nampoothiri[1], Prasada Chowdari Gurram[1], Sairaj Satarker[1], Dinesh Upadhya[2], Gayathri Shamabhat[3], Fayaz Shaik Mahammad[3]*

[1]Department of Pharmacology, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, India.
[2]Centre for Molecular Neurosciences, Kasturba Medical College Manipal Academy of Higher Education, Manipal, India.
[3]Department of Biotechnology, Manipal Institute of Technology, Manipal Academy of Higher Education, Manipal, India.

ARTICLE HISTORY

Received on: 05/08/2023
Accepted on: 02/01/2024
Available Online: 05/02/2024

Key words:
Differentially expressed genes, protein-Protein interactions, network analysis, regulatory clusters, Hub proteins.

ABSTRACT

The most predominant form of dementia is Alzheimer's disease (AD), which most often manifests as loss of cognitive ability and episodic memory. Repressor element-1 silencing transcription factor (REST), generally referred to as neuron-restrictive silencer factor, is a transcriptional repressor that is typically expressed throughout embryogenesis and is essential for regulating the genes that are unique to neurons. The genes modulating neurotransmitter synthetases, synaptic vesicle proteins, transporters, receptors, and various ion channels in the central nervous system are regulated by REST. In neurons from the hippocampus and prefrontal cortical regions, there was a discernible decline in the nuclear REST level in AD patients. Despite the importance of REST, very little is known regarding the regulatory mechanism of REST. In this study, we have computationally explored the role of REST in differential expression of genes in AD by the construction of gene/protein interaction networks. In addition, we have also investigated the interaction between REST and other transcription factors (TFs) in the regulation of genes. When the gene expression data of AD samples were compared with the control samples, 97,457 genes from the 850,125 total examined genes displayed differential expression. 33 genes among the DEGs regulated REST, while 364 genes were controlled by REST. Twenty important TFs were discovered to be directly involved in the REST regulation among the DEGs. In addition, among the DEGs, 17 TFs were found to share common targets with REST that are involved in AD. Gene annotation analysis has shown that REST along with other TFs regulated genes that are involved in processes such as synaptic signaling, neuronal death, metabolic processes etc. The results demonstrated the critical regulatory role of REST in AD pathogenesis.

INTRODUCTION

The most harmful form of dementia, Alzheimer's disease AD, has been studied for the past 50 years, but its root cause and optimal treatment are still unknown. It has been strongly linked to pathogenic factors including tau, or microtubule-associated protein, and amyloid (Aβ). The combination of both of these risky elements contributes to the emergence of neurofibrillary tangles. [1]. Numerous essential transcription factors (TFs) have a substantial impact on the root causes and emergence of AD [2]. Repressor element-1 silencing transcription factor (REST), generally assigned the name "neuron-restrictive silencer factor, is an essential transcriptional repressor that is typically expressed throughout embryogenesis and plays a critical role in regulating the enormous neural genes that have distinct roles assigned specifically to neurons. It has been discovered that the majority of the genes that regulate neurotransmitter synthetases, synaptic vesicle proteins, transporters, receptors, and some ion channel-modifying genes play substantial functions in the central nervous system (CNS). However, many of the aforementioned facts are still not fully explored due to the lack of minimum research on this particular TF [3–7]. But since REST's probable role in causing AD is still

*Corresponding Author
Fayaz SM, Department of Biotechnology, Manipal Institute of Technology, Manipal Academy of Higher Education, Manipal, India.
E-mail:fayaz.shaik @ manipal.edu

being critically studied, further research is needed in this area. We do, however, highlight some important research from the body of literature that supports the impact of REST on AD. In AD patients, there was a noticeable decrease in the nuclear REST level in neurons from the memory-focused region, particularly those from the CA1, CA3, and CA4 regions of the hippocampus, as well as prefrontal cortical neurons [8]. In contrast to cognitively healthy control subjects, a recent study underscored the diminished REST levels in plasma neuronal-derived exosomes from stable mild cognitive impairment (MCI) patients, MCI patients who are transitioning to AD, and AD people [9]. REST deficit consequently manifests in sporadic AD and persists in differentiated neurons, indicating that it might be the primary etiology of AD. Nuclear translocation deficit has been established as the defining feature of REST-related diseases, including AD [8] and Parkinson's disease [10]. However, it was found that augmented REST nuclear translocation from the cytoplasm is a pathological feature in Huntington's disease [11]. Despite conflicting evidence in this paradigm, the principal impacts of the loss of REST function in the neurons of sporadic AD patients have been recognized as nuclear translocation defect from the cytoplasm to neurons and nuclear lamina disruption [12]. Lue and colleagues showed the neuroprotective role of REST in AD patients by triggering oxidative stress resistance genes and suppressing apoptosis-inducing genes that promote Aβ toxicity [8]. Age-related diseases like AD have been speculated to be significantly influenced by cellular senescence. In the brains of AD patients and AD animal models, the senescence phenomenon attributed to crucial brain components such as neurons, astrocytes, and microglia was visible [13]. Importantly, REST was associated with aging and neurodegenerative conditions. REST was required to halt the senescence characteristic in mouse primary neurons [14]. REST deficit has the extraordinary capacity to alter the autophagy process, cause proteostasis to break down, increase oxidative stress, and accelerate cell mortality, making this TF an essential epigenetic entity during aging [14]. Long-lived daf-2 mutants with loss-of-function mutations of REST ortholog genes spr-3 and spr-4 in the *C aenorhabditis elegans*, were reported with diminished life expectancies and augmented neuronal excitation [15]. Thus, REST is linked to increased longevity and controls neuronal excitation in the aging brain [15]. Along with suppressing several apoptotic genes such as p38 map kinase MAPK11, Tumor necrosis factor receptor type 1-associated DEATH domain protein, and death domain associated protein (DAXX), REST also targets γ-secretase complex essential components that stimulate Aβ synthesis [8]. The repressive influence of REST on these AD-causing genes states the epigenetic remodeling mechanism crucial to progressive neurodegeneration.

