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The mRNA Expression Levels of General Transcription Factors Altered in Alzheimer Cases Possibly Due to Amyloid Beta 1-42 Exposure

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ABSTRACT

Introduction: Given the global gene expression alterations associated with amyloid beta (Aβ), a hallmark of Alzheimer's disease (AD) pathology, this study aimed to investigate its potential role in modulating gene expression through the regulation of specific transcription factors (TFs).

Methods: Using a combination of protein-protein interaction prediction tools and transcriptional regulatory interaction databases, we identified JUN, FOS, ATF2, ATF4, RELA, NF-κB, SMAD3, STAT1, STAT3, and SP1 as potential candidate TFs that might be involved in Aβ1-42 related pathways. We then conducted in vitro studies to demonstrate a direct effect of Aβ on these TFs and a case-control study to investigate any alterations of selected TFs in human samples. In vitro studies included HEK293 T cells treated with 0.09 μM and 10 μM Aβ1-42. The expression levels of the TFs were assessed by qRT-PCR. The mRNA expression levels of selected target transcription factors that have the highest PPI scores, namely JUN, FOS, and RELA, were also investigated in blood samples from core Alzheimer's disease (AD) cerebrospinal fluid (CSF) biomarker-confirmed AD cases and plasma ALZpath pTau217-confirmed healthy subjects.

Results: In vitro studies indicated that the mRNA expression of most of the TFs was altered due to either the dose of Aβ or the period of treatments. JUN, FOS, NFKB, and SP1 mRNA expression were increased, while STAT1 and ATF2 were decreased within 24 hours of at least one dose of Aβ treatment. At 48 hours of treatment, FOS, STAT1, STAT3, ATF2, and SP1 were higher, whereas RELA, SMAD3, and NFKB were lower in Aβ-treated groups. At 72h of treatments, the ATF4 and NFKB expressions were high, whereas JUN FOS, RELA, STAT1, STAT3, ATF2, and SP1 were low in Aβ treated groups. Human samples showed that the mRNA levels of JUN and RELA were significantly higher in blood samples from AD cases compared to those from healthy individuals.

Conclusion: Alterations in the expression levels of TFs in response to Aβ exposure may explain the alterations of the expression levels of genes that these TFs regulate. Given that, understanding the transcriptional effects of Aβ and its regulatory role on TFs may provide a perspective for the physiological roles of Aβ and the molecular pathways underlying AD pathogenesis.

Keywords: Aβ1-42, Alzheimer's disease, transcription factors, ALZpath pTau217, CSF

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INTRODUCTION

Amyloid beta (Aβ) is a product of the cleavage of a transmembrane protein, the amyloid precursor protein (APP) (1). The insoluble plaques that are produced by the accumulation of Aβ in the brain are known as a major hallmark of Alzheimer's disease (AD). Aβ is thought to be involved in a series of events that ultimately result in the degeneration of neurons and the cognitive decline associated with AD. Aβ has been shown to disrupt neuronal signaling, impair synaptic plasticity, and promote neuroinflammation and oxidative stress. Additionally, Aβ has been shown to induce tau hyperphosphorylation, resulting in the development of neurofibrillary tangles, another hallmark of AD (1–6). Recent findings suggest that Aβ may have significant functions in normal physiological processes within the brain, including synaptic plasticity,

Highlights

- **The study investigated Aβ-transcription factors relation in vitro and in AD cases**
- **Aβ pathways may involve JUN, FOS, ATF2, ATF4, RELA, NF-κB, SMAD3, STAT1, STAT3, SP1**
- **The mRNA levels of JUN and RELA were significantly higher in blood samples of AD cases**
- **TF level changes from Aβ exposure may explain altered expression of their target genes**

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neuronal development, neuronal survival, formation of ion channels, kinase activation, and regulation of cholesterol transport (7,8).

