FEBS Letters 586 (2012) 4357–4361

journal homepage: www.FEBSLetters.org

Characterization of the novel protein P9TLDR (temporal lobe down-regulated) with a brain-site-specific gene expression modality in Alzheimer's disease brain

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ARTICLE INFO

Article history:
Received 19 September 2012
Revised 5 October 2012
Accepted 29 October 2012
Available online 15 November 2012

Edited by Jesus Avila

Keywords:
Alzheimer's disease
Amyloid
Brain
Mapt
Neurotoxicity
Neurodegeneration
Tau

ABSTRACT

Alzheimer's disease (AD) is an aging-related neurodegenerative disorder characterized by irreversible loss of higher cognitive functions. The disease is characterized by the presence of amyloid plaques and neurofibrillary tangles (NFT). In the current study we isolated from an intra-cerebral brain-site-specific (AD temporal lobe vs. AD occipital lobe) polymerase chain reaction (PCR)-select cDNA suppression subtractive hybridization (PCR-cDNA-SSH) expression analysis the novel gene P9TLDR, potentially a microtubule-associated protein involved in neuronal migration, with an altered expression pattern: down-regulated in the temporal lobe cortex of early stage AD brains. In an in vitro AD-related cell model, amyloid-β peptide (Aβ)-treated neurons, reduced P9TLDR expression correlated with increased tau protein phosphorylation. In conclusion, interference with the P9TLDR signalling pathways might be a therapeutic strategy for the treatment of AD.

1. Introduction

As a progressive neurodegenerative disorder of the central nervous system (CNS), AD is characterized by impaired memory and the deterioration of higher cognitive functions [1,2]. Though the exact mechanism that leads to the clinical manifestations of sporadic or familial AD has yet to be fully understood, it is postulated to be a multifactorial syndrome that includes causes as diverse as lifestyle, environmental and genetic factors [3,4]. The pathological hallmarks of AD include deposition of extracellular amyloid plaques, cerebrovascular amyloidosis and intracellular NFTs. NFTs are formed by hyper-phosphorylation of the microtubule-associated protein tau (MAPT), while proteolytic processing of the Amyloid beta Precursor Protein (APP) generates the neurotoxic Aβ peptide, which has been implicated in the formation of neuritic amyloid plaques [5,6]. Neurodegeneration (ND) in AD progresses sequentially, starting firstly in predisposed induction sites from the medial temporal lobe, advancing in topographically predictable sequences and ultimately expanding to the temporal association cortex. Some neuronal types, cortical areas and subcortical nuclei remain almost untouched, whereas others sustain severe damages. While the occipital lobe cortex retains nearly normal function, even in terminal stage patients, the temporal lobe cortex, by contrast, as one of the most fragile parts of the brain, is extremely vulnerable to neuronal death [7–10]. Thus, it might be possible to identify in the temporal lobe those genes that are causative for AD, and in the occipital lobe eventually those genes that are capable to prevent ND in this area. Accordingly, we previously compared the genetic expression profile in the occipital and temporal lobes of a patients with AD using the state-of-the-art inter- and intra-cerebral brain-site-specific PCR-cDNA-SSH technology, that had various advantages over conventional methods such as GeneChip microarrays, to present a gene expression profile of a number of known genes, such as MAP1B, NCALD, FKBP14, p33MONOX, CLIPR-59, TRIM32/37, HSP90 or RTN3 that undergo brain-site-specific changes in AD, and discussed their potential involvement in progressive ND in AD brains [11–15].

In the current study we specifically searched for novel genes that were previously down-regulated (unpublished) in the temporal lobe (=up-regulated in the occipital lobe) of AD patients in our inter-cerebral brain-site-specific (AD temporal lobe vs. control temporal lobe and AD temporal lobe vs AD occipital lobe) analysis [12] to isolate the novel thus far unknown gene P9TLDR that

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0014-5793/$36.00
http://dx.doi.org/10.1016/j.febslet.2012.10.050

showed now also a down-regulation in the temporal lobe cortex in our intra-cerebral brain-site-specific PCR-cDNA-SSH differential screening (AD temporal lobe vs. AD occipital lobe) analysis and we disclose its potential neurobiological features using molecular and cell biological studies as well as bio-computational analyses.

2. Materials and methods

2.1. Reagents

Unless indicated, all reagents used for biochemical methods were purchased from Sigma–Aldrich (St. Louis, MO, USA). Recombinant human brain-derived neurotrophic factor (BDNF) was obtained from PeproTech (Rocky Hill, NJ, USA). Aβ (1–40) was purchased from Peptide Institute Inc. (Osaka, Japan) and a stock-solution prepared at a concentration of 1 mg/ml in phosphate-buffered saline (PBS) pH 7.4 with a 24 h pre-incubation period at 37 °C before cell culture experiments were performed [16,17].

