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Review

# Roles of p75NTR in the pathogenesis of Alzheimer's disease: A novel therapeutic target

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ABSTRACT

Alzheimer's disease (AD), the most common form of dementia, is characterized by the deposition of amyloid plaques, accumulation of fibrillary tangles in neurons, neurite degeneration, loss of neurons, and a progressive loss of cognitive function. The pathogenesis of AD is not fully understood, and no strong disease-modifying therapies are currently available. Recent studies suggest that the pan-neurotrophin receptor, p75NTR, is a critical factor involved in the pathogenesis of AD. In this review, we have discussed the roles of p75NTR in the production of amyloid-beta (Aβ), neuronal death, neurite degeneration, tau hyperphosphorylation, cell cycle re-entry and cognition decline in AD, and proposed that p75NTR is a potential target for the development of therapeutic drugs for AD. Finally we provide perspectives in developing various therapeutic strategies targeting different aspects of AD hallmarks which relate to p75NTR functions and breaking the p75NTR-mediated positive feedback loop which promotes the cascades in the pathogenesis of AD.



**Contents**



## 1. Introduction

Alzheimer's disease (AD) is the most common form of dementia and is an aging associated neurodegenerative disease that affects aging population in all countries. It is clinically characterized by progressive loss of memory, cognitive dysfunctions, mood disorders

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and finally loss of life. Pathological diagnostic hallmarks of the disease in the brain include senile plaques consisting of beta-amyloid (Aβ) deposition, degenerative neurites, activated microglia and astrocytes, intraneuronal hyperphosphorylated Tau-positive neurofilamentary tangle, loss of neurons and reduction in the brain volume. Majority of late onset sporadic disease (LOAD) lacks obvious genetic mutations whereas familial cases (account for less than 5% of total AD patients) can be traced with genetic mutations in genes of amyloid precursor protein (APP) and its processing enzyme of presenilins. However, a number of genes related to cholesterol metabolisms or signal transduction, such as apolipoprotein E4 and SorLA are obviously associated with the LOAD. The precise molecular mechanism underlying the development of the disease remains controversial despite that intensive studies have pointed to the central role of Aβ in the pathogenesis of the disease. However, almost all clinical trials targeting Aβ have failed, suggesting the urgency in developing new drugs for this devastating disease focusing on alternative targets. In this review, we have focused on the recent progress in the roles of the p75 neurotrophin receptor (p75NTR) in the pathogenesis of AD, and have proposed future research on validating p75NTR as a potential drug target.

p75NTR was first identified about 25 years ago as the receptor for nerve growth factor (NGF) and was subsequently found to be a receptor for all other neurotrophins including brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT3) and neurotrophin-4/5 (NT4/5) [1,2]. p75NTR belongs to the tumor necrosis factor receptor superfamily which consists of ten different trans-membrane (type I) glycoproteins [3]. The role as a pan-receptors for neurotrophins enables p75NTR to play diverse roles in regulating cell survival, neuronal degeneration and cell death. It can activate at least three signaling pathways including neuronal growth, apoptosis and synapse plasticity, and most recently this receptor is also found to be involved in the neuronal cell cycle re-entry, which is considered as a key pathological mechanism underlying the development of AD and other neuronal degenerative diseases [4].

The structure of the human p75NTR gene was first described in 1996 [5]. It was identified as 75 kD in size containing 10 exons and nine introns. Sharing an analogous structure and function with TNF receptor, p75 NTR is a transmembrane protein that consists of an extracellular domain, a transmembrane domain and an intracellular domain. The extracellular domain consists of a stalk domain which links transmembrane domain and four cysteine-rich repeat domains that facilitate neurotrophin binding. There is clear evidence that the third and fourth cysteine repeats are the binding site for neurotrophins, because the mutant form of p75NTR that lacks these two domains can not bind neurotrophins. The intracellular part of p75NTR contains an 80-amino acid 'death domain' module [6]. It connects the transmembrane domain through a flexible linker region N-terminal domain. The flexibility of the linker domain possibly plays an important role in multiple signal transduction. In addition, the intracellular, cytoplasmic region of p75NTR does not exhibit an intrinsic ligand-inducible enzymatic function, and this is distinctly different from tropomyosin receptor kinase (Trk) receptors. Although p75NTR is a member of the TNF receptor family, there are some differences between p75NTR and other TNF receptors. The death domain of p75NTR is a type-2 molecule, which is different from the type-1 molecules of other TNF receptors. Furthermore, unlike other TNF receptors, p75NTR does not self-associate in solution [6].

## 2. Roles of p75NTR in the pathogenisis of AD

Recent studies have revealed that p75NTR is involved in different critical hallmarks of AD, including Aβ production and deposition, neuronal death, neurite degeneration, Tau phosphorylation, cell cycle re-entry and cognition, as discussed below.