While the roles of Aβ in both physiological and pathological conditions are not entirely understood, it is known that Aβ can have a profound impact on gene expression in the brain. Aβ has been shown to affect the expression of various genes involved in inflammation, oxidative stress, and synaptic function. Such alterations ultimately lead to synaptic dysfunction, neuronal death, and cognitive decline seen in AD. Furthermore, reports have indicated that Aβ1-42 is present in the nucleus and can interact with DNA (7,9,10). We and others have shown that Aβ1-42 has the potential to regulate amyloidogenic pathway-related genes (amyloid precursor protein (*APP*), beta-secretase 1 (*BACE1*), presenilin 1 (*PSEN1*) and *PSEN2*), tau pathology-related genes (*TAU*, glycogen synthase kinase 3 beta (*GSK3β*) and cyclin-dependent kinase 5 (*CDK5*)), learning- and memory-related genes (glutamate ionotropic receptor NMDA type subunit 1 (*GRIN1*), *GRIN2A*, *GRIN2B*, *GRIN2C*, *GRIN2D* and *GRIN3A*), AD-related genes (apolipoprotein E (*APOE)* and triggering receptor expressed on myeloid cells 2 (*TREM2*)), cholecalciferol pathway-related genes (vitamin D receptor (*VDR*), 24-hydroxylase (*CYP24A1*), 1α-hydroxylase (*CYP27B1*)) and calcium metabolism-related genes (calcium voltage-gated channel subunit alpha 1 C (*CACNA1C*)) at transcriptional level (7,9–13). Among these, VDR and Aβ1-42 relations gained particular attention, given that VDR has proven to be a mitochondrial TF (14,15). Given this background, the main questions were: 1) Does this alteration depend on the direct effect of Aβ on the gene expression? 2) Does it occur due to alterations in the expressions of general TFs in response to Aβ exposure? 3) Does it occur due to an interaction of Aβ and the TFs? Based on these possibilities, first, we have investigated the proteins that have the potential to interact with the precursor protein of Aβ1-42, APP, using the FpClass protein-protein interaction (PPI) prediction program. We have determined that APP can interact with over a hundred TFs (16). Then, we utilized the TRRUST v2 database to identify the TFs (5) that regulate the genes that we have already shown to be affected by Aβ1–42 treatment (11–13). Finally, we compared these TFs with APP-interacting TFs. We have selected the TFs with the highest PPI scores as the candidate TFs that can be affected by the Aβ peptide. These TFs were Jun, Fos, activating transcription factor 2 (Atf2), activating transcription factor 4 (Atf4), RelA, nuclear factor kappa B (NF-κB), Smad3, signal transducer and activator of transcription 1 (STAT1), signal transducer and activator of transcription 3 (STAT3) and Sp1 (5). To answer the second question, we aimed to investigate the possible changes in the expressions of relevant TFs at different doses of Aβ1-42 and any alteration of TFs in blood samples of core AD CSF biomarker confirmed AD cases and plasma ALZpath pTau217 confirmed healthy subjects in this study.

METHODS

Determining the candidate TFs that might be regulated by Aβ1-42

Our previous study indicated 1133 partners for APP (16). After reanalyzing the data with the TRRUST v2 database (17), we merged the data from the FpClass tool and the TRRUST database and identified 17 TFs *in silico* (5). In the present study, we investigated the mRNA levels of top 10 scoring TFs (Jun, Fos, Atf2, Atf4, RelA, NF-κB, Smad3, STAT1, STAT3, and Sp1) (Table 1) in response to Aβ1-42 treatments *in vitro*, and the levels of selected TFs that have the highest PPI scores (Table 1) namely Jun, Fos, and RelA in AD cases and healthy subjects, to investigate whether the current set-up will support the previous *in silico* data.

Cell culture and Aβ1-42 treatment

HEK293T cells (ATCC, CRL-3216) were seeded at 10% confluency per well in a 6-well plate in DMEM (Gibco, 41966–029) containing 10% FBS (Gibco, 10270–098) and maintained at 37°C and 5% CO_2 in an incubator. The medium was refreshed every 2–3 days. To investigate the potential effects of Aβ1-42 under physiological and toxic conditions, two different concentrations were used—one representing a non-toxic dose and the other the maximum toxic dose—based on our previous publications and findings from our studies. The cells were treated with Aβ1-42 when they reached 70–80% confluency. Aβ1-42 (Millipore AG912) was reconstituted in phosphate-buffered saline as previously described (11,18). HEK293T cells were treated with either 0.09 μM or 10 μM Aβ1-42. The cells were incubated for 24 h, 48 h, or 72 h. Medium was not changed after Aβ1-42 treatments. Three independent experiments were performed. Cytotoxicity levels were assessed using a Cytotoxicity Detection kit (Roche, 11644793001) according to the manufacturer's instructions, as previously reported (11). Each sample was tested in triplicate.

AD cases and healthy subjects

Twenty-five AD CSF core biomarker-confirmed AD cases, and 23 plasma ALZpath pTau217 confirmed age-matched control subjects were included in this study. Given that the lumbar puncture is an invasive method, CSF sampling was performed only on cases and the control subjects were confirmed with blood biomarker, namely plasma ALZpath pTau217. NIA-AA 2011 criteria were utilized for clinical diagnosis (19). Routine measurements of CSF Aβ1-42, total Tau (t-Tau), and phosphorylated Tau (p-Tau181) were conducted at the Brain and Neurodegenerative Disorders Laboratory, Department of Neuroscience, Institute of Neurological Sciences, Istanbul University-Cerrahpasa. This laboratory is an active participant in the Alzheimer's Association Quality Control program. Core AD biomarkers were analyzed in CSF samples using ELISA (MultiSkanEX, Thermo) with the following FUJIREBIO kits: INNOTEST β-AMYLOID (1–42) Sandwich ELISA Kit (81576), INNOTEST hTAU Ag Sandwich ELISA Kit (81572), INNOTEST PHOSPHO-TAU (181P) Sandwich ELISA Kit (81574). All assays were performed in accordance with the manufacturers' protocols. Plasma levels of the pTau217 biomarker in control subjects were measured using the SIMOA-SRX platform (Quanterix, MA, USA) and the Simoa ALZpath p-Tau 217 Advantage PLUS assay kit (104570), also following the manufacturer's instructions. Participants with autoimmune, inflammatory, infectious, chronic heart, or psychiatric disorders, as well as those with significant laboratory abnormalities or a history of diabetes mellitus or stroke, were excluded from the study. Additional assessments included age, disease onset, and Mini-Mental State Examination (MMSE) scores. Subject demographics are detailed in Table 2. All procedures followed the ethical principles of the World Medical Association's Declaration of Helsinki, and informed consent was obtained from all participants. The study was approved by the Clinical Research Ethics Committee of Cerrahpasa Faculty of Medicine, Istanbul University-Cerrahpaşa, with the numbers 02.01.2023–573754 and 26.05.2022–389678.

