Molecular Neurobiology (2019) 56:2838–2844
https://doi.org/10.1007/s12035-018-1242-2

DAPK1: a Novel Pathology and Treatment Target for Alzheimer's Disease

Ling-zhi Xu [1,2,3,4,5,6] · Bing-qiu Li [1,2,3,4,5,6] · Jian-ping Jia [1,2,3,4,5,6]

Received: 3 May 2018 / Accepted: 12 July 2018 / Published online: 31 July 2018

Abstract
Alzheimer's disease (AD) is the most common neurodegenerative disease and seriously damages the health of elderly population. Clinical drug research targeting at classic pathology hallmarks, such as amyloid-β (Aβ) and tau protein, failed to achieve effective cognitive improvement, suggesting that the pathogenesis of AD is much complicated, and there are still other unknown and undetermined important factors. Death-associated protein kinase 1 (DAPK1) is a calcium/calmodulin-dependent serine/threonine kinase that plays an important role in various neuronal injury models. Mounting evidence has demonstrated that *DAPK1* variants are associated with AD risk. The activation of DAPK1 is also involved in AD-related neurodegeneration in the brain. Exploring the roles of DAPK1 in AD might help us understand the pathogenic mechanisms and find a novel promising therapeutic target in AD. Therefore, in this review, we comprehensively summary the main progress of DAPK1 in the AD studies from genetic risk, neuropathological process, and clinical potential implications.

Keywords Death-associated protein kinase 1 · Alzheimer's disease · Variants · Neuropathology · Therapeutics

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder leading to dementia. It is estimated that about 40 million people around the world, mostly older than 60 years old, are suffering from this disease [1]. Rapid increase of AD prevalence is a challenge to public health and also brings huge social and economic burdens worldwide [1–4]. The past 30 years of AD research have demonstrated that AD is neuropathologically characterized by the accumulation of amyloid-β (Aβ) plaques and of hyperphosphorylated tau containing neurofibrillary tangles (NFTs). These neuropathological alterations are related to neurodegenerative processes in AD [1, 5]. This classical Aβ hypothesis has influenced drug discovery and development for AD more than 20 years. But there are no successful therapeutic drugs to reach the desired therapeutic effects. The incomplete understanding of complexity and multicausality of AD may account for this predicament. Many researchers propose that there may be other key factors in the etiology and progression of AD still unknown [1, 5–7].

Death-associated protein kinase 1 (DAPK1) belongs to DAPK protein family. DAPK1 is a calcium/calmodulin (Ca^{2+}/CaM)-dependent serine/threonine kinase and is responsible for several types of cell death, including apoptosis and autophagy [8, 9]. DAPK1 is composed of 1430 amino acids. From N-terminal to C-terminal, the protein structure of DAPK1 contains catalytic domain, Ca^{2+}/CaM binding domain, ankyrin repeats, cytoskeletal binding region, a death domain, and a serine-rich tail in sequence (see Fig. 1). DAPK1 is abundantly expressed in the brain, especially in the cerebral cortex, and is related to many neurological diseases, such as stroke, depression, and AD. The activation of DAPK1 is regulated by autophosphorylation of Ser308 within its Ca^{2+}/CaM binding domain; once DAPK1 is dephosphorylated from the phosphorylated physiological status, it becomes

✉ Jian-ping Jia
jiajp@vip.126.com

1 Innovation Center for Neurological Disorders, Department of Neurology, Xuan Wu Hospital, Capital Medical University, Beijing, People's Republic of China

2 Beijing Key Laboratory of Geriatric Cognitive Disorders, Beijing, People's Republic of China

3 Clinical Center for Neurodegenerative Disease and Memory Impairment, Capital Medical University, Beijing, People's Republic of China