### 2.1. Expression of p75NTR in AD

It is well known that cholinergic neurons in the basal forebrain which is severely affected in AD, especially in the nucleus basalis of Meynert (NBM), express p75NTR, TrkA, TrkB and TrkC [7]. Strikingly, neurons in other brain regions normally express little or no p75NTR. Previous reports on the levels of p75NTR expression in AD patients and during aging remain controversial. Some research find that the expression of NGF receptors (including p75NTR) is increased in both cortical neurons and CA1, CA2 subfields of hippocampus in AD patients compared with controls [8,9]. But some other results suggest a significant reduction of p75NTR in AD brain [7,10,11]. Meanwhile, no significant difference in expression levels for p75NTR was observed across controls, mild cognitive impairment and AD in other research [12–14]. The discrepancy in p75NTR expression in AD may be due to the differences in investigated brain regions and measurements. Most of the studies have consistently found the decrease in both immunohistochemical reactivity and mRNA levels in NBM cholinergic neurons, which are most vulnerable in AD brain. This reduction may be due to the loss of p75NTR positive cholinergic neurons in AD. Some other studies find no significant change in p75NTR mRNA levels in the individual NBM neurons [12,14], even though the protein level of p75NTR in this region is reduced [14]. This may be the result of a compensatory response at p75NTR mRNA level in a few remaining active NBM neurons. The increased p75NTR levels in the hippocampus and temporal lobe may be resulted from neurons which are exposed to pathological stimuli i.e. Aβ. Another important factor for the discrepancy could be the difference in severity of the disease. The more the loss of the cholinergic neurons is, the less the presence of p75NTR in the brain. Recent animal studies show the increase of p75NTR expression in animal models of AD. A study has found that p75NTR expression is significantly increased in two different strains of transgenic AD mice, the triple transgenic mice (3xTg-AD, harboring PS1M146V, APPswe and tau P301L) and APPswe/PS1dE9 mice. In these animals p75NTR expression is associated with the age-dependent rise in Aβ [15]. Consistently, we found that p75NTR expression increases in an age-dependent manner in wild type mice, and is higher in APPswe/PS1dE9 mice relative to their wild type littermates at the same age [16]. *In vitro* study shows that Aβ promotes p75NTR expression in the membrane of SH-SY5Y human neuroblastoma cells [15]. Although most of the human studies show the reduction of p75NTR level in the brain which is the result of the loss of p75NTR positive cholinergic neurons, these animal studies suggest that p75NTR expression increases with aging and is further activated by Aβ. The brain neurons of the transgenic animal models are more resistant to Aβ toxicity as reflected by very few neuron loss in the brain of the animal models relative to humans [17].

### 2.2. p75NTR-mediated neurite degeneration

Neurite degeneration is a key event of AD and a main contributor of the memory loss. Aβ is an important factor which leads to neurite degeneration in AD patients, but its receptor pathways and mechanisms are still unknown [18]. p75NTR is involved in the regulation of axonal elongation or collapse by neurotrophins as well as several myelin components. The roles of p75NTR in the neurite degeneration in AD remains elusive. It is suggested that the myelin-derived protein Nogo is increased and contributes to the neurite degeneration in AD brain [19,20]. It is worthy to study whether the neurite degeneration induced by myelin-derived proteins is mediated by p75NTR in AD, and whether targeting these proteins are effective in rescuing the neurite degeneration in AD [21]. We have observed abundant degenerative fibers and neurites in neocortex and hippocampus

which also express p75NTR in APPswe/PS1dE9 mice, suggesting that p75NTR may play a role in neurite degeneration [16]. Studies have suggested that intact p75NTR mediates Aβ-induced neurite degeneration *in vitro* and *in vivo* via the c-Jun pathways, a known mediator of Aβ-induced deleterious signaling. Both the neurite degeneration and loss of basal forebrain cholinergic neurons in chronic AD model and Aβ-induced toxicity are significantly reduced by the removal of p75NTR extracellular domain which suggests that p75NTR mediates Aβ-induced neurite degeneration [22]. Meanwhile, a recent study found that the sympathetic innervation is severely impaired in p75NTR-deficient AD model, this suggests that p75NTR not only interacts with APP and Aβ to induce neuronal toxicity, but also promotes NGF and TrkA signaling which is neuroprotective, especially for sympathetic nervous system [23].

The reduction of NGF has also been suggested to be involved in the pathogenesis of AD, but the role of its precursor (proNGF) in AD remains unknown. It is reported that proNGF is the predominant form of this neurotrophin in human brain [24], and it binds to p75NTR more strongly than mature NGF. ProNGF level is increased in the cerebral cortex in AD brain [24,25], and is posttranslationally modified to become more resistant to processing enzymes and more toxic to neurons via p75NTR compared to proNGF from controls [26]. Blocking proNGF can rescue neuronal loss [27–29]. We investigated the effect of proNGF on neuron death and neurite growth, *in vitro* and *in vivo*, and found that proNGF is localized to the Aβ plaques in AD mice brain, and induces the neuron death and neurite degeneration of different neuronal cell lines and primary neurons, likely dependent on the expression of p75NTR [30]. These studies suggest that p75NTR is a key receptor modulating neurite degeneration in AD, and it may become an important target to block Aβ and proNGF neurotoxicity.

### 2.3. p75NTR-mediated neuronal death

#### 2.3.1. Aβ-induced neuronal death

It was reported that Aβ is a ligand of p75NTR and trigger p75NTR mediated death signals [31]. Both soluble oligomeric and aggregated Aβ can specifically bind to p75NTR [31–38], with $K_D$ of 3–23 nM [31,33], but not to TrkA [32], the nerve growth factor co-receptor that mediates neuronal survival. The soluble Aβ has a higher affinity than its aggregated form [31]. This is consistent with the current concept that soluble Aβ oligomers are the most toxic form of Aβ [39,40]. The amino acids within the 29–35 region of the Aβ sequence are crucial for the effects mediated through p75NTR, because the different length forms of Aβ containing the domain of 29–35 amino acids of Aβ peptide, but not reverse peptides (40–1) or truncated peptides (1–28), also interact with and activate p75NTR signaling.

Since Yaar et al. firstly proposed involvement of p75NTR in extracellular Aβ-induced cytotoxicity [31], numerous studies so far have confirmed that extracellular Aβ exerts cytotoxicity by directly interacting with p75NTR in different neuronal tumor cell lines, including NIH-3T3 cells, human SK-N-MC cells, F11 neuronal hybrid cells, at micromolar concentrations which is thousands times higher than the concentration of 4 nM found in the CSF of early-onset AD patients [41]. Recently an *in vivo* evidence indicates that p75NTR plays a critical role in the early and characteristic loss of cholinergic neurons in response to Aβ in the septohippocampal pathway that occurs in AD [42]. A recent study suggests that two distinct pathways are involved in p75NTR-mediated Aβ neurotoxicity, one is caspase-3-related caspase pathway and the other is Gi protein (heterotrimeric G proteins), c-Jun N-terminal kinase (JNK), NADPH (nicotinamide adenine dinucleotide phosphate-oxidase) oxidase pathway [35].