mRNA Expression Analysis

RNA was isolated with PureLink RNA Mini Kit (Thermo Fisher, 12183018A) from cell cultures and with QIAmp RNA Blood Mini Kit (Qiagen, 51303) from K3EDTA treated blood samples of AD cases and healthy individuals following the manufacturers' protocols. cDNA synthesis was performed using iScript cDNA synthesis kit (Biorad, 1708891) with a fixed amount of RNA (20 ng) from each sample. The expression levels of the *JUN*, *FOS*, *ATF2*, *ATF4*, *RELA*, *NFKB*, *SMAD3*, *STAT1*, *STAT3* and *SP1* mRNAs were investigated by qRT-PCR with Universal Probe Library (UPL) probes, a LightCycler 480 Probe Master Mix kit (Roche, 04707494001), and LightCycler 480 II Instrument (Roche Applied Biosystems). *ACTB*, *RPL13A* and *B2M* were used as endogenous reference genes for normalization. The primers and probes were used as follows: *JUN*: ENSG00000177606.6, UPL probe #41 (Roche, 04688007001); *FOS*: ENSG00000170345.9, UPL probe #46 (Roche, 04688066001); *ATF2*:ENSG00000115966.16, UPL probe #65 (Roche, 4688643001); *ATF4*:ENSG00000128272.14, UPL

Table 1. Transcription factors selected by combining data obtained from FpClass tool and TRRUSTV2 database and related publications†

		Transcription factors									
		JUN	**FOS**	**RELA**	**ATF2**	**SMAD3**	**NFKB1**	**ATF4**	**STAT1**	**STAT3**	**SP1**
Aβ1-42 Related Genes	APP	+							+		+
	APOE							+			+
	BACE1			+			+				+
	PSEN1										+
	PSEN2										
	GSK3A			+			+				
	GSK3B						+				
	GRIN1			+			+				+
	iNOS	+	+	+			+		+		
	NGF	+	+								
	VDR	+				+				+	
	CYP24A1										
	CYP27B1			+			+				
APP FpClass PPI Score		**0.8826**	**0.8826**	**0.8391**	**0.7955**	**0.7895**	**0.7459**	**0.7167**	**0.6906**	**0.6126**	**0.5159**

Aβ: Amyloid beta; APP: Amyloid precursor protein; APOE: Apolipoprotein E; ATF2: Activating transcription factor 2; ATF4: Activating transcription factor 4; BACE1: Beta-secretase 1; CYP24A1:24-hydroxylase; CYP27B1:1α-hydroxylase; GSK3A: Glycogen synthase kinase 3 alpha; GSK3B: Glycogen synthase kinase 3 beta; GRIN1: Glutamate ionotropic receptor NMDA type subunit 1; iNOS: Inducible nitric oxide synthase; NGF: Nerve growth factor; NFKB: Nuclear factor kappa B; PPI: Protein-protein interaction; PSEN1:Presenilin 1; PSEN2: Presenilin 2; STAT1: Signal transducer and activator of transcription 1; STAT3: Signal transducer and activator of transcription 3; VDR: Vitamin D receptor
†Gezen-Ak, D., et al., The Transcriptional Regulatory Properties of Amyloid Beta 1–42 may Include Regulation of Genes Related to Neurodegeneration. Neuromolecular Med, 2018. 20(3): p. 363–375.
Dursun, E., D. Gezen-Ak, and S. Yilmazer, A novel perspective for Alzheimer's disease: vitamin D receptor suppression by amyloid-beta and preventing the amyloid-beta induced alterations by vitamin D in cortical neurons. J Alzheimers Dis, 2011. 23(2): p. 207–19.
Dursun, E., D. Gezen-Ak, and S. Yilmazer, Beta amyloid suppresses the expression of the vitamin d receptor gene and induces the expression of the vitamin d catabolic enzyme gene in hippocampal neurons. Dement Geriatr Cogn Disord, 2013. 36(1–2): p. 76–86.
Dursun, E., D. Gezen-Ak, and S. Yilmazer, A new mechanism for amyloid-beta induction of iNOS: vitamin D-VDR pathway disruption. J Alzheimers Dis, 2013. 36(3): p. 459–74

probe #76 (Roche, 04688996001); *RELA*: ENSG00000173039.18, UPL probe #21 (Roche, 04686942001); *NFKB*: ENSG00000109320.11, UPL probe #22 (Roche, 04686969001); *SMAD3*:ENSG00000166949.15, UPL probe #22; *STAT1*:ENSG00000115415.18, UPL probe #1 (Roche, 04684974001), *STAT3*:ENSG00000168610.14, UPL probe #65 and *SP1*:ENSG00000185591.9, UPL probe #12 (Roche, 04685113001). Primer sequences were given in Supplementary Material 1. Each PCR amplification was performed in triplicate as previously described (11,18).

