The role of *UNC5C* in Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is a chronic progressive neurodegenerative disease in adults characterized by the deposition of extracellular plaques of β-amyloid protein (Aβ), intracellular neurofibrillary tangles (NFTs), synaptic loss and neuronal apoptosis. AD has a strong and complex genetic component that involving into multiple genes. With recent advances in whole-exome sequencing (WES) and whole-genome sequencing (WGS) technology, *UNC5C* was identified to have association with AD. Emerging studies on cell and animal models identified that aberrant *UNC5C* may contribute to AD by activating death-associated protein kinase 1 (DAPK1) which is a new component involved in AD pathogenesis with an extensive involvement in aberrant tau, Aβ and neuronal apoptosis/autophagy. In this review, we briefly summarize the biochemical properties, genetics, epigenetics, and the speculative role of *UNC5C* in AD. We hope our review would bring comprehensive understandings of AD pathogenesis and provide new therapeutic targets for AD.

Keywords: Alzheimer's disease (AD); apoptosis/autophagy; activating death-associated protein kinase 1 (activating DAPK1); tau; *UNC5C*

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Introduction

Alzheimer's disease (AD) is the most common chronic neurodegenerative disorder which is characterized by progressive memory loss and ultimately dementia (1,2). The pathogenesis of AD is multifactorial which involves in the interaction of complex genetic, epigenetic, and environmental factors (3). AD is commonly categorized into two types, early-onset AD (EOAD) and late-onset AD (LOAD) based on the onset time (4). The EOAD cases (<60 years old; 5–10%) are Mendelian forms of the disease caused by rare and dominantly inherited mutations in the amyloid-β protein precursor (*APP*), *presenilin 1* (*PSEN1*) and *PSEN2* (5). The LOAD (onset ≥65 years), is the major type of AD accounting for >95 % of all cases (6). The pathology of LOAD is multi-factorial with biological, genetic and environmental factors interacting with each other to aggravate the process of AD pathology (7). Up to now, the *ε4 isoform of apolipoprotein E* (*ApoE4)* has been widely accepted as the only genetic risk factor for LOAD (8). With recent advances in whole-exome sequencing (WES) and whole-genome sequencing (WGS) technology, to identify rare variants with large effect sizes associated with the disease has been proven to be feasible (9,10). Compared with this putative variant, recently the *UNC5C* gene was also revealed to have significant association with AD pathogenesis via combining WES, WGS and linkage analyses in large LOAD pedigrees in European populations (11). *UNC5C* plays an important physiological role during neural development by directing axon extension and cell migration (12,13). Thus, discussion on in which way the aberrant expression of *UNC5C*

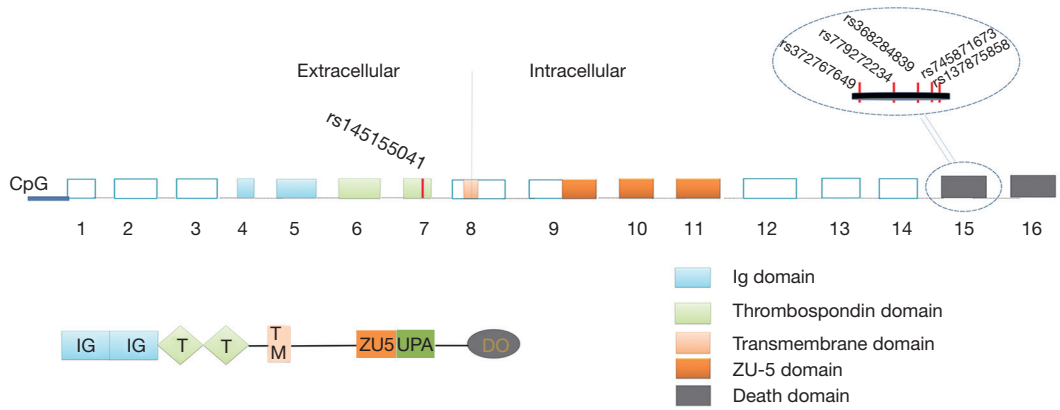

Figure 1 Genomic features of the *UNC5C* gene with some reported SNPs in corresponding exon domains. The schematic representation of the *UNC5C* gene is shown in this study including exon-intron structure, location of CpG island, corresponding encoded protein domains and the site of filtered SNPs. The locations of rs137875858, rs145155041, rs372767649, rs368284839, rs779272234, rs745871673 highlighted by the red line means six main risk loci among UNC5C variants in AD. AD, Alzheimer's disease; DD, death domain.