However, p75NTR does not always mediate Aβ-induced neuron death, it is also proposed to exert protective effect against Aβ toxicity in both cell line and primary neuron cells [34,36]. p75NTR has been found to play different and opposite roles in cytotoxicity induced by the fibrillar and soluble oligomeric forms of Aβ [36]. p75NTR is involved in death signaling of fibrillar Aβ but exerts a protective role against the cytotoxicity of soluble oligomeric Aβ. This protective role of p75NTR against Aβ is also found in human neuron primary culture. Incubation of primary human neurons in culture with Aβ peptide results in up-regulation of p75NTR. Such neurons are relatively resistant to the toxicity of Aβ and this resistance is reversed by incubation with an antisense construct to p75NTR or an antibody to its extracellular domain [34]. Low concentration of Aβ at low nM levels behaves as a neurotrophic factor like NGF to promote neurite outgrowth and neuron survival via p75NTR [37], whereas at a higher concentration it acts as an antagonist to NGF which reduces the neurite of GABAergic neurons and alter their morphology [43]. The survival pathway responsible for p75NTR-mediated neuroprotection against extracellular Aβ remains unclear. In neuronal culture, the increase of p75NTR activates the phosphorylation of PI3K and Akt survival pathway which is independent of TrkA [36,44]. Whether other p75NTR-linked survival pathways are involved, such as neurotrophin-mediated survival through ceramide in subplate neurons and NGF-activated survival through RIP2-TRAF (TNF-R-associated factor) in Schwann cells, need to be investigated [45,46]. A recent study also shows that Aβ can activate phosphorylation of TrkA and convert it from its pro-survival effect to pro-apoptosis effect via activation of the phospholipase C gamma (PLCgamma) pathway [47]. Such phosphorylation seems associated with alpha- and gamma-secretase-mediated p75NTR processing.

Several explanations could be proposed for the discrepancy observed in p75NTR pro-apoptotic and pro-survival functions. The pro-apoptotic effects of p75NTR against extracellular Aβ are mainly observed in the neuroblast cell lines, while the pro-survival effects are mainly occurred in cultured primary neurons. This difference might indicate differential activation of signal transduction pathways in primary neurons versus tumor cell lines, cell-type or species-specific effects of Aβ, or differential expression of the other neurotrophic receptors [34]. Considering that the activation of p75NTR-mediated pathway needs the roles of its specific co-receptors, and that most studies were confined to *in vitro* model, further investigation about how p75NTR mediates Aβ-induced neurotoxicity needs to be carried out in *in vivo* models [48]. Using a NGF-deficit transgenic AD mouse model (NGF antibody transgenic AD11 mice) to dissect roles of TrkA from roles of p75NTR in the neurodegeneration and AD pathology, Capsoni et al. shows that TrkA plays a critical role in the survival of cholinergic neurons and suppresses Aβ accumulation whereas p75NTR plays an important role in suppressing Tau-hyperphosphorylation [49].Meanwhile, the neurotoxic or protective effects of p75NTR in response to Aβ is related to the different intracellular domains of the receptor. Intracellular sequence corresponding to the death domain is involved in the death effect of fibrillar Aβ, whereas with soluble oligomers, the protective role was associated with the function of the juxtamembrane intracellular sequence [36].

#### 2.3.2. ProNGF induced neuronal death

ProNGF is another major neurotoxic factor in AD brain. Some research suggests that proNGF from the injured spinal cord induces apoptosis in culture among p75NTR positive, but not p75NTR negative oligodendrocytes, and its action can be blocked by proNGF specific antibody. ProNGF can eliminate damaged cells by activating the apoptotic machinery of p75NTR [50]. Other research also found that proNGF secreted by astrocytes under the

stimulation of peroxynitrite can specifically cause motor neuron death via the engagement of p75NTR [51]. As for AD, some studies demonstrated that proNGF level increases in glial cells and in cortical and hippocampal neurons, and this level is closely related to the progression of AD. Moreover, proNGF extracted from AD brain can obviously induce apoptotic neuronal death through p75NTR [26]. Nevertheless, some researchers speculate the possibility that the loss of proNGF mediated signaling may reduce the TrkA receptors within cholinergic basal forebrain (CBF) neurons, affecting cell death [25]. A recent study indicated that cleavage-resistant mutated forms proNGF can both promote neurite outgrowth, increase cell survival and cause apoptotic cell death through phosphorylation of TrkA and ERK1/2 or initiation of apoptotic pathway by cleavage of caspase 3. So the final balance will be shifted from cell viability to apoptotic effects when proNGF:NGF and p75NTR:TrkA ratios increase in AD brain [52]. p75NR is also essential for the neutrotrophic effects of mature neurotrophins in AD. In a transmitochondrial hybrid cell expressing mitochondrial genes from patients with sporadic AD, activation of p75NTR as well as TrkA is required for the enhanced viability by NGF [53].

### 2.4. p75NTR mediates Aβ production

Aging is the most important risk factor for AD. Recently p75NTR has been identified as a molecular link between normal aging and AD. That is, during aging p75NTR increases whereas TrkA decreases, the p75NTR-ceramide pathway is activated which increases steady-state levels and activity of BACE1 downstream and eventually accelerates Aβ generation [54]. Caloric restriction and nSMase (neutral sphingomyelinase) inhibitors can reduce Aβ generation by interrupting this signaling pathway. Both the up-regulation of p75NTR expression and the acceleration of Aβ generation follow an age-dependent fashion. In the further study of this research shows that signaling through insulin-like growth factor-1 receptor (IGF1-R) controls the level of TrkA and p75NTR in both human neuroblastoma cell lines and primary neurons from mouse brain, and IGF1-R acts upstream of p75NTR-ceramide pathway and regulates Aβ production [55].

