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REVIEW

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Neural stem/progenitor cells in Alzheimer's disease

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Alzheimer's disease (AD) is the most prevalent neurodegenerative disease and a worldwide health challenge. Different therapeutic approaches are being developed to reverse or slow the loss of affected neurons. Another plausible therapeutic way that may complement the studies is to increase the survival of existing neurons by mobilizing the existing neural stem/progenitor cells (NSPCs) — i.e. "induce their plasticity" — to regenerate lost neurons despite the existing pathology and unfavorable environment. However, there is controversy about how NSPCs are affected by the unfavorable toxic environment during AD. In this review, we will discuss the use of stem cells in neurodegenerative diseases and in particular how NSPCs affect the AD pathology and how neurodegeneration affects NSPCs. In the end of this review, we will discuss how zebrafish as a useful model organism with extensive regenerative ability in the brain might help to address the molecular programs needed for NSPCs to respond to neurodegeneration by enhanced neurogenesis.

INTRODUCTION

Alzheimer's disease (AD) is characterized by the chronic loss of neurons and synapses in the cerebral cortex and by a significant loss of brain mass in a progressive manner [1]. AD is the most-common form of dementia [2]. World Alzheimer Report estimates about 46.8 million people worldwide were living with dementia in 2015, and that figure is expected to double over the course of the next two decades. As there is no cure, there is an urgency to better understand the causes of AD in order to carry out prevention strategies. Equally, and maybe more importantly, is to design novel and unconventional therapeutic approaches that not only target the affected neurons, but also the stem cell pool of an adult brain.

Cellular therapies for neurodegenerative diseases are one of the most promising alternatives, along with drug treatments. Cellular replacement implicates the substitution of specific neuronal subtypes lost in disease and successive grafting into affected areas. The newly transplanted cells should incorporate and recapitulate a neural network similar to the healthy brain. Stem cells could provide an environmental support to residing neurons by producing neurotrophic factors and creating additional neural networks in affected areas. Environmental enrichment of stem cells with growth factors, such as glial-derived neurotrophic factor

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†Abbreviations: AD, Alzheimer's disease; ADAM10, A disintegrin and metalloproteinase domain-containing protein 10; ADNP, activity-dependent neuroprotective protein; APOE, Apolipoprotein E; APP, Amyloid precursor protein; Aβ, Amyloid beta; AB40; amyloid beta 40; BACE, beta-site APP cleaving enzyme; BDNF, Brain-a derived neurotrophic factor; BMP, Bone morphogenic protein; CBL, Cerebrolysin; CNS, central nervous system; CSF, cerebrospinal fluid; CTF, C-terminal fragment of amyloid precursor protein; DCX, doublecortin; DG, Dentate gyrus of the hippocamps; ESC, embryonic stem cells; FAD, familial Alzheimer's disease; GDNF, glial cell-derived neurotrophic factor; GZ, granular zone; IGF2, insulin growth factor 2; IL, Interleukin; IL-1RA, Interleukin-1 receptor antagonist; iPSC, induced Pluripotent stem cells; MSC, mesenchymal stem cells; NEP, Neprilysin; NFT, neurofibrillary tangle; NGF, neural growth factor; NLRP3: NACHT, LRR, and PYD domains-containing protein 3; NPC, neural progenitor cell; NSPC, neural stem/progenitor cell; PDGF, Platelet-derived growth factor; PS-1 and PS-2, Presenilin 1 and 2, respectively; SAD, sporadix Alzheimer's Diease; SGZ, subgranular zone; sNEP, soluble neprilysin; SVZ, subventricular zone of the lateral ventricle; TGFBN, transforming growth factor beta N; NSC, nueral stem cell; TLR, toll-like receptor; TREM, triggering receptor expressed on myeloid cells; VEGF, Vascular endothelial growth factor

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(GDNF), nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF) would provide a support at the main site of the disease [3-6].

