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THOUGHT LEADERS INVITED REVIEW

CD2AP in Alzheimer's disease: Key mechanisms and therapeutic potential

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Alzheimer's disease affects millions worldwide as one of the most devastating neurodegenerative conditions, characterized by two distinct pathological features: amyloid plaques (composed of clustered β-amyloid peptides) and neurofibrillary tangles (made of hyperphosphorylated Tau protein). These hallmark changes trigger a cascade of events, including progressive synaptic dysfunction, inflammation, and the breakdown of the protective blood–brain barrier. Recent breakthrough research through genome-wide association studies has identified CD2-associated protein (CD2AP) as a significant risk factor in developing Alzheimer's disease, with this crucial adaptor protein emerging as a key player in several disease mechanisms due to its fundamental role in cellular transport and cytoskeletal architecture. Growing evidence reveals that CD2AP influences multiple aspects of Alzheimer's disease pathogenesis, from β-amyloid metabolism and deposition to Tau-mediated neurotoxicity, synaptic integrity, blood–brain barrier function, and microglial activation states. Understanding CD2AP's physiological and pathological roles in the nervous system, particularly its cell type-specific functions, is crucial for developing effective therapeutic strategies that target CD2AP levels for Alzheimer's prevention and treatment, requiring a comprehensive understanding of CD2AP biology in neuronal cells.

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Alzheimer's disease (AD) is a neurodegenerative disease characterized by impairments in cognitive functions, especially in learning and memory. The primary pathological features observed in the brain tissues of deceased patients with AD include extracellular amyloid plaques composed of β-amyloid (Aβ) peptides and intracellular neurofibrillary tangles (NFTs) formed by hyperphosphorylated Tau proteins (1). Due to an aging society worldwide, the number and proportion of people with AD or other dementias are expected to grow in the coming years. In 2019, some 55 million people were estimated to have dementia across the world, a figure predicted to increase to 139 million by 2050, according to the WHO. The annual cost of dementia was estimated to be US $1.3 trillion in 2019, with this figure expected to more than double by 2030 to $2.8 trillion (2).

AD can be classified into early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease (LOAD) based on the age of onset (before or after 65 years old), with EOAD accounting for 5%–10% of the incidence (3). Studies indicate that EOAD is often linked to familial genetic mutations, particularly in the genes encoding β-amyloid precursor protein (APP), presenilin-1 (PS1), and presenilin-2 (PS2) (4, 5). In contrast, the majority of LOAD cases are typically sporadic and associated with multiple factors, including environmental influences. Since the identification in 1993 of the Apolipoprotein E (APOE) ε4 allele as a significant genetic risk factor for LOAD (6, 7), genome-wide association studies (GWAS) have uncovered additional genes related to LOAD, such as *TREM2*, *BIN1*, *MS4A4*, *CD33,* and *CD2AP* (8–10). *CD2AP* encodes CD2-associated protein (CD2AP), also referred to as Cas ligand with multiple SH3 domains (CMS) (8–11). In this article, we provide a concise review on the latest research advancements concerning the functional role of CD2AP in AD.

CD2AP Introduction

The human *CD2AP* gene is located on chromosome 6 and comprises 18 exons (Figure 1A). It encodes a protein consisting of 639 amino acids with a molecular weight of approximately 71 kDa. The mouse *Cd2ap* gene is located on chromosome 17 and contains 18 exons, encoding a protein of 637 amino acids. The CD2AP protein is a scaffold protein that was initially identified due to its interaction with the transmembrane protein CD2 in T cells. This interaction facilitates CD2 clustering and stabilizes the connection between T cells and antigen-presenting cells, leading to its naming in 1998 (12).

CD2AP is primarily composed of three consecutive SH3 domains near the N-terminus, a proline-rich region in the middle, and a coiled-coil domain at the C-terminus [Figure 1A, with the three-dimensional structure of CD2AP derived from AlphaFold 3 (13, 14)]. The SH3 domains of CD2AP specifically recognize target protein sequences composed of extended polyproline type II helices. They are essential for CD2AP interaction with various cellular components, including cytoskeletal regulators, multiple signaling molecules, and apoptosis regulatory factors (15–17). The central proline-rich region of CD2AP mediates ligand-dependent interactions with actin-binding proteins, facilitating their recruitment to endocytic CD2AP-Cbl-epidermal growth factor receptor complexes (18). The C-terminal coiled-coil domain of CD2AP is indispensable for its actin-binding capability, as this region contains a conserved sequence of approximately 20 residues, known as the CARMIL peptide that specifically interacts with actin-capping protein (CP). This interaction enables CP to bind to the barbed ends of actin filaments, thereby capping the filaments and regulating actin monomer addition and loss. Furthermore, the C-terminal region of CD2AP contains specific binding sites for membrane proteins such as nephrin and podocin, highlighting its multifunctional role in cellular processes (19–23).