REST has lately been studied in neurodegenerative diseases irrespective of its connection with neurodevelopment [10,12,16,17]. The regulatory mechanism of REST in neurological disorders, especially AD, is not clear and demands more research in this area. In addition, the targets of REST and the essential corepressors of REST have not been entirely explored in AD. Therefore, it is crucial to identify the interacting partners of REST and the resulting biological function that they regulate under the circumstances of AD.

We hypothesize that REST is a key regulatory protein that has a beneficial role in AD, through its interactions with the proteins involved in the progression of AD. However, no studies have been conducted on how REST regulates the differentially expressed genes (DEGs) in AD or how other DEGs in AD regulate REST. Hence, the objective of this study is to investigate the regulatory mechanism of REST via several DEGs in AD including multiple TFs that regulate REST during AD conditions. Similar studies have been carried out in other diseases such as atherosclerosis and cervical cancer, which involve the identification of DEGs and protein–protein interaction networks [18,19]. However, the methodology adopted in this study to delineate the mechanism of a transcriptional regulator is novel and has not been reported elsewhere to the best of our knowledge.

MATERIALS AND METHODS

Gene expression data

The gene expression omnibus (GEO) provided a wealth of knowledge on the expression of genes [20]. For this analysis, we used the microarray gene expression information of 17 human brain samples with AD and 19 healthy control samples (GEO accession number GSE138260). The healthy control samples do not have any history of neurological or psychiatric illness. The DEGs ended up being identified using the GEO2R program, which assessed the raw gene expression data. The *p*-value of 0.05 and logFC values were used to figure out DEGs that were statistically significant as described previously [19]. DEGs went up when logFC values were positive and diminished when logFC values were negative.

REST regulating genes

The REST regulating genes were identified as described previously [21]. It was feasible to determine the genes governing REST and the genes that it controls from the TF-Gene interactions by using the pertinent data from the TRRUST [22], hTFtarget [23], and transcription co-factors (TcoF-DB) [24] database. TRRUST is a database of transcriptional regulatory networks for humans and mice. This collection contains the TF-target regulatory relationships of 800 human TFs that articulate small-scale experimental studies of transcriptional control. Additionally, it offers details pertaining to the type of regulation (activation or suppression). Large-scale ChIP-Seq data of human TFs (7,190 experiment samples of 659 TFs) in 569 settings (399 types of cell line, 129 classes of tissues or cells, and 141 kinds of therapies) have been compiled by hTFtarget to create complete TF-target regulations. The Database of TcoF-DB and transcription factor interactions makes it easier to investigate the genes encoding for proteins that regulate gene transcription in humans and mice by attaching to regulatory regions of DNA (TFs) and the genes encoding for proteins that have interactions with TFs but are unable to attach directly to regulatory DNA regions (transcription co-factors). For this study, only REST interactions among humans were taken into account from all of these datasets.

Protein-protein interactions

The interactions among the REST regulating proteins were identified as discussed previously [18]. We used the STRING database, which is widely recognized for illustrating data pertaining to interactions between proteins [25]. Using this database, we were able to determine the DEGs responsible for the regulatory framework for REST through their interactions (physical and functional links, both direct and indirect). To ensure that all interactions were empirically validated and, therefore, legitimate in order to be taken into consideration for this investigation, the minimum needed interactions score was set to the highest confidence level of 0.9. The first shell interactions that involved the query proteins only were considered. The results were retrieved in the form of tabular text.

Gene annotation

Gene annotation was carried out as per a previously reported study [19]. The annotation information such as biological processes, cellular components, and tissue expression of the genes involved in the regulatory mechanism of REST was retrieved from the database for annotation, visualization, and integrated discovery database [26]. This database provides a full range of functional annotation tools that allow researchers to gain insight into the biological relevance of a huge number of genes.