contributes to the mechanisms of LOAD is essential.

Accumulation of evidence from cell models showed that a *UNC5C* variant could lead to AD pathogenesis by activating death-associated protein kinase 1 (DAPK1) which was involved in modulating tau protein accumulation, β-amyloid protein (Aβ) toxicity and neuronal apoptosis/autophagy (11,14). However, in view of the complexity of AD pathogenesis, there are still no complete cellular or animal models demonstrating all pathological traits of AD. In addition, the definition of pathogenesis and effective therapies remain unsolved (15). Therefore, it is more essential to define the specific role of any molecule in AD pathogenesis. In this review, we focus on the role of *UNC5C* in AD pathogenesis. We briefly summarize the current genetics findings, the potential epigenetics and speculative roles of *UNC5C* in AD. Besides, we believe that further studies on *UNC5C* may be of great value to understand the mechanism of AD and *UNC5C*-targeted therapeutics will present the recent challenges and advances.

Structure and biochemical properties of UNC5C

UNC5C was the first to be identified to have association with AD in 2014 by combining WGS, WES and linkage analyses in large LOAD pedigrees in European populations (11). *UNC5C* gene localizes on chromosome 4q22.3 and encodes 16 exons, which can translate into 950 amino acid polypeptides (16). The UNC5C protein is a typical transmembrane protein that contains two Ig domains (Ig), two thrombospondin domains (TS), a transmembrane domain (TM), a zona occludens-5 domain (ZU-5), a UPA domain, and a death domain (DD) (16) (*Figure 1*). *UNC5C* is a member of UNC-5 family including *UNC5A*, *UNC5B*, *UNC5C* and *UNC5D*, which are widely expressed in the nervous system as well as the heart and seems to be enriched in the hippocampus of AD brain (17). So far, among these members, only *UNC5C* is reported to be associated with AD (18). *UNC5C* is universally known as the receptor of neurin-1, playing a crucial role in mediating axon repulsion of neuronal growth cones and cell migration in the developing nervous system (19,20). UNC5C is also known as a dependence receptor which is responsible for the regulation of neuronal apoptosis and whether UNC5C acts the role of pro- or anti-apoptotic molecule depends on its binding to netrin-1 (21,22). Dysfunctional UNC5C will cause relative cells to be misrouted and to fail to receive survival signals, ultimately triggering cell death (23). Previous studies revealed that mice homozygous for mutations in *UNC5C* are ataxic and have cerebellar hypoplasia and laminar structure defects (16,17), which indicated that *UNC5C* plays an indispensable role in the development of nervous system. Additionally, the altered *UNC5C* expression is associated with many types of cancers including colorectal, breast, stomach, lung, ovary, uterus, or kidney cancers (22). Recently, a *UNC5C* variant (T835M) was found to markedly shorten cell survival time up to 50% compared with controls *in vitro* experiment, suggesting a significant role of *UNC5C* in the regulation of

Table 1 Rare coding variants of *UNC5C* related to LOAD

UNC5C SNPs	Risk allele	AA variation	Exon location	P	Population
rs137875858	A	T835M	Exon 15	0.0095	European population
rs145155041	T	D353N	Exon 7	N/A	European population
rs372767649	G	Q860H	Exon 15	0.017	Han Chinese
rs368284839	A	T837K	Exon 15	0.13	Han Chinese
rs779272234	G	S843G	Exon 15	0.36	Han Chinese
rs745871673	G	V836V	Exon 15	0.36	Han Chinese