CD2AP is expressed throughout the body, with relatively high levels in the stomach, duodenum, colon, and kidneys. CD2AP is particularly enriched in podocytes of the glomeruli (24). In glomerular cells, CD2AP plays a crucial role by interacting with proteins such as nephrin and podocin at the slit diaphragm, anchoring these proteins to the actin cytoskeleton. This interaction is essential for maintaining the function of podocytes and the slit diaphragm during the glomerular filtration process (25, 26). CD2AP is indispensable for normal glomerular function. Mice with a complete knockout of the *Cd2ap* gene exhibit progressive glomerular dysfunction due to the loss of podocyte foot process integrity and typically die of renal failure within 6 to 7 weeks after birth (27).

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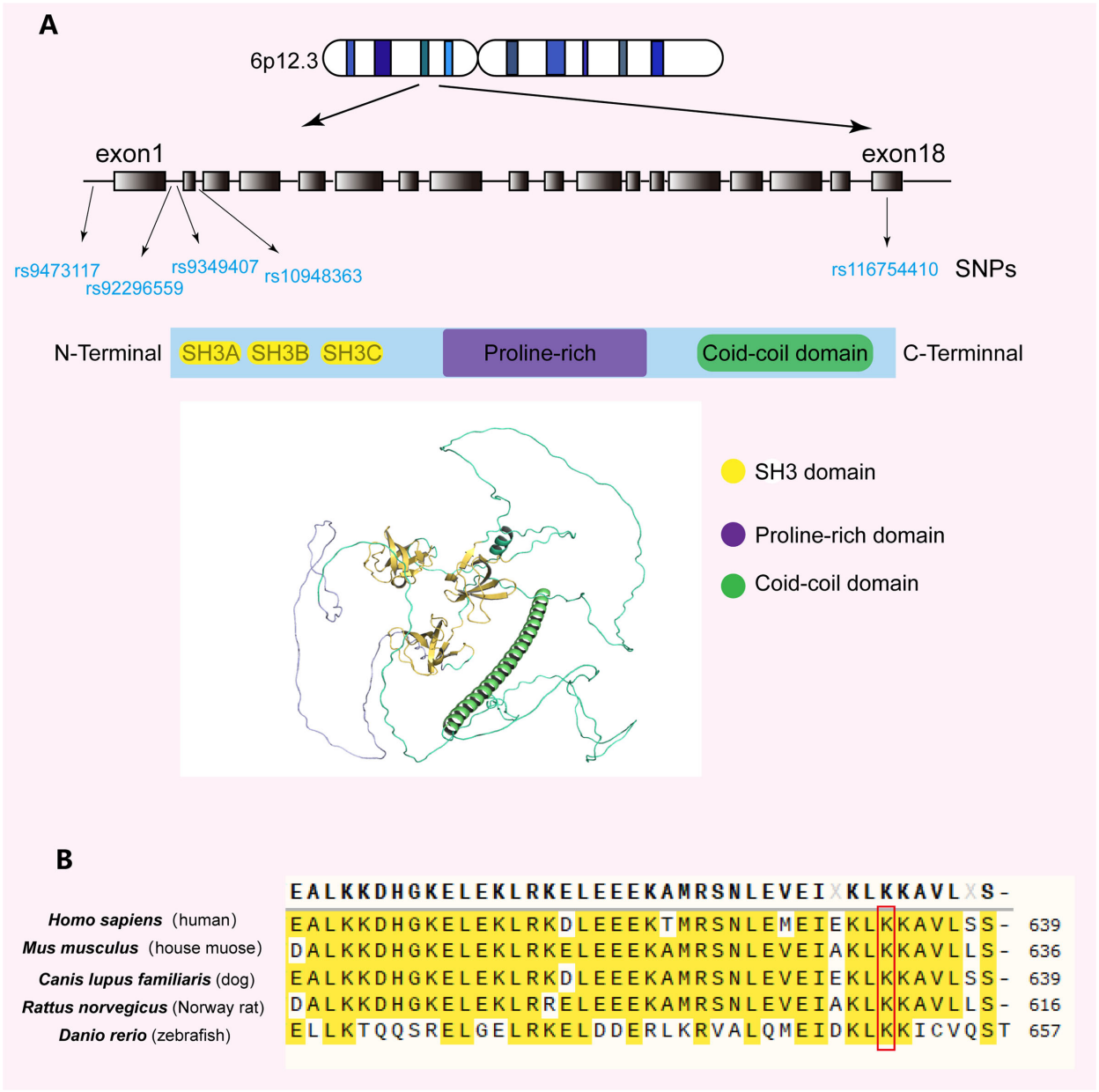