Network construction and analysis

The networks of protein interactions and REST regulatory systems were built using Cytoscape v3.9.0. [27]. It is a free and open-source software platform for portraying intricate networks and merging them with all attribute data. The maximal clique centrality strategy employed by CytoHubba was implemented to pinpoint the hub proteins in the protein-protein interactions of the DEGs that operate via REST [28]. A number of topological techniques are used by the Cytoscape plugin, CytoHubba to anticipate and explore significant nodes and subnetworks in a given network [18]. The hub proteins have been demonstrated to have greater interactions (degrees) than other proteins, relative to the protein-protein interaction network. During the process of developing new drugs, they provide essential information for selecting or classifying targets. Additionally, another Cytoscape plugin, MCODE, was employed to establish the network's strongly interconnected regions or clusters [29,18].

RESULTS

Gene expression data analysis

The microarray study involved 19 samples (violet) from AD patients and 17 samples (green) from healthy controls (Fig. 1a). The median of each of the chosen samples has been normalized, and their values are identical. It guarantees that each sample that was chosen could be used for differential expression analysis. The DEGs are depicted using a volcano plot (Fig. 1b). From the Venn diagram, it is evident that 97,457 genes -are differential expressed with p_{adj} value <0.05 among the 850,125 total analyzed genes in AD samples when compared with the control samples (Fig. 1C). The logFC was in the range of −.5 to 2.5. There are 256 genes that are downregulated (logFC < −1) and 1,523 genes upregulated (logFC >1).

Regulatory mechanism of REST in AD

Overall, there are 33 DEGs regulating REST and 364 DEGs that are regulated by the REST. Further, two genes (GATA1 and AR) were found to act in a feedback manner, where these two genes have the potential to modulate as well as be modulated by REST (Fig. 2). Among the top 250 DEGs, BRD2 regulates REST, and Chromogranin A (CHGA) and PPP1R16A were found to be regulated by REST (Fig. 3a).

REST-TFs interactions in AD

Among the top 250 DEGs, only SP1 was involved in the regulation of REST (Fig. 3b). However, when the whole set of DEGs was analyzed, 20 crucial TFs were found to be directly involved in the REST regulation (Fig. 4). Out of these 20 TFs, 17 TFs were found to share common targets with REST that are involved in AD (Table 1).

Interactions of REST regulatory proteins in AD

The protein-protein interactions of the DEGs involved in the regulatory mechanism of REST demonstrate that most of them are interconnected with each other and are involved in either

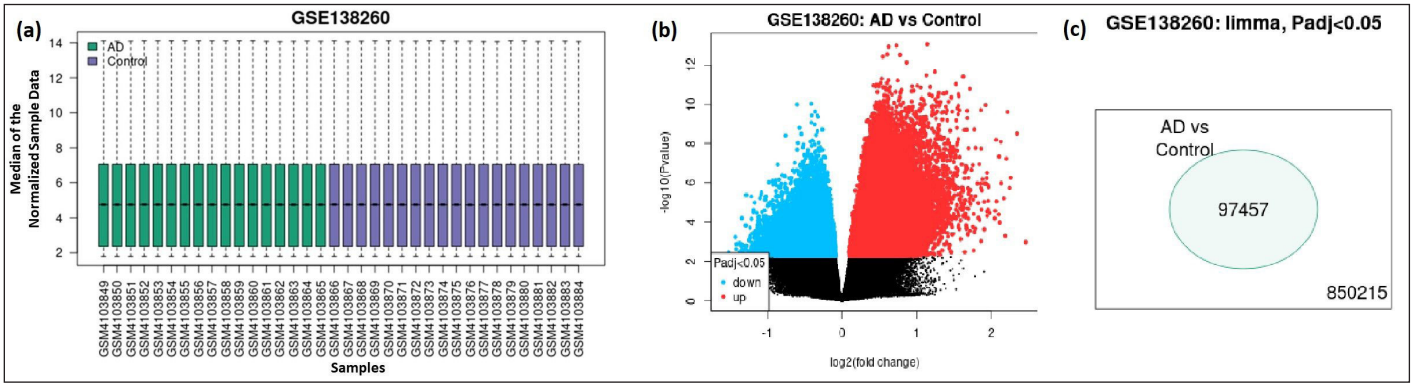

Figure 1. Gene expression data. (a) Boxplot showing the distribution of the normalizedexpression data of the samples. (Boxplot is used to view the distribution of the values of the selected samples. The samples are colored according to groups. Viewing the distribution can be useful for determining if your selected samples are suitable for differential expression analysis), (b) volcano plot, (c) venn diagram of the overlapping differentially expressed genes (DEGs).