4 Center of Alzheimer's Disease, Beijing Institute for Brain Disorders, Beijing, People's Republic of China

5 Key Laboratory of Neurodegenerative Diseases, Ministry of Education, Beijing, People's Republic of China

6 National Clinical Research Center for Geriatric Disorders, Beijing, People's Republic of China

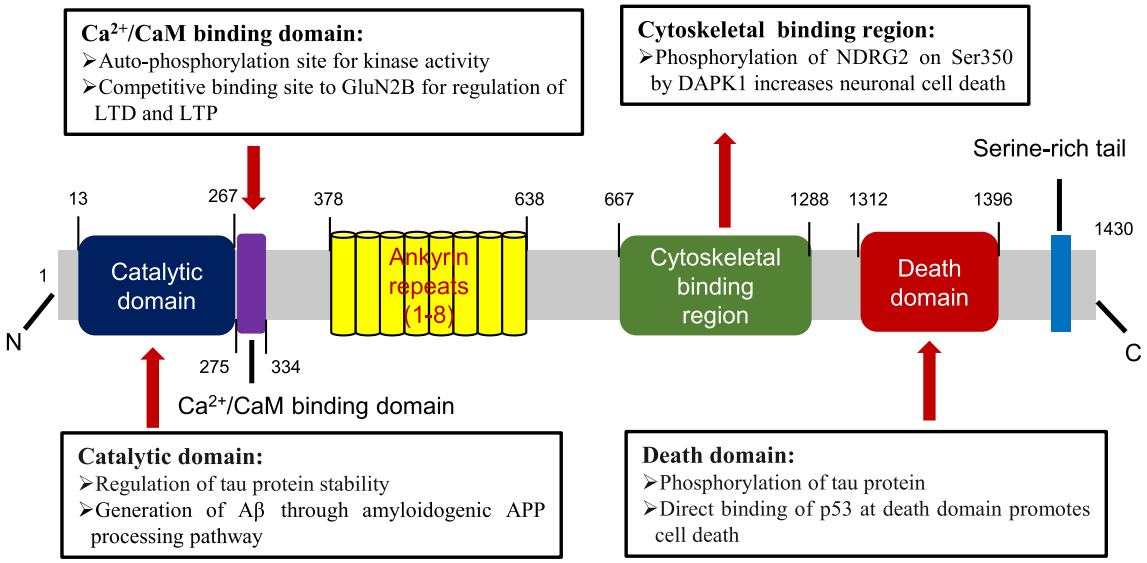

Fig. 1 Summary of the key domains of DAPK1 and their roles in the pathogenesis of AD. DAPK1 is mainly comprised of catalytic domain, ankyrin repeats, cytoskeletal binding region, and death domain. The potential biological roles of different domains of DAPK1 in the AD-related pathogenesis and synaptic damages are also depicted in this figure

activated [10, 11](Fig. 1). DAPK1 is a key mediator of cell death and is also involved in neuronal and synaptic damage in central nervous system (CNS).

Studies on *DAPK1* variants and DAPK1 protein in AD are increasing in recent years, while there are still many uncertain issues in understanding the susceptibility and pathogenicity of DAPK1 in AD. Here, we reviewed the recent findings of DAPK1 from genetics, neuropathology to clinical treatment, in AD-related studies. The purpose of the review is to help us better understand the important roles of DAPK1 in AD.

DAPK1 Variant and the Risk of AD

AD is highly heritable, and has complex genetic architecture, which makes its genetic analysis difficult [1, 3–5]. DAPK1 is highly expressed in the brains of AD patients and AD animal models, and its genetic variants are also associated with AD. *DAPK1 gene* is located in chromosome 9 in human. Li et al. firstly reported *DAPK1* variants are associated with late-onset Alzheimer's disease (LOAD) in 2006 [12]. They found that the two single nucleotide polymorphisms (SNPs) of *DAPK1*, *rs4878104* and *rs4877365*, were significantly associated with LOAD. Even the two SNPs are located within an intron of *DAPK1*; *DAPK1* transcript shows significant differences in allelic expression. This indicates that the two SNPs might possess the potential to directly or indirectly modulate the kinase activity of DAPK1. Thereafter, researchers carried out a lot of studies on the association between *DAPK1* polymorphisms and AD in different populations. In 2009, Schjeide et al. reported that the *DAPK1 rs4878104* in Caucasian population is a significant association with AD risk in the case-control (AlzGene) meta-analyses [13]. In 2010, Laumet et al. showed that *DAPK1 rs4878104* and *rs4877365* are a weak nominal association with AD risk in French population [14]. In 2011, Wu et al. examined the genetic variations of *DAPK1 rs4877365* and *DAPK1 rs4878104* in Chinese LOAD patients. There are significant differences in genotype and allele frequencies of *DAPK1 rs4878104* but not of *DAPK1 rs4877365* between LOAD patients and controls, and the "C" allele of *rs4878104* worked as a protective factor of LOAD in the Han Chinese [15]. The studies on association of *DAPK1 variants* with AD were summarized and described in Table 1.

However, there are also some negative results on *DAPK1* variants in AD [13, 16, 17]. In 2009, Minster et al. examined the two SNPs *rs4878104* and *rs4877365* in *DAPK1* in a large case-control cohort of Caucasian Americans LOAD subjects, and did not detect any association with AD for the two variations [17]. Tedde et al. examined the genotype and allele distributions of *rs4878104* and *rs4877365* in 681 Italian subjects, including patients with LOAD and frontotemporal dementia (FTD). They did not find the association with LOAD, but a positive association between *rs4878104* and FTD. In Schjeide et al. study, they also did not find *DAPK1* variation associated with AD risk in family-based samples in Caucasian population [13]. Recently, Hu et al. carried a meta-analysis [17] to figure out the potential association between *rs4878104* and AD. They found that *rs4878104* is significantly associated with AD risk in American population or Chinese population in subgroup analysis, but not in pooled population. They also found *rs4878104* T allele could significantly regulate the increase of DAPK1 expression in the European population [18].

