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Review

The role and therapeutic implication of protein tyrosine phosphatases in Alzheimer's disease

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ABSTRACT

Protein tyrosine phosphatases (PTPs) are important regulator of neuronal signal transduction and a growing number of PTPs have been implicated in Alzheimer's disease (AD). In the brains of patients with AD, there are a variety of abnormally phosphorylated proteins, which are closely related to the abnormal expression and activity of PTPs. β-Amyloid plaques (Aβ) and hyperphosphorylated tau protein are two pathological hallmarks of AD, and their accumulation ultimately leads to neurodegeneration. Studies have shown that protein phosphorylation signaling pathways mediates intracellular accumulation of Aβ and tau during AD development and are involved in synaptic plasticity and other stress responses. Here, we summarized the roles of PTPs related to the pathogenesis of AD and analyzed their therapeutic potential in AD.

1. Introduction

Alzheimer's disease (AD) is an irreversible degenerative disease and is characterized by abnormal deposition of β-amyloid plaques and aggregation of neurofibrillary tangles [1]. These abnormal proteins are neurotoxic, resulting in symptoms such as cognitive impairment, emotional instability, and decreased judgment, which eventually lead to memory loss, abnormal behavior, and loss of self-care ability [2,3]. According to statistics, there are nearly 50 million patients with AD in 2018, and the number is expected to exceed 152 million by 2050, of which 13.8 million will be patients over the age of 65 [4,5]. Patients will bring a serious burden to the family and society. So, it is urgent to understand the pathogenesis of AD and develop effective drugs for the treatment of AD.

The pathogenesis of AD has not been fully elucidated, but scientists have proposed some widely accepted hypotheses, such as the Aβ cascade hypothesis, the tau protein hyperphosphorylation hypothesis, the cholinergic hypothesis, the neuroinflammation hypothesis, and the metal ion disorder hypothesis [6–8]. In addition, scientists have drawn attention to the role of mitochondrial dysfunction in neurodegenerative diseases [9]. Based on the above hypothesis, a series of drugs were designed and used in clinical, but the expected effect was not achieved. For example, elenbecestat (E2609), a β-secretase inhibitor developed by Amgen, which aims to reduce the production of Aβ, failed in 2019 due to its phase III clinical trial results showing that patients' cognitive function deteriorated [10]; Swiss Roche launched RG7129, which acts on BACE, and the clinical phase III results proved that it has severe liver toxicity [11,12]; the azeliragon developed by VTV Therapeutics in the United States for the RAGE target, and phase III clinical results showed that it failed to reach the primary efficacy endpoint and had to withdraw from the study [13,14]. There are countless examples of AD-related treatments that have failed in clinical trials. In addition to traditional

Abbreviations: APP, Amyloid precursor protein; APOE, Apolipoprotein E; DUSPs, Dual-specificity phosphatases; CDK5, Cyclin-dependent kinase-5; EGF, Epidermal Growth Factor; ER, Endoplasmic reticulum; HGF, Hepatocyte growth factor; IFN, Interferon; IRS, Insulin receptor substrate; JAK2, Janus kinase 2; LMWPTP, Low mass weight protein tyrosine phosphatases; MCI, Mild cognitive impairment; NFTs, Neurofibrillary tangles; NETs, Neutrophil extracellular traps; PTK, Protein tyrosine kinase; PTPN3, Protein tyrosine phosphatase non-receptor type 3; PTP1B, Protein Tyrosine Phosphatase1B; PDK1, Phosphoinositide-dependent protein kinase-1; PKC, Protein kinase C; RAGE, Receptor for advanced glycation end product; SUMO, Small-ubiquitin-related modifier; SHP2, Src homology2(SH2) domain-containing protein tyrosine phosphatase; SMAP, Small acidicprotein; TNIK, TRAF2 And NCK Interacting Kinase; TrkB, Tyrosine Kinase receptor B.

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drug treatment, scientists have proposed other treatment methods, such as hyperbaric oxygen therapy [15], monoclonal antibodies [16,17], vaccines [18], and plasma therapy [19,20]. Because of the lack of randomized clinical trial analysis for the number of samples or only effective for a certain type of cognitive dysfunction, the exact efficacy of these treatments on AD requires further research. There are four main types of FDA-approved anti-AD drugs: acetylcholinesterase inhibitors (e.g., donepezil, 1996 [21]; galantamine, 2001 [22]), NMDA receptor antagonists (Memantine, 2003 [23]), Aβ inhibitors (adumumab, 2021 [17,24]), and intestinal flora regulators (GV-971, 2019). These listed drugs can only improve the symptoms of patients or delay the development of the disease but cannot reverse the disease process. At present, researchers have not fully understood the pathogenesis of AD; therefore, it is difficult to develop effective drugs. Effective targets are the basis for new drug development and are powerful tools to treat AD.

Increasing evidence has shown that the AD pathogenesis is closely related to abnormal protein tyrosine phosphatases (PTPs). Inhibition of DUSP22 activity results in hyperphosphorylation of tau protein, which promotes its dissociation from microtubule-associated proteins, ultimately leading to synaptic loss and neuronal death. Increased PTP1B activity in the brains of AD patients inhibits GSK3 activation, which further inhibits the activation of downstream signaling proteins, resulting in neuronal loss and accelerated AD development. In addition, according to a recent report, the expression of SHP2 is upregulated in the hippocampus of patients with AD. Its interaction with tau is enhanced and the tau-SHP2 complex is abundantly present in neurofibrillary tangles. Although there are relatively few reports on the relationship between PTPs and AD, and the specific mechanism remains unclear, the roles of PTPs in the pathogenesis of AD cannot be ignored. PTPs is expected to be an important direction and a potential breakthrough for AD research. Therefore, we reviewed the abnormal PTPs in AD, and introduced the role of related inhibitors in AD to provide theoretical support for follow-up research.

2. PTPs family

2.1. Classification of PTPs

PTPs refer to a group of proteins with PTP homologous catalytic domains encoded by more than 100 genes. The amino acid sequences of the catalytic domains of various enzymes are different; thus, they have substrate specificity [25]. PTPs can be divided into four categories [26,27]: Class I contains the H/VC(X)SRS/T catalytic motif and has 99 members, of which 38 are classical tyrosine-specific phosphatases and the other 61 are dual-specificity phosphatases [28,29]; Class II is encoded by a single gene ACP1 alone, called LMWPTP; Class III is Tyr/Thr-specific phosphatase, including three members, CDC25A, CDC25B, CDC25C respectively; and the Class IV have four proteins, EYA1, EYA2, EYA3, and EYA4, dephosphorylating pSer as well as pTyr. The first three types use Cys as the catalytic core, while the fourth type uses Asp as the core; therefore, the catalytic mechanism is completely different from the first three types. It depends on the presence of cations and has Tyr/Thr phosphatase activity [30]. Among these, the crystal structures of dual-specificity phosphatases and low-molecular-weight phosphatases show greater similarity [31]. In the PTP superfamily, the [I/V] HCXXGXXR [S/T] sequence is preserved and relies on the cysteine residue in the catalytic active center as a nucleophilic site to form a covalent structure with phosphonothioate. Simultaneously, unchanged arginine residues play a role in stabilizing the regulatory state and maintaining substrate coordination affinity [32].