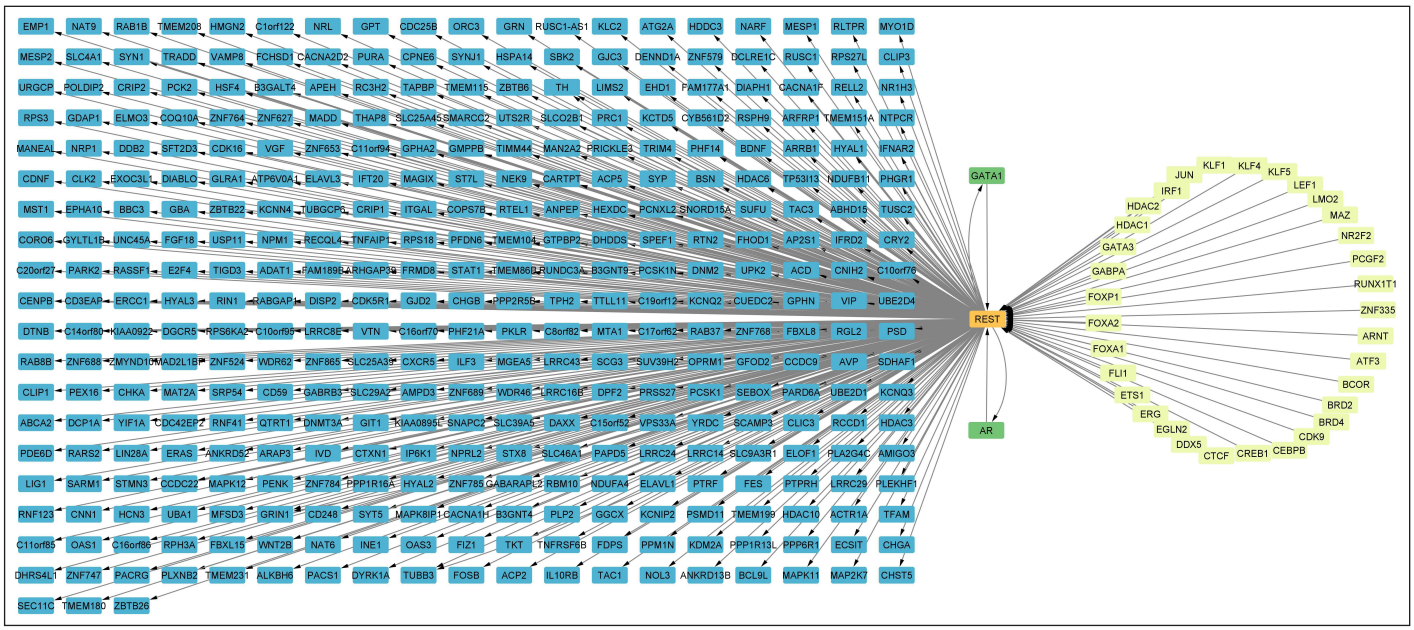

Figure 2. DEG Regulation related to REST

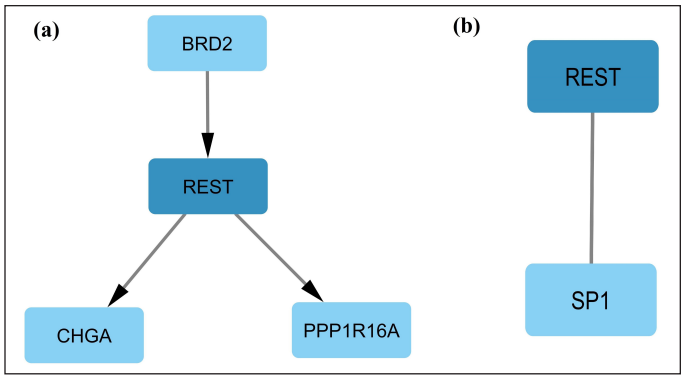

Figure 3. The role of REST among the top 250 DEGs. a) TF BRD2 regulating REST which in turn regulates genes CHGA and PPP1R16A. b) Interaction of REST and SP1.

physical or functional regulation. Only a few proteins are sparsely spaced apart and are only briefly interconnected. HDAC1, JUN, and HDAC2 showed maximum interaction with other proteins. HDAC1 interacted with 21 other proteins. Likewise, JUN and HDAC2 interacted with 16 and 11 other proteins.

Hubs and regulatory modules

CytoHubba identified 10 hub proteins in the REST regulatory network involving the products of DEGs (Fig. 6). In addition, three closely interconnected clusters were obtained from MCODE (Fig. 7). The first module contained five proteins, the second had four proteins, and the third involved three proteins.

Annotation of REST regulatory genes

The REST regulatory genes are involved in a variety of bodily functions, and the bulk of them are expressed in the brain and CNS (Table 2).