Table 1 Summary of the articles on the association between DAPK1 variants and AD

Title	Author	Year	Journal	Variant	Subjects/ population	Association(±)
DAPK1 variants are associated with Alzheimer's disease and allele-specific expression.	Li et al.	2006	Hum Mol Genet	rs4878104 rs4877365	LOAD/Caucasian	rs4878104/+ rs4877365/+
No association of DAPK1 and ABCA2 SNPs on chromosome 9 with Alzheimer's disease	Minster et al.	2009	Neurobiol Aging	rs4878104 rs4877365	LOAD/Caucasian Americans	rs4878104/− rs4877365/−
Assessment of Alzheimer's disease case-control associations using family-based methods.	Schjeide et al.	2009	Neurogenetics	rs4878104	FAD/Caucasian	rs4878104/− rs4877365/−
Systematic analysis of candidate genes for Alzheimer's disease in a French, genome-wide association study	Laumet et al.	2010	J Alzheimers Dis	rs4878104 rs4877365	LOAD/French Caucasian	rs4878104/+ rs4877365/−
Association of DAPK1 genetic variations with Alzheimer's disease in Han Chinese	Wu et al.	2011	Brain Res	rs4878104 rs4877365	LOAD/Chinese	rs4878104/+ rs4877365/−
DAPK1 is associated with FTD and not with Alzheimer's disease.	Tedde et al.	2012	J Alzheimers Dis	rs4878104 rs4877365	LOAD and FTD/Italian	LOAD rs4878104/− rs4877365/− FTD rs4878104/+

LOAD late-onset Alzheimer's disease, *FAD* familial Alzheimer's disease, *FTD* frontotemporal dementia

As to the inconsistent findings, we speculate that there may be two important reasons that cause the variations. Firstly, the two common SNPs in *DAPK1* are both located in the intron, so the functional effects and their phenotypic consequences are complicated to predict. Secondly, the ethnicity can partly account for the inconsistent findings in different population. However, the association between *DAPK1* gene polymorphisms and AD cannot be ignored; there are more studies have demonstrated that DAPK1 protein level and kinase activity in AD patients and animal models were obviously elevated.

DAPK1 and Classical AD Pathology

It is well known that the characterized pathologies of AD are the extracellular senile plaques and the intracellular neurofibrillary tangles, and most AD studies are based on this theory. The amyloid-β (Aβ) is the major component of plaques, and hyperphosphorylated microtubule-associated tau is the major protein component of the tangles. Recent studies have confirmed that DAPK1 is involved in the pathological changes of Aβ and tau. Hainsworth et al. firstly reported that DAPK1 is markedly seen in somata, nuclei, and dendrites of large cortical neurons in the brain. The DAPK1 level in the frontal cortex is higher in severe LOAD cases than that in control aged human [19]. They also detected the difference in the DAPK1 level in the frontal cortex between aged (16–21 months) Tg2576 mice (a transgenic mouse model overexpressing a mutant form of *APP*, *APPK670/671L*) and their wild-type littermate controls, but no difference was found [19]. Shu et al. [20] detected the DAPK1 level and activity in the early stage of AD animal model. They found that DAPK1 is involved in the neurodegenerative changes of AD-related brain region in the early stage of AD. In their study, DAPK1 is selectively activated in excitatory pyramidal neurons, a one of the most vulnerable and the earliest affected brain cells, in the entorhinal cortical layer II region ($ECII_{PN}$) in AD mice. And selective inhibition of DAPK1 can protect against the impairment in the $ECII_{PN}$ synaptic transmission and function, rescue spines loss, and improve spatial learning and memory in AD mice [20].

Interestingly, DAPK1 is also contributed to the production of Aβ via the amyloidogenic processing [21], and previous studies have reported that *DAPK1* variants are significantly associated with the Aβ levels in cerebrospinal fluid (CSF) [22]. Overexpression of DAPK1 significantly increases Aβ secretion, and inhibition of DAPK1 can decrease Aβ40 and Aβ42 secretion in cultured cells. As to the mechanisms underlying DAPK1 promoting the amyloidogenic processing, DAPK1 can directly interact with APP and phosphorylate APP at the Thr668 site. Downregulation of DAPK1 expression or inhibition of DAPK1 can remarkably reduce the phosphorylation of APP at Thr668 and the secretion of Aβ40 and Aβ42 in cultured cells and Tg2576 mice [21].

These evidences indicate that DAPK1 plays a critical role in the pathogenesis and progression of AD through involvement in the neurotoxicity of Aβ and regulating Aβ production. However, some new puzzles need further exploration. Such as, which of Aβ and DAPK1 is the initiating factor? How DAPK1 is involved in the pathological process of AD? Is there a complicated feedback loop between DAPK1 and Aβ?

In addition to affecting the production of Aβ, DAPK1 is also involved in the pathological changes of tau protein.

DAPK1 is elevated in the hippocampus and cortex in the *hTau* transgenic mice [23], and DAPK1 can directly affect tau protein stability via phosphorylation of multiple AD-related sites of tau in vitro and in vivo, including Thr231, Ser262, and Ser396 [10, 23–25]. The phosphorylation of tau can be induced through direct interaction between DAPK1 and tau [23, 24] or through some key kinases activated by the catalytic domain or death domain of DAPK1, such as Pin1 and MARK1/2 [25, 26] (Fig. 1). The pathological effects of DAPK1 on tau protein mainly include microtubule assembly, neuronal apoptosis, spine damages, etc. Overexpression of DAPK1 can significantly increase tau phosphorylation at the AD-related sites, which lead to degeneration of synaptic transmission. While inhibition of DAPK1 can effectively increase the microtubule assembly and promote the neurite outgrowth and axonal formation [20, 24–26]. Interestingly, hyperphosphorylation of tau by DAPK1 can in turn inhibit proapoptotic process of DAPK1 [23]. These intriguing findings may be explained as the hyperphosphorylation of tau in the early phase of AD may have protective effects against DAPK1-induced cell damage and loss in the brain.