P value was determined using Fisher exact test. LOAD, late-onset Alzheimer's disease; SNP, single-nucleotide polymorphism; N/A, not applicable.

cell survival (11). More recently, a genome-wide association study (GWAS) revealed a single nucleotide polymorphism (SNP) in the 3'UTR of *UNC5C* has close association with embryonic development in mammals, which may affect the binding site of microRNAs and further change the expression levels of mRNA and UNC5C protein (24). Given those mentioned above, aberrant expression of *UNC5C* is likely to cause diverse disease development. In view of the important function of *UNC5C* in nervous system, a more comprehensive study on it may offer a deeper understanding of the AD pathogenesis as well as helpful insights into tumor context.

Genetics of UNC5C in AD

To date, more than 20 loci have been revealed to be associated with AD risk, among which the total *APOE* with frequent [1–5% minor allele frequency (MAF)]variants are irrefutably recognized as the major susceptibility gene for LOAD (25). What's more, in 2014, a *UNC5C* SNP rs137875858 T835M was identified to predispose to LOAD with a similar effect size to that of *APOE* ε4 allele (26) by linkage analyses, segregating with disease in two independent families (11). Wetzel-Smith *et al.* also demonstrated that a *UNC5C* SNP predisposed to increasing risk of sporadic AD (odds ratio =2.15, P=0.0095, 95 % CI: 1.21–3.84) in four independent data sets including 8,050 LOAD cases and 98,194 controls (11). Furthermore, Jiao *et al.* replicated *UNC5C* in Chinese population with 360 AD cases and 400 controls and revealed four highly conserved *UNC5C* SNPs associated with LOAD (27). However, *UNC5C* T835M failed to be replicated in Chinese population, but four novel loci (p.S843G, p.Q860H, p.V836V, p.T837K) showed to confer certain risk of AD (27). The four loci only existed in sporadic AD cases but not in controls, among which p.Q860H variant showed stronger association with AD risk with a P value 0.017 (27). More recently, rs145155041 (D353N) of *UNC5C* located in exon 7 which encodes an extracellular TS was found to be involved in AD occasionally during the study focusing on *TREM2* (28). Apparently, *UNC5C* variants were found in different datasets and close association between *UNC5C* and AD was highlighted. The detailed information of *UNC5C* variants are shown in *Table 1*.

Recently, a neuroimaging study by Sun *et al.* demonstrated that *UNC5C* gene polymorphisms had a notable effect on the brain structure in AD-associated regions (29). Some loci near rs145155041 and rs137875858 showed significant association with brain atrophy; rs34585936 is related to the volume atrophy in right middle temporal; rs72672784, rs13120458, and rs34875919 would promote the atrophy rate in crucial regions especially the left hippocampus; rs72672784, rs74690179 and rs2001246 are associated with right precuneus atrophy (29). What's more, the study by Sun *et al.* (29) also showed that effect of *UNC5C* gene polymorphisms on brain structures was independent of *APOE* genotype, indicating that *UNC5C* may be an independent risk factor for AD. Given those mentioned above, *UNC5C* gene polymorphisms play a significant role in AD and thus deeper studies will be of great value in exploring *UNC5C* induced pathways in AD.

The epigenetics of UNC5C in AD

Epigenetics is referred to as the processes involving changing gene expression without altering the DNA sequence (30). The *UNC5C* promoter contains a special methyl group which is called CpG dinucleotides (31),

and methylation in these CpG islands or any correlated modifications in histone complexes can disorder the process of gene transcription in an epigenetic manner (30,32) (*Figure 1*). In addition, research showed that the aberrant methylation of *UNC5C* was a universal phenomenon in cancers, and the level of mRNA was markedly reduced by the aberrant methylation (13,33). In the context of tumors, the aberrant *UNC5C* methylation is negatively correlated with its protein expression (34). However, due to the bidirectional effect of aberrant DNA methylation in protein expression, methylation in gene promoter would lead to the increase in protein expression and reversely methylation in gene bodies would lead to the reduction in protein expression (30,35). Following this logic, the aberrant *UNC5C* methylation in neurons seems warranted.