Various types of stem cells, including embryonic stem cells (ESC), mesenchymal stem cells (MSC), induced pluripotent stem cells (iPSCs), and neural stem/progenitor cells (NSPC), have been studied as a cellular therapy in neurodegenerative diseases. Bone marrow-derived MSC transplantation into AD mouse model rescued AD-like pathology via microglial activation [7]. Restorative therapy with ESC-derived neural progenitor cell implantation into AD rat model improved the cognitive function and implanted ESC cells preserved neuronal phenotype. However there are multiple concerns, including immune rejection and/or tumor formation [8,9]. Programming of somatic cells or fibroblasts into iPSCs and iPSC-derived NSCs are another option for stem cell-based therapy for neurodegenerative diseases. iPSCs do not bear immunological complications, but similar to ESCs, have a risk of tumorigenesis in *in vivo* transplantation. Therefore, to use iPSCs in treatments, safety is an important issue [10]. The development of patient-derived iPSCs gives an exclusive basis to understand the molecular mechanisms in neurodegenerative diseases by providing platforms to perform drug screens, which could otherwise not be possible *in vivo* [11,12].

One particular way for providing stem cell-based input into the nervous system is to mobilize the endogenous NSPCs. In a healthy brain, the NSPCs are the multipotent stem cells that are capable of proliferation, self-renewal and generation of new neurons, astrocytes, and oligodendrocytes. Enhancing their proliferation rate and differentiation capacity combined with approaches aiming to increase the survival and integration of neurons into circuitry, elevated levels of newly born neurons might provide a regenerative input in a highly unfavorable neurodegenerative environment. Therefore, it is important to understand the behavior of NSPCs during neurodegeneration. In this review, we will elaborate on the current knowledge of how NSPCs are affected by AD and how they affect the AD pathology. In the last section, we will give an outlook on potential uses of model organisms that are capable of regeneration toward understanding the molecular basis of NSPC plasticity and regenerative activity.

THE PATHOLOGY OF AD

AD develops as a result of multiple factors rather than a single cause. Advanced age and certain genetic polymorphisms are the predominant risk factors, yet diabetes, cardiovascular diseases, traumatic brain injury, hypertension, fatty diet, gender, endocrine conditions, oxidative stress, inflammation, stroke, smoking, depression, infection, tumors, vitamin deficiencies, immune and metabolic conditions, and chemical exposure also contribute to the likelihood of developing AD dementia [13-16]. The classical neuropathological hallmarks associated with AD are presence of intracellular and extracellular misfolded protein aggregates: senile plaques and the neurofibrillary tangles (NFTs) [17].

Over the past decades, several studies portrayed the evidence of two competing hypotheses that evolved around AD [18]. The amyloid hypothesis suggests that the depositions of Amyloid precursor protein (APP) cleavage products (39 to 42 amino-acid-long Amyloid β peptides) inside or outside the neuron are the fundamental cause of AD. Amyloid Beta (Aβ) was initially thought to be an abnormal peptide, but studies later showed that it is produced constitutively during normal cell metabolism but the imbalance in amyloidogenic cleavage cascade leads to excessive production of Aβ peptides, which are naturally cleared from the brain by either enzyme degradation [19] or by the process of peptide efflux and influx mechanism [20]. Alternatively, the tau hypothesis states that the hyperphosphorylated tau protein forms the NFTs inside neurons, which in turn acts as the stimulus for the disease progression. Though AD pathogenesis is complicated and elucidating the exact mechanism is difficult, genetic and pathological evidence strongly support the amyloid cascade hypothesis of AD, in which the accumulation of Aβ has an early and critical role to trigger a cascade of events leading to synaptic dysfunction, tau pathology, gliosis, and neuronal loss [21,22].

The major etiology of AD is aggregation of Amyloid protein cleavage products — mainly Aβ42 peptide — either extracellularly or intracellularly [23-30]. Senile plaques, also known as amyloid plaques, are composed of Aβ peptides that exist in extracellular β-pleated sheet conformation in the brain parenchyma [31]. Aβ deposits have also been reported to be found as vascular amyloid in the walls of meningeal and cerebral blood vessels, usually referred to as cerebral amyloid angiopathy [32,33]. Lately, presence of Amyloid deposits inside the neurons have gained much attention as various lines of research suggest that intracellular aggregates of amyloid cleavage products might constitute the early toxicity during the course of neurodegeneration [34].