Statistical Analysis

Relative expression levels of the target genes were determined using the formula $\Delta Ct=2^{(\text{Geometric mean of housekeeping genes - Ct target gene})}$. Graphpad Prism 8 was used to analyze the raw data for each group. Data were compared using one-way ANOVA, and subsequently, a Tukey-Kramer multiple comparisons test in cases where the data followed a normal distribution and the difference between the obtained standard deviations (SD) is not significant. When data was not distributed normally or the difference between the SDs is significant, a Kruskal-Wallis test was utilized to compare data, followed by a Dunn's multiple comparisons test. $p<0.05$ was considered to be statistically significant. Data are given as mean (SD). All data regarding human samples were analyzed via Independent Samples t-Test. The given p values represent the 2-tailed significance. Equality of Variances and means checked by Levene's Test for Equality of Variances and t-test for Equality of Means. The distribution of gender was analyzed by the Chisquare (χ^2) via IBM Statistical Package for Social Sciences (SPSS) program version 24.0.

Protein-Protein Interaction and Pathway Analysis

Potential PPIs were analyzed by STRING which is a predicted protein–protein interaction network (https: //string-db. org/) (20), and pathway analysis of APP and the target TFs were done by Reactome Pathway Browser 3.7, a curated database of pathways and reactions in human biology (21).

RESULTS

Alterations in the mRNA Expression Levels in Cell Cultures

At 24 h of the treatments, *JUN*, *FOS*, and *SP1* expressions were increased in the cells treated with 0.09 μM Aβ1-42 ($p<0.01$, $p<0.0001$ and $p<0.0001$, respectively), and *JUN*, *NFKB* expression was increased while *STAT1* expression was decreased in the cells treated with 10 μM Aβ1-42 ($p<0.05$, $p<0.0001$ and $p<0.001$, respectively) compared to the untreated cells. Forty-eight hours after the treatments, the expression level of *FOS*, *STAT1*, *STAT3*, *ATF2*, and *SP1* was elevated in 10 μM Aβ1-42 group ($p<0.01$, $p<0.0001$, $p<0.01$, $p<0.01$, and $p<0.0001$, respectively), where *RELA* and *NFKB* was reduced in 0.09 μM Aβ1-42 group ($p<0.01$, and $p<0.0001$, respectively). At 72h, 0.09 μM Aβ1-42 treated cells had lower RELA, STAT1, STAT3, ATF2, and SP1 expressions ($p<0.0001$, $p<0.01$, $p<0.05$, $p<0.0001$, and $p<0.01$, respectively), and 10 μM Aβ1-42 treated cells had lower *JUN*, *STAT1*, *ATF2* and *SP1* expressions ($p<0.01$, $p<0.01$, $p<0.0001$, and $p<0.001$, respectively) while had higher *ATF4* and *NFKB* expression ($p<0.001$ and $p<0.01$, respectively) in comparison to the untreated cells (Fig. 1). Cytotoxicity results were given in Supplementary Material 2.

Human Samples

There was no significant difference in the mean age or gender distribution between the healthy subjects and the AD cases ($p>0.05$). Alzheimer's disease cases had significantly lower MMSE scores compared to healthy individuals ($p<0.0001$). The demographics of all groups are given in Table 2.

Mean ± SD of Aβ1-42 was 450.0±154.0 pg/ml, pTau (181) was 93.3±38.2 pg/ml, and tTau was 631.0±225.4 pg/ml in AD cases. AT (N) classification was determined based on cutoffs for A (Aβ1-42): 813pg/ml, T (pTau181): 52pg/ml, and (N) (tTau): 375pg/ml as previously described (22). Given that AT (N) distribution of the AD cases were as follows: A+ (100.0%), A- (0%); T+ (84.0%), T- (16.0%); (N)+ (92.0%), (N)- (8.0%). The mean ± SD of plasma pTau217 was 0.16±0.08 pg/ml in healthy subjects. Each individual in the healthy control group had a concentration of less than 0.66 pg/ml, indicating the absence of amyloid beta pathology (100% A-).