These evidences indicate that DAPK1 plays a critical role in the state of tau protein and its function in the degenerative progress of AD. However, the interesting interaction between DAPK1 and tau still need more studies in the future. We summarize the specific location of DAPK1 protein and potential signals involve in classical pathology of AD in Fig. 1 and Fig. 2.

DAPK1 and Neuronal and Synaptic Dysfunction

Neurons and synapses are the two most important structures in the brain, and their biological roles are closely related to the memory and other cognitive function. As neuronal loss and synaptic damage are essential events in AD progression and eventually leads to cognitive impairment and even dementia, and the critical roles and mechanisms of DAPK1 in neuronal cell death and synaptic damage have been substantiated in many studies.

The symptoms of AD begin with early alterations of synaptic plasticity and efficacy prior to neuronal degeneration, and that the synaptic dysfunction may be caused by multiple factors [27]. Long-term potentiation (LTP) and long-term depression (LTD) are the two opposing forms of synaptic plasticity underlying learning, memory, and other cognition [28]. DAPK1 has been reported to involve in LTP and LTD [29–31]. LTP and LTD inductions require activation of *N*-methyl-*D*-aspartate receptors (NMDARs), which triggers a signaling cascade that induces the alterations of postsynaptic protein and trafficking or endocytosis of related receptors [32, 33]. NMDARs are the predominant receptors for controlling

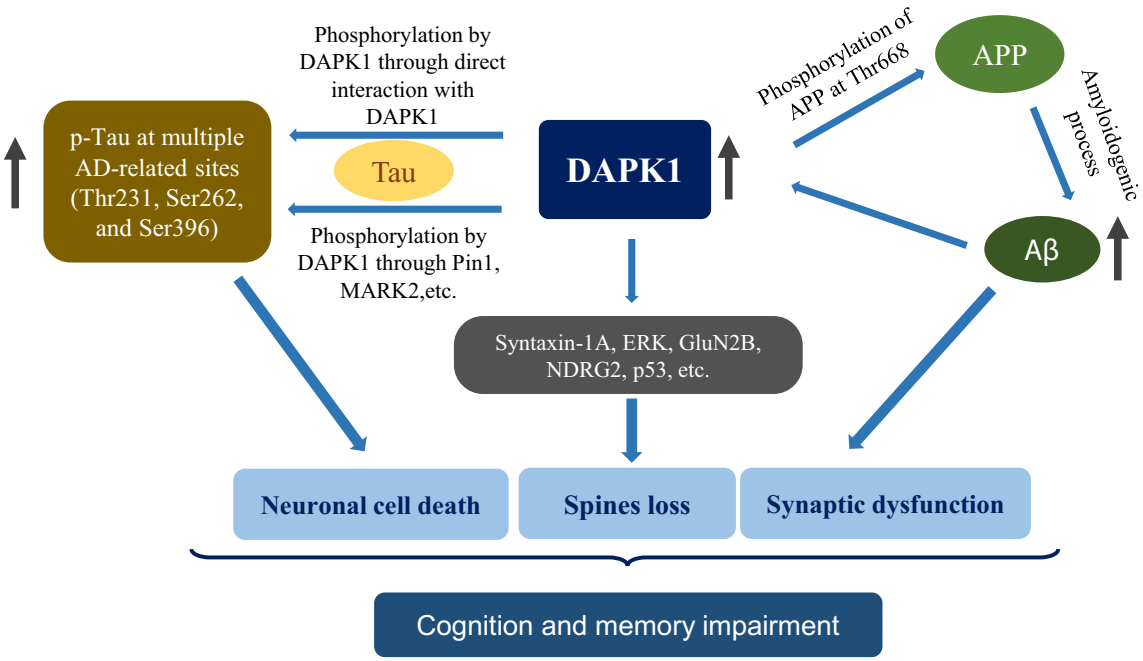

Fig. 2 DAPK1 involved in the potential mechanisms of AD-related pathology and cognition impairment. Endogenous or exogenous Aβ can upregulate DAPK1 expression and its activity, in turn DAPK1 can promote the amyloidogenic processing of APP and increase Aβ production through phosphorylation of APP at Thr668. DAPK1 can directly interact to and phosphorylate tau or indirectly phosphorylate tau through activation of other molecules (Pin1, MARK2, etc.). DAPK1, through interaction with ERK, GluN2B, syntaxin-1A, NDRG2, p53, etc., also may engage in neuronal cell death, spines loss, and synaptic dysfunction. The progress of neurodegeneration will further exacerbate the cognition and memory impairment