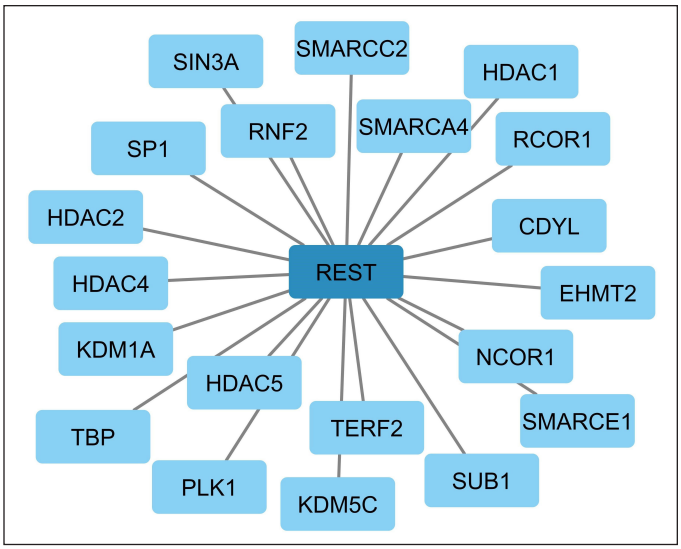

Figure 4. Overall interaction of REST with other TFs among the DEGs in AD

DISCUSSION

REST is a crucial TF that represses several genes involved in various neurological disorders including AD. Understanding the regulatory mechanism of REST during AD would provide novel insights into the disease mechanism and identify potential disease targets. This could be achieved by analyzing the relation of REST with the DEGs in AD. In addition, it is critical to demonstrate the REST-TF interactions in AD since REST can interact with and influence other TFs that are differently expressed in AD.

Among the top 250 DEGs in AD, CHGA and PPP1R16A are regulated by REST (Fig. 3a). CHGA is a neuroendocrine secretory protein found in neurons and neuroendocrine cells.

CHGA levels in the brain tissue of AD patients were substantially greater than those of healthy individuals. [30,31]. It was reported that CHGA could potentially be used as a biomarker for AD [32]. CHGA, expressed in amyloid plaques in AD, activated microglia to a reactive neurotoxic phenotype [33]. This is probably the bridge between AD-related neuronal, glial, and inflammatory pathways. PPP1R16A, which is also known as MYPT3, is involved in actin binding and GCPR signaling [34]. The role of GPCR and actin protein in AD pathology have been discussed elsewhere [35,36]. We have observed that REST is in turn regulated by BRD2. BRD2 is involved in the histone acetylation landscape and its dysregulation aids in the etiology of AD [37]. Although our study showed the interaction between BRD2 and REST, it is still unclear how both TFs regulate CHGA and PPP1R16A.

Table 1. Transcription factors that share common target genes with REST.

Sl. No.	Transcription factor	No. of common target genes
1	CREB1	5
2	EGR1	5
3	SP1	7
4	PIAS1	2
5	ESR1	3
6	ATF3	2
7	CTNNB1	2
8	ATF1	2
9	LEF1	2
10	STAT6	2
11	STAT3	3
12	JUN	3
13	HDAC1	2
14	HIF-1α	2
15	STAT1	2
16	RELA	3
17	NFKB1	3

Yet another important interaction that we have observed among the top 250 DEGs is between REST and TF SP1 (Figs. 3b and 4). SP1 is a REST activator [38] that regulates the genes linked to the development of amyloid plaques and governs the genes relevant to neuronal death, oxidative stress, tau phosphorylation, and inflammation, all of which likely have an impact on the evolution of AD [39,40]. It shares seven common target genes with REST (Table 1).

Apart from the top 250 DEGs, when the overall network was analyzed, we noted that REST interacted with 20 other TFs (Fig. 4) which included SMARCA4 (known as BRG1), RNF2, SIN3A, KDM1A, NCOR1, HDAC family proteins, etc. A chromatin remodeling factor called SMARCA4 is involved in the transcriptional stimulation of genes that is fundamental to neural development. SMARCA4 levels have been detected to be more abundant in individuals with AD than in controls. [41]. RNF2, a transcriptional enhancer, boosts the expression of genes that contribute to brain development by binding to certain DNA regions. The establishment of glutamatergic synapses in the hippocampus is encouraged by RNF2 [42]. SIN3A controls