2.2. Activity of PTPs

PTP activity is regulated by various ways, including phosphorylation of serine/threonine residues [33], phosphorylation of tyrosine residues [34], calpain-mediated proteolysis [35], caspase reactions [36], protease-mediated proteolysis [37], reversible oxidation of reactive oxygen species [38], small ubiquitin-like modifications [39], and prenylation modifications [40].

Reversible oxidation is widespread in the regulation of the PTP superfamily activity. The catalytically active site of PTP contains a cysteine residue. If it is oxidized by reactive oxygen species, it loses its nucleophilicity and the enzymatic activity is inhibited immediately. Cysteine is usually only oxidized to S-OH; if it is further oxidized to S-O2H or S-O3H, it undergoes irreversible oxidation [41–43]. However, LMWPTP differs from classical PTPs in that the former has two cysteine residues in the active site, one of which is oxidized and instantly forms a disulfide bond with the other to prevent further irreversible oxidation. The newly formed disulfide bond can be reduced to -SH after exposure to a reducing agent. These two procedures effectively ensure transient and reversible modification of the enzyme [44].

PTPs are also regulated by autophosphorylation, mainly at the serine, threonine, and tyrosine residues. For example, the activity of PTP-SHP2 is greatly increased after phosphorylation by receptor-type tyrosine kinase, and then the phosphorylated SHP2 binds to Grb2/SOS, activating the Ras/Erk signaling pathway, and finally enhancing tumor metastasis [45]. After phosphorylation at Ser39/Ser434, the activity of PTP-PEST was significantly reduced, resulting in the down-regulation of downstream signaling pathways [33]. The phosphorylation of different PTPs has different effects on the signaling pathways in which the enzymes are located, and these pathways are closely related to life activities, such as cell proliferation, differentiation, growth, and metastasis [46,47].

Researchers found that PTP_S can be modified by small-ubiquitin-related modifier (SUMO) as well [48]. There are four types of SUMO proteins in the human body. When these proteins bind to target proteins, they change their intracellular localization, catalytic activity, and spatial conformation of the target protein. Moreover, recent research has revealed that SUMO may induce protein degradation and affect protein stability. PTP1B was the first protein found to localize in the endoplasmic reticulum after SUMO. SUMO not only alters the subcellular localization of PTP1B but also significantly reduces its catalytic activity [49]. If the amino acid residue covalently bound to the corresponding site of the SUMO protein is mutated, PTP1B cannot be modified [50].

2.3. Function of PTPs

PTPs regulate the dephosphorylation of downstream signaling proteins [51,52]. Most enzymes do not have a single function and usually participate in several signaling pathways, regulating the phosphorylation balance of proteins together with PTKs. PTP dysfunction is implicated in many human diseases, including diabetes, cancer, inflammation, and AD.

Abnormal signal transduction mediated by SHP2 plays an important role in tumor development. Under the stimulation of cytokines, such as EGF, IFN, and HGF, SHP2 can participate in p53-related signaling pathways and regulate DNA damage and replication in cancer. SHP2 can also bind to Gab1, activate the PI3K/Akt signaling pathway, and regulate tumor cell proliferation, apoptosis, and drug resistance [53,54].

The protein tyrosine phosphatase non-receptor type 3 (PTPN3) signal transduction function is regulated by MAPK and PIK3, which are closely related to tumor cell growth, metastasis, invasion, and other processes. Studies have found that inhibiting PTPN3 activity in lung NETs can promote lymphocyte activation and prevent cancer, which is expected to provide a new therapeutic method for human beings to overcome cancer [55,56].

Over the past decade, numerous reports have shown that LMWPTP is highly expressed in chronic myeloid leukemia, resulting in the hyperactivation of Src and Bcr-Abl kinases, followed by accelerated glucose metabolism and increased lactate production, which in turn facilitates the pentose pathway (one of the key processes for antioxidant and protective effects). Research explored the relationship between

Table 1
PTP_S associated with AD.

PTPs categories	Name	Expression site	Function
Classical Tyrosine-specific phosphatases	STEP [61]	striatum cortex hippocampus	Activity of STEP modulates synaptic connectivity
	SHP2 [62]	hippocampus	Upregulation of SHP2 expression promotes phosphorylation of Tau
	PTP1B [63]	hippocampus	Increased PTP1B activity induces neuroinflammatory responses in AD
Dual-specific phosphatases	DUSPs [64]	cortex hippocampus	DUSPS family members mediate accumulation of Aβ and tau proteins, causing synaptic loss

LMWPTP and autophagy and found that the reduction of LMWPTP content would lead to a decrease in SOD levels, and then stimulate the process of autophagy [56].

3. PTPs in AD

3.1. Pathological features of AD

AD is the most common form of dementia, accounting for 50–60 % of all cases. Its pathological characteristics include the deposition of extracellular β-amyloid protein to form senile plaques and the accumulation of hyperphosphorylated tau protein in cells to form neurofibrillary tangles. Both abnormal proteins are neurotoxic and can cause loss of synapses and neuronal cell death, ultimately leading to memory impairment and cognitive dysfunction in patients [57]. Throughout the development of AD, protein phosphorylation mediates a series of signal transduction processes. White et al. constructed a network of unusually phosphorylated proteins in AD through statistical analysis, including TNIK pS680, BRSK2 pS423, phosphorylated CDK5, and phosphorylated CDK18, providing a clear idea for the study of AD pathological processes. With the continuous development of molecular biology and cell biology, an increasing amount of evidence has shown that PTP_S is closely related to AD. In patients with AD, the expression level and activity of PTPs are altered; for example, STEP level obviously increases about 6-month old AD mice and they are accompanied by behavioral and cognitive impairments [58]; Upregulation of SHP2 expression leads to increased interaction with tau [59]; Increased activity of PTP1B mediates neuroinflammation in AD [60,61]. The above deviant phosphatase activity or content is associated with AD symptoms, suggesting that phosphatases are expected to become a key breakthrough point in elucidating the pathogenesis of AD.