synaptic plasticity and memory function [34]. Most NMDARs are comprised of the two structural GluN1 subunits and two regulatory GluN2 subunits. GluN2A- and GluN2B-containing NMDARs are considered the major isoforms of functional NMDARs in CNS neurons [35–38]. DAPK1 affects the synaptic plasticity mainly through binding to extrasynaptic GluN2B-containing NMDARs. The DAPK1 binding to extrasynaptic GluN2B subunit at a site overlapping the Ca^{2+}/CaM-dependent protein kinase II-α (CaMKIIα) binding site which phosphorylate GluN2B subunit at the S1303 site [29–31, 39, 40]. DAPK1 and CaMKII are both CaM kinases and bind to the GluN2B subunit at Ser1303. Hence, researchers speculate that DAPK1 and CaMKIIα might compete for binding to this same region on GluN2B subunit. CaMKII plays an essential role for LTP; DAPK1 mediates the suppression of CaMKIIα/GluN2B binding and competition for binding to GluN2B subunit during LTD [29].

DAPK1 is involved in the modulation of neuronal and synaptic function through modulating the expression of synapse-related proteins and neurotrophic pathway. DAPK1 plays an important role in regulating synaptic transmission [41]. DAPK1 can directly bind to syntaxin-1A and phosphorylate syntaxin-1A at Ser188 site via its C-terminal domains, and then the interaction between syntaxin-1A and munc18-1 is decreased. Munc18-1 is a protein that modulates the synaptic vesicles docking/priming process and is important for synaptic transmission [41]. Extracellular signal-regulated kinase (ERK) is a key molecule in DAPK1 signaling, and DAPK1 can directly interact with ERK through a docking sequence within its death domain and ERK also function as an upstream to activate DAPK1 by phosphorylating DAPK1 at Ser735 [38, 42]. Further, DAPK1 interaction with ERK can promote the cytoplasmic retention of ERK and inhibits ERK nuclear translocation, which contributes to neuronal apoptosis [43]. As known, BDNF is an important neurotrophic factor in CNS and plays a crucial role in modulating neuronal and synaptic function, and BDNF is associated with many CNS disease, such as AD, depression, etc. [44–50]. When DAPK1 is activated under some pathological conditions in the brain, the CREB-BDNF signaling is significantly downregulated and synaptic proteins are also deficit. On the contrary, when DAPK1 is inhibited or knocked down, the downregulation of neurotrophic process can be rescued in the brain [31, 36, 38, 40].

DAPK1 is also involved in the neuronal dysfunction through neuronal death process [10, 23, 24, 51, 52]. Under some pathological conditions like ischemia insults, DAPK1 is activated during ischemic injuries, then catalyzes and phosphorylates p53 at serine-23 (pS^{23}) via a direct binding of DAPK1 death domain (DAPK1DD) to the DNA binding motif of p53 (p53DM). The functional forms of pS^{23} mediate apoptotic neuronal death in mouse cortical neurons and induce the expression of proapoptotic genes in the nucleus. In contrast, inhibition of DAPK1 or blocking interaction of DAPK1-p53 effectively inhibits neuronal death and loss [10, 51, 52]. N-myc downstream-regulated gene 2 (NDRG2) has been demonstrated as a novel substrate of DAPK1, and NDRG2 can be phosphorylated at Ser350 by DAPK1. The phosphorylated NDRG2 and DAPK1 levels in the hippocampus are significantly increased in AD patients and in AD transgenic mice [53]. And interaction between DAPK1 and NDRG2 results in the increase of NDRG2-derived neuronal cell death through caspase-dependent pathway. In contrast, inhibition of DAPK1 can effectively reduce phosphorylation of NDRG2 at Ser350 and rescue neuronal cell death and loss.

Additionally, recent studies have also demonstrated that DAPK1 can directly interact with tau protein and phosphorylate tau protein at Ser262 (pS^{262}). Eventually, DAPK1 causes synaptic damage and neuronal death via the formation of indissoluble tau and accumulation in the dendritic spines in cortical neurons of stroke mice. On the contrary, deletion of DAPK1 kinase domain or interrupting the interaction between DAPK1 and tau distinctly reduced ischemia-induced spine loss and the impairment of synaptic plasticity [10, 24].

The potential mechanisms underlying DAPK1 signals in the AD-related neuronal and synaptic dysfunction and cognition impairment are summarized in Fig. 1 and Fig. 2. Deepening study on DAPK1, synaptic plasticity and their function will help us better understand the important role of DAPK1 in learning and memory process.

DAPK1 and Potential Biomarker or Treatment Target?

DAPK1 is involved in many CNS diseases, including stroke, depression, and AD. Manipulations of DAPK1 have shown significant neuroprotective effects in preclinical studies. This makes DAPK1 possess huge potential for clinical diagnosis and treatment.