The level of p75NTR is significantly elevated with aging and further activated by Aβ in AD brain, but the meaning of this appearance remains unclear. Our study shows that knockout of p75NTR gene in APPswe/PS1dE9 transgenic mice reduces the Aβ production in the cortical neurons, suggesting that p75NTR signaling is able to promote Aβ production [16]. Based on the results mentioned above, we speculate that Aβ activates the expression of p75NTR in AD brain, and the activated p75NTR in turn promotes Aβ production. Thus they form a vicious cycle and finally result in Aβ over-production (Fig. 1). This hypothesis can explain the phenomenon why there is an acceleration of Aβ production in AD brain during aging [56], and why 95% of AD patients (sporadic AD) do not have gene mutation relating to Aβ production [57]. The positive feedback loop in p75NTR expression and Aβ production is an important issue worthy of further investigation.

### 2.5. p75NTR inhibits Aβ deposition

Aβ mainly deposits in cerebral neocortex, hippocampus and vessel walls, which are the projection area of cholinergic neurons and sympathetic neurons expressing p75NTR. We found that in the cerebral cortex and hippocampus of APPswe/PS1dE9 transgenic AD mice, more than 90% of the Aβ plaques contain p75NTR positive fibers. More importantly, the p75NTR positive fibers are mostly located in the cores of Aβ plaques, while the p75NTR negative degenerated ones are around the plaques [16]. These findings indicate that p75NTR expressed on the fibers is probably an initiating or promoting factor for Aβ deposition.

P75NTR is cleaved by metalloproteases mainly TNF alpha-converting enzyme (TACE, ADAM17) in the normal metabolic process, and then extracellular domain of p75NTR (p75NTR-ECD) is released [58]. The physiological function of p75NTR-ECD remains elusive. In our research, insoluble Aβ deposition is significantly increased in the brain after deleting p75NTR-ECD gene in APPswe/PS1dE9 transgenic mice, recombinant p75NTR-ECD inhibits Aβ oligomerization and fibrillation in a dose-dependent manner *in vitro*, and injection of p75NTR-ECD in hippocampus reduces local Aβ plaques [16]. Based on these findings, it can be concluded that p75NTR-ECD, which is released during metabolic process of p75NTR, is a key regulatory factor in inhibiting Aβ aggregation and facilitating disaggregation of Aβ fibrils. It may act as an Aβ-sequestering molecule to clear Aβ *in vivo*. Seeking the Aβ binding sites on p75NTR-ECD is critical for revealing the mechanism about how p75NTR regulates Aβ deposition. After that, the effective control and interference with the deposition and clearance of Aβ can be achieved.

In the progression of AD, the level of p75NTR increases and is correlated with the Aβ load in the brain. How is the extracellular

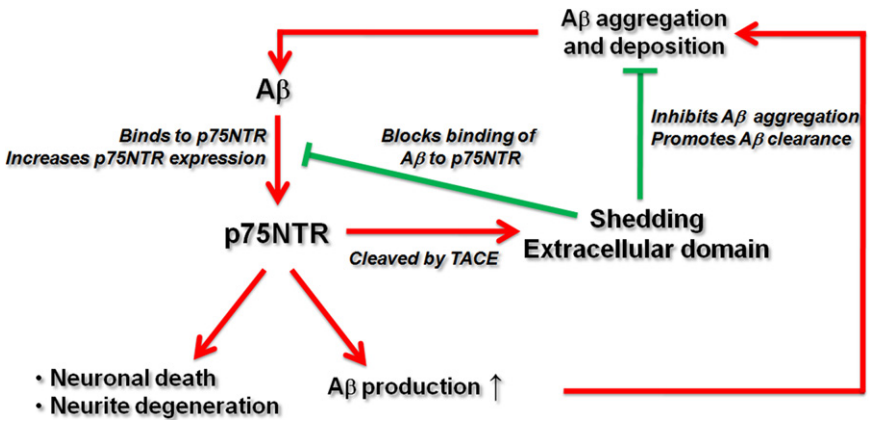


**Fig. 1.** Positive feedback loop between Aβ and p75NTR in AD brain. In the AD brain, p75NTR expression is elevated with the aging process and further activiated by Aβ. p75NTR is a receptor of Aβ. Aβ/p75NTR signaling increases the Aβ production and induces neuronal death and neurite degeneration. Overproduction of Aβ increases the accumulation of Aβ in the brain, which further activates the p75NTR expression and exerts its neurotoxicity via p75NTR, thus forms a positive feedback loop between Aβ and p75NTR, which accelerates the course of AD. Cleavage of p75NTR by TACE sheds the soluble extracellular domain, which exerts protection against Aβ, by blocking the binding of Aβ to p75NTR, attenuating the Aβ-activated p75NTR expression, reducing Aβ production, blocking Aβ neurotoxicity, inhibiting Aβ aggregation and faciliating Aβ clearance.

shedding of p75NTR regulated *in vivo*? Is there any change of p75NTR-ECD level in the AD brain, cerebral spinal fluid, blood or urine? Are the function and metabolism of p75NTR-ECD impaired in AD patients? Can Aβ influence p75NTR-ECD production? Are there any single nucleotide polymorphisms in the p75NTR gene associated with the risk of AD? All these important questions need to be answered in further studies.