3.2. AD-related PTPs

Recent studies have reported a close relationship between several PTPs and AD. Next, the known PTPs associated with AD will be reviewed and the main pathological results are summarized in Table1.

3.3. STEP in AD

3.3.1. Introduction of STEP

STEP is one of the important members of the PTP family, encoded by the human *PTPN5* gene. STEP is a MAPKs-specific phosphatase with a total of 5 subtypes, and STEP61 and STEP46 are mainly found in neurons of the central nervous system [65]. The complete STEP contains not only the classical PTP catalytic domain, the KIS domain that determines substrate specificity, and the KIM domain binding to the substrate, but also two TM domains which can help target ER as well as PSD and the PR1 and PR2 domains bind to Fyn and Pyk2, respectively [66]. Similar to classical PTPs, the catalytic domain of STEP phosphatases contains abundant α-helices and β-sheets, among which there are also some

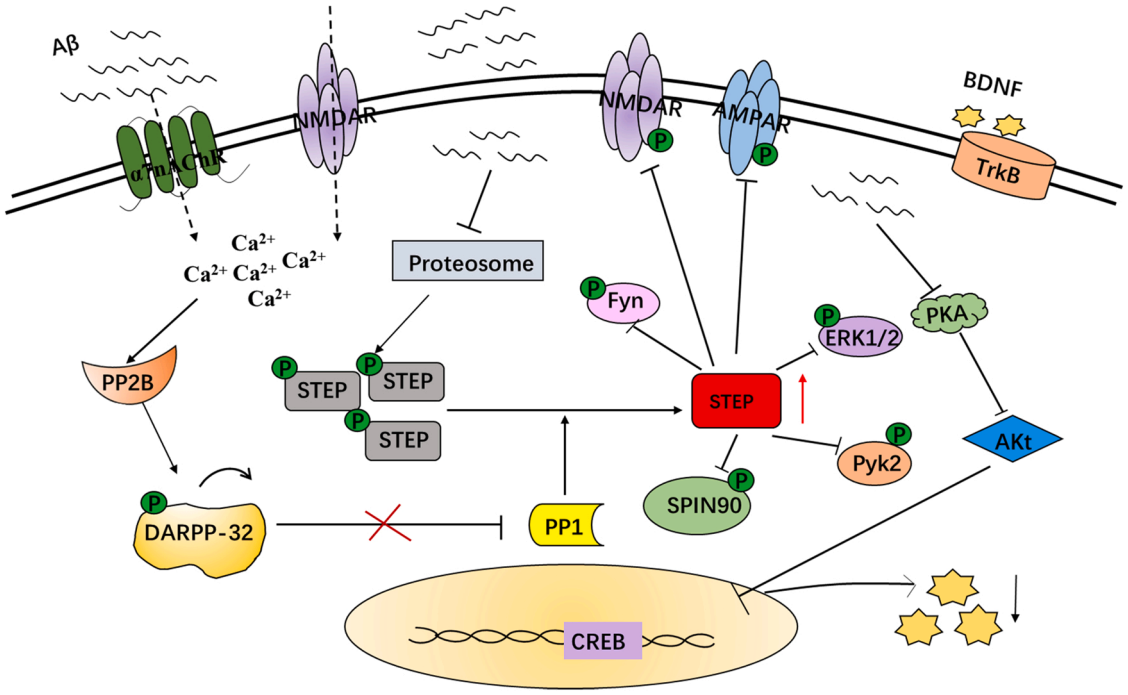


Fig. 1. The mechanism of reduced synaptic plasticity and dendritic spines caused by abnormal STEP. There are several pathways causing increased levels of STEP: ①soluble Aβ oligomers bind to α7nAChRs, promoting influx of ca2+. PP2B dephosphorylates DARPP-32, which makes DARPP-32 fail to inhibit PP1 activity. PP1 dephosphorylates STEP, activating STEP. ②Aβ oligomers destroy Proteosome systems, which prevents STEP from being ubiquitinated, increasing levels of phosphorylated STEP. ③ Endocytosed Aβ can inhibit activities of PKA and Akt, which does harm to CREB regulating transcription and translation of BDNF. Finally, abnormal BDNF/TrkB signaling elevates STEP contents. STEP can dephosphorylate Fyn, ERK1/2, Pyk2, SPIN90, NMDAR, AMPAR, etc. These will lead to endocytoses of NMDARs and AMPARs, then contributing to loss of synapses as well as dendritic spines and reduced synaptic plasticity.

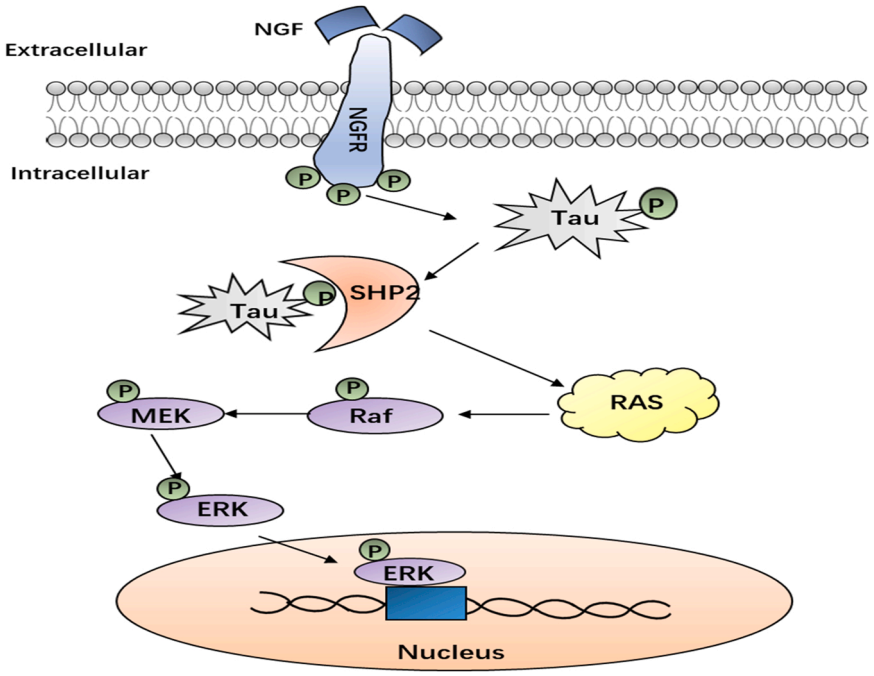


Fig. 2. Schematic diagram of activation of Ras/MAPK pathway by SHP2-tau interaction. Under NGF stimulation, the content of p231tau in nerve cells increases, which adds the number of SHP2-tau complexes. Finally, the Ras/MAPK pathway is activated.

atypical α-helices, denoted as "n_s" [67]. Different from PTP1B, the β5 of STEP is divided into two small parts, β5' and β5''. The WPD loop is located between β5'' and β6 in an open conformation, and its characteristic motif is changed from Gly-Val-Pro to Lys-Thr- Pro. The atypical α-helix between β7 and α3 is immediately adjacent to the WPD loop, which may be beneficial to stabilize the catalytic domain conformation and exert its unique catalytic activity [68,69]. Notably, the maintenance of the open conformation of the WPD loop also relies on the 3_{10} helix, forming hydrogen bonds between Thr440 and Arg443, Pro441, and Ala444, which is not found in other tyrosine phosphatases. The main role of KIS is to regulate the binding of KIM to the substrate, and its C-terminus has a greater impact on binding. The KIM is the specific binding region of STEP and MAPKs. The phosphorylation level of this region significantly affects the activity of STEP enzyme, which is mainly regulated by PKA (Ser221, Ser449) and PP1 [70,71].