Figure 1. The scheme of CD2AP. (A) Human *CD2AP* gene and CD2AP protein. The *CD2AP* gene is located on chromosome 6p12.3 and has 18 exons. The CD2AP protein contains three SH3 domains, a proline-rich domain and a coil-coil domain. The three-dimensional structure of CD2AP is derived from AlphaFold 3. SNPs associated with AD are listed. (B) Comparison of CD2AP sequences of different species around K633 (highlighted by a red box).

CD2AP also participates in tumor growth but shows diverse effects in different cancers. For example, CD2AP was found to display a specific expression pattern in human urogenital organs but with distinct expression patterns in several types of kidney tumors (28). Another study revealed a reduction of CD2AP expression in renal clear cell carcinoma (ccRCC) and an association of lower CD2AP expression level with worse patient prognosis, implicating that CD2AP may be a prognostic biomarker for ccRCC (29). In addition, CD2AP was found to form a scaffold protein complex with TKS4 for regulating the migration and epithelial-mesenchymal transition pathways of HCT116 colon cancer cells (30). Furthermore, CD2AP could promote cell adhesion and influence cytoskeletal assembly by interacting with the protein CAPZA1, thereby regulating the metastasis of gastric cancer cells (31). Recently, we also revealed that CD2AP was upregulated in glioblastoma, in which CD2AP could enhance the NF-κB signaling by interacting with TRIM5, thereby promoting the malignant behavior of glioblastoma (32).

Since the identification of the association between CD2AP and AD, the function of CD2AP in the brain has been attracting more and more attention. The mRNA data from the Allen Brain Atlas suggest that although CD2AP may be expressed at low levels in neurons, it is relatively enriched in highly plastic brain regions such as the hippocampus, cortex, and cerebellum (33, 34). In addition, high expression of CD2AP was observed in dendritic endosomes of primary cultured mouse neurons (34). Since neurons share morphological similarities with podocytes, as both possess abundant actin-rich projections and have common actin regulators such as synaptopodin and cortactin (35), CD2AP might play a significant role in neurons as it does in podocytes. Indeed, the absence of CD2AP in neurons was shown to cause synaptic damage (36–38). Moreover, we recently discovered that CD2AP was expressed at higher levels in microglia compared to neurons in mice and that CD2AP could regulate microglial activation in response to Aβ toxicity (39). These findings indicate that CD2AP also plays a critical role in the central nervous system.

Relationship Between CD2AP and AD

CD2AP Single-Nucleotide Polymorphisms Are Associated with AD

In 2011, Naj *et al.* and Hollingworth *et al.* independently conducted genome-wide association studies (GWAS) using large samples and consistently identified that the single-nucleotide polymorphism (SNP) rs9349407 in *CD2AP* intron 1 significantly associated with LOAD (8, 9). Subsequent replicative studies reported controversial results on the association between rs9349407 and AD, with both positive (40–42) and negative (43–46) correlations suggested. However, most negative studies used relatively small sample sizes. Another work studying deceased individuals who underwent complete neuropathological evaluations found that the rs9349407 locus was related to neuritic plaque pathology (47).

The work by Hollingworth *et al.* further identified that the SNP rs9296559 in *CD2AP* intron 1 was also associated with LOAD (9), and this association was confirmed in the southern Han Chinese population (42). Other studies identified additional SNPs in the *CD2AP* gene to associate with AD, such as rs10948363 in *CD2AP* intron 2 (48, 49) and rs116754410 in *CD2AP* exon 18 (50), of which the latter results in a missense mutation (K633R) in CD2AP. The amino acid K633 is located in the coiled-coil domain of CD2AP, and one recent study found that CD2AP K633R overexpression in neurons could increase spine density and volume. In contrast, its overexpression failed to rescue impaired spine density in CD2AP-deficient neurons (37). Herein, we also evaluated the conservation of K633 and found it conserved from humans to zebrafish (Figure 1B), further implicating the importance of K633 for CD2AP function; this requires further investigation. Moreover, The SNP rs9473117 located upstream of *CD2AP* was reported to be associated with EOAD (51).