2.2. Antibodies

Anti-MAPT (microtubule-associated protein tau, 1:1000, mouse monoclonal (TAU-5); Cat-No: 577801, recognizes the ~45–68 kDa tau protein; Calbiochem, Millipore, Tokyo, Japan) and anti-phosphorylated MAPT (p-MAPT, 1:1000, mouse monoclonal (AT-8), Ser202/Thr205; Thermo Scientific Pierce, Rockford, IL, USA).

2.3. Human subject

A patient with sporadic AD (early stage, low incidence; with neuropathological changes in the limbic system [5–7,18–22] Table 1) received a pathological diagnosis of AD according to the criteria of the Consortium to Establish a Registry for AD (CERAD) and the Braak stage [7,23,24]. The patient was also cognitively evaluated by neuropsychological tests using the mini-mental state examination (MMSE) and Hasegawa's dementia scale (HDS, or the HDS revised version (HDS-R)) which is commonly utilized in Japan as we have previously reported [12,24–26]. The brain was obtained from the brain bank of the Choju Medical Institute of Fukushimura hospital (Toyohashi, Aichi, Japan), and the protocols utilized were independently approved by the local ethics committees of the Brain Function Research Institute (Osaka, Japan) and the Fukushimura hospital [12]. The scientific use of human material was conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from the guardians of the patient. The brain was weighed at the time of autopsy, snap frozen with liquid nitrogen, and stored at −80 °C. The case we selected had not been on life support with artificial ventilators. In particular, we carefully selected a relatively young (75-year-old) test subject who

Table 1
Characteristic features of the human brain tissue samples.

Patient No ([12])	Pathological diagnosis	Gender	Age (years)	Stage of amyloid deposits (–, A, B, C)	NFTs stage (I–VI)	PMI (h)	Cerebral cortex area
V	SDAT	Female	75	C	III–IV	3	Temporal/ Occipital

SDAT: Senile dementia with Alzheimer's type.
NFTs: neurofibrillary tangles.
PMI: post-mortem-interval in hours.
– = none, A = rare or a few, B = mild or moderate, C = numerous or marked.
Temporal lobe, Brodmann's area No. 21 (the 'T2' area).
Occipital lobe, Brodmann's area No. 19 (near the lateral occipital gyrus).

Gene ID: 100128226
UniGene: Hs.694587
Gene symbol: LOC100128226
Location: Human Chromosome 11q23.1
UniProtKB/TrEMBL: A4PB32
GenBank: Protein-ID: BAF51963.1; LOCUS: AB128931; 1589 bp
Length: 77 amino acids, **Molecular weight:** 9,039 Da, **Theoretical pI:** 11.25, **Aliphatic index:** 60.91,
Protein Sequence:
MLGRKALAKG CYVQGHRQWS ACRSAACHKR PNTFYLFFFS FFLFRSCHPG WSAVSRYRTT LHSSLGDRPR LRLKKIK

UniRef cluster member(s):
- A4PB32_HUMAN, Homo sapiens, 77aa (P9TLDR)
- G3SGA0_GORGO, Gorilla (Lowland gorilla), 75aa
- F7IAR5_CALJA, Callithrix jacchus (White-tuftedear marmoset), 73aa

Features:
- structural protein, cytoplasm/mitochondria,
- aa44 – aa75: region with high homology to NEK5 and NAV1.

Fig. 1. Characteristic features of the novel protein P9TLDR.