3.3.2. Mechanisms of STEP in AD

The study found that in the Tg-2576 and 3×Tg-AD mouse models, the level of STEP was basically normal at the early stage. However, about 6 months onwards, the STEP content in the brain increased, following by mice's behavioral and cognitive impairments. In the water maze and novel object recognition test, STEP-KO mice showed better learning and memory ability than WT mice, which was closely related to the increased levels of phosphorylated GluN2B, GluA1, ERK1/2, Fyn, and Pyk2 in the brain. Elevated Aβ levels can be found in the brains of early AD patients [72–74]. On one hand , Aβ can directly bind to α7nAChRs and stimulate NMDARs, resulting in the opening of ca^{2+} channels and then increasing influx of ca^{2+}. Ca^{2+} activates calmodulin PP2B and PP2B dephosphorylates DARPP-32, rendering the lattter inactive and incapable of repressing PP1, which in turn dephosphorylates to activate STEP [75]. At the same time , Aβ can also inhibit the Proteosome after endocytosis into the cytoplasm, resulting in the inability of STEP to be ubiquitinated [76]. On the other hand , PKA inactivates under Aβ stimulation, which leads AKT to dephosphorylate and CREB not to be activated via PKA/Akt pathway [77]. CREB regulates BDNF transcription and translation in cholinergic neurons, and its inactivation does harm to BDNF/TrkB signaling [78,79]. These factors ultimately contribute to the increased activity and level of STEP in neurons. STEP not only dephosphorylates its numerous substrates, including ERK1/2, Fyn, AMPA, NMDA, SPIN90, and Pyk2, but also mediates NMDA and AMPA receptor endocytosis, causing loss of dendritic spine as well as synapse, and reduced synaptic plasticity, which finally damage patients' learning and cognitive abilities. If STEP is inactivated, in addition to direct activation of Fyn, Fyn can be activated via Pyk2 as well. Subsequently, Fyn phosphorylates the subunit GluN2B of NMDAR, helping ameliorate synaptic plasticity and cognitive impairment (Fig. 1) [80,81].

3.4. SHP2 in AD

3.4.1. Introduction of SHP2

SHP2 is encoded by PTPN11; therefore, it is also called PTPN11. It is mainly located in the cytoplasm and contains the classical PTP catalytic domain. Most PTPs downregulate downstream signal transduction pathways by dephosphorylating substrate proteins, whereas SHP2 plays a signal-amplifying role in the signaling cascade. SHP2 contains two Src-homologous SH2 domains (N-SH2 and C-SH2), a catalytic PTP domain, and a hydrophobic C-terminus with a tyrosine-phosphorylation site [82,83]. In the inactive state, the two SH2 domains surround the phosphatase domain, while N-CH2 protrudes into the catalytic cleft, interacting polarly with key amino acid residues, such as Cys459/Arg465, thereby blocking the PTP active site. Furthermore, the loop between β-helices 4 and 5 is stabilized by forming a hydrogen bond network with Gly60, Gln506, and Gly503. This maintains SHP2 in an autoinhibited state [84]. Most of these three functional domains are polar contacts; therefore, the interaction is weak, and many water molecules bind to the contact interface of any two domains [83]. The PTP domain has nine α-helices and 14 β-sheets (of which 10 β-sheets are paired to form parallel/antiparallel β-sheets surrounding the α-helix 5). There is a PTP characteristic motif (HCSAGIGRS) between β-sheet 13 and α-helix 7, in which nucleophilic Cys and other functional groups play important roles in phosphatase binding and catalysis. In both N-SH2 and C-SH2 domains, four β-sheets were located between the outer sides of the two α-helices. The phosphopeptide binding sites of the two SH2 domains are roughly perpendicular to each other, and the substrate binds to SH2 in an extended conformation. The N-SH2 domain acts as a molecular

switch, and its conformation changes immediately upon binding to one site of the phosphopeptide ligand, preventing the PTP domain from binding to another site of the ligand. This also leads to intramolecular dissociation between PTP and SH2, thus restoring SHP2 catalytic activity. Notably, the position of the second α-helix in N-SH2 is different from that in other SH2 domains, possibly due to the fact that the valine at position 4 of the second β-sheet is changed to an alanine, favoring free transition between the repressed state and the active state. Moreover, tandem structures of C-SH2 and N-SH2 are crucial for enzyme activation and normal physiological functions. The SHP2 C-terminal tail and SH2 domains regulate the catalytic function of the enzyme [85–87].

3.4.2. Mechanisms of SHP2 in AD

It is well-known that the RAS-MAPK signaling pathway is associated with various life processes of cells, such as proliferation, differentiation, growth, and metastasis. In addition, tau protein is involved in the activation of this signaling pathway, and T231 phosphorylation plays an essential role [88]. AD is a progressive disease. pY18-tau and tau-SHP2 complexes have been observed in neurofibrillary tangles in AD patients, which intrigues scientists' strong curiosity about the relationship between tau and SHP2 [62]. Researchers first confirmed the combination of tau and SHP2 in nerve cells by a co-immunoprecipitation assay, and then used densitometry to show that after NGF stimulation, the interaction between pT231 tau and SHP2 was enhanced (Fig. 2). The number of complexes increased significantly and exhibited membrane localization characteristics [62]. Comparing the numbers of DG, CA3, CA1, and tau-SHP2 complexes in the inferior horn of the NCI, MCI, and severe AD patients, it was found that the NCI samples were the least abundant, and the severe AD patients had significantly increased SHP2 expression and the largest number of complexes. After tau binds to microtubule-related proteins, its ability to bind to SHP2 is dramatically reduced. Whereas, pT231 of tau is difficult. This reduces binding to microtubule-related proteins and ultimately affects the formation of microtubules, which is one of the factors that induce AD. Interestingly, although researchers found a large amount of pY18-tau in Neutrophil extracellular traps (NFTs) of AD patients, some pathological tau did not contain pY18 [89], leading to the speculation that tyrosine phosphatase was involved. It has also been reported that SHP2 binding to Gab2 may be associated with AD, as GAB2 gene mutations increase the risk of late-onset AD [90,91]. Taken together, these results imply that SHP2 is inseparable from the pathogenesis of AD.