### 2.6. p75NTR and Tau phosphorylation

Whether p75NTR is involved in Tau phosphorylation in AD remains unknown. However, several lines of evidence suggest a role of p75NTR in the formation of neurofibrillary tangles (NFTs) which is another pathological character of AD. It is well known that Aβ triggers hyperphosphorylation of Tau and the formation of neurofilamentary tangles [59,60]. But the signal pathways linking Aβ and Tau hyperphosphorylation are not known. In cultured hippocampal neurons, NGF from astrocytes increases Tau phosphorylation in a p75NTR dependent manner [61]. A small molecule p75NTR antagonist which blocks the p75NTR signal can suppress Aβ-induced Tau phosphorylation and the activation of AD pathological signals such as cdk5 and GSK3β in cultured neurons, suggesting the role of p75NTR in Tau phosphorylation [62]. In AD patients, a large proportion of these p75NTR expressing neurons is co-localized with hyperphosphorylated tau, suggesting that p75NTR may be involved in the formation of NFTs [8]. Whether p75NTR plays any roles in the formation of neurofilament tangle and Tau phosphorylation remains to be investigated *in vivo*.

### 2.7. p75 NTR and neuronal cell cycle re-entry

Adult neurons in the brain are classically thought to remain in a state of terminal differentiation permanently, effectively precluded from cell division. A decade ago, it was shown that there was an activated cell cycling activity in the susceptible cortical and hippocampal neurons of AD brains, suggesting that neurons in AD re-enter the cell cycle. Accumulating evidence indicates that neuronal cell cycle re-entry represents an early and critical event in AD, recapitulating known hallmarks of the disease such as Tau hyperphosphorylation and Aβ plaques. Such a cell cycle re-entry also occurs in other neurodegenerative disease, suggesting that the cell cycle re-entry hypothesis may be applicable in many disease processes in nervous system.

The mechanism by which the neurons activate the cell cycles in AD remains unclear, although some studies suggest that interaction of APP with the APP-binding protein (APP-BP1) plays a role in triggering signal pathways leading to the cell cycle re-entry [63,64]. Recently several lines of evidence shows that p75NTR might play important roles in cell cycle re-entry in AD. Firstly, it is demonstrated that, during the development of central nervous system (CNS), the activation of p75NTR by an endogenous source of NGF or possibly proNGF can trigger cell cycle re-entry and tetraploidization of retinal ganglion cells [65–67]. Thus, a novel hypothesis for AD based on neuronal tetraploidy induced by p75NTR has been proposed [4]. According to this hypothesis, somatic tetraploidy induced by p75NTR in neurons plays a major role in the initiation and propagation of the neuropathological signs of AD. It is intriguing to speculate that p75NTR has similar effects on neurons in the basal forebrain and hippocampus which are most vulnerable in AD. Secondly, several p75NTR intracellular interactors have been identified, and many of them have been known to regulate cell cycle. These proteins include Schwann cell factor 1 (SC1), neurotrophin receptor intereacting MAGE homolog (NRAGE), neurotrophin receptor interacting factor (NRIF1/2) and Sal-like protein 2 (sall2), a newly identified p75NTR interacting protein involved in the NGF-mediated cell cycle progression and neurite outgrowth [68–72]. Finally, p75NTR becomes up-regulated in response to stress in affected brain regions including AD affected neurons. p75NTR is a well-known stress- responsive receptor. The p75NTR expression in both neurons and glial cells becomes increased in response to oxidative stress, which is linked to cell cycle re-entry in neurons [73,74]. The roles of p75NTR in inducing cell cycle re-entry of neurons in AD need to be further investigated.

### 2.8. p75NTR and cognition

Degenerated cholinergic neurons in the basal forebrain are closely related to the impaired learning and memory processes in AD patients. Some research has found that deletion of exon III or IV of the p75NTR gene increases the number of cholinergic neurons in the medial septal nucleus by 13% and 28% respectively in mice [75]. This neuronal increase is sure to improve cognition to some degree [76]. A recent study shows that deletion of p75NTR gene enhances long-term potentiation in the Schafer collateral fiber synapses and increases the choline acetyltransferase activity of the hippocampus in a p75NTR gene-dose dependent manner. Deletion of p75NTR gene also improves the performance in multiple cognition tests including the Barnes maze and the open field test [77]. As p75NTR is very sparsely expressed in the adult hippocampus and has a potent effect on hippocampal choline acetyltransferase activity, the effects of p75NTR on hippocampal function are likely to be mediated by its actions on basal forebrain cholinergic neurons.

## 3. p75NTR as a target for the treatment of AD

Due to the failure in clinical trials targetting Aβ (active or passive vaccination against Aβ and inhibitors of β- and γ-secretases), it is imperative to discover new therapeutic targets for AD. Based on multiple functions of p75NTR in the pathogenesis of AD as discussed above, we propose that p75NTR is a potential target for the development of therapeutic drugs for AD. Future studies should focus on validating ways targeting different aspects of AD hallmarks which are regulated by p75NTR and breaking up the p75NTR-mediated positive feedback loop which promotes the cascades on the pathogenesis of AD (Fig. 2).

### 3.1. Enhancement of the neurotrophin/p75NTR/TrkA signaling

Cholinergic neurons in the basal forebrain express both p75NTR and TrkA, and NGF is a neurotrophic factor for the function and survival of these neurons. Protection of these neurons in AD patients may improve the cognitive functions and delay the development of the disease. In the presence of TrkA, p75NTR interacts with TrkA and significantly enhances NGF signaling and activation of TrkA phosphrylation and down streaming Akt/PI3K cell survival pathways [78]. Thus, the NGF/p75NTR/TrkA signaling pathway in the basal forebrain may play a critical role in balance of the neurotrophic and neurodegenerative status of cholinergic neurons and maintenance of the healthy brain. In recent years, strong evidence using NGF antibody transgenic mice has shown that the NGF signaling pathway not only maintains the function of cholinergic neurons and cognition, but also plays important roles in the Aβ deposition and Tau phosphorylation [79]. Simply depletion of NGF in mice with NGF antibody transgene increases Aβ plaques and Tau phosphorylation and reduces cognitive functions, and the development of AD in these mice can be abolished by nasal delivery NGF [80,81]. Recent studies suggest that the increased level of Aβ in the brain of AD is due to the lower neurotrophic activity. The dysfunction of neurotrophic activity and reduction in brain-derived neurotrophic factor (BDNF) and mature NGF has been found in AD brain [24,82]. BDNF can reduce