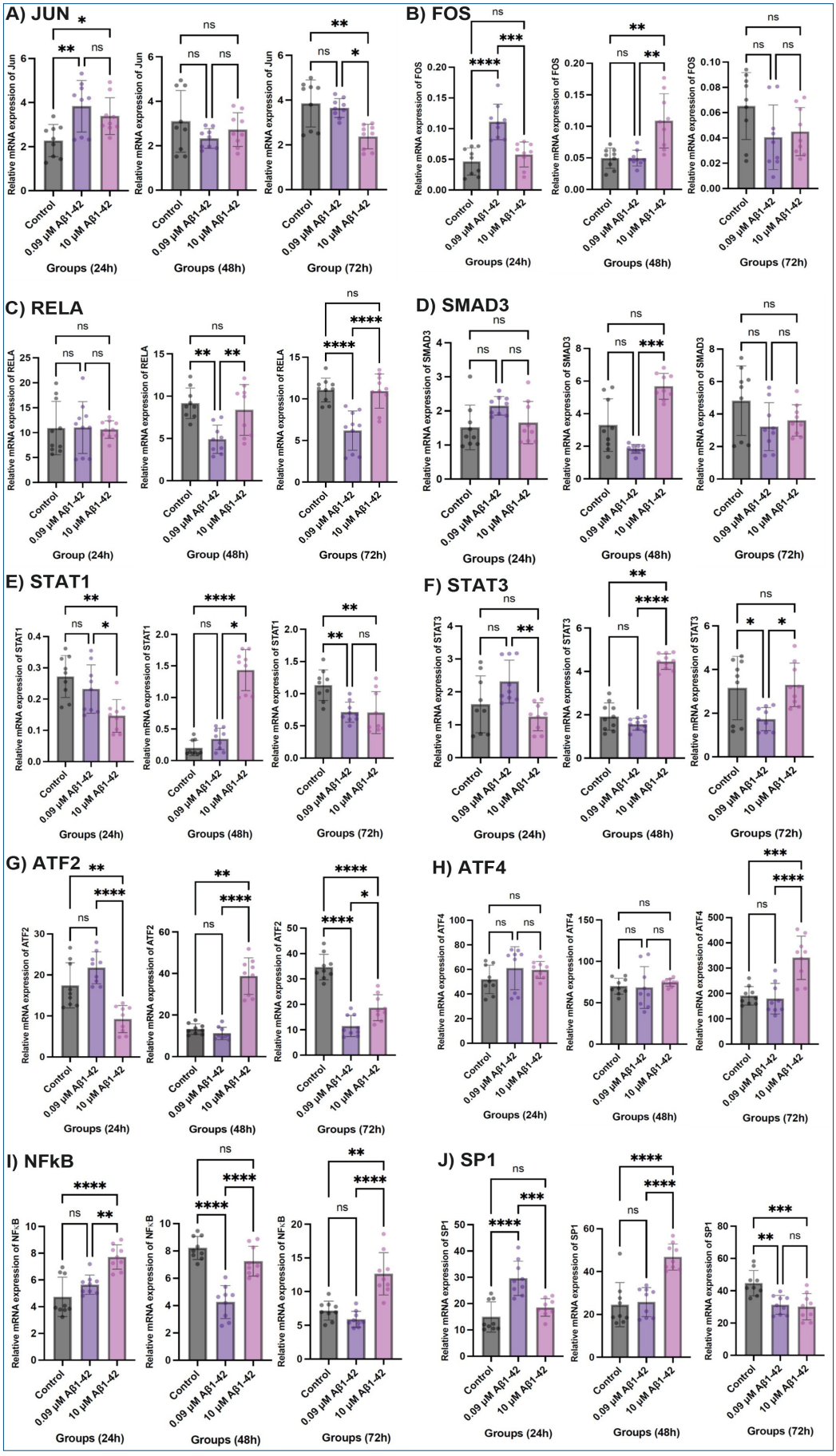

Figure 1. mRNA expression levels of transcription factors (relative mRNA expression levels of JUN, FOS, ATF2, ATF4, RELA, NFKB, SMAD3, STAT1, STAT3 and SP1 mRNAs at 24, 48 or 72 h. Data are presented as the mean (SD). *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001).

The mRNA Expression Levels of Transcription Factors JUN, FOS, and RELA in Human Samples

The mRNA expression levels of JUN and RELA were significantly higher in blood samples from AD cases compared to healthy individuals (p=0.0001 and p=0.001, respectively). Although the mRNA expression levels of FOS were relatively high in AD cases, they were not statistically significant (Table 2).

Protein Interactions and Pathways

STRING analysis showed that APP might interact with Jun (Combined Score: 0.790), Fos (Combined Score: 0.543), RelA (Combined Score: 0.552), NF-κB (Combined Score: 0.870), STAT1 (Combined Score: 0.483) and STAT3 (Combined Score: 0.753) directly (Fig. 2). Reactome analysis revealed that APP and the target TFs may be associated, particularly in the

Table 2. The demographics of the cohort and the relative mRNA expression levels of JUN, FOS, RELA

	Healthy subjects (n=23)	AD (n=25)	p Value
Age (years)	*64.44±6.89	67.64±10.71	p>0.05
Age of onset (years)	-	62.36±9.49	-
Gender: Female (F); Male (M) (%)	F (56.5%); M (43.5%)	F (56.0%); M (44.0%)	p>0.05
MMSE	29.20±0.77	17.00±7.79	**p<0.001**
CSF Aβ1-42 (pg/ml)	-	450.0±154.0	-
CSF pTau181 (pg/ml)	-	93.3±38.2	-
CSF total Tau (pg/ml)	-	631.0±225.4	-
Plasma ALZpath p-Tau 217 (pg/ml)	0.16±0.08	-	-
A	**A+ (0%), A- (100.0%)**	**A+ (100.0%), A- (0%);**	
T	-	**T+ (84.0%), T- (16.0%);**	
(N)	-	**(N)+ (92.0%), (N)- (8.0%)**	
JUN mRNA expression	0.83±0.35	2.19±1.65	**p=0.0001**
FOS mRNA expression	37.10±20.07	48.47±32.63	p=0.15
RELA mRNA expression	2.61±0.48	3.18±0.68	**p=0.001**