Post-translational processing of APP occurs in two different pathways: amyloidogenic pathway and non-amyloidogenic pathway [35]. The former pathway features the sequential action of two different enzymes, namely β-secretase (β-site APP-cleaving enzyme, BACE) and γ-secretase, showing a proteolytic action on the APP [26]. BACE cleaves at the N-terminus of the Aβ sequence, releasing a soluble fragment sAPPβ, and another 99 amino-acid-long C-terminal fragment (CTF99) attached to the cellular membrane. The CTF99 fragment is then cleaved by γ-secretase at the C-terminus of the Aβ domain to release the full-length Aβ 40-residue peptide (Aβ40). A small proportion of the longer form of Aβ, a 42-residue peptide Aβ42, is also generated depending on the site of γ–secretase cleavage and is considered to be more cytotoxic [23]. The non-amyloidogenic pathway processes APP with physiological proteolytic cleavage by α-secretase.

ADAM10, a disintegrin and metalloprotease component of α-secretase, cleaves APP on the C-terminal side of the Aβ sequence [36-38]. This leads to the destruction of amyloidogenic component, thus preventing the formation of cytotoxic peptides.

Despite the substantial knowledge on the pathological features, the mechanism initiating or leading to the development of AD remains poorly understood. Two forms of AD, namely familial AD (FAD) and sporadic AD (SAD), are known to occur [39]. Early onset FAD shows mutation in three genes: APP, presenilin 1 (PSEN1), and presenilin 2 (PSEN2). The mutations in these genes increase the production of Aβ42 peptide [40]. In the case of the more prevalent late-onset SAD, the main risk factor is the interaction between the genetic susceptibility factors and environment leading to the expression of the ε4 allele of the apolipoprotein E gene (APOE) [41]. The association of early onset FAD with mutations in the APP and γ-secretase components provides a potential tool of generating animal models of the disease. Although various aspects of neuropathophysiology of AD were modeled in various animal models of AD, to date no transgenic animal model fully recapitulated the whole spectrum of the human pathology [42,43].

Lately, preclinical and genetic studies have shown the role and the importance of immune system in AD. Inflammation, various inflammatory cascades, and immune cells seem to contribute to the overall pathology of AD [44]. The link between immune alterations in AD was documented with mutations or deficiencies in microglial or myeloid cell-dependent genes: triggering receptor on myeloid cells 2 (TREM2), myeloid surface antigen CD33, and complement receptor 1 in patients. TREM2 deficiency in AD mice model was shown to enhance the hippocampal Aβ accumulation [44]. CD33 expression was upregulated on microglia in postmortem human AD brains. In contrast to this observation, single-nucleotide polymorphism related with the downregulation in CD33 expression lead to a decrease in Aβ levels [45].

Inflammatory response was mainly generated by central nervous system (CNS)-resident cells, microglia, perivascular myeloid cells, and astrocytes, but also by endothelial cells [46]. It has been showed that receptors, which are expressed by microglia, including CD14, CD36, CD48 and Toll-like receptors (TLRs), can detect soluble Aβ oligomers and Aβ fibrils [47-50]. The binding of Aβ to CD36 or TLR4 results in the production of various inflammatory chemokines and cytokines such as interleukin-1β (IL-1β), IL-6, IL-12, IL-23, and tumor necrosis factor-α, which influence the pathology of AD [51-53]. IL-12 and IL-23 were shown to be increased in the cerebrospinal fluid (CSF) of AD patients [54]. Neutralization studies of these cytokines in AD-like mice models resulted in the reduction of AD-like pathology [55,56]. Regulatory cytokine transforming growth factor β (TGFβ) found to be increased in the plasma, CSF, and brain in AD [57]. Blocking of TGFβ in genetic AD mouse model resulted in reduction in pathology [58].