CD2AP Expression Alteration in AD

It was reported that *CD2AP* expression decreased in peripheral blood lymphocytes in patients with LOAD (42). However, we recently noticed that in one proteomic study with large datasets (52), CD2AP protein levels were significantly increased in the brain of patients with AD compared to control subjects and asymptomatic patients with AD (39). We also found that CD2AP levels significantly increased in the hippocampus of the 5xFAD AD model mice at pathological stages but not at pre-pathological stages, and such an increase probably occurred specifically in microglia (39). Our findings implicate that CD2AP alterations in AD occur after pathological changes. Consistent with our results, an earlier study also reported that CD2AP levels were increased in the brain of the APP/PS1 AD model mice (53).

Although several SNPs around *CD2AP* have been reported to be highly associated with AD, only a few studies have explored the effects of some of these SNPs on *CD2AP* expression so far. In a study analyzing human brain gene expression data, researchers found that the minor allele of rs9349407 was only associated with decreased *CD2AP* expression in the cerebellar cortex (54). While the study showed that rs9473117 associates with EOAD, the minor allele of rs9473117 was found to associate with increased *CD2AP* expression in the thalamus and cerebellar cortex (51). In addition, Pavešković *et al.* leveraged new paired single-nucleus RNA-sequence and whole genome sequencing data and found that the risk variant of rs9473117, together with those of rs7767350 and rs9369716 that are in strong linkage disequilibrium with rs9473117, increases human *CD2AP* mRNA expression in both excitatory and inhibitory neurons, as well as in microglia (36).

CD2AP Regulates APP Transport and Aβ Production

One major pathological feature of AD is the formation of amyloid plaques composed of Aβ, which is derived from APP through sequential cleavages. First, APP is cleaved by the β-secretase (BACE1) to generate soluble extracellular APP (sAPPβ) and a C-terminal fragment (CTFβ). APP CTFβ is then cleaved by the γ-secretase to produce Aβ fragments of 40 or 42 amino acids in length, namely Aβ40 and Aβ42 (55, 56). The cleavage of APP is determined by the subcellular localization of APP and its interactions with BACE1 and γ-secretase during membrane, endosome, and lysosome trafficking (57, 58).

CD2AP is an actin-associated adaptor protein that, along with several members of the Rab family, participates in the docking process of vesicles to target membranes and regulates endosome morphology (19). Several studies have suggested that CD2AP is involved in the intracellular transport and cleavage of APP for Aβ production. Furusawa *et al.* found that overexpression of CD2AP at the cellular level accelerated the transport of APP from early endosomes to late endosomes, thus initiating the degradation process of APP without affecting its degradation rate. In contrast, knocking down CD2AP in cells significantly increased intracellular APP levels (59). Ubelmann *et al.* also showed that CD2AP could keep APP and BACE1 apart in early endosomes in neurons: CD2AP deficiency increased the trapping of APP at the limiting membrane of early endosomes and thus reduced its sorting for degradation in dendrites so that APP and BACE1 had elevated convergence in early endosomes for increased Aβ generation (34). However, Liao *et al.* reported that in the N2a-APP695 cell line, overexpressing APP, knocking down CD2AP reduced cell membrane APP levels and Aβ release and lowered the Aβ42/Aβ40 ratio. Moreover, they found that in 1-month-old APP/PS1 mice with complete loss of CD2AP, the Aβ42/Aβ40 ratio was decreased. While, CD2AP haploinsufficiency had no effect on Aβ deposition up to 7 months of age in APP/PS1 mice (60). One recent study also reported that in APP/PS1 mice with neuron-specific CD2AP knockout, Aβ levels were not altered at 4.5 months of age (61). Due to the inconsistency in different studies, the specific role of CD2AP in APP processing and Aβ requires further in-depth investigation. Table 1 summarizes reported studies on the effects of CD2AP on APP trafficking/Aβ generation and other AD-related processes.

CD2AP Modulates Tau-mediated Neurotoxicity

Neurofibrillary tangles formed by hyperphosphorylated Tau protein represent another important pathological feature of AD. In one study using immunohistochemical assays to explore the association between CD2AP expression and AD pathologies in postmortem human brain samples, CD2AP was found not associated with Aβ deposits in vessels or parenchymal plaques. Instead, CD2AP immunodetection in neurons was positively associated with Braak neurofibrillary stage (62). Furthermore, the AD-associated *CD2AP* SNP rs10948363 was found to associate with NFTs (63), the AD-associated *CD2AP* SNP rs9349407 was found to associate with an increase in total Tau protein levels in cerebrospinal fluid, and the rs9381563 variant in *CD2AP* was correlated with changes in phosphorylated Tau levels in cerebrospinal fluid (64).