3.5. PTP1B in AD

3.5.1. Introduction of PTP1B

PTP1B was the first tyrosine phosphatase to be discovered in humans. It was originally isolated and purified from the human placenta. The study of its structural and dynamic properties provides a reference for research on all PTP family members.

The full-length PTP1B molecule contains 435 amino acid residues, and there is an endoplasmic reticulum localization sequence in the -COOH tail. If this sequence is truncated, PTP1B will have different subcellular localization. However, its activity is comparable to that of PTP1B purified from human embryos and can function in a variety of physiological processes [92]. The truncated PTP1B consists of 321 amino acid residues with a molecular weight of 37KD, eight α-helices, and 12 β-sheets, of which 10 β-strands together form the β-sheet [93,94]. There is a conserved tyrosine phosphatase motif in the substrate-binding pocket, His214-Arg221, which contains Cys necessary for catalysis and other residues that bind phosphate substrates [95]. Arg221 in active PTP1B and dual-specificity phosphatases usually remain unchanged. Experiments have shown that replacing Arg221 with any amino acid leads to a loss of enzymatic activity. In addition, GxGxxG motifs are present in many phosphatases, and this sequence contains four sites that can bind to phosphate groups: Gly218–Arg221. Gly218 is located in loop15, and the other residues are located in α4 [95,96]. Cys215 is a thioanion under physiological conditions that can be used as a nucleophile to participate in substrate binding. If mutated, the enzymatic activity is completely lost. His214 does not function directly. It forms the first hydrogen bond with the carbonyl group of Cys215 through the -NH of the side chain, and the N atom of the other side chain forms a second hydrogen bond with the hydroxyl group of the side chain of Tyr124, thereby stabilizing Cys215 and the phosphate-binding loop conformation. If replaced, enzymatic activity is reduced [92]. Most of the structure required for PTP1B to recognize phosphates and catalytic substrates is provided by the conserved motif His214-Arg221, and the active pocket formed by Asp48, Lys116, Lys120, and Tyr46 side chains interacts with the substrate tyrosine moiety. Other amino acid residues of the substrate interact with bumps or grooves on the surface near the catalytic site. These factors may affect the substrate selectivity of PTP1B [97,98]. PTP1B and similar classical PTP_S rather than serine/threonine proteins are selective for phosphotyrosine substrates. The latter, having side chains that are too small to penetrate deep into the cleft to interact with the phosphate binding site, may be the key reason. The regulation of PTP1B activity depends mainly on four mechanisms: phosphorylation, oxidation, SUMOylation, and proteolysis. The phosphorylation patterns at the different sites were different. For example, phosphorylation of Ser50 is regulated by AKT; phosphorylation of Tyr152 and Tyr153 is regulated by IR kinase; and Ser352 and Ser386 are cell cycle-dependent. In addition, ROS-induced reversible oxidation occurs at Cys215, SUMO sites are Lys335 and 347, respectively, and PTP1B is activated immediately after calpain cleaves the C-terminal ER-targeting region. Notably, Arg221 is tightly linked to phosphatase catalytic activity [99] and Gly259 is a determinant of substrate-specific recognition [100]. The C-terminal fragment of PTP1B is hydrophobic, which facilitates endoplasmic reticulum membrane localization, while affecting enzymatic activity. In the human body, PTP1B exists in a phosphorylated form that maintains its spatial structure and catalytic activity, thereby regulating processes such as cell growth, differentiation, and proliferation.

3.5.2. Mechanisms of PTP1B in AD

Interest in PTP1B stems from its strong negative regulation of insulin and leptin signaling. It has long been considered as an ideal target for the treatment of diabetes, obesity, and breast cancer. Interestingly, insulin, leptin, endoplasmic reticulum stress, and other pathways are abundant in the hippocampal and cortical neurons of postmortem AD patients, where PTP1B plays a pivotal regulatory role. PTP1B dephosphorylates IR, IRS-1, leptinR, and its downstream signaling factor JAK2, inhibiting their activation and signaling. Notably, these signaling pathways are closely related to the regulation of synaptic plasticity, cognition, and memory formation, and PTP1B is involved in the TrkB and nSOC signaling pathways, which are associated with synaptic stability. Endoplasmic reticulum stress involving PTP1B may also be a major mechanism of AD pathogenesis. It was later found that PTP1B actively regulates cell proliferation and growth [63] and can be an important target for the treatment of familial AD [101]. Familial AD is a neurodegenerative disease caused by mutations in the amyloid precursor protein (APP) gene. Mutant APP metabolizes abnormally, increases extracellular Aβ, and produces greater cytotoxicity [102,103]. Konrad et al. found that inhibition of PTP1B with a reversible, non-competitive natural drug, trodusquemine, increased the phosphorylation levels of IRS1 and GSK3β in hippocampal neurons of familial AD model mice after insulin stimulation, and significantly improved behavioral performance and spatial memory in AD mice [104]. Interestingly, systemic inhibition of PTP1B reduces inflammatory cytokine levels in the hippocampus of familial AD mice, but ablation of PTP1B in specific neurons does not reduce the inflammatory response [104]. PTP1B ablation did not reduce Aβ levels and plaque number, but reduced the Aβ plaque area. In conclusion, either inhibition of PTP1B or ablation of PTP1B in glutamatergic neurons rescued neuronal loss and improved spatial learning and memory in hAPP-J20 mice [104]. GSK-3β is a key factor that