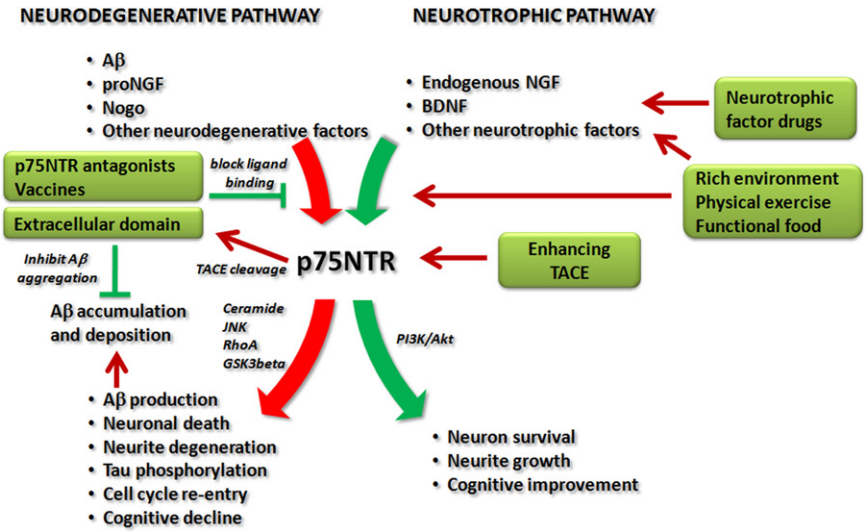


**Fig. 2.** Neurodegenerative and neurotrophic pathways of p75NTR signaling, and potential therapies targeting p75NTR. In the AD brain, neurodegenerative substances such as Aβ, proNGF, Nogo and other factors exert detrimental effects via p75NTR signaling, including Aβ overexpression, neuronal death, neurite degeneration, Tau hyperphosphorylation, cell cycle re-entry and cognitive decline. Meanwhile, neurotrophic factors such as endogenous NGF, BDNF and other factors exert protective effects via p75NTR signaling, including neuron servival, neurite growth and cognitive improvement. Therapeutic effects could be achieved by targeting p75NTR signaling. p75NTR antagonists, vaccines and recombinant extracellular domain of p75NTR are able to block the interaction of Aβ, proNGF and other neurodegenerative ligands with p75NTR, thus to protect the neurons from the neurotoxicities. Furthermore, extracellular domain is also able to inhibit Aβ deposition and faciliate Aβ clearance from brain. Enhancement of TACE could increase shedding of soluble extracellular domain of p75NTR. Neurotrophic factor drugs, rich environment, physical exercise and functional food are able to enhance neurotrophin/p75NTR/Trk signaling to promote neuron survival, neurite growth and improve the cognition.

amyloidogenic processing of APP via up-regulating expression of SorLA, the VPS 10 receptor controlling APP trafficking and linked to LOAD [83]. In addition, IGF1-R and insulin receptor are down-regulated in AD brain and the reduction in IGF1 and insulin signaling is associated with the increased plaque formation in AD brain [84]. The main signaling pathway activated by neuritrophins/p75NTR/Trk is the Akt/PI3K pathway, which normally enhances neuronal survival and prevents the activation of GSK3beta. GSK3beta activation leads to increases in Aβ production, Tau phosphorylation and other neurodegenerative events [84]. Thus it is reasonable to increase neurotrophic activity by introduction of exogenous neurotrophins or enhance the process of proneurotrophins by over-expression of furin or other proneurotrophin processing enzymes. Introduction of insulin, NGF and BDNF all enhances the cognitive functions in human and in AD animals. These neurotrophic drugs are powerful agents to suppress the amyloidogenic pathway and reduce Aβ production. Neurotrophic treatment also enhances the non-amyloidogenic processing of APP and increases the production of sAPPα which not only precludes the production of Aβ but also is a neurotrophic agent to trigger the Trk/Akt signaling and suppress the neurodegeneration [85]. NGF increases the expression of ADAM-17 which increases the alpha-processing of APP and the processing p75NTR which generates extracellular domain [85].

There are a number of ways to develop neurotrophic drugs for AD. *Ex vivo* gene delivery of NGF has proven effective in patients with AD who experienced improvements in cerebral metabolism and cognition compared with pre-operative function without adverse events. Clinical trials using AAV-NGF gene into AD patients have generated promising results and has also proven the concept of neurotrophic hypothesis [86,87]. However it is clearly disadvantageous to use this method to treat a large number of patients due to the limitation of invasiveness and risks associated with the surgical operation. Non-invasive delivery of neurotrophic factors is possible to treat AD [88]. Nasal application of NGF or other neurotrophic molecules is a clearly advantageous method to activate neurotrophic system in the brain. It is known that nasal olfactory neurons express p75NTR, Trk and other neuronal receptors which would act as a naturally occurring delivery vehicle for the axonal transport of neurotrophins and other neurotrophic molecules such as insulin and IGF. It is likely that these neurotrophic molecules are transported to the brain and released via olfactory axons when they are delivered via nasal mucosa. Further studies should be focused to test different neurotrophic factors and to elucidate possible mechanisms of how exogenous neurotrophic factors in the periphery may cross the blood-brain barrier to reach the CNS. In addition to nasal route, neurotrophins may also be transported to CNS by primary sensory neurons or motor neurons via the mechanisms of retrograde and anterograde transport [89]. Our previous studies have demonstrated injection of BDNF into the footpad or sciatic nerve can affect the regeneration of spinal cord neurons and improve functional recovery after spinal cord injury [90]. The non-routine CNS delivery route should be tested to improve the neurotrophic activities of AD brain.