CD2AP also affects the neurotoxicity caused by Tau. In a fruit fly AD model expressing human Tau, researchers found that knockdown of the cindr gene (the human homolog of *CD2AP*) robustly enhanced Tau toxicity (65). Xue *et al.* also found that the specific knockout of CD2AP in neurons in APP/PS1 mice resulted in a significant increase in the phosphorylation levels of endogenous Tau protein. In contrast, the total Tau protein levels remained unchanged (61). Additionally, the deficiency of CD2AP led to elevated P38 phosphorylation levels in these mice. Treatment with P38 phosphorylation inhibitors attenuated the increased phosphorylation of endogenous Tau protein caused by the loss of CD2AP (61). It is known that P38 can phosphorylate Tau (66, 67). However, although some studies consistently reported that high glucose and TGFβ treatments decreased CD2AP while increased P38 phosphorylation (68, 69) and that CD2AP deficiency enhanced TGFβ-induced P38 activation (70), the precise mechanism by which CD2AP influences P38 phosphorylation remains unclear and deserves further scrutiny.

CD2AP Regulates Synaptic Growth and Development

Synapses are the core structures for signal transmission between neurons, and abnormalities in synaptic function are closely linked to cognitive impairment. In the early stages of AD, synaptic dysfunction appears, although the number of synapses does not significantly change at this stage. However, in the mid to late stages of AD, there is a significant loss of synapses and neuronal death, leading to a sharp decline in cognitive abilities (71–76). Ojelade *et al.* found that the cindr gene was involved in the development and maturation of synapses during the growth of fruit flies. Mutations in cindr disrupted the release and recycling of synaptic vesicles, impairing synaptic plasticity (38). They also noticed decreased levels of some synaptic proteins in CD2AP knockout mice (38). Additionally, they showed that cindr interacted with 14-3-3ζ to regulate the ubiquitin

Table 1. Current knowledge on the contribution of CD2AP to various AD-related processes

Study system	Findings	References
APP and Aβ		
Cells (HEK293, COS-7, N2a, neurons)	CD2AP overexpression enhances APP transport from early endosomes to late endosomes and APP degradation. CD2AP knockdown has opposite effects	(59)
Cells (N2a, neurons)	CD2AP knockdown stalls APP at the limiting membrane of early endosomes, increases the encounter of APP and BACE1, and promotes Aβ generation	(34)
N2a-APP695 cells	CD2AP knockdown reduces Aβ40 and Aβ42 and Aβ42/40 ratio, reduces cell surface levels of APP but not total APP	(60)
PS1APP mice with CD2AP KO	No significant change of Aβ40 and Aβ42, but decreased Aβ42/40 ratio in 1-month old mice	(60)
PS1APP mice with CD2AP haploinsufficiency	No significant change of Aβ40 and Aβ42 and Aβ plaques at 7 months old. Only decreased PBS-soluble Aβ42/40 ratio in 7-month-old female mice	(60)
APP/PS1 mice with neuron-specific CD2AP KO	Aβ not altered in 4.5-month-old mice.	(61)
Tau		
Flies expressing human Tau	CD2AP knockdown enhances Tau toxicity	(65)
APP/PS1 mice with neuron-specific CD2AP KO	Increased synaptic deficits and synaptic protein loss at 4.5 months old	(61)
Synapse		
Neurons	CD2AP knockdown reduces spine density and size and neuronal activity	(37)
Neurons	CD2AP knockout disrupts neuronal and synaptic morphology	(36)
Flies	CD2AP deficiency impairs synapse maturation and function	(38)
CD2AP KO mice	Decreased certain synaptic proteins at 5 months old	(38)
CD2AP heterozygous and homozygous KO mice	Abnormal pre-synaptic release with increased paired-pulse facilitation at 5 to 8 weeks old	(36)
CD2AP homozygous KO mice	Perturbation of proteins involved in synaptic function at 5 weeks old	(36)
5xFAD mice with microglial CD2AP haploinsufficiency	Improved synaptic damage at 7 months old	(39)
Microglia		
CD2AP-deficient microglia	Reduced phagocytosis ability	(39)
5xFAD mice with microglial CD2AP haploinsufficiency	Attenuated microgliosis at 7-months old	(39)
Blood–brain barrier (BBB)		
CD2AP KO mice with CD2AP transgene expression in the kidney	Compromised BBB integrity	(85)
Behaviors		
CD2AP heterozygous KO mice	Subtle impairments in discrimination learning at 2.5-months old	(36)
Nestin-Cre mediated brain CD2AP KO mice	No obvious cognitive and motor behavior changes at 3.5- and 12-months old	(36)
APP/PS1 mice with neuron-specific CD2AP KO	Accelerated cognitive deficit onset at 4.5-months old	(61)
5xFAD mice with microglial CD2AP haploinsufficiency	Improved cognitive behaviors at 7-months old	(39)
CD2AP KO mice with CD2AP transgene expression in the kidney	Normal behaviors	(85)