AT (N) classification of AD cases was determined based on cutoffs for A (Aβ1-42): 813pg/ml, T (pTau181): 52pg/ml, and (N) (tTau): 375pg/ml as previously described. Amyloid pathology (A) of healthy control group determined based on cutoff 0.66 pg/ml for plasma ALZpath p-Tau 217. All data were analyzed via Independent Samples t-Test. The given p values represent the 2-tailed significance. Equality of Variances and means checked by Levene's Test for Equality of Variances and t-test for Equality of Means. The distribution of gender was analyzed by the Chisquare (χ^2). Statistically significant values were presented in bold. AD: Alzheimer's disease.

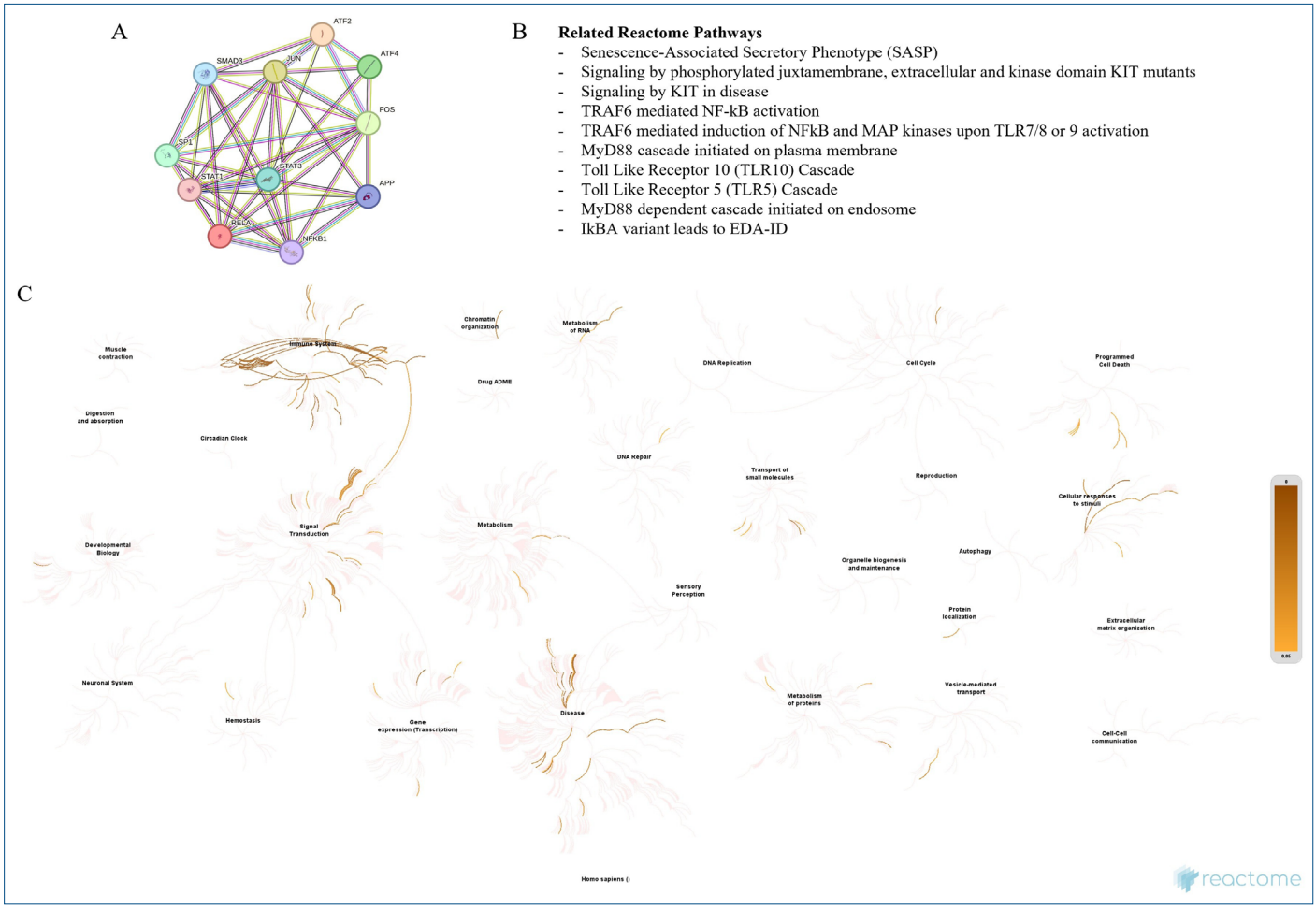

Figure 2. PPI and pathway analysis (A: STRING analysis shows that APP is related with Jun, Fos, RelA, NF-κB, STAT1 and STAT3; B: Top 10 related Reactome pathways (see also Supplementary Material 3); C: Overall Reactome pathways

immune system and signal transduction pathways. The pathways and false discovery rate (FDR) scores are presented in Fig. 2 and Supplementary Material 3.