Mutations in the inflammasome complex NLRP3 or NLRP3-related gene, caspase 1, reduced AD-like pathology in AD mouse model of AD, along with an alteration in microglial phenotype [59]. CD36, the upstream regulator of NLRP3 involved in the inflammation, could enhance the clearance of Aβ in AD, but more *in vivo* experiments should be conducted to understand the function of CD36 in AD pathology [60]. A deficiency in monocyte-related CC chemokine receptor type 2 leads to Aβ deposition in transgenic mouse model of AD [61]. Another chemokine receptor, CX3CR1, had a positive effect on amyloid deposition, but drastically worsens tau pathology in AD mice [62]. As a potential therapeutic target for AD, roles of IL-12, IL-23, IL-10, and TGFβ cytokines, NLRP3-related molecules (caspase-1, CD36, etc.), and specific chemokine receptors should be more extensively studied. Like myeloid cells, astrocytes are one of the key players in AD pathology. Astrocytes also lead to Aβ plaque-related astrogliosis and possibly contribute to the cognitive impairment in mouse models of AD. The expression of Aβ-degrading enzymes in these cells were upregulated upon the exposure of Aβ peptides *ex vivo* [63]. Endothelial cells, oligodendrocytes, and neurons have a role in the pathogenesis of AD in neuroinflammatory manner. Complement components that are expressed by oligodendrocytes may contribute to the neuroinflammation by enhanced expression levels in AD brain [64]. Neurons ameliorate the pathology of AD by reducing the expression of anti-inflammatory proteins such as CD59 and CD200 [65,66]. Pro-inflammatory cytokines, IL-1β, IL-6, and CCL2 chemokine were produced by endothelial cells in human AD brains via JNK-AP1 signaling pathway, which is one of the Aβ-induced neuroinflammatory pathways [67]. Since immune-related components are among the main contributors to the pathology of AD, combination therapy of drugs targeting Aβ and/or tau, and modulation of inflammation may be an ultimate way to offset the progression of the disease.

CHARACTERISTICS OF NSPCS

NSPCs are multipotent cells that generate the cell types of the nervous system: neurons, glia, and oligodendrocytes [68]. In vertebrate development, multipotent neuroepithelial cells progressively differentiate into cell types of the nervous system, while sparing undifferentiated cells that maintain glial identity and act as resident stem/progenitor cells of the adult nervous system [69-72]. Stem cell niches in vertebrates show diverse localizations. In adult mammalian brain, neurogenic stem cell niches are restricted to the telencephalon [70], where neural stem cells are found in distinct neurogenic niches: the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone of the dentate gyrus (DG) in the hippocampus (SGZ) [69,73-75]. Recently, the SGZ and

the striatum were suggested to be stem cell niches in the human brain [76,77]. In non-mammalian vertebrates, the proliferative and germinal zones in the brain are more widespread [78-82]. Thus, there is a fundamental difference in plasticity responses of vertebrate neural stem cells. This is evident in the regenerative capacity of adult vertebrate brains. While lower vertebrates such as teleost fish, frogs, and salamanders can regenerate their CNS [83-89] using an inducible set of molecular programs [90-92], mammalian brains are poorly regenerative [87]. For instance, our aging brains are prone to neurodegeneration, but we are unable to counteract neuronal loss by regenerating lost cells. Patients with neurodegenerative conditions progressively lose neurons yet cannot form new neurons that would replace the lost ones — namely, we humans lack the proper "plasticity response." Even though the neuropathological outcome in neurons could be hampered, we would still need a neurogenic input from stem cells to replenish the lost neurons. However, as we will elaborate in subsequent sections, most of the neurodegenerative pathology (e.g. Aβ42 deposition) has a negative effect on stem cell proliferation, and even if newborn neurons could be generated, they cease to survive in such an unfavorable environment. Therefore, we might consider neurodegenerative diseases of humans to some degree as "stem cell diseases." Thus, either providing input through exogenous NSPCs or mobilizing the endogenous stem cells in mammalian brains to proliferate and generate more neurons using "intrinsic" molecular programs of regenerating vertebrates could serve as an alternative (though challenging) therapy option.