Abbreviation: KO, knockout.

proteasome system, thereby affecting the conversion of synaptophysin and plasma membrane calcium ATPase (PMCA); and the absence of cindr increased PMCA levels and decreased cytosolic calcium (38). Research by Mirfakhar *et al.* found that CD2AP knockdown in neurons resulted in decreased spine density and size and decreased neuronal activity (37). They also proposed that CD2AP controls the formation and growth of dendritic spines by regulating the balance of F-actin polymerization and depolymerization (37). Pavešković *et al.* also observed a marked reduction in the number of synapses and impaired synaptic plasticity in the hippocampus of CD2AP-deficient mice (36). In addition, CD2AP was suggested to regulate the length and complexity of neuronal axons and the number of filopodia at growth cones through coordinating nerve growth factor signaling (77). Moreover, we recently found that specific deletion of CD2AP in microglia attenuated synaptic damage in 5xFAD mice at pathological stages, though this is attributed to reduced synapse phagocytosis by CD2AP-deficient microglia (39). These findings collectively suggest that CD2AP plays a crucial role in synaptic development in neurons, and its alteration may contribute to synaptic dysfunction in AD. A summary of the regulation of APP, Tau, and synapses in neurons by CD2AP is illustrated in Figure 2.

CD2AP Regulates Microglial Activity

In addition to Aβ plaques and Tau tangles, AD is also characterized by neuroinflammation. Microglia are primary immune cells of the brain and are activated in response to toxicity to exert protective function during the early stages of AD. However, in the later stages of AD, excessively activated microglia can exacerbate disease progression by releasing toxic proinflammatory factors and phagocytosing functional synapses (78–81). CD2AP was initially discovered as a ligand for CD2 in T cells, implicating its significant role in immune cells (12). We recently found that CD2AP