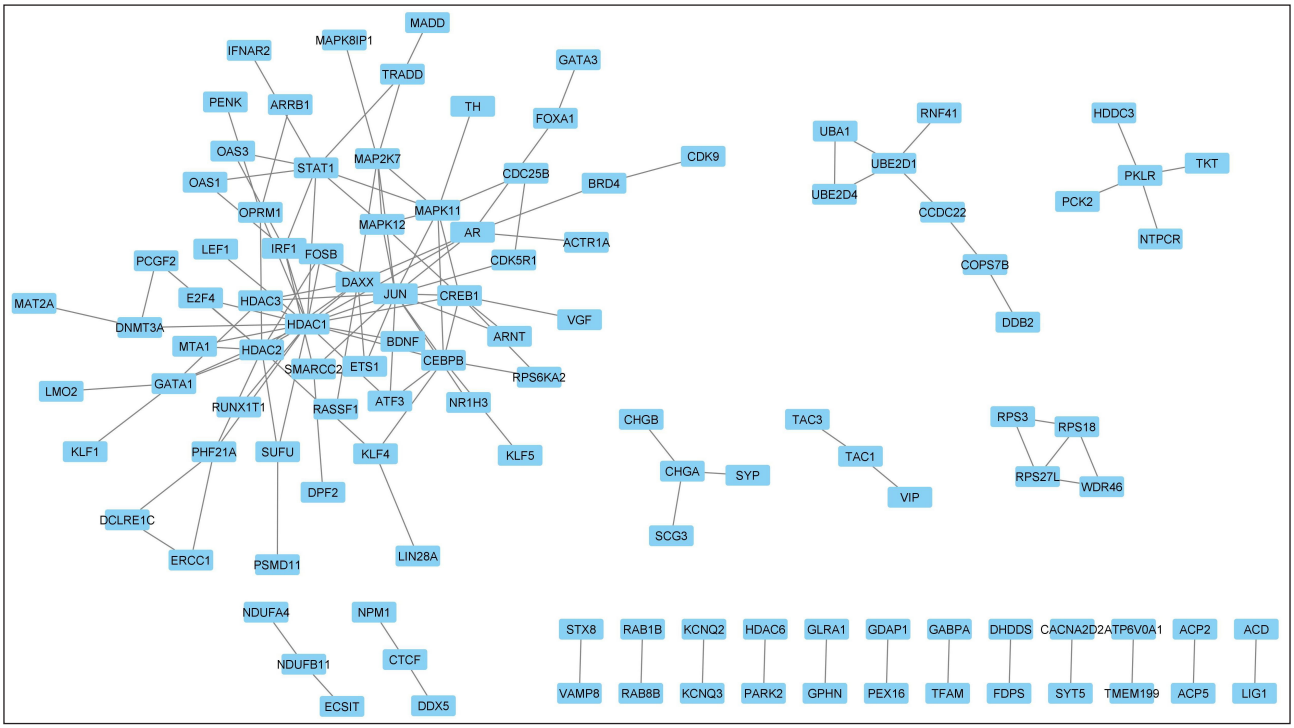

Figure 5. Physical protein interactions and functional associations of the proteins related to the DEGs regulated by REST.

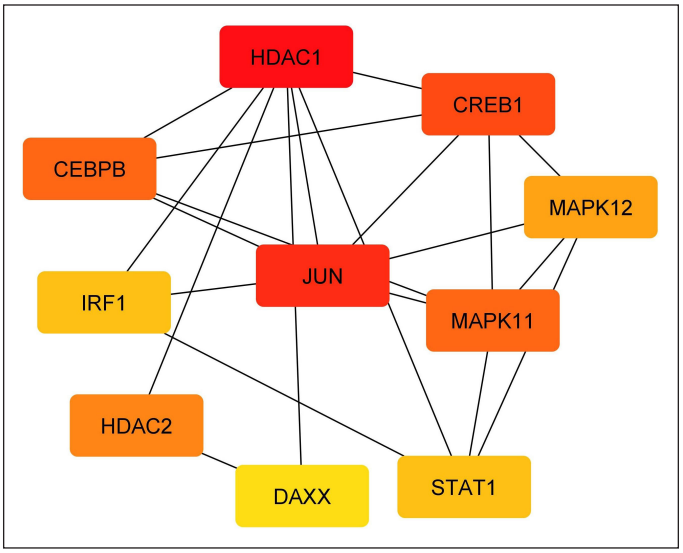

Figure 6. Interactions of the Hub proteins related to the DEGs regulated by REST. (Generated by CytoHubba). The color indicates the order of ranks, red is rank 1 and yellow is rank 10.

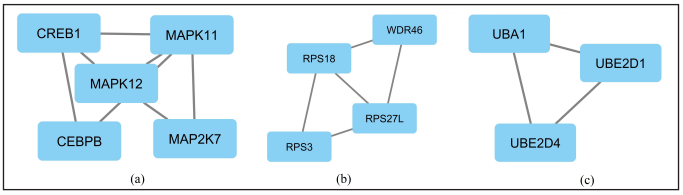

Figure 7. Clusters (highly interconnected regions) in the interaction network of proteins related to the DEGs regulated by REST. (Generated by MCODE).

the metabolism of Aβ peptides, and Soluble Aβ peptides accumulated extensively as a consequence of loss-of-function mutations in SIN3A [43]. According to studies on the role of REST in the regulation of these TFs, SMARCA4 is a REST-interacting protein that forms epigenetic repressor complexes during the development of the brain by restricting the activity of specific genes [44]. Similarly, SIN3A acts as a transcriptional corepressor that engages with the REST and serves as crucial to modulating gene expression [45].