As a matter of fact, the AD pathogenesis is multifactorial. The risk factors are not only genetic variants and environmental factors but also epigenetic abnormalities, such as changes in DNA methylation or modifications of the proteins that package the DNA (36). Previous studies have revealed that epigenetic modifications may affect AD pathogenesis, such as increased microtubule-associated protein tau (MAPT). Methylation could suppress the MAPT expression, which could affect the levels of tau protein (37). However, whether aberrant *UNC5C* DNA methylation alters in AD requires more in-depth investigation. Interestingly, the epigenetic changes can be reversible under certain circumstances (34), thus further research is needed on the epigenetics of *UNC5C*. Targeting the epigenome may provide new opportunities in neuroprotection and therapy for AD.

The speculative role of UNC5C in AD

The initial finding of *UNC5C* in AD was detected by Wetzel-Smith *et al.* (11) with the variant T835M, suggesting the involvement of *UNC5C*-induced neuronal death pathways, tau pathology and Aβ-associated pathways. Subsequently, a study by Hashimoto *et al.* focusing on molecular mechanisms of the association between *UNC5C* and AD, demonstrated that *UNC5C* leading to neuron death was mediated by an intracellular death-signaling cascade through the sequentially activating DAPK1/protein kinase D (PKD)/apoptosis signal-regulating kinase 1 (ASK1)/JNK/NADPH oxidase/caspases (14). Among the signal transduction processes, activated DAPK1 is the central component in initiating the pathology of AD. Interestingly, the death-signaling cascade in UNC5C partially overlapped with APP-mediated death-signaling pathway at ASK1 (14). However, as *UNC5C* is a novel risk gene in AD, the correlative study on it is modest compared with that of *APOE*, *MAPT*, and clusterin (*CLU*) for less available data. In view of the fact that *UNC5C* variants play a pronounced role in neuronal death, in-depth investigation of potential molecular pathways in AD is required. Following this logic, we reviewed the current available studies on *UNC5C*, which summarized thoughts in AD with tumors contexts and elaborated the following speculative pathways.

UNC5C-induced signaling pathway and Aβ

Abnormal Aβ aggregation and accumulation forming the amyloid plaques is well known as a major pathological hallmark of AD (38). As Aβ accumulation acts as a putative central factor in initiating the AD pathogenesis, it is essential to explore the role of *UNC5C* in Aβ pathways. Accordingly, the initial study was to explore the effect of *UNC5C* on the production of Aβ. Aβ is generated by sequential proteolytic cleavages of amyloid precursor protein (APP) by β-secretase and γ-secretase (39) (*Figure 2*). Aβ is 38–43 amino acid residue peptides including two major isoforms $A\beta_{1-40}$ (account for 90%) and $A\beta_{1-42}$ (account for 5–10%), in which $A\beta_{1-42}$ is more prone to assemble into neurotoxic oligomers (40,41). However, cell models to alter the expression levels of *UNC5C* showed no evidence of affecting the generation of $A\beta_{1-40}$ and $A\beta_{1-42}$, indicating that *UNC5C*-induced neuronal death did not affect the process of APP cleavage (11). Additionally, a deeper investigation of the association between *UNC5C* and Aβ showed that overexpressed *UNC5C* and *UNC5C*-T835M cell had higher propensity to death compared with normal controls in Aβ-incubated rat hippocampal neurons, indicating that the aberrant *UNC5C* increased the susceptibility to Aβ-induced neurotoxicity (11). Meanwhile, the study also revealed that the aberrant *UNC5C* increases the susceptibility of neurons not only to Aβ but also to other neurotoxic insults in a similar manner (11), indicating that the role of *UNC5C* in neuronal death did not depend on Aβ. However, deeper exploration is required for the explanation of why *UNC5C*-induced neuronal death was intensified in the existence of Aβ. Until 2016, Hashimoto *et al.* revealed the signaling pathway of *UNC5C* contributing to neuronal death was involved in DAPK1/PKD/ASK1/JNK/NADPH oxidase/caspases pathways (14). During the