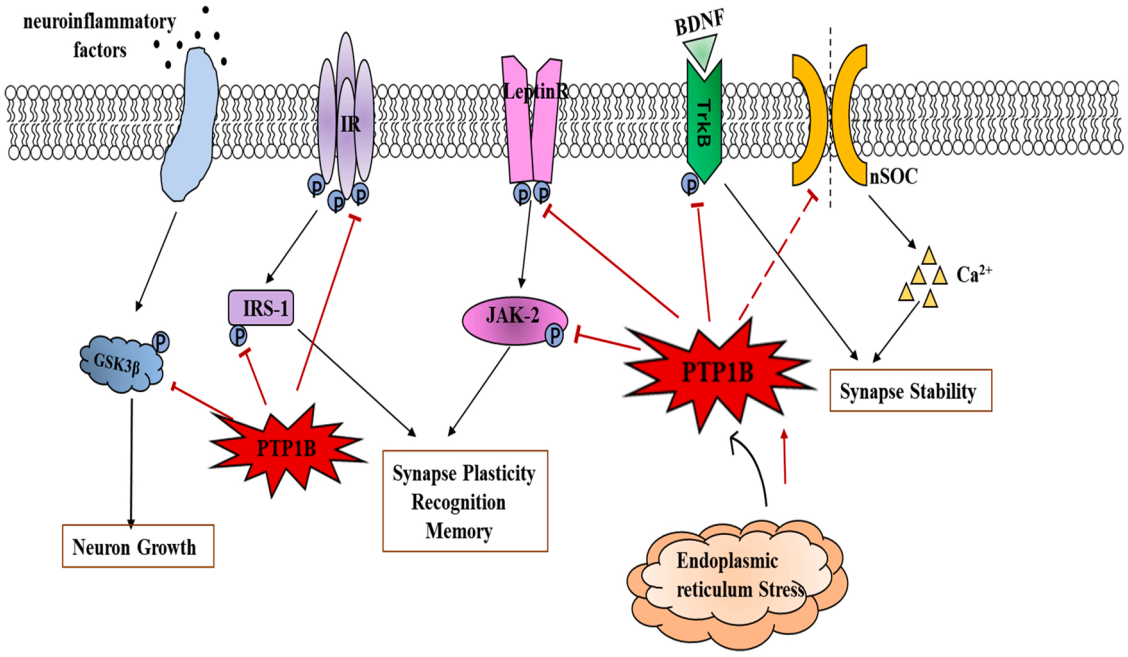


Fig. 3. Effects of PTP1B on AD development. Under neuroinflammatory factors stimulation and endoplasmic reticulum stress, levels of PTP1B elevate in neurons, which can dephosphorylate IR, IRS-1, leptinR, JAK2, GSK3β and TrkB, and inhibits the nSOC signaling pathway indirectly. These signaling pathways are closely germane to the regulation of synaptic plasticity, cognition, memory formation and synaptic stability.

regulates the hyperphosphorylation of tau protein and the formation of NFTs. PKCε can inactivate GSK3β by activating Akt, and simultaneously, inhibit the activity of PTP1B and increase the phosphorylation level of IRS-1, depending on the IRS-1/PI3K/PDK1/Akt axis inactivation of GSK3β; the combination of these two methods can more significantly reduce tau hyperphosphorylation and improve spatial learning ability and memory deficits in 5× FAD mice (Fig. 3) [103]. These signaling pathways are closely germane to the regulation of synaptic plasticity, cognition, memory formation and synaptic stability. It can be seen that PTP1B plays a key role in AD pathology, and it is expected to become a new target for the development of AD drugs [105].

3.6. Dual-specificity phosphatases in AD

3.6.1. Introduction of DUSPs

The dual-specificity phosphatase family is comprised of a heterogeneous group of proteins encoded by different genes. It can be divided into seven sub-categories: MKPs (11), myotubularins (16), CDC14s (4), slingshots (3), PTENs (5), PRLs (3), and atypical DSPs (19) [106,107]. The active sites of different members of the DUSP family have a loop (containing the HCX5R motif) and a WPD loop (containing Asp residues and nucleophilic action), but catalytic domains have their own characteristics for different subtypes of DUSP, for instance, distinct active sites and surface charge distributions, which is one of the important reasons for the substrate specificity of DUSP. Typical $DUSP_S$ contain a MAPK-binding (MKB) domain at the N-terminus and a phosphatase catalytic domain at the C-terminus. They participate in the MAPK signal transduction pathway by reversibly regulating MAPK phosphorylation, which in turn regulates cell growth, differentiation, and apoptosis. Although atypical DUSPs do not contain MKB, most also have MAP kinase catalytic activity [108].

Members of the DUSP family can catalyze the dephosphorylation of serine/threonine and tyrosine protein substrates, all of which contain a PTP loop. A WPD loop (composed of Trp-Pro-Asp) is adjacent to the PTP loop, where Asp acts as a nucleophile [109] The catalytic domain of [110,111] may change for different DUSPs. For example, the WPD loop of DUSP3 is shortened to only Asp [111]. Active pocket structures and cleft depths of different $DUSP_S$ also vary, which may determine enzyme substrate specificity. By overlapping all structures, it is not difficult to find that the core catalytic domains of each DUSP are aligned; however, there are certain deviations in other domains and secondary structures [111]. Moreover, there are varying degrees of truncation or extension at the N- or C-termini. Different DUSP have different structures. For example, DUSP12contains helix α6, which is not found in other $DUSP_S$. This helix may be involved in the folding of the C-terminal domain of DUSP12 [108]; the P and D loops of DUSP11 do not overlap well with the P and D loops of DUSP5, especially the large displacement of the D loop, but DUSP5 still has a typical DUSP structure that can exert enzymatic activity [112]. DUSP8 has two ion-binding sites, so it can bind to double phosphorylated substrates, whereas DUSP12 has only one binding site [108]. Additionally, DUSP exhibits a loop-chain conformational switch. The loops near the active pockets of different DUSPs were distinct. For example, DUSP3 has a typical P-loop and closed D-loop [113], whereas the P-loop of DUSP6 is shifted from the typical conformation and the D-loop is open [114]. Simultaneously, the P-loop side chains also differ, which may be related to substrate specificity [115]. The redox behavior of various DUSPs is also helpful for understanding the structural differences between them [116]. All DUSPs lost their activity when treated with high concentrations of hydrogen peroxide, but some were still active when low concentrations were used. Moreover, the reversibility of different DUSPs also varies greatly after treatment with high-concentration hydrogen peroxide, which may be related to Cys. For example, there is another Cys residue near the active site, Cys, of RPL1. The two S atoms are close to each other and can form a disulfide bond to prevent the active site Cys from being over-oxidized, resulting in irreversible inactivation of the enzyme. For enzymes with low recovery rates, such as DUSP15, there are more hydrophobic amino acids in the active pocket, which is beneficial for improving the affinity of hydrogen peroxide for key amino acids at the active site, causing irreversible inactivation of the enzyme [117]. In summary, the structures of all DUSP family members are similar and different. These similarities facilitate the understanding of the catalytic mechanism of enzymes and the search for key active sites. However, differences determine substrate specificity and are conducive to the development of