REST actively interacts with the HDAC family of TFs such as HDAC1, HDAC2, HDAC4, and HDAC5 (Fig. 4). HDAC1 is involved in the formation of amyloid plaques and the regulation of tau protein, which are a hallmark of AD [46]. HDAC1 seems to play a part in controlling the expression of specific genes linked to synaptic plasticity. In AD models, HDAC1 was reported to be elevated similarly to HDAC2 [47]. REST interacts with HDAC1 to regulate gene expression. REST binds to HDAC1 and modifies the chromatin structure, which in turn affects gene expression [48–51]. Interestingly, SIN3A recruits its corepressor HDAC2 to the target promoter genes to preserve a suitable repressive state [52]. REST binds to HDAC2 and inhibits its activity, thus preventing the transcription of target genes which is important for maintaining the proper balance of gene expression in the nervous system

Table 2. Biological processes, cellular compartments and the tissues in which the REST regulatory proteins are involved.

Biological Process	Cellular Component	Tissue Expression
Negative regulation of nucleobase-containing compound metabolic process	Membrane-bounded organelle	Erythroleukemia cell
Negative regulation of rna metabolic process	Intracellular organelle	Cervical carcinoma cell
Negative regulation of cellular biosynthetic process	Intracellular membrane-bounded organelle	Nervous system
Negative regulation of transcription by rna polymerase	Intracellular	Central nervous system
Response to stress	Somatodendritic compartment	Brain
Negative regulation of cellular metabolic process	Dendrite	Head
Negative regulation of transcription, dna-templated	Neuron projection	
Negative regulation of macromolecule biosynthetic process	Nucleoplasm	
Regulation of nucleobase-containing compound metabolic process	Cell projection	
Negative regulation of metabolic process	Axon	
Response to stimulus		
Synaptic signaling		
Regulation of neuron death		
Regulation of cell death		

[48–50]. In our study, HDAC1 and HDAC2 were found to be the crucial hub genes that interact with most of the other proteins involved that come under the REST regulation (Fig. 6). Thus, we speculate that the REST via HDAC1 and HDAC2 regulates the other proteins involved in AD.

Two histone deacetylases, HDAC4 and HDAC5, have been tied to the cause of AD. They play an integral part in controlling the regulation of the expression of genes, and the malfunctioning of any of them has been attributed to the appearance of AD. Boosted HDAC4 has been found in AD patients' brains, according to studies [53], which contributes to the buildup of Aβ. Additionally, transgenic mice with ApoE4, the sole genetic risk factor for late-onset AD, have higher nuclear HDAC4 levels [54]. HDAC4 controls age-associated declines in memory generally. Neuner *et al.* [55]. HDAC5 gets elevated in AD patients' brains, hinting that it could be contributing to the emergence of AD [56]. HDAC5 additionally performed an essential part in controlling the process of beta-amyloid synthesis. In addition, it has been established that REST interacts with HDAC5, and regulates the genes necessary for neural differentiation. As a result, REST is vital to the stage of neuronal differentiation [57].

Another REST interacting TF KDM1A, also known as lysine-specific demethylase 1 (LSD1), is a well-characterized co-repressor [58,59] that has been connected to the onset of AD. For instance, in CNS disorders, the repressor complex LSD1-REST-CoREST-HDAC1/2 largely controls the developmental program and modifies neuronal morphology [60]. REST along with LSD1 actively contributes to the repression of REST targets. Similarly, REST along with Chromodomain Y Like (CDYL) represses neuronal genes in non-neuronal tissues CDYL can suppress the transcription of genes [61–63].

REST interacts with NCOR1, which is a transcriptional corepressor and controls the brain's gene expression related to a variety of processes including synaptic plasticity, learning, and memory as well as neuronal growth. In addition to controlling neurotransmitter release, NCOR1 is also linked to the etiology of AD [64]. REST also interacts with TRF2 or TERF2 whose expression was significantly lower in the peripheral blood serum of AD patients compared to the control. This decrease in expression is likely related to the reduction in telomere length observed in AD patients [65]. TERF2 was suggested to be an important factor in regulating telomere shortening in AD [66].

The protein-protein interaction and network analysis identified certain hub proteins forming clusters (Fig. 5). These hub proteins are DAXX, MAPK11, CREB1, and MAPK12 (Figs. 6 and 7). Understanding the role of these genes would help in elucidating the REST regulation in AD. Because these are the main cell death genes involved in AD pathology [8].

The p38 MAP kinases (MAPK11 and MAPK12) are implicated in tau phosphorylation [8]. CREB1 is crucial for controlling gene expression in the brain and contributes to the onset of AD [67–69]. CREB activation induces REST expression in the context of neuroinflammation [70]. In addition, the TF CREB1 shares five common target genes with REST (Table 1).