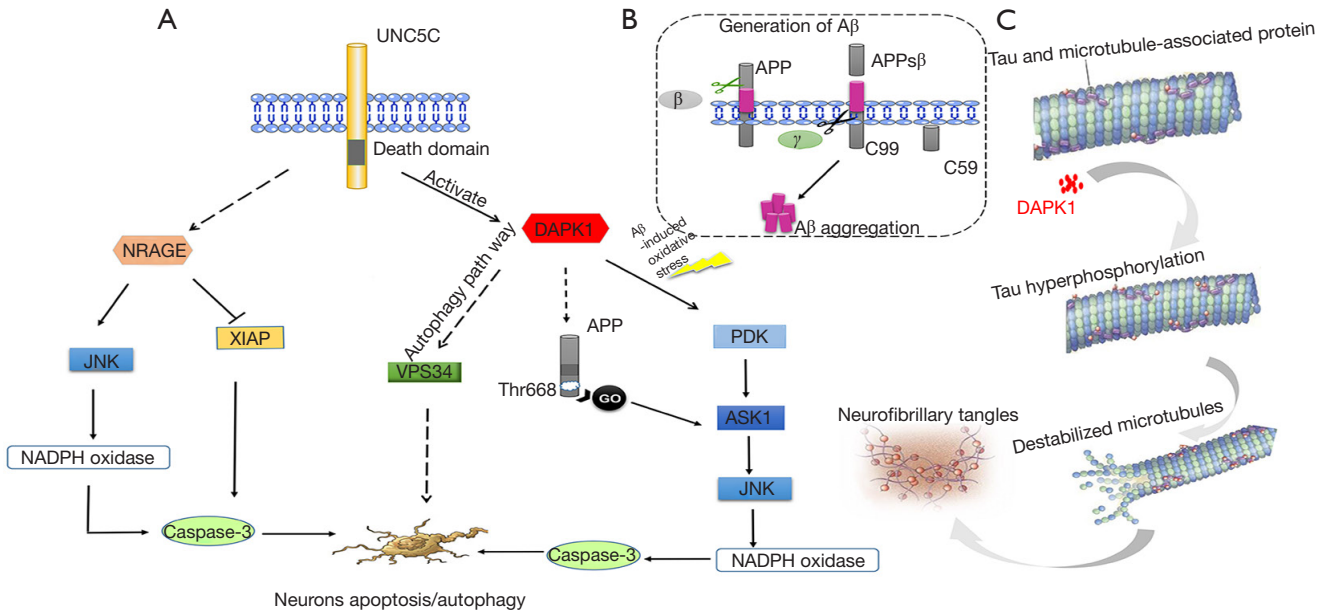

Figure 2 Summary of the speculative roles of *UNC5C* in AD pathogenesis. (A) Aberrant *UNC5C* would activate the expression of DAPK1 then activated DAPK1 would sequential activate its downstream of PKD, ASK1, JNK, NADPH oxidase, caspases and ultimately led to a common caspases-dependent neuronal apoptosis. DAPK1-induced Vps34 pathways also may be a possible pathway to trigger neuronal autophagy. In addition, activated DAPK1 could phosphorylate APP at Thr668, which would lead to neuronal death by Aβ-independent GO protein pathway. On the other hand, the *UNC5C* also may be possible to be related to NRAGE-associated pathway. The aberrant NRAGE may activate its downstream of JNK, which would ultimately lead to caspases-dependent neuronal death. What's more, the NRAGE may also degrade the caspase inhibitor XIAP, which would trigger the increase of caspases and result in promoting to neuronal apoptosis; (B) Aβ is generated via cleaving fragment of APP via β-secretase and γ-secretase. Firstly, APP is cleaved by β-secretase at the corresponding site and then releases APPsβ ectodomain. Secondly, the remaining carboxy-terminal fragment is cleaved by γ-secretase and then Aβ is released; (C) aberrant *UNC5C* over activate DAPK1, overexpression of DAPK1 will lead to tau protein hyper phosphorylation and ultimately promote to the form of NFT. AD, Alzheimer's disease; DAPK1, death-associated protein kinase 1; PKD, protein kinase D; ASK1, apoptosis signal-regulating kinase 1; APP, amyloid-β protein precursor; Aβ, β-amyloid protein; NRAGE, neurotrophin receptor p75-interacting melanoma-associated antigen homolog; XIAP, X-chromosome-linked inhibitor of apoptosis protein; NFT, neurofibrillary tangle.