NSPC-BASED THERAPIES FOR AD

Multipotent NSPCs have been on attention for a considerable time as a cell replacement therapy to prevent the loss of learning and memory function in AD [93-95]. A large portion of the studies using NSPCs undertook transplantation of exogenous mammalian NSPCs. Several studies showed that NSPCs could be used as a potential cell-based treatment in AD mice models. In the mouse model of nucleus basalis of Meynert (NBM) lesion, which manifests as a significant disruption of the working memory, the injection of mouse ESC-derived neural stem cells (NSC) showed improvement in working memory in concordance with the formation of choline acetyltransferase-positive neurons and migration to the cortical cortex [96]. Transplantation of adult mouse NSCs into the hippocampus of the inducible transgenic model with neuronal ablation improved survival, migration, and differentiation of NSCs into neurons, astrocytes, and oligodendrocytes, as well as a significant recovery in memory skills [97].

Transgenic animal models of AD, which recapitulates many of the significant features of the disease, were used to examine the therapeutic effects of mammalian NSPCs (Table 1). Transplantation of postnatal NSPCs to the hippocampi of 3xTg-AD mice recovered behavioral tasks, context-dependent novel object recognition, as well as enhancement in hippocampal synaptic density due to the positive effect of BDNF secreted by NSPCs without changing Aβ or tau pathology [4]. Another mouse model of AD, containing P301S mutation in the Tau gene displays overt Tau pathology, progressive neuronal loss with associated astrogliosis in the cerebral cortex. When fetal NSPCs were injected, astrocytes resulted in improved neuroprotective effect of cortical neurons by the increase in neurotrophins, in particular the GDNF and activity-dependent neuroprotective protein (ADNP). Although the underlying mechanisms are unknown, the differentiation of NSPCs to astrocytes or transplantation of exogenous astrocytes could be the reason for such a neuroprotective effect [98]. Recent studies showed that transplantation of embryonic NSPCs into APP/PS1 double transgenic mice rescued impaired memory and learning ability, along with enhanced long-term potentiation, regeneration of neurons, new synapses, and elevation of neurotrophic factors (NR2B, Trkb/BDNF, SYP and PKCζ), which potentially protect neural function [99]. However, Aβ plaques were not cleared in either of the studies.

A potential reason underlying the improvement in learning and memory in APP/PS1 mice at 10 weeks post-transplantation of NSPCs could be the downregulation of inflammation-related pathways TLR4, MyD88, TRIF, p-P38, MAPK, and NFκB because NSPC transplantation also leads to reduced microglial activation [100]. NSC inoculation into AD mice was shown to significantly improve the number of mitochondria and the amount of mitochondria-related proteins (mitochondrial fission factors) [101]. Since a defect in mitochondrial biogenesis is one of the early and prominent features of AD, the level of restoration of the impaired spatial learning and memory could be due to enhanced mitochondrial biogenesis. Fetal NSPCs were also transplanted into the brains of adult Tg2576 mice and showed improvements on cognitive defects, reduction of phosphorylated tau levels, and amyloid plaque levels in the cortex [102]. These outcomes could be due to elevated levels of vascular endothelial growth factor (VEGF) and postsynaptic density protein 95 (PSD-95) at the early stages (12-month-old) of Tg2576 AD model. Similarly, significant improvement in spatial learning and memory were observed in 3xTg-AD mice implanted with NSPCs [103].