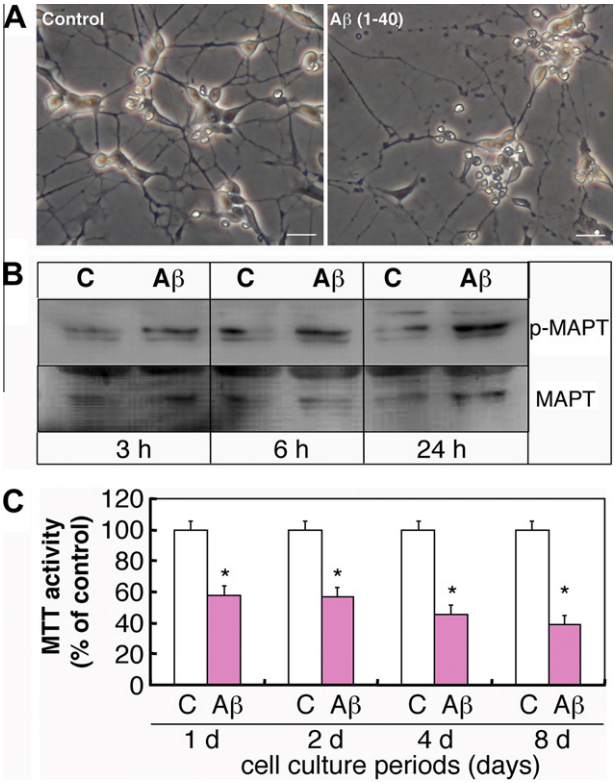

Fig. 2. Establishing an AD-related in vitro cell death system confirmed by various means. (A) Morphological cell analysis by microscopy revealed neurite degeneration induced by Aβ (1–40) in human differentiated neuronal SH-SY5Y cells. Pictures were taken 4 days after Aβ (1–40) (20 μM) treatment. Control: vehicle control, Aβ: Aβ (1–40) (20 μM) stimulation. Scale bar: 50 μm. (B) Western blot analysis of tau (MAPT) protein phosphorylation induced by Aβ (1–40) in human differentiated neuronal SH-SY5Y cells. Western blots were performed using anti-phosphorylated microtubule-associated protein tau (p-MAPT) and anti-MAPT (as internal control for equal protein loading) antibodies, respectively. C: vehicle control, Aβ: Aβ (1–40) (20 μM) stimulation. Upper panel shows a schematic representation of the time-dependent increased MAPT phosphorylation mediated by Aβ. (C) Time-course of Aβ (1–40) (20 μM)-induced cytotoxicity in human differentiated neuronal SH-SY5Y cells. MTT assay. C: vehicle control, Aβ: Aβ (1–40) (20 μM) stimulation. Cells were incubated for the indicated periods of days. $^{*}P < 0.05$.

was in the early/intermediate stage of AD in order to avoid effects other than the onset of AD, such as aging.

2.4. Human tissue RNA isolation, generation of a PCR-cDNA-SSH library, reverse transcription reaction, cDNA cloning, RT-PCR, P9TLDR mRNA and protein sequence analyses, cell culture, cell lysis and protein extraction, SDS–PAGE and western blot analysis

These procedures were described previously in detail (Supplementary materials and methods) [12,15–17,24,27–30].

2.5. MTT assay

Cell viability was assessed using the colorimetric MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay (Sigma, according to the manufacturer's protocol) which offers a quantitative method for evaluating neurons' response to Aβ (1–40) (2–20 μM), whether it be e.g. a decrease in growth due to apoptosis. Briefly, upon Aβ (1–40) (2–20 μM) stimulation, MTT was added at a final concentration of 0.3 mg/ml and incubated for 4 h at 37 °C/5% CO_2. Thereafter, the reaction was terminated with the same volume of detergent (10% SDS containing 1 mM NH_4OH) as that of culture medium. After further incubation for 24 h at 37 °C, the absorbance was quantified by spectrophotometric means at 550 nm. Experiments were performed twice, with each set repeated in triplicates [16].

2.6. Statistical analysis

The results are presented as mean ± S.D. The data were subjected to a Student's *t*-test (two-tailed; $P < 0.05$ was considered significant).