REST has also been observed to regulate gene expression via a synergistic mechanism, i.e., REST along with other TFs regulates common genes. For instance, the transcriptional regulator STAT3 is involved in neuroinflammation, transcriptional regulation, and the accumulation of amyloid and tau fragments. STAT1 and its interactions with STAT3 affect tau accumulation and synaptic plasticity [71–75]. STAT3 shares three common target genes with REST (Table 1). Recent research has proposed that STAT6-mediated promotion of M2 polarization of microglial cells may improve the cognitive ability of AD mice [76]. STAT6 shares two common target genes with REST (Table 1).

HIF-1 boosts the formation of Aβ, and diminishes the functioning of microglia, induces neuroinflammation and microglia mortality, all of which contribute to the genesis of AD [77,78]. REST suppresses HIF-1, and this in turn slows the uptake of glucose and lactate generation driven by hypoxia. REST restricts HIF-1-dependent transcription in order to perform its role as a repressor of gene expression [79]. But direct HIF-1α -REST interplay needs to be elucidated in AD. HIF-1α shares two common target genes with REST (Table 1).

The NF-κB pathway plays a negative role in the development of AD with inflammatory characteristics. REST and NF-κB 1 share three target genes in common (Table 1). Aβ and other pro-inflammatory molecules trigger NF-KB in AD, which boosts the level of expression of pro-inflammatory cytokines and chemokines. By encouraging neuronal death and hindering synaptic plasticity, this heightened inflammation is believed to speed up the manifestation of AD. NF-κB activation is additionally linked to the occurrence of amyloid plaques, an identifiable feature of AD [80–82].

To summarize, REST mediates the regulation process through other TFs such as NCOR1, TERF2, KDM1A, and HDAC family proteins to regulate hub proteins such as DAXX, MAPK11, CREB1 and MAPK12. In addition, it regulates target gene expression synergistically with other TFs such as HIF-1, STAT1, NF-κB, etc., thus are involved in crucial processes of AD pathology.

CONCLUSION

Understanding the regulation of beneficial TFs like REST in a complex disease like AD would be helpful to comprehend the underlying mechanism of the disease. In the regulatory networks involving DEGs in AD, active TFs influencing REST and the potential molecular mechanism of REST-DEGs interaction were identified. REST was found to physically interact with key TFs like SP1. Ten proteins produced by the DEGs were identified as hubs that might comprise direct (physical) and indirect (functional) associations with most of the proteins involved in the regulatory mechanism of REST. These hubs are critically involved in the pathogenesis of AD. Three clusters that are tightly regulated and involved in the REST regulation were identified. Seventeen TFs in the DEGs were found to share common targets with REST. The proteins in the REST regulatory network were involved in the biological processes associated with neuronal death.

Further in-depth research on the regulatory mechanism of REST for the treatment of AD under both *in vitro* and *in vivo* conditions can be carried out using this study as a stepping stone. In addition, because REST is a member of the category of epigenetic repressors, it is crucial to establish the relevance of other vital repressors and their corepressors under the epigenetic perspective of AD. Investigations on the inhibition of hub proteins reported in this study, which are involved in the pathogenesis of AD, can be performed to develop novel therapeutic molecules. Similar studies can be carried out to delineate the regulatory role of key TFsin other diseases.

ACKNOWLEDGMENTS

The authors acknowledge the Council of Scientific & Industrial Research, Government of India, New Delhi, for providing the Senior Research Fellowship to Mr. Ajmal Nassar and Manipal Academy of Higher Education, Manipal for providing financial and infrastructural support for the research activities. Ms. Gayathri S acknowledges the Indian Council of Medical Research (ICMR), for providing the Senior Research Fellowship.

AUTHOR CONTRIBUTIONS

Fayaz Shaik Mahammad: Conceptualization, Methodology, Formal analysis, Investigation, Writing, Reviewing & Editing, Project administration. Ajmal Nassar: Methodology, Investigation, Writing, Reviewing & Editing.

Gayathri S: Methodology, Investigation, Writing, Reviewing & Editing. Prasada Chowdari Gurram: Data collection and Reviewing. Sairaj Satarker: Data collection and Reviewing. Madhavan Nampoothiri: Methodology, Formal analysis, Writing, Reviewing & Editing. Dinesh Upadhya: Methodology, Formal analysis, Writing, Reviewing & Editing.

FINANCIAL SUPPORT

This work was supported by the Council of Scientific & Industrial Research 08/602(0007)2019-EMR-1 and the Manipal Academy of Higher Education. Ms. Gayathri S has received financial support from the Indian Council of Medical Research (ICMR) (Grant No: BMI/11(65)/2020).

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

PUBLISHER'S NOTE

This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

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How to cite this article:
Nassar A, Nampoothiri M, Gurram PC, Satarker S, Upadhya D, Gayathri S, *et al.* Deciphering the molecular mechanism of REST regulation through DEGs and TFs in Alzheimer's disease. J Appl Pharm Sci. 2024;14(02):083–092.