NSPC derived from human tissues also showed ameliorating effects on the cognitive decline in various AD mouse models. hNSCs genetically modified to express hNGF differentiated into functional neurons and astrocytes after transplantation helped to improve the learning abilities of a mouse model of cognitive dysfunction [104]. BDNF-producing human CNS-derived NSPCs were injected into hippocampi of 3xTg-AD mice and efficaciously rescued the cognitive defects and upregulated the expression of synaptic and growth-related markers, but did not alter the Aβ or tau pathology [105], similar to other studies [100,101]. Consistent with these

Table 1: Effects of various factors on NSPCs and AD pathology

Factor	*Effect on NSPCs*	*Effect on AD pathology*	*Mice model(s)*	*NSPC type(s)*	*Reference*
BDNF, GDNF, ADNP	*Increased NSPC proliferation *Synaptic remodeling	*Repair of cognitive impairment	3x Tg-AD P301S	Fetal	Blurton-Jones et al. 2009, Hampton et al., 2010
TLR4 and TLR4-related pathways	*Decrease glial activation	*Deteriorate the course of the disease	APP/PS1	Fetal	Zhang et al., 2015a
Mitochondria-related	*Enhanced differentiation into neurons, astrocytes, oligodendrocytes	*Restoration of spatial learning and memory	APP/PS1	Fetal	Zhang et al., 2015b
VEGF	*Increased NSPC proliferation	*Improvement on cognitive defects *Reduction of phosphorylated tau levels and Aβ plaques	Tg2576	Fetal	Kim et al., 2015
NGF	*Differentiation into functional neurons and astrocytes	*Improvement on learning abilities	Cognitive dysfunction model	Fetal	Lee et al., 2012
Akt/GSK3β pathway	*Differentiation into neuronal and glial cells	*Inhibit tau phosphorylation	NSE/APPsw	Fetal	Lee et al., 2015
IL-1RA	*Microglial proliferation	*Reduction in Aβ plaque formations *Recovery of cognitive impairment	Tg2576	Postnatal	Ben-Menachem-Zidon et al., 2014
Neprilysin	*Enhancement of synaptic connectivity *Enhanced NSPC survival	*Reduction in Aβ-induced toxicity	3xTg-AD	Postnatal	Blurton-Jones et al., 2014

reports, promising therapeutic studies were also performed with fetal hNSCs and hNSC cell lines in AD mouse models. When fetal NSCs were introduced into the cerebral lateral ventricles of an APP mouse model that displays Aβ deposits but not plaques, increased levels of neurotrophic factors led to the activation of Akt/GSK3β pathway, which inhibits tau phosphorylation, while implanted cells migrated into the SVZ and differentiated into various types of neuronal and glial cells, improving spatial memory without any adverse effects [106]. Treating Tg2576 mice with neurotrophic drugs combined with injected hNSC cells improved endogenous neurogenesis by the increase in early neurons expressing doublecortin (DCX), inhibit further cognitive impairment and decreased the Aβ levels [107].

Potential NSC-based therapies for AD aim to provide a convenient microenvironment to suppress neurodegeneration and to sustain the survival of mature neurons by supplying neurotrophic factors. For instance, infusions of NGF in aged murine models have been shown to improve cognitive function [108-110]. Phase 1 clinical trials of NGF gene therapy were also performed in AD patients and resulted in an improvement in cognitive behavior and activation of neuronal responses with no adverse effects

[5,111]. Delivery of Aβ-degrading enzyme endopeptidase Neprilysin (NEP) or NEP-derived Neuropeptide Y into APP transgenic resulted in neuroprotective activity and led to a reduction of Aβ deposition and inflammation [112,113]. BDNF gene delivery into mice, rat, and non-human primate models of AD resulted in reversing synapse loss, cognitive decline, and neuronal atrophy by normalizing the cell survival pathways [114]. Intraventricular BDNF infusion into APP/PS1 mice showed decreased Aβ peptide and enhanced N-acetylaspartate, which is the precursor of the most abundant neuropeptide N-acetylaspartylglutamate in mouse brain [115]. Infusion of bone morphogenic protein 9 (BMP9) or Insulin-like growth factor 2 (IGF2) in APP/PS1 mice models resulted in reduced amyloid plaques and the enhancement of neurotrophic factors such as NGF and BDNF [116,117]. Injection of an adeno-associated virus into the hippocampal region of APP and APP/PS1 mice to express anti-inflammatory glycoprotein CD200 restored the number of differentiated neurons in DG, improved neurogenesis in the SGZ area, and reduced the neuroinflammation and soluble Aβ42 levels [118].