DAPK1 rs4878104 and *rs4877365* are associated with AD risk. Individuals who carry the risk variants might be at high risk of AD, and these high-risk individuals should be given extra attention in clinic, including early prevention and diagnosis. A number of studies have demonstrated that DAPK1 is consecutively expressed in the brain in healthy aged subjects and AD patients, especially highly expressed in the latter [19, 53]. Because these findings are all resulted from the postmortem of AD patients, DAPK1 expression in the brain cannot be easily detected in living aged subjects or AD patients clinically. Other studies have demonstrated that DAPK1 can be a potential peripheral biomarker in diagnosis of some cancers, leukemia, and other conditions. However, there is no evidence that DAPK1 in the peripheral blood can be used as an early diagnostic indicator of AD. Whether DAPK1 can be used as an early diagnostic indicator for prevention and intervention of AD need further investigation in the future.

Based on the preclinical studies we referred above, DAPK1 is associated with the impairment of performance of cognition and memory [54], and intervention of DAPK1 exhibits significant neuroprotective roles in tau phosphorylation, Aβ production, and synapse loss. Therefore, there are some reasons to suggest that DAPK1 may be a potential target for AD treatment: (1) DAPK1 is highly expressed in the brain of AD patients, especially in the brain areas closely related to memory and cognition, such as hippocampus and cortex; (2) DAPK1 is involved in the amyloidogenic process of APP and Aβ-induced toxicity; (3) DAPK1 can phosphorylate tau at multiple AD-related sites through direct or indirect interaction with tau protein; (4) DAPK1 is involved in degenerative changes of synapses in the early stage of AD, and the neuronal loss and death in the late stage of AD. Hence, the intervention targeting to DAPK1 might effectively delay the development of AD and improve the conditions of AD.

Conclusion and Future Directions

In this review, we mainly summarize the recent literatures on *DAPK1 variants* and DAPK1 signals in AD, and mounting evidences have confirmed that DAPK1 plays a crucial role in the development of AD. On the other side, inhibition of DAPK1 can improve AD-related pathological changes and exhibit significant protective effects in AD models. However, there are still many unsolved issues in the roles of DAPK1 in AD. These issues are including (1) the causative relationship between DAPK1 and the key pathological hallmarks of AD; (2) the dynamic changes in the expression and activity of DAPK1 in pathogenesis of AD; (3) the association between DAPK1 and the other important factors of AD pathological changes, such as oxidative stress reaction, immune inflammation, etc.; and (4) the potential role of DAPK1 in early diagnosis and early intervention in AD. This review may provide new insights into a better understanding of the etiology and pathogenesis of AD. In conclusion, we hold the opinion that DAPK1 may be a promising target for intervention and treatment for AD.

Acknowledgments We thank Su-xia Li from the National Institute on Drug Dependence and Peking University for the revision of this work.

Funding Information This work was supported by Beijing Municipal Natural Science Foundation (7184215); Beijing Talents Foundation (2017000020124G251); the key project of the National Natural Science Foundation of China (81530036); the National Key Scientific Instrument and Equipment Development Project (31627803); Mission Program of Beijing Municipal Administration of Hospitals (SML20150801); Beijing Scholars Program; Beijing Brain Initiative from Beijing Municipal Science & Technology Commission (Z161100000216137); China-Canada Joint Initiative on Alzheimer's Disease and Related Disorders (81261120571); and Beijing Municipal Commission of Health and Family Planning (PXM2017_026283_000002).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, Van der Flier WM (2016) Alzheimer's disease. Lancet (London, England) 388(10043):505–517
2. Jia J, Zhou A, Wei C, Jia X, Wang F, Li F, Wu X, Mok V et al (2014) The prevalence of mild cognitive impairment and its etiological subtypes in elderly Chinese. Alzheimer's Dement 10(4):439–447
3. Jia J, Wang F, Wei C, Zhou A, Jia X, Li F, Tang M, Chu L et al (2014) The prevalence of dementia in urban and rural areas of China. Alzheimer's Dement 10(1):1–9
4. Jia J, Wei C, Chen S, Li F, Tang Y, Qin W, Zhao L, Jin H et al (2018) The cost of Alzheimer's disease in China and re-estimation of costs worldwide. Alzheimer's Dement 14(4):483–491
5. Karran E, Mercken M, De Strooper B (2011) The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. Nat Rev Drug Discov 10(9):698–712
6. Leinenga G, Langton C, Nisbet R, Gotz J (2016) Ultrasound treatment of neurological diseases–current and emerging applications. Nat Rev Neurol 12(3):161–174
7. Karran E, Hardy J (2014) A critique of the drug discovery and phase 3 clinical programs targeting the amyloid hypothesis for Alzheimer disease. Ann Neurol 76(2):185–205
8. Singh P, Ravanan P, Talwar P (2016) Death associated protein kinase 1 (DAPK1): a regulator of apoptosis and autophagy. Front Mol Neurosci 9:46
9. Bialik S, Kimchi A (2006) The death-associated protein kinases: structure, function, and beyond. Annu Rev Biochem 75:189–210
10. Wang S, Shi X, Li H, Pang P, Pei L, Shen H, Lu Y (2017) DAPK1 signaling pathways in stroke: from mechanisms to therapies. Mol Neurobiol 54(6):4716–4722
11. Shohat G, Spivak-Kroizman T, Cohen O, Bialik S, Shani G, Berrisi H, Eisenstein M, Kimchi A (2001) The pro-apoptotic function of death-associated protein kinase is controlled by a unique inhibitory autophosphorylation-based mechanism. J Biol Chem 276(50): 47460–47467
12. Li Y, Grupe A, Rowland C, Nowotny P, Kauwe JS, Smemo S, Hinrichs A, Tacey K et al (2006) DAPK1 variants are associated with Alzheimer's disease and allele-specific expression. Hum Mol Genet 15(17):2560–2568
13. Schjeide BM, McQueen MB, Mullin K, Divito J, Hogan MF, Parkinson M, Hooli B, Lange C et al (2009) Assessment of Alzheimer's disease case-control associations using family-based methods. Neurogenetics 10(1):19–25
14. Laumet G, Chouraki V, Grenier-Boley B, Legry V, Heath S, Zelenika D, Fievet N, Hannequin D et al (2010) Systematic analysis of candidate genes for Alzheimer's disease in a French, genome-wide association study. J Alzheimers Dis 20(4):1181–1188
15. Wu ZC, Zhang W, Yu JT, Zhang Q, Tian Y, Lu RC, Yu NN, Chi ZF et al (2011) Association of DAPK1 genetic variations with Alzheimer's disease in Han Chinese. Brain Res 1374:129–133
16. Tedde A, Piaceri I, Bagnoli S, Lucenteforte E, Piacentini S, Sorbi S, Nacmias B (2012) DAPK1 is associated with FTD and not with Alzheimer's disease. J Alzheimers Dis 32(1):13–17
17. Minster RL, DeKosky ST, Kamboh MI (2009) No association of DAPK1 and ABCA2 SNPs on chromosome 9 with Alzheimer's disease. Neurobiol Aging 30(11):1890–1891