DISCUSSION

The transcriptional effects of Aβ have been an emerging field of investigation in recent years as researchers seek to comprehend the molecular mechanisms that underlie AD. We and others have demonstrated that Aβ can translocate to the nucleus (10,23) and bind to DNA (7,24). These findings have raised questions about whether Aβ itself may act as a TF or not. On the other hand, given the presence of studies showing that Aβ alters the expression of many genes, we hypothesized the possibility of Aβ affecting such a large number of genes by regulating the expression of general TFs instead of regulating these genes directly itself.

TFs are key regulators of gene expression. TFs regulate a variety of signaling pathways and cellular processes, including development, cell division, differentiation, cell metabolism, and immune response (25). Jun (c-Jun, JunB, and JunD) and Fos (c-Fos, FosB, Fra-1, and Fra-2) proteins are the major constituents of the activator protein-1 (AP-1) complex, which controls neuronal survival and death (26–30). c-Jun is the major nuclear substrate of c-Jun N-terminal kinase (JNK), which mediates a dual-natured response that can result in either neurodegeneration or neuroprotection (31). Increased c-Jun protein levels were found in the CA1 region of the AD hippocampus (32). Likewise, we found that peripheral blood samples of AD cases had higher levels of JUN mRNA compared to the healthy subjects. In *in vivo* AD model, rats, and primary astrocytes treated with Aβ showed that the total c-Jun level remained unchanged while the phosphorylated c-Jun level increased (33). There are studies indicating that Jun regulates inducible nitric oxide synthase (iNOS) (34,35), nerve growth factor (NGF) (36), and VDR (37), and binds to the promoter sequence of *APP* (38), which we showed in our previous studies that the expression levels of each altered by Aβ1-42 treatment (11–13,18). In this study, we observed that the expression level of JUN altered in a dose and time-dependent manner in response to Aβ treatments.

c-Fos is suggested to play a protective role against neurodegeneration and is considered an indicator of neuronal activation (39). APP was shown to be involved in the regulation of c-Fos in APP-transgenic mice (40). Another study showed that both c-Fos and c-Jun showed intense immunolabeling in the hippocampus of Alzheimer's patients (41). However, the specific mechanism underlying the role of c-Fos in the pathophysiology of AD is unclear. The studies have shown that c-Fos is one of the TFs that regulate iNOS (34,35) and NGF (36), which are known to be associated with AD and whose levels have been shown to change with Aβ1-42 administration by our previous studies (11,18). We observed significant alterations in FOS expression levels in response to Aβ treatments, which might be considered a root factor for the changes in FOS-dependent genes in AD. We observed a relatively high mRNA expression of FOS in AD cases, yet it was not statistically significant. Atf2 and Atf4 are also members of the AP-1 complex and belong to the basic region-leucine zipper family. Studies have shown that Atf2 is involved in neuronal migration during development and also promotes nerve cell death (42). Atf2 expression in the hippocampus of AD brains was found to be reduced (42). Yamada et al. demonstrated that Atf2 localized in the cytoplasm of cortical neurons in AD patients, suggesting that the nuclear transport of Atf2 might be prevented, which could be associated with the early pathological changes of AD (43). In the study, we observed that the expression level of ATF2 increased with 10 μM Aβ1-42 treatment at 48h, while decreasing with 0.09 μM Aβ1-42 at 72 h. Atf4 is essential for development, metabolism, and memory formation (44). Atf4 protein level in the cortex of AD brains has been reported to increase 1.9 fold than that of age-matched controls (45). The expression levels of Atf4 have been shown to be elevated in AD transgenic mice (46). In the study, we found an increase in *ATF4* expression level after 10 μM Aβ1-42 treatment at 72 h. Atf4 was suggested to be a mediator of the neurodegenerative signal in AD pathology (47). Some studies suggest that the AD is associated with abnormal gene expression regulation via Atf4 (44). Geng et al. found an interaction between Atf4 and the promoter of *APOE*, a risk factor for AD. Moreover, they demonstrated that Atf4 overexpression resulted in increased *APOE* expression, whereas knockdown of Atf4 resulted in attenuation of the gene's expression (48). Significant alterations in the expression of c-Jun, c-Fos, Atf2, and ATF4 in response to Aβ exposure in our study may indicate a possible dysregulation of the AP-1 complex, which controls neuronal survival and death in AD-type pathology.