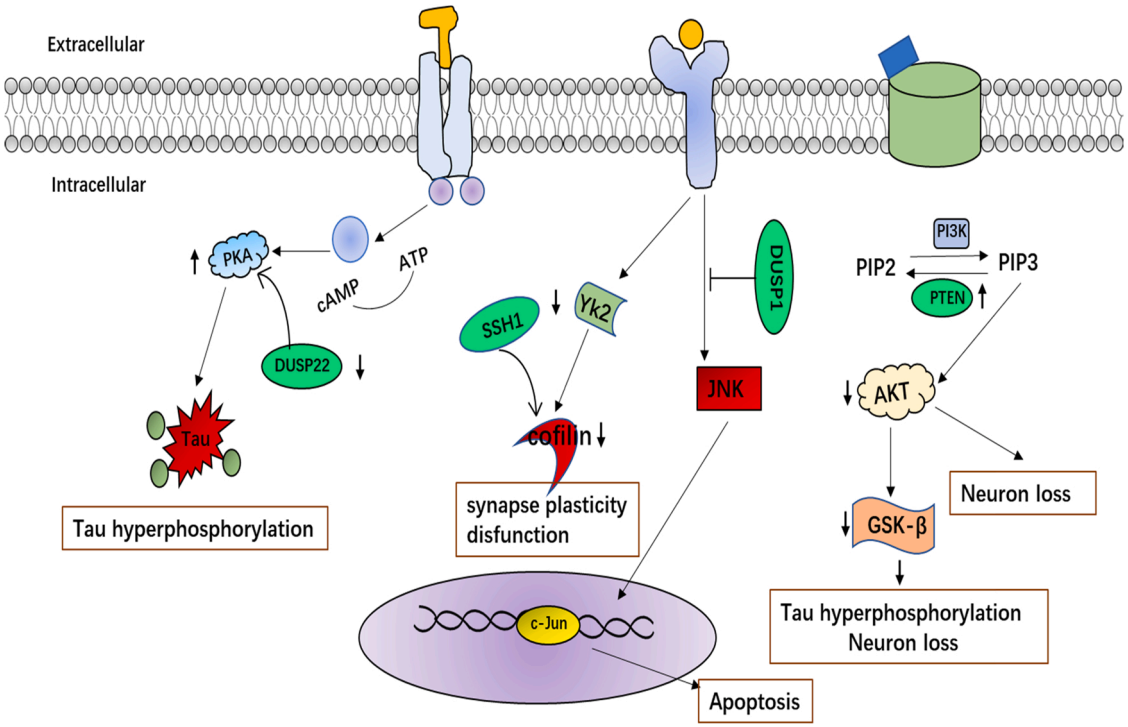


Fig. 4. Diagram showing the relationship between some DUSPs abnormalities and the pathogenesis of AD. ①SSH1 inactivation→Cofilin1 inactivation→uncontrolled neuronal plasticity regulation②DUSP1 attenuates Aβ-induced apoptosis, oxidative stress, and neuroinflammation through the JNK signaling pathway③The decreased level of DUSP22→increased activity of protein kinase A→increased phosphorylation level of tau ④Increased PTEN activity→inhibiting transformation from PIP2 to PIP3→Akt inactivation→GSK-β inactivation→neuron loss and tau hyperphosphorylation.

selective inhibitors.

3.6.2. *Mechanisms of DUSPs in AD*

A variety of DUSPs are abnormal in the brains of AD patients. For example, DUSP1 can reduce Aβ amyloidosis and extracellular Aβ levels by inhibiting the ERK/MAPK pathway, thereby improving cognitive ability in APP/PS1 mice. However, DU et al. found that the content of DUSP1 in the hippocampus and temporal cortex of patients was significantly decreased [118]; DUSP26 mutations produce inactive enzymes, altering APP processing and reducing Aβ production, suggesting that DUSP26 may be involved in AD pathogenesis [119], and PTEN is recruited to synapses, where it mediates Aβ-induced neurotoxicity. Simultaneously, in CA1, inferior horn, and entorhinal cortex of neurons, Griffin et al. observed that PTEN moves out of the nucleus to the cytoplasm and nears the NFT_S [120,121]. Deletion of the PDZ-binding domain of PTEN attenuates the toxic effect of Aβ on postsynaptic neurons [122]. What's more, SOD can be increased via PI3K/AKT/PTEN pathway, which does good to neuronal protect. [123]. In AD patient brains, PTEN levels are elevated, which inhibits PIP3 production, thereby preventing AKT and GSKβ from activation, ultimately leading to neuronal death and tau hyperphosphorylation [124]. It can be seen that PTEN plays a decisive role in AD. In addition to $DUSP_S$, SSH1, SSH3, and DUSP22 may also be involved in the occurrence and development of AD, but the specific mechanism is not complete (Fig. 4). In conclusion, there are still many mysteries regarding the inner connection between DUSP family members and AD waiting for human beings to explore.

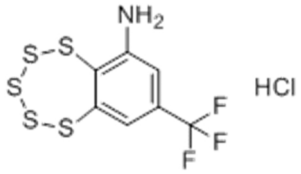
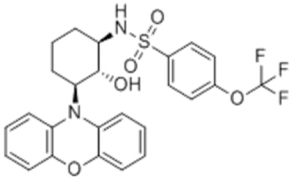
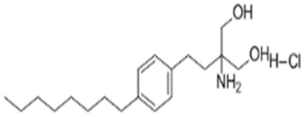
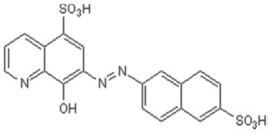
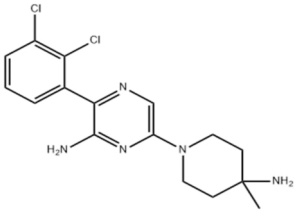
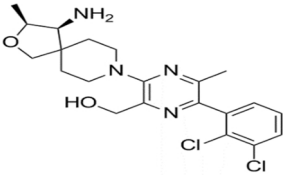
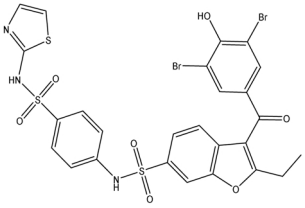
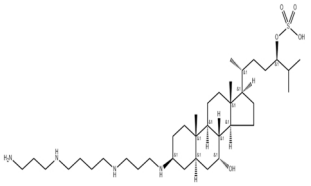
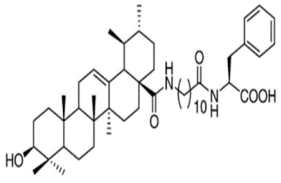
3.7. *Other PTPs in AD*