18. Hu Y, Cheng L, Zhang Y, Bai W, Zhou W, Wang T, Han Z, Zong J et al (2017) Rs4878104 contributes to Alzheimer's disease risk and regulates DAPK1 gene expression. Neurol Sci 38(7):1255–1262
19. Hainsworth AH, Allsopp RC, Jim A, Potter JF, Lowe J, Talbot CJ, Prettyman RJ (2010) Death-associated protein kinase (DAPK1) in cerebral cortex of late-onset Alzheimer's disease patients and aged controls. Neuropathol Appl Neurobiol 36(1):17–24
20. Shu S, Zhu H, Tang N, Chen W, Li X, Li H, Pei L, Liu D et al (2016) Selective degeneration of entorhinal-CA1 synapses in Alzheimer's disease via activation of DAPK1. J Neurosci 36(42): 10843–10852
21. Kim BM, You MH, Chen CH, Suh J, Tanzi RE, Ho Lee T (2016) Inhibition of death-associated protein kinase 1 attenuates the phosphorylation and amyloidogenic processing of amyloid precursor protein. Hum Mol Genet 25(12):2498–2513
22. Kauwe JS, Wang J, Mayo K, Morris JC, Fagan AM, Holtzman DM, Goate AM (2009) Alzheimer's disease risk variants show association with cerebrospinal fluid amyloid beta. Neurogenetics 10(1): 13–17
23. Duan DX, Chai GS, Ni ZF, Hu Y, Luo Y, Cheng XS, Chen NN, Wang JZ et al (2013) Phosphorylation of tau by death-associated protein kinase 1 antagonizes the kinase-induced cell apoptosis. J Alzheimers Dis 37(4):795–808
24. Pei L, Wang S, Jin H, Bi L, Wei N, Yan H, Yang X, Yao C et al (2015) A novel mechanism of spine damages in stroke via DAPK1 and tau. Cereb Cortex 25(11):4559–4571
25. Kim BM, You MH, Chen CH, Lee S, Hong Y, Hong Y, Kimchi A, Zhou XZ et al (2014) Death-associated protein kinase 1 has a critical role in aberrant tau protein regulation and function. Cell Death Dis 5:e1237
26. Wu PR, Tsai PI, Chen GC, Chou HJ, Huang YP, Chen YH, Lin MY, Kimchi A et al (2011) DAPK activates MARK1/2 to regulate microtubule assembly, neuronal differentiation, and tau toxicity. Cell Death Differ 18(9):1507–1520
27. Iqbal K, Grundke-Iqbal I (2011) Opportunities and challenges in developing Alzheimer disease therapeutics. Acta Neuropathol 122(5):543–549
28. Kandel ER, Dudai Y, Mayford MR (2014) The molecular and systems biology of memory. Cell 157(1):163–186
29. Goodell DJ, Zaegel V, Coultrap SJ, Hell JW, Bayer KU (2017) DAPK1 mediates LTD by making CaMKII/GluN2B binding LTP specific. Cell Rep 19(11):2231–2243
30. McQueen J, Ryan TJ, McKay S, Marwick K, Baxter P, Carpanini SM, Wishart TM, Gillingwater TH et al (2017) Pro-death NMDA receptor signaling is promoted by the GluN2B C-terminus independently of Dapk1. Elife 6
31. Li SX, Han Y, Xu LZ, Yuan K, Zhang RX, Sun CY, Xu DF, Yuan M et al (2018) Uncoupling DAPK1 from NMDA receptor GluN2B subunit exerts rapid antidepressant-like effects. Mol Psychiatry 23(3):597–608
32. Tu S, Okamoto S, Lipton SA, Xu H (2014) Oligomeric Aβ-induced synaptic dysfunction in Alzheimer's disease. Mol Neurodegener 9:48
33. Sheng M, Kim MJ (2002) Postsynaptic signaling and plasticity mechanisms. Science 298(5594):776–780
34. Li F, Tsien JZ (2009) Memory and the NMDA receptors. N Engl J Med 361(3):302–303
35. Furukawa H, Singh SK, Mancusso R, Gouaux E (2005) Subunit arrangement and function in NMDA receptors. Nature 438(7065): 185–192
36. Hardingham GE, Fukunaga Y, Bading H (2002) Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways. Nat Neurosci 5(5):405–414
37. Cull-Candy S, Brickley S, Farrant M (2001) NMDA receptor subunits: diversity, development and disease. Curr Opin Neurobiol 11(3):327–335