Although direct application of neurotrophins and other neurotrophic factors in CNS and in the periphery is an obvious approach to tackle the progression of the disease and improve the cognitive functions, other approaches such as changes of life styles may also improve the balance of neurotrophic and neurodegenerative status of AD patients. It is well known that exercise and environmental richness are simple and efficient ways to up-regulate neurotrophins and their receptors. In particular, exercise can increase expression of BDNF [91], which would counteract the neurodegenerative metabolism of the brain. Environment richness in animals can also up-regulate BDNF gene expression, and reduce Aβ production and prevent cognitive decline in AD mice [92]. Clinical studies have shown that playing board games is beneficial to prevent the cognitive decline in aging population [93]. These simple changes in life styles are very effective to increase BDNF and other neurotrophic functions and should be recommended for aging population. A number of phytochemicals and polyphenols from food and extracts of plants have been shown to regulate NGF and BDNF expressions [94]. Future studies should be directed to discover functional food which affects gene expression and processing of neurotrophins and their receptors and to suppress progression of AD.

### 3.2. Development of therapies to block p75NTR-mediated neurodegenerative signals

The predominant functions of p75NTR in the pathological conditions such as in AD are to transduce neurodegenerative signals from extracellular ligands i.e. Aβ, proneurotrophins, myelin associated inhibitory molecules and axonal repulsive molecule ephrins [95–98]. Aβ, proneurotrophins and myelin associated inhibitory molecules are present in the AD brain as dominant and degenerating signals [99]. As p75NTR is up-regulated in AD brain and Aβ is a positive signal to up-regulate p75NTR expression, p75NTR is an obvious target for developing drugs to antagonize these extracellular toxic signals to break the positive feedback loop in the AD cascade. Two different p75NTR antagonists have been developed: cyclic peptide antagonist which binds extracellular ligand-binding site and non-peptide chemicals which can antagonize p75NTR signaling of Aβ and other toxic signals. Yarr et al. have demonstrated *in vitro* that a p75NTR antagonistic cyclic peptide (CATDIKGAEC) interferes with Aβ binding to p75NTR and displaces Aβ on the binding site and rescues neurons from Aβ-induced toxicity [100]. At 250 nM, the peptide reduced Aβ (1–40)-induced phosphorylation of JNK by 71.8% and protected neurons from Aβ-induced toxicity. The KGA motive in the antagonist is also present in Aβ and NGF sequence and may serve as a competitive motive to antagonise Aβ toxicity. Subsequent *in vivo* studies showed that the p75NTR antagonist injected into the cortex together with Aβ can significantly suppress the inflammation, suggesting the p75NTR antagonist may have therapeutic value [101]. Further studies are required to see whether *in vivo* application can protect neurons from apoptosis, reduce Aβ production and amyloid plaques in AD model. The other non-peptide small molecule p75NTR antagonist has also been developed by an independent group [62]. These small ligands bind to p75NTR, inhibit Aβ-induced neurite degeneration and death of cultured primary neurons and cultured brain slices. These molecules can promote survival of neurons which are exposed to Aβ via suppression of Aβ evoked signaling molecules in the pathogenesis of AD such as Calpain/cdk5, GSK3beta, and c-JUN. These molecules also prevent inactivation of Akt and CREB induced by Aβ. These studies suggest that the small chemical ligands may have therapeutic potential to antagonise p75NTR signaling and suppress the progression of AD induced by Aβ-p75NTR signaling [62]. It would be interesting to see whether these small molecule ligands also antagonize proneurotrophin-induced neurodegeneration and whether application of these molecules *in vivo* improves the cognitive functions and attenuates AD pathology in AD mice.

One of the important features of AD is the axonal degeneration and dystrophic neurites, which are likely derived from signals activating Rho-GTPase-ROCK pathway, which is also involved in the production of Aβ [102]. These features of AD are likely due to the neurodegenerative signals derived from degrading myelin associated proteins, Nogo A, MAG and OMgP [103,104]. These inhibitory factors bind to Nogo receptors (NgR), activating Rho-GTPase via the p75NTR receptor [105]. Vaccines of recombinant DNA against the inhibitory factors have been developed to treat spinal cord injury and generated significant beneficial results [106]. This approach should be tested to treat AD for the prevention of neurodegeneration via p75NTR signaling pathways [107]. The antibodies generated after the treatment with the DNA vaccine would block the actions of inhibitory factors on NgR and p75NTR, thus promote nerve regeneration and reduce the production of Aβ and Tau phosphorylation.

### 3.3. To develop drugs targeting the shedding of the extraceullular domain of p75NTR

Our recent study has found that p75NTR molecule has multiple actions on Aβ production and deposition [16]. Full length molecule mediates signals to promote Aβ production in the brain of AD mice whereas the extracellular domain of p75NTR plays an opposite role in the Aβ deposition. In APPswe/PS1dE9 transgenic mice with p75NTR gene deletion, there is a dramatic increase in Aβ deposition in the brain as detected by histology and the insoluble Aβ as detected by ELISA is also increased in the brain. In contrast, the soluble Aβ in the brain and plasma Aβ are significantly reduced. These differential actions of p75NTR in Aβ metabolism reflect two distinct mechanisms of p75NTR in regulation of Aβ metabolism. The full-length p75NTR positively regulates Aβ production by neurons via ceramide signal [54]. The up-regulation of Aβ by p75NTR is most likely ligands-dependent. The reduction in soluble Aβ and serum Aβ by p75NTR knockout *in vivo* further supports this notion by Constantini et al. [55]. However, the net outcome of Aβ pathology and inflammatory response are much more severe than the control mice, suggesting that p75NTR may have an overall beneficial function for Aβ pathology. Simply down-regulation of p75NTR may be unwise in the treatment of AD. We hypothesize that the extracellular domain of p75NTR shed by TACE may be the key component to play the beneficial function. Indeed, we test this hypothesis and found that recombinant p75NTR extracellular domain can suppress the Aβ oligomerization and fibrillation. Injection of recombinant extracellular domain into the hippocampus of AD mice can reduce the local Aβ plaques [16].