caspases-dependent cell death pathway, DAPK1 played an initial role in this signaling transduction and acted as a regulator of PKD and was indispensable for the activation of JNK signaling in oxidative stress condition (42). It is well recognized that Aβ showed wide neurotoxicity including increasing oxidative stress in cells (41,43). Based on these concepts, we hypothesize that the Aβ-induced oxidative stress condition would promote the signaling activation of PDK and JNK by DAPK1. That seems to be a plausible explanation of why *UNC5C* variant increased cell death in the existence of Aβ without affecting Aβ levels. Taken together, aberrant *UNC5C*-induced neuronal death was independent of Aβ. Meanwhile, Aβ-induced oxidative stress condition would promote DAPK1-induced death signaling (*Figure 2*). However, the direct molecular mechanism of the association between *UNC5C* and Aβ pathways remains to be further verified.

Interestingly, previous studies revealed that *APP* also had an Aβ-independent pathway associated with neuronal apoptosis and lysosomal-autophagy in AD by a heterotrimeric G protein Go pathways (44-48) (*Figure 2*). What's more, *UNC5C* revealed a common death-associated signaling pathway with *APP*-induced cell death at ASK1 during the G protein Go pathways (14). However, there is still no direct link between *APP* and *UNC5C*-induced signaling pathway. Based on the important roles of both in AD, it will be of great value in exploring the possible link between *UNC5C* and *APP*.

Hence, an in-depth investigation of whether *UNC5C* interacts with *APP* is required in further study.

The speculative role of UNC5C in tau

Recently, aberrant *UNC5C* expression was revealed to notably increase the levels of extracellular tau proteins in cell models (11). Tau is a natively microtubule-associated protein widely distributed in the neurons of central nervous system, playing a role in the assembly and stabilization of microtubules (49). Tau protein phosphorylation is a physiological process to regulate microtubule dynamics and promote neuronal differentiation (50,51). However, hyperphosphorylated tau triggering aberrant tau accumulation in neurons was the center of many neurodegenerative diseases including AD (15,52). Overall, when tau protein is abnormally hyperphosphorylated and modified, it will lose its physiological function in binding to microtubules and then generate pathological insults in neurons. The recent study by Wetzel-Smith *et al.* revealed that a *UNC5C* variant (T835M) would notably increase the levels of extracellular tau proteins and decrease the cell survival *in vitro* cell models (11). It is obvious that the aberrant *UNC5C* expression had a close association with increasing tau levels. Though the underlying mechanisms of the association between *UNC5C* and tau remain unclear, prospective correlative pathways were introduced in the following.