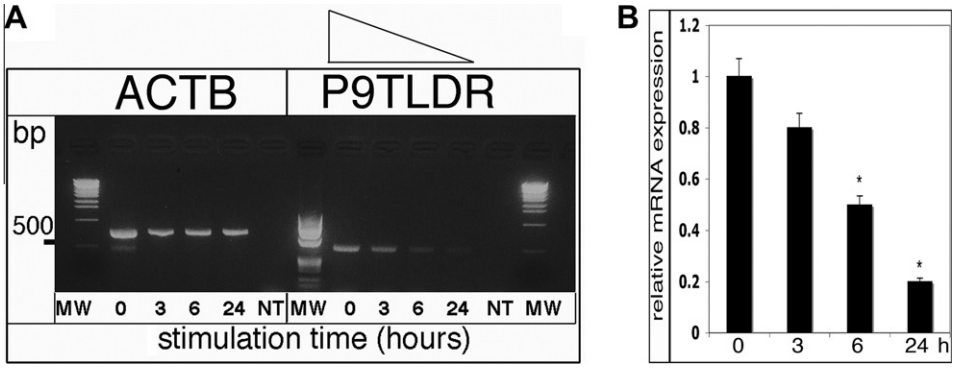

Fig. 3. Quantitative RT-PCR analysis of P9TLDR mRNA expression in Aβ (1–40) (20 μM)-treated human differentiated neuronal SH-SY5Y cells as described in Fig. 2. (A) Agarose gel analysis of the PCR products obtained by RT-PCR as described in materials and methods. Time duration of Aβ treatment shown in hours; NT: no template, control without mRNA template; MW: molecular weight marker (base-pairs (bp)). Upper panel shows a schematic representation of the time-dependent decrease in Aβ-mediated P9TLDR expression normalized to ACTB. A representative gel is shown. (B) Quantitation of the P9TLDR transcripts shown in (A). Values represent the ratios of the densitometric scores for P9TLDR and ACTB PCR products ± S.D. of three independent analyses (*$P < 0.05$ compared with controls at 0 h).

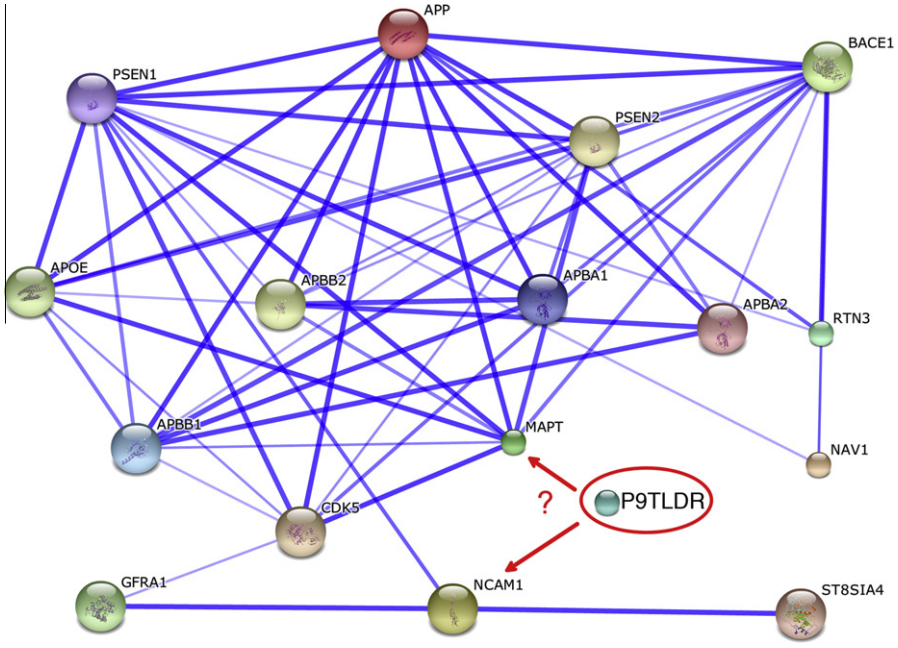

Fig. 4. STRING-9.0 analysis (at http://string-db.org/; default mode) of P9TLDR's potential interactive signalling pathways. The functional significance of P9TLDR within the APP and MAPT networks remains to be elucidated. APP, amyloid beta (A4) precursor protein; APBA1, APP-binding, family A, member 1; APBA2, APP-binding, family A, member 2; APBB1, APP-binding, family B, member 1 (Fe65); APBB2, APP-binding, family B, member 2; APOE, apolipoprotein E; BACE1, beta-site APP-cleaving enzyme 1; CDK5, cyclin-dependent kinase 5; GFRA1, GDNF family receptor alpha 1; MAPT, microtubule-associated protein tau; NAV1, neuron navigator 1; NCAM1, neural cell adhesion molecule 1; p9TLDR; PSEN1, presenilin 1; PSEN2, presenilin 2; RTN3, reticulon 3; ST8SIA4, ST8 alpha-*N*-acetyl-neuraminide alpha-2,8-sialyltransferase 4.

3. Results

3.1. Bio-computational characterization of the novel P9TLDR mRNA and protein sequences

We identified the novel gene P9TLDR (Fig. 1) that showed a significant down-regulation in our previous inter-cerebral brain-site-specific expression study in the lateral temporal lobe cortices of AD patients (not disclosed; [12]) which was herewith confirmed by our intra-brain-site-specific mRNA expression analysis (RRS-level (relative to the reverse-subtracted probes as described previously) [12]: 1.9 (temporal lobe vs occipital lobe)) .

Bio-computational sequence analyses revealed that P9TLDR seems to be a member of a novel protein family that comprises so far only two other uncharacterized proteins of 75 and 73 amino acids (aa), respectively.