p75NTR is cleaved extracellularly to generate a 50 kD extracellular domain by ADAM17 (TACE) [58], the same enzyme that cleaves APP at the alpha-site to prevent Aβ production [108]. The TACE cleavage of p75NTR is followed by the receptor regulated intramembrane gamma-secretase processing (RIP) to generate intracellular domain, which binds TRAF6 and moves into nuclear to regulate apoptosis [109]. TACE mediated p75NTR shedding of sympathetic neurons is regulated by extracellular ligands such as BDNF, which activates apoptotic signaling through p75NTR via activation of the stress kinase, JNK, which subsequently regulates the gene expression of TACE. The interaction of BDNF/proBDNF/p75NTR produces a positive feedback loop to generate cascade of signals promoting apoptosis of neurons by activating a biphasic shedding of p75NTR [109]. The first phase of shedding is produced by constitutive TACE expressed by neurons but the second phase is involved in the gene expression of TACE activated through JNK signaling pathway and p75NTR intracellular domain nuclear translocation [109]. The functions of extracellular domain of p75NTR is not clear after shedding, but Ahmed et al. provide the first evidence that the shed extracellular domain plays a beneficial role in the suppression of neurite inhibitory molecules such as NgR ligands [110]. The extracellular domain of p75NTR can promote the neurite outgrowth and disinhibits the effect of CNS myelin neurite growth inhibitory factors. TACE is highly expressed in both neurons and glia, colocalizes with amyloid plaques [111], and plays critical roles in neuron development and in AD pathogenesis [112]. Our study shows that p75NTR is also associated with amyloid plaques [16]. It is likely that the effect of TACE-mediated alpha-processing of APP on Aβ production may also affect p75NTR processing and extracellular domain shedding. Thus, targeting TACE to treat AD may have double beneficial effects via both APP non-amloidogenic pathway and p75NTR pathway to prevent the neurotoxic effect of Aβ. For example, interleukin-1 beta (IL1beta) up-regulates TACE and enhances alpha-cleavage of APP in neurons to generate more sAPPα and C83, but suppresses beta-cleavage, resulting in less production of Aβ40/42 in human neuroblastoma SK-N-SH cells [113]. It is worthwhile to examine whether such regulation by IL1beta also occurs on the processing of p75NTR, in particular *in vivo* conditions in the AD brain where IL1beta and TACE may be increased [114], and whether suppression of inflammation or inhibition of IL1beta aggregate AD progression. The treatment with the molecular chaperone phenylbutyric acid in AD transgenic mice reduces amyloid plaques and improves cognitive behaviour, likely through the up-regulation of

ADAM 10 and TACE in the brain [115]. It is apparent that targeting TACE with drugs to treat AD may be associated with serious side effects as there are numerous target proteins which are critical for their physiological functions [116].

Based on the concept from the shedded extracellular domain TNFα receptor, which is useful in antagonizing TNFα for anti-inflammatory functions, and clinical effectiveness and tolerance of Etanercept for the treatment of rhumatoid aruthritis in patients [117], it is reasonable to use the p75NTR extracellular domain for the treatment of AD. The extracellular domain of p75NTR may also play a role in antagonizing its toxic ligands such as Aβ, proneurotrophins, myelin inhibitory factors and other neurite degenerating and apoptotic molecules. Our study provides additional evidence that extracellular domain of p75NTR suppresses Aβ deposition. We also provide evidence that the extracellular domain can suppress the effects of Aβ and proNGF on apoptosis [16,30]. Whether the application of such molecule in the periphery affects CNS neurons and alters the progress of AD is not clear, but based on our study that peripheral application of single chain antibody to Aβ reduce CNS Aβ plaques and improves cognitive functions in AD mice [118,119], it would worth to try such approach for the treatment and prevention of AD in the future studies. Although administration of the extracellular domain of p75NTR may have side effects as this molecule may intercept endogenous mature neurotrophins from sensitive neurons. However, such side effects may not prevail as neurons in the periphery and CNS often express high affinity receptors Trk which can bind endogenous neurotrophins with much higher affinity than the extracellular domain of p75NTR, therefore the extremely low concentration of endogenous mature neurotrophin may still be functional on Trk expressing neurons in the presence of the therapeutic extracellular domain of p75NTR.

## 4. Conclusion remarks

Since the discovery of p75NTR as the neurotrophin receptor more than two decades ago, it has become clear that this molecule has diverse functions particularly linked with neuron development, aging, stress and neuropathological conditions. Recent studies have found that p75NTR not only mediates signals promoting protection of nervous system by its interaction with neurotrophins and Trk receptors, but also mediates signals of neurodegenerative molecules such as Aβ, proneurotrophins, axonal repulsive molecules and myelin associated inhibitory factors. Thus p75NTR appears to play a critical role of balancing signals derived from both physiological and pathological conditions which control life and death of neurons. In pathological conditions such as AD, p75NTR is involved in the pathogenesis of almost all hallmarks, starting from the generation and removal of Aβ, Aβ-induced neuronal death and neurite degeneration, to the Aβ deposition and associated neuroinflammation. We have proposed that targeting p75NTR for the development of therapeutics for AD may open a new avenue of research to fight against the disease.

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