Emerging studies revealed that DAPK1 could notably increase tau protein phosphorylation and improve tau stability (53). In cell and animal model studies, the DAPK1 knockout mice showed an evident decrease of tau protein stability and even an abolition of phosphorylated tau (53), which indicated that DAPK1 played a critical role in the regulation of tau protein. The cellular molecule studies revealed that DAPK1 would phosphorylate tau protein at Ser262, Thr231 and Ser396 sites by inhibiting the function of Pin1 (53). Pin1, a phosphorylation-dependent peptidyl-prolyl cis-trans isomerase, played an important role in restoring the conformation of phosphorylated tau (53,54). Obviously, the DAPK1 inhibited the protective function of Pin1 and thus led to enhancing tau stability and promoting tau phosphorylation which was prone to form pathological aggregation and trigger neurodegeneration (53) (*Figure 2*). Given that aberrant *UNC5C* could activate DAPK1 expression and increase tau levels, *UNC5C*-induced DAPK1 activation may be a prospective mechanism associated with tauopathies. Although aberrant *UNC5C* elevated tau levels, the underlying mechanisms involved in DAPK1 remains to be further verified in cell and animal experiments.

The speculative role of UNC5C in apoptosis/autophagy

Accumulative evidence suggested that inappropriate apoptosis and impaired autophagic processes were extensively involved in neurodegenerative diseases including AD (55-57). A recent study revealed that *UNC5C* overexpression and *UNC5C*-T835M in neurons brought higher levels of annexin V, an early apoptotic marker (11,58), which indicated that aberrant *UNC5C* was involved in LOAD by mediating neuronal apoptosis process. UNC5C emerges as a dependence receptor including a DD which is responsible for cell death (59) and the knockout of the C-terminal DD would markedly abolish cell death (14). Accordingly, it is clear that *UNC5C*-induced neuronal death depends on the DD. The DD contains a caspase cleavage site in the intracellular region where it is cleaved by caspase-3 (60). This cleavage will lead to the generation of a pro-apoptotic fragment called addiction/dependence domain (ADD) (61,62), which acts as a scaffold to recruit and activate caspases which have been termed "executioner" proteins, ultimately leading to cell apoptosis, or programmed cell death (63). In addition, a mechanistic study in cell models identified that DAPK1 was activated in the aberrant *UNC5C* cell and the interaction of activated DAPK1 with the DD was the initial component in triggering neuronal death. DAPK1 interacted with the DD and triggered a series of highly regulated steps including sequential activation of PKD, ASK1, JNK, NADPH oxidases and caspases, ultimately leading to caspases-dependent neuronal apoptosis (14,64). As for the role of DAPK1 in UNC5C-induced neuronal apoptosis, DAPK1 was an initial factor which was indispensable for PDK and JNK phosphorylation and DAPK1 inhibitor could almost nullify the *UNC5C* variant-induced cell death in cell culture model (42). DAPK1 was identified to be involved in AD pathogenesis with an up-regulated expression in AD brain (65). In addition, SNPs (rs4878104 and rs4877365) in *DAPK1* were identified to be risk factors for AD, which indicated the negative association of DAPK1 with AD (66-68).

As a death-associated kinase protein, DAPK1 is identified as a new component of the neuronal death signaling complex involved in a wide range of cellular processes,

including apoptosis and autophagy (69). Therefore, DAPK1 could not only mediate apoptotic caspase-dependent cell death pathway but also be recognized as a mediator of cell autophagy to mediate a non-apoptotic caspases-independent programmed cell death (69). The molecular mechanisms of DAPK1 in cell autophagy were mainly associated with the Vps34-associated signaling pathways and the process of Vps34 activation included two independent pathways (69). The first pathway involved a kinase cascade, in which DAPK1 bound and phosphorylated PKD and further phosphorylated and activated Vps34. In the other pathway, DAPK1 can directly phosphorylate Beclin1, a necessary component of the Vps34 complex, and further activate Vps34 by releasing Beclin1 from its inhibitors, B-cell lymphoma 2 (Bcl-2) (69). Although DAPK1 can induce cell autophagy, the mechanisms underlying *UNC5C*-induced cell autophagy in AD context remain to be further elucidated.