In addition to this, several other PTPs have also been reported to be abnormally expressed in AD models. However, the correlation with AD pathology is not explained or the content is not detailed. Therefore, we do not specifically describe it here. It is reported that in brains of AD patients, LMWPTP activity is downregulated. By analyzing the nature and abundance of LMWPTP at the cytoplasm and nerve endings, researchers found that it plays an crucial role in synaptic function [125]. Besides , In vitro tests , when exposed to H_2O_2, LMWPTP can form intramolecular disulfide bonds to block oxidative stress damage. Excessive oxidative stress is an important pathological feature in the brain of AD patients, which will injury mitochondrial severely. [126, 127]. These specific impact mechanisms need to be further studied. Cdc25 is a class of cell cycle-dependent proteins. Cdc25A regulates the G1/S phase transition; Cdc25B and Cdc25C are involved in G2/M progression. The structural hallmarks of AD neurodegeneration, neurofibrillary tangles and neuritic plaques, were prominently immunolabeled with Cdc25A antibodies. CDK5 phosphorylates and activates various isoforms of CDC25, which in turn activate CDK1, CDK2, CDK4, and finally lead to neuronal death after Aβ treatment [128]. At the same time , Aβ can induce apoptosis via Ras/Cdc25 pathway [129]. Cdc25A participates in mitotic activation during neurodegeneration, which is involved in tau hyperphosphorylation [130]. EYA protein belongs to the fourth type of PTPs family, with Asp as the catalytic core, has tyrosine phosphatase activity, and is closely related to cell growth [131]. However, there are few studies related to AD.

4. Function of drugs targeting PTPs in brain diseases

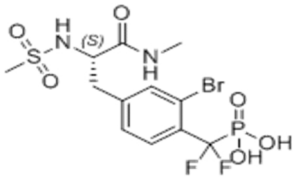
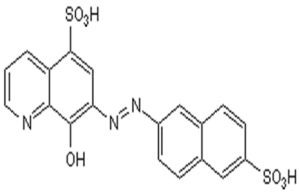
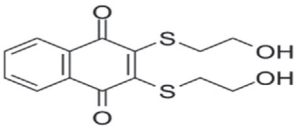
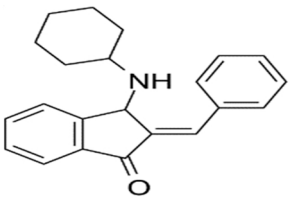
Studies have found that a variety of PTPs are abnormally expressed in brain diseases, and selective inhibitors of different phosphatases have a certain therapeutic effect on these diseases. For instance, TC-2153 can directly bind to STEP and irreversibly inhibits STEP activity, increasing NMDA/AMPA receptor expression on synapses and ultimately ameliorating synaptic plasticity and connectivity. SC222227 is a selective inhibitor of PTP1B that modulates the ER stress-autophagy axis via PERK signaling in microglia and alleviates deleterious microglial activation and neuronal damage after ischemic stroke. NSC-87877 selectively inhibits SHP2, which modulates AβPP processing through the c-Kit signaling pathway, ultimately increasing AβPP phosphorylation,

Table 2
Drugs targeting PTPs and their functions in brain diseases.

Targets	Compound	Structure	Function
STEP	TC-2153 [132]		Increases synaptic plasticity and connectivity; Ameliorates learning and cognitive impairments
	SMAP [133]		Prevents neuron damage; Improves cognitive impairment
	FTY720 [134]		Improves neurological function and apoptosis
SHP-2	NSC-87877 [135]		Reduces Aβ levels
	SHP-099 [136]		Targeted therapy for glioblastoma with PDGFRα activation
	RMC-4550 [137]		Inhibition of SHP2 in the RAS-MAPK pathway for glioblastoma treatment
PTP1B	SC222227 [132]		Attenuate microglial activation; Protect neuronal damage
	Trodusquemine [63]		Improves behavioral disorders; Reduces neuroinflammation; Prevents neurodegeneration
	UA0713 [138]		Enhanced BDNF signaling and Rescues phenotype of MeCP2-deficient mice

(*continued on next page*)

Table 2 (*continued*)

Targets	Compound	Structure	Function
	CPT-157633 [139]		Relieves Rett Syndrome Symptoms
DUSPs	NSC-87877 [135]		Reduces hypoxia-induced Aβ production
	NSC-95397 [140]		Alleviate symptoms of depression
	BCI [141]		Alleviate bipolar disorder

reducing Aβ levels, and enhancing AβPP surface localization. This indicates that effective PTP-selective inhibitors will become another breakthrough in the development of AD drugs. We summarized drugs targeting PTP and their role in brain diseases in Table2.

5. Conclusion and future perspectives

We summarized the roles of AD-related PTP members and small-molecule compounds that modulate their activity in AD pathology in this paper. The effects of these abnormal PTPs on AD pathology are substantial, involving synaptic plasticity, neuroinflammation, tau hyperphosphorylation, and accumulation of Aβ plaques. Some other PTPs have also been reported to be directly or indirectly related to the occurrence of AD, such as the class II PTPs of LMWPTP, the receptor PTPs of PTPRR, and the key transcriptional regulatory protein EYA. However, their specific roles and mechanisms are unclear, and need to be further investigated.

The research and development of AD therapeutic drugs has become the focus of current research. Because the mechanism has not been fully elucidated, many drugs are ineffective in clinical trials or have serious side effects. For example, RG7129 caused severe liver toxicity. These side effects have greatly prevented the clinical use of AD drugs. There is an urgent need to elucidate the pathogenesis of AD and identify practical and effective therapeutic targets.

Emerging evidence points to PTPs as promising therapeutic targets AD treatment. As mentioned above, PTPs are closely related to AD abnormally expressed kinases and can alter tau phosphorylation levels, affect Aβ deposition, reduce synaptic plasticity and mediate neuroinflammatory responses. Inhibitors or activators targeting these PTPs significantly improved the pathological features and clinical symptoms of brain diseases which showed great potential for treating brain disorders. However, their role in AD progression still needs to be fully understood. In addition, there are approximately 110 members of the PTP family, but there are few reports regarding AD. Numerous mysteries between PTP_S and AD remain waiting for exploration. The existing data have laid a foundation for studying the role of PTPs in the pathogenesis of AD and have provided researchers with a new direction for exploration.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Data Availability

No data was used for the research described in the article.

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CRediT authorship contribution statement

X.Z. and G.L. conceived and initiated the manuscript. L.X., L.S. L.L. and P.H. participate in wrote and revised the manuscript. All authors have read and approved the final manuscript. All authors contributed to drafting or revising the article, agreed on the journal to which the review will be submitted, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Author contributions

X.Z. and G.L. conceived and initiated the manuscript. L.X., L.S. L.L. and P.H. participate in wrote and revised the manuscript. G.L. submitted the manuscript on behalf of other authors.

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