Nuclear factor-kappa B (NF-κB) is generated by the integration of five different proteins: p50, p52, RelA (p65), RelB, and c-Rel (49). NF-κB regulates target genes in the central nervous system in a pleiotropic manner, regulating both pathological neurodegenerative processes and normal function (50). NF-κB factors play a crucial role in regulating inflammation and apoptosis, and they also influence the pathophysiology of various neurodegenerative diseases and the programming of systemic aging in the brain (51,52). RelA subunit and its post-transcriptional modifications have a crucial role in the initiation of neurodegeneration induced by Aβ toxicity (50). Researchers found that injecting Aβ into mice and macaques increased the levels of NF-κB in the hypothalamus (53). In addition, dysregulation of NF-κB has been linked to neurodegeneration mechanisms in the AD brain (54). Another study demonstrated that Aβ1–42 stimulated the synthesis of prostaglandin E2, a major mediator of inflammation, and cyclooxygenase-2, a key enzyme in prostaglandin synthesis, through an NF-κB-dependent mechanism in human astrocytoma cells, suggesting a link between Aβ1–42 and NF-κB (55). Our current study has shown that *RELA* expression levels decreased after treatment with 0.09 μM Aβ1-42 at both 48 h and 72 h, and *NFKB* expression levels increased with 10 μM Aβ1-42 treatment at 24 h. On the other hand, we found that AD cases had higher levels of *RELA* compared to the healthy individuals.

Smad3 is a key intracellular mediator of the transforming growth factor-β (TGF-β) signaling pathway (56). Smad signaling is recognized for its crucial role in macrophage phagocytosis. Macrophages with inhibited Smad2/3 signaling exhibit an enhanced ability to phagocytose Aβ (57). Its role in macrophage phagocytosis of Aβ was also confirmed in primary cell cultures and AD animal models (58). Interestingly, decreased nuclear localization of Smad3 was observed in neurons containing tangles in AD, while association of cytoplasmic Smads with tau were demonstrated in other neurodegenerative disorders (59). In the current study, we observed an increase in *SMAD3* mRNA expression level with 10 μM Aβ1-42 treatment at 48 h.

Signal transducers and activators of transcription (STAT) factors mediate the effects of cytokines, growth factors, and hormones and organize numerous cellular processes including cell proliferation, differentiation, apoptosis, and development (60,61). Among the members of the STAT family, STAT1, 3, 5, and 6 are variably expressed in the brain (62,63). A study reported that STAT1 was more abundant in AD patients compared to healthy ones (64). Aβ was suggested to lead memory impairments by disrupting JAK2/STAT3 pathway in hippocampal neurons. On the other hand, the studies suggested that the level of phospho-STAT3 is decreased in both AD mouse models and hippocampal neurons of AD patients (65), and nuclear STAT3 levels were attenuated in neurons of AD brains (66). STAT1 was shown to regulate expression of APP and iNOS (67,68) while STAT3 interacts with VDR (69). We observed that both STAT1 and STAT3 expressions were altered in response Aβ exposure.

Sp1 has previously been shown to affect the expression of several AD-related genes (70) including *APP* (71), *BACE1* (72), *PSEN1* (73), *APOE* (74) and *GRIN1* (75), which we already demonstrated that their expression levels were altered by Aβ1-42 (13). A coordinated control of the transcription factors Sp1, AP-1 suggested to be a feasible method for treating neurodegeneration (76). Several studies have found Sp1 dysregulation in AD (77). According to Cao et al., Sp1 may simultaneously contribute to neuronal apoptosis and accelerate neuronal death in AD patients (78). In the current study, we showed that *SP1* expression level was elevated after 0.09 μM Aβ1-42 treatment at 24 h, while decreased at 72 h.

Consequently, our findings showed that the expression levels of *JUN*, *FOS*, *ATF2*, *ATF4*, *RELA*, *NFKB*, *SMAD3*, *STAT1*, *STAT3*, and *SP1* changed in response to Aβ1-42 administration, and these changes varied depending on the dose and duration of administration. Additionally, a significant increase was observed in the expression levels of JUN and RELA in AD cases, as a possible alteration of the general transcription factor was also confirmed in human samples. Moreover, a recent study we published showed that Mitochondrial Phosphoenolpyruvate Carboxykinase 2 which is regulated by Jun, Fos, and RELA, was significantly reduced in the CSF of AD cases (79). We should note that we investigated the TFs, given that most of their target genes had altered expression levels in our previous studies. The present study indicates that such alteration in the gene expressions seen in AD might be the result of more general dysregulation that involves the alterations of TFs. Another possibility is that the existence of a DNA-TF complex involving Aβ serves as a regulatory component, where any factor altering the binding duration of a DNA-binding protein may affect gene regulation (80). The cellular concentration of a TF protein can contribute to transcription activity (81). This suggestion also shows the importance of the expression levels of TFs for cell behavior and their possible relation with Aβ. The data suggest that Aβ1-42 might play a role in the regulation of gene expression through changing the expression of general TFs and influences many cellular processes such as inflammation, immune response, differentiation, apoptosis, and cell growth. However, it would be best to confirm this hypothesis via mechanisms of Aβ-DNA or Aβ-TF interactions with further studies.

SUPPLEMENTARY

https://www.noropsikiyatriarsivi.com/uploads/NPA_29229_EN_SUPPL.pdf

Ethics Committee Approval: No ethical approval is required for in vitro studies given the research was done with commercially purchased HEK293T cells. The study was approved by the Clinical Research Ethics Committee of Cerrahpasa Faculty of Medicine, Istanbul University-Cerrahpaşa with the numbers 02.01.2023-573754 and 26.05.2022-389678.

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Conflict of Interest: The authors declared that there is no conflict of interest.

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