Inflammasome complex NLRP3 is involved in the immunomodulation of AD pathogenesis. NLRP3 regulates the activity of caspase-1, which is involved in the cleavage of proinflammatory Type-1 cytokines such as IL-1 and IL-18. Elevated levels of active caspase-1 and IL-1 have been detected in AD patients [59,119]. IL-1 can affect AD pathology in both detrimental and beneficial ways, such as by stimulating the expression of APP [120,121] or by leading to a reduction in amyloid pathology by microglia-dependent plaque degradation [122-124]. In a study where Neural Progenitor Cells (NPCs) from IL-1 receptor antagonist transgenic mice were transplanted into Tg2576 mouse model, there was a significant increase in hippocampal cells producing BDNF, microglial proliferation, and alleviation of cognitive decline even one month after the transplantation [125]. This study is the first example for the use of genetically manipulated NSPCs in the treatment of AD, and also shows that usage of anti-inflammatory agents can improve the beneficial effects of NSPCs.

Proteolytic enzyme NEP is one of the most potent Aβ degradation enzyme, shown to be found in low levels in AD brains [126,127]. In order to deliver NEP, murine NSCs that overexpress secreted NEP (sNEP) were generated. Modified NSCs were implanted into 3xTg-AD mice and sNEP expressing NSCs drastically decreased Aβ-induced toxicity, enhanced synaptic connectivity, NSCs survived, and continually produced sNEP after the transplantation [128]. Combining NSC implantation with systemic treatment of Cerebrolysin™ (CBL) — a peptide mixture having neurotrophic-like properties — into hAPP transgenic mice showing defects in neurogenesis, high levels of Aβ production, and behavioral deficits significantly improved NSC survival and increased BDNF levels. However, the exact underlying mechanism for this improvement is not clear [129].

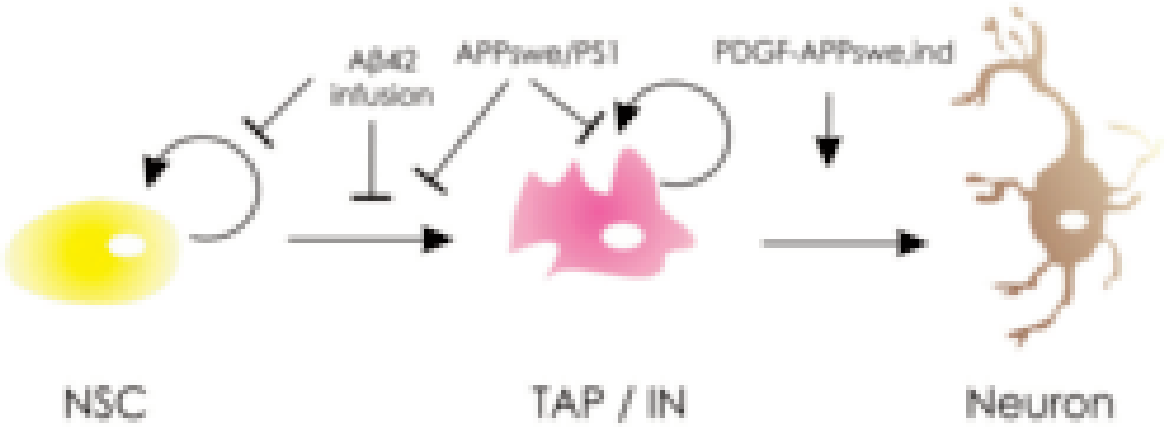
Despite the promising results, some limitations need to be clarified before hNSCs and hNSC cell lines can be used for AD treatment primarily because of the immune rejection [130]. Generation of iPS-derived NSPCs from patients is one possible way to overcome graft rejection. Generation of NSPCs from mouse fibroblasts has been reported using stromal feeder co-culture, lentiviral, or retroviral transduction with neural lineage-specific transcription factors Sox2, Klf4, Myc, Pou3f4, and E47/Tcf3; treatment with retinoic acid, or culturing with the mitogens fibroblast growth factor 2 (FGF2) and EGF2. These methods are able to convert stem cells into all three lineages of the CNS in vitro: neurons, astrocytes, and oligodendrocytes [131-136]. Studies showed restricted graft survival but improved functional recovery following implantation of mouse and/or human-derived iNSCs into an animal model of spinal cord injury without tumor formation, revealing the therapeutic potential of this approach in neurodegenerative diseases [137,138]. Although iPS-derived NSPC transplantations generate a quick response on neurodegenerative disease models, they are invasive methods and the long-term effects are still unknown [139]. Therefore, NSPCs can enable major functional improvements in AD animal models both endogenously and exogenously, nevertheless the exact mechanism remains tentative.