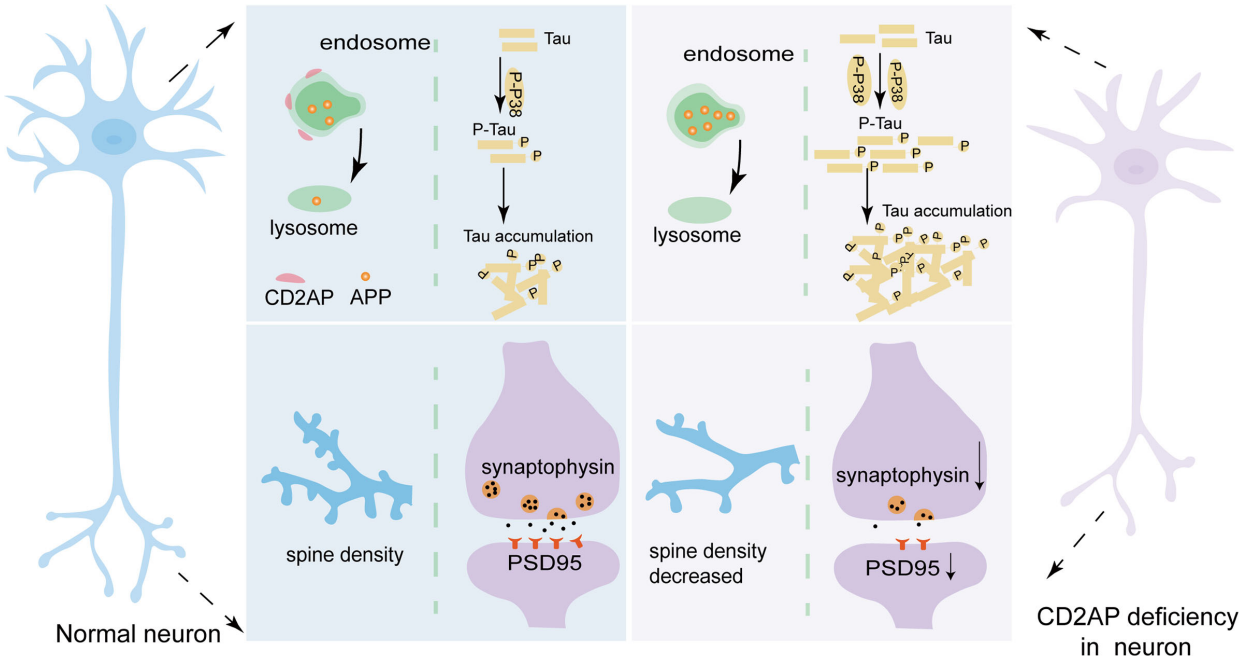

Figure 2. Impact of CD2AP function in neurons. CD2AP regulates APP transport from endosomes to lysosomes, Tau phosphorylation, and synapse formation and maintenance in neurons. CD2AP deficiency results in increased APP retention in endosomes for elevated Aβ generation, increased Tau phosphorylation and accumulation, and reduced synapse numbers and synaptic proteins such as synaptophysin and PSD95.

deficiency reduced microglial response to Aβ and microglial phagocytosis ability. Notably, we showed that in contrast to the deteriorating effect of neuronal knockout of CD2AP in APP/PS1 mice (61), microglial CD2AP deficiency attenuated cognitive defects, synaptic damage, and disease-associated microglia (DAM) in 5xFAD mice at pathological stages (39). We further suggested that one possibility for such a rescuing effect was that CD2AP could interact with the critical microglial survival factor, colony stimulating factor 1 receptor (CSF1R), so that CD2AP deficiency ameliorated the CSF1R signaling–mediated microglial activation and downstream expression of the C1q complement, which is crucial for synapse phagocytosis, and the formation of DAMs triggered by toxic Aβ (Figure 3) (39). The seemingly contradictory data regarding the effects of microglial CD2AP and neuronal CD2AP on Aβ pathologies are likely stem from distinct action mechanisms in each investigated cell type. However, it is also possible that they are caused by different experimental models used in these studies. However, so far, our understanding of the role of CD2AP in microglia and other cell types lags behind that in neurons. There are urgent requirements for elucidating the pathophysiological functions of CD2AP in different cell types and parallelly comparing their contributions to AD.

CD2AP Participates in the Integrity of the Blood–Brain Barrier

The blood–brain barrier (BBB) provides a physical barrier to protect the brain from harmful materials in the peripheral environment. The disruption of the BBB can lead to the influx of neurotoxic bloodborne debris, cells, and microbial pathogens into the brain, triggering inflammatory responses and related immune reactions, which may initiate various pathways leading to neurodegenerative diseases such as AD (82–84). MRI studies have shown that the BBB function is impaired in patients with early AD and other neurodegenerative diseases. Analyses of postmortem tissues of AD patient brain tissues also support this conclusion (82). Brain microvascular endothelial cells, which express high levels of CD2AP, are key components of the BBB (85). CD2AP homozygous knockout mice with CD2AP transgene expression in the kidney attenuated their mortality rate. Such mice showed overall normal behaviors. However, they had compromised the integrity of the BBB so intraperitoneally administered pentylenetetrazol increasingly penetrated into the brain to induce seizures in much shorter latency periods in these mice than in controls (85). This finding implicates that abnormal expression of CD2AP in brain microvascular endothelial cells, if any, may lead to BBB dysfunction and facilitate AD progression.

Conclusion

CD2AP is intricately involved in intracellular protein transport and degradation, vesicle trafficking, cell signaling, and cytoskeleton remodeling. As a risk factor for AD, abnormalities in CD2AP in the nervous system may contribute to the pathogenesis of AD through various mechanisms, including influencing the transport and processing of APP and thus Aβ generation, participating in Tau-mediated neurotoxicity, disrupting synaptic function and vesicle release, modulating microglial activation, and compromising the integrity of the BBB. However, the specific molecular mechanisms by which CD2AP participates in these processes have yet to be fully elucidated. Moreover, CD2AP in different neural cell types may have contradictory effects on AD pathologies. Further detailed research into the pathophysiological roles of CD2AP in the nervous system, especially in various cell types, will provide new insights into the pathogenesis of AD. With a comprehensive understanding of the exact pathophysiological functions of CD2AP in different neural cells, it is also possible to design cell type–specific drugs to promote CD2AP levels in those whose CD2AP deficiency is pathogenic (e.g., neurons) and to reduce CD2AP levels in those whose CD2AP elevation is pathogenic (e.g., microglia) as potential therapeutic approaches for AD.

Author Contributions

Y.W. wrote a draft. Y.-w.Z. reviewed and revised the manuscript.