38. Lai TW, Zhang S, Wang YT (2014) Excitotoxicity and stroke: identifying novel targets for neuroprotection. Prog Neurobiol 115:157–188
39. Tu W, Xu X, Peng L, Zhong X, Zhang W, Soundarapandian MM, Balel C, Wang M et al (2010) DAPK1 interaction with NMDA receptor NR2B subunits mediates brain damage in stroke. Cell 140(2):222–234
40. Liu SB, Zhang N, Guo YY, Zhao R, Shi TY, Feng SF, Wang SQ, Yang Q et al (2012) G-protein-coupled receptor 30 mediates rapid neuroprotective effects of estrogen via depression of NR2B-containing NMDA receptors. J Neurosci 32(14):4887–4900
41. Tian JH, Das S, Sheng ZH (2003) Ca2+−dependent phosphorylation of syntaxin-1A by the death-associated protein (DAP) kinase regulates its interaction with munc18. J Biol Chem 278(28):26265–26274
42. Chen CH, Wang WJ, Kuo JC, Tsai HC, Lin JR, Chang ZF, Chen RH (2005) Bidirectional signals transduced by DAPK-ERK interaction promote the apoptotic effect of DAPK. EMBO J 24(2):294–304
43. Xiong W, Wu Y, Xian W, Song L, Hu L, Pan S, Liu M, Yao S et al (2018) DAPK1-ERK signal mediates oxygen glucose deprivation reperfusion induced apoptosis in mouse N2a cells. J Neurol Sci 387:210–219
44. Boots EA, Schultz SA, Clark LR, Racine AM, Darst BF, Koscik RL, Carlsson CM, Gallagher CL et al (2017) BDNF Val66Met predicts cognitive decline in the Wisconsin Registry for Alzheimer's Prevention. Neurology 88(22):2098–2106
45. Lim YY, Hassenstab J, Cruchaga C, Goate A, Fagan AM, Benzinger TL, Maruff P, Snyder PJ et al (2016) BDNF Val66Met moderates memory impairment, hippocampal function and tau in preclinical autosomal dominant Alzheimer's disease. Brain 139(Pt 10):2766–2777
46. Buchman AS, Yu L, Boyle PA, Schneider JA, De Jager PL, Bennett DA (2016) Higher brain BDNF gene expression is associated with slower cognitive decline in older adults. Neurology 86(8):735–741
47. Beeri MS, Sonnen J (2016) Brain BDNF expression as a biomarker for cognitive reserve against Alzheimer disease progression. Neurology 86(8):702–703
48. Cattaneo A, Cattane N, Begni V, Pariante CM, Riva MA (2016) The human BDNF gene: peripheral gene expression and protein levels as biomarkers for psychiatric disorders. Transl Psychiatry 6(11):e958
49. Bennett MR, Lagopoulos J (2014) Stress and trauma: BDNF control of dendritic-spine formation and regression. Prog Neurobiol 112:80–99
50. Lu B, Nagappan G, Guan X, Nathan PJ, Wren P (2013) BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases. Nat Rev Neurosci 14(6):401–416
51. Wang X, Pei L, Yan H, Wang Z, Wei N, Wang S, Yang X, Tian Q et al (2014) Intervention of death-associated protein kinase 1-p53 interaction exerts the therapeutic effects against stroke. Stroke 45(10): 3089–3091
52. Pei L, Shang Y, Jin H, Wang S, Wei N, Yan H, Wu Y, Yao C et al (2014) DAPK1-p53 interaction converges necrotic and apoptotic pathways of ischemic neuronal death. J Neurosci 34(19):6546–6556
53. You MH, Kim BM, Chen CH, Begley MJ, Cantley LC, Lee TH (2017) Death-associated protein kinase 1 phosphorylates NDRG2 and induces neuronal cell death. Cell Death Differ 24(2):238–250
54. Yukawa K, Tanaka T, Bai T, Li L, Tsubota Y, Owada-Makabe K, Maeda M, Hoshino K et al (2006) Deletion of the kinase domain from death-associated protein kinase enhances spatial memory in mice. Int J Mol Med 17(5):869–873