EFFECT OF AMYLOID DEPOSITION ON ENDOGENOUS NSPCS

In the past, many studies conducted on various model organisms of AD suggested that the disease modulates the neurogenesis. However, the results still remain contradictory. A considerable portion of the published literature suggests that AD and amyloid deposition has a negative effect on stem cells [99-104], while opposing findings do exist [140-143] (Figure 1).

According to a group of studies, the proliferation of NSPCs and neurogenesis in general are enhanced in the presence of Aβ peptide. One key study showed increased neurogenesis in the hippocampus of postmortem brains of AD patients. The markers for early neurons (TUC-4 and DCX) were overexpressed in the SGZ as well as the Grandular Zone (GZ) of the hippocampus in AD patients compared to healthy controls [140], suggesting enhanced neurogenesis. Further studies on transgenic platelet-derived growth factor (PDGF)-$APP_{SW,IND}$ mouse model of AD supported the previous findings (Figure 1). They were able to show a significantly increased number of BrdU-immunopositive cells in the SGZ of the DG of 3-month-old, as well as year-old transgenic mice. The same hypothesis stood true also for the number of proliferating stem cells in the SVZ of the year-old, but not 3-month-old mice. The different rate of neurogenesis at the two neurogenic zones of murine brain could be explained by earlier pathology in hippocampus compared to SVZ [141]. Similar results of enhanced neurogenesis were obtained

Figure 1: Effect of Alzheimer's disease on NSPCs.



A simplified sketch showing the effects of Aβ deposition in mouse brain on stem cell proliferation, transient amplifying progenitor proliferation, neuronal differentiation and maturation. Aβ42 through infusion or transgenic APP_{swe}/PS1 suppressed NSPC proliferation, while PDGF-driven $APP_{Swe,Ind}$ increases the differentiation of progenitors to neurons. NSC: neural stem cell; TAP: transiently amplifying cells, IN: immature neuron. See text for details.

from in vitro studies with cultured NSCs from striatum and hippocampus of rat and mouse [142]. The cells were treated with different concentrations of Aβ peptide at different time points. An average of a threefold increase of the number of neurons was observed. However, the increase was noticed to be time-point and dose-dependent. Moreover, the rate of proliferating NSCs in culture was unchanged, thus suggesting that the effect of Aβ is on neurogenic precursors rather than NSCs [144]. These results suggest that Aβ deposition might force the NSPCs to differentiate rather than proliferate, which in the end would deplete the stem cell pool.

An opposing view favors detrimental effects of Aβ peptides on NSPC plasticity. Impaired neurogenesis in the DG and significant reduction in proliferation, survival, and migration of NSPCs in SVZ of adult transgenic mice for mutant APP or in mice infused with Aβ25-35 or Aβ42 in the lateral ventricles were shown [145,146] (Figure 1). The results were consistent with the negative effects of amyloid deposition in NSPCs neurosphere cultures of human embryonic cerebral cortex, possibly due to dysregulated cellular calcium homeostasis [100,109]