Besides, we unraveled that P9TLDR (aa44 – aa75) has to some parts of the human neuron navigator 1 protein (NAV1 (1877aa), microtubule-associated protein involved in neuronal migration [31]), a 50% identity (over a sequence length of 31 aa). As such, it is interesting to note that the same sequence of 31 aa is also found to be homologous to NEK5 (NIMA (never in mitosis gene a)-related kinase 5)′, thus indicating that P9TLDR might be epigenetically controlled and eventually found in post-mitotic differentiated neurons only. Taking these findings into account it is worth to mention that NCAM1 (neural cell adhesion molecule 1) is also located on Chr 11q23.1 close to P9TLDR.

3.2. Expression of P9TLDR in Aβ-treated neurons

In order to understand the potential relationship between P9TLDR expression and AD, we applied an in vitro AD-related cell culture model where neuronal cell death was induced by the treatment with Aβ. At first, the AD-related Aβ-mediated cell death system was established in human differentiated neuronal SH-SY5Y cells (American Type Culture Collection (ATCC), Manassas, VA, USA) and confirmed by (i) morphological changes (Fig. 2A), (ii) the time-dependent phosphorylation of the tau protein MAPT (Fig. 2B) and (iii) Aβ-mediated neuronal cell death by MTT analysis (and confirmed by a lactate dehydrogenase (LDH) cytotoxicity assay (data not shown)) (Fig. 2C). This in vitro AD cell culture model was previously introduced by others and was also used by us to show a correlation between JNK (c-jun N-terminal kinase) and MAPT phosphorylation [16,32].

Accordingly, semi-quantitative RT-PCR analysis was performed at the indicated time points upon Aβ treatment (Fig. 3). Although Aβ-treated neurons showed significant neuronal cell death only by day 4 (Fig. 2A) [16,32], MAPT protein phosphorylation in Aβ-treated neurons occurred already 3 h after Aβ treatment, and JNK phosphorylation after 6 h (data not shown) [16,32]; the expression of P9TLDR progressively decreased at an earlier stage as well – at 3 h upon Aβ stimulation (Fig. 3).

4. Discussion

Due to its homologue region to NAV1 and NEK5 and its chromosomal location near NCAM1 it is tempting to speculate that P9TLDR may have a microtubule-associated functional role related to neuronal migration. The fact that P9TLDR showed reduced expression in the temporal lobes of comparatively early-stage AD patients and progressively reduced neuronal expression upon Aβ stimulation, suggests that its signalling pathways might be involved in neuropathophysiological processes that may play a pivotal role at early stages of AD with mild cognitive symptoms (Fig. 4).

Taking into consideration that the decreased expression of P9TLDR correlated in the in vitro AD model with early MAPT and JNK phosphorylation [16,32] – much earlier than the appearance of significant neuronal cell death – it seems that the function of P9TLDR might be disturbed prior to neuronal cell death.

Recently, it has been hypothesized that a prion-like transmission of misfolded hyper-phosphorylated MAPT or Aβ aggregates from neuron to neuron is one possible explanation for AD-associated anatomical regularity and progression which appears in the absence of both MAPT lesions in the transentorhinal region as well as cortical Aβ pathology. Misfolded MAPT in the neuronal cytoplasm may function as seed that triggers hyper-phosphorylation and misfolding of the natively unfolded MAPT protein. Disease progression is thus associated with the intercellular transfer of pathogenic proteins such as hyper-phosphorylated MAPT aggregates [33–35]. This sheds new light on the discussion that an impairment of the ubiquitin proteasome system (UPS) is affected at early stages of AD [36,37] and is in agreement with our previous data showing that pivotal proteins of the chaperone/proteasomal pathways, such as HSP90, FKBP14 and TRIM32/37, are changed at early stages of AD [12]. Accordingly, P9TLDR may also have a crucial role within an impaired chaperone/proteasomal degradation system that may contribute to the prion-like inter-neuronal transmission of protein aggregates eventually correlating with clinical symptoms at early stages of AD.

Concluding, our data provide a new perspective for further regional examination of brain P9TLDR expression levels in normal, AD and brains of other neurodegenerative diseases which might give a clue as to whether P9TLDR is involved in the disturbed higher brain functions. Further investigations also need to identify what triggers the down-regulation of P9TLDR in AD and under what circumstances this protein gets activated to interfere eventually with MAPT protein phosphorylation and the chaperone/proteasomal degradation system in order to develop better therapeutics for the treatment of AD.

Acknowledgements

This work was supported by the Hanyang University, the Brain Function Research Institute Inc. (Osaka, Japan) and by a grant from the Miyauchi Project of the Life Science Center of the Tsukuba Advanced Research Alliance (TARA; University of Tsukuba).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.febslet.2012.10.050.

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