All authors have read and approved the manuscript. All authors take full responsibility for all data, figures, and text and approve the study's content and submission. No related work is under consideration elsewhere. All authors state that all unprocessed data are available, and all figures accurately present the original data.

Corresponding author: Professor YwZ for any aspect of the work. This corresponding author takes full responsibility for the submission process.

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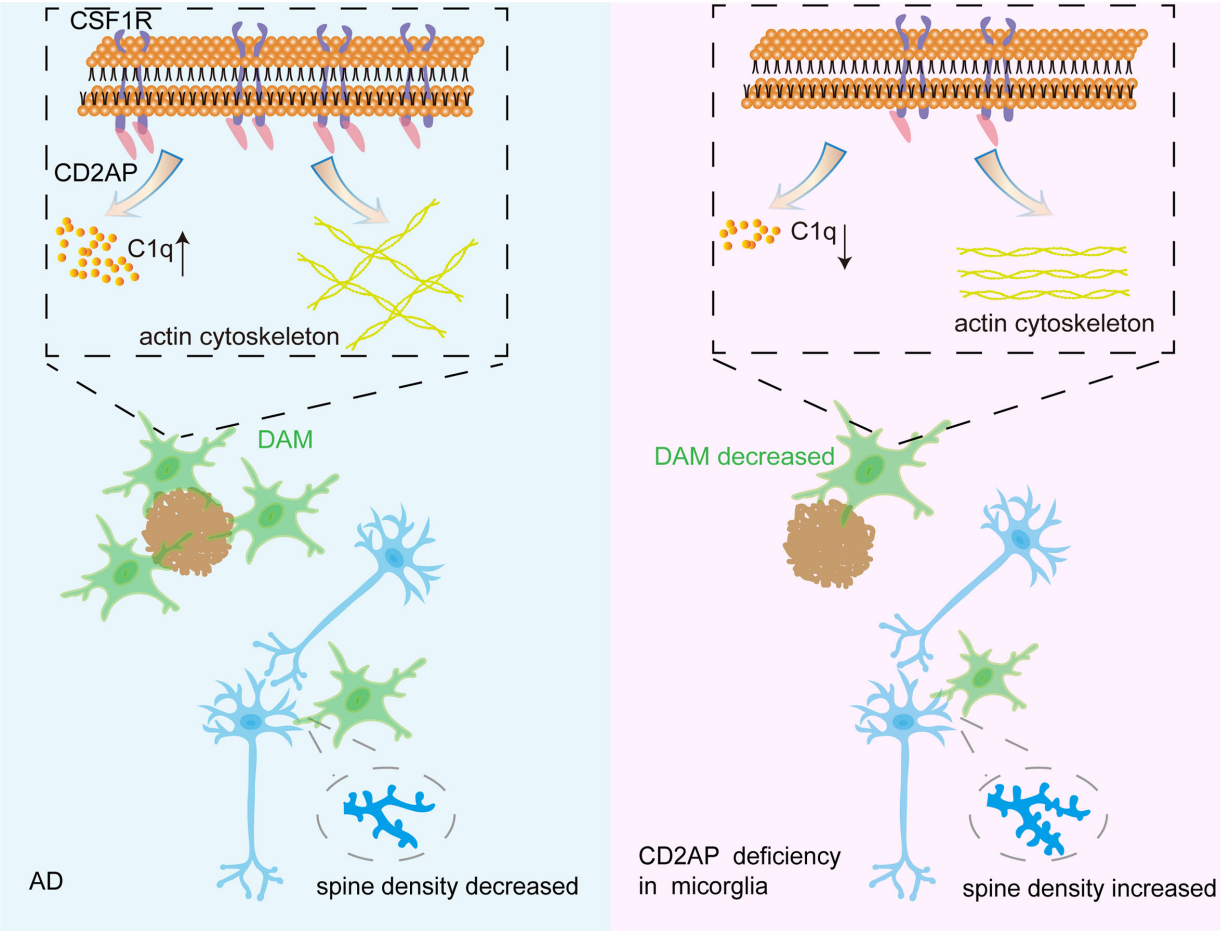

Figure 3. Impact of CD2AP deficiency in microglia in AD. Microglial CD2AP levels are increased in AD, leading to elevated CSF1R signaling and C1q expression and cytoskeleton remodeling in microglia, resulting in the formation of disease-associated microglia (DAM) and elevated microglial phagocytosis of synapses. CD2AP deficiency in microglia attenuated these changes to protect against AD.

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Author Disclosures

The authors have confirmed that no conflict of interest exists.

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