In addition, based on the studies on *UNC5A*-induced death-signaling pathway, other possible signaling molecules may also be involved in the *UNC5C*-induced neuronal apoptosis. Neurotrophin receptor p75-interacting melanoma-associated antigen homolog (NRAGE), a UNC-5 family interacting protein, was revealed to participate in *UNC5A*-induced apoptosis via two ways (70). In one way, NRAGE is involved in the degradation of the X-chromosome-linked inhibitor of apoptosis protein (XIAP) which is a caspase inhibitor, and in another way, NRAGE could participate in activating pro-apoptotic JNK signaling pathway (70). However, it is a fact that the binding affinity of NRAGE to UNC5C is weaker than that to UNC5A (70). Thereby whether these signaling molecules participated in *UNC5C*-induced apoptosis needs further study. In conclusion, the role of UNC5C in neuronal death was involved in several mechanisms including cell apoptosis and autophagy process (*Figure 2*). The *UNC5C*-induced DAPK1 pathway in apoptosis has been identified in AD associated cell and animal models. However, the UNC5C-induced DAPK1 pathway in autophagy and the UNC5C-induced NRAGE pathway in AD are still unclear and remain to be elucidated in future research. In view of the importance role of DAPK1 in triggering neuronal death, we sincerely expect that blocking DAPK1 can be a new therapeutic target for AD.

UNC5C as a therapeutic target for AD

Given together, the potential pathways underpinning roles of *UNC5C* in AD pathogenesis demonstrated above have provided new insights into further investigations and intervention in the disease.

As demonstrated above, aberrant *UNC5C*-induced LOAD is mainly mediated by DAPK1-dependent cell death signaling pathways. Therefore, blocking the DAPK1 signal transduction seems feasible in *UNC5C*-associated AD. Calmodulin-like skin protein (CLSP) acts on JNK, the downstream molecular of DAPK1, as an endogenous inhibitor was identified to have marked neuroprotective effects in aberrant *UNC5C* cell models. For this reason, the deeper study of applying CLSP in *UNC5C*-associated AD treatment will be of great value. Interestingly, studies focusing on netrin-1 revealed that it prevented cell apoptosis by binding to UNC5C on the cell surface and suppressed UNC5C-induced death (14). Additionally, previous studies also reported netrin-1 could interact with APP and regulate Aβ levels in animal models (71). Combining the above evidence with the fact that netrin-1 has been successfully applied as an anti-apoptotic agent against hypoxic injury of the brain tissue (72,73), we can conclude that netrin-1 is promising to present a new therapeutic approach for *UNC5C*-induced AD. In view of the strong risk factor of *UNC5C* gene polymorphism for LOAD, *UNC5C* gene targeted therapy such as antisense oligonucleotides and RNA interference would offer a new therapeutic opportunity for *UNC5C*-associated AD. Finally, given the potential roles of *UNC5C* to AD pathogenesis, we sincerely hope that these new findings of *UNC5C* may open up avenues for further novel therapeutic approaches.

Conclusions

UNC5C is widely expressed in the adult hippocampus and cerebellum neurons. As for its biological function, it acts as a chemotropic molecule in mediating axon growth and neuronal migration in neuronal development and acts as a dependence receptor in the regulation of cell apoptosis. Up to now, six SNPs in *UNC5C* have been reported to increase the risk of LOAD. Although the association between *UNC5C* and LOAD risk has been well replicated in Chinese population, all these findings need to be further identified in more ethnic groups. To our knowledge, this review is the first study to summarize the role of *UNC5C* in AD. Although the potential mechanisms of *UNC5C* in AD are unclear, emerging data suggests that aberrant *UNC5C* predisposing to LOAD was mediated by DAPK1-induced

cell death signaling pathway. However, further study should be conducted in cell culture and animal models to validate the speculative pathological pathways including DAPK1-induced APP phosphorylation, aberrant tau accumulation, neuronal autophagy in *UNC5C*-associated AD. Other possible pathways, such as synaptic plasticity, iron homeostasis and lipid metabolism, also remain to be further investigated before being translated into clinical practice. Finally, we sincerely hope that in-depth studies on the association of *UNC5C* with AD will point to novel pathogenesis and thus provide insights into novel therapeutic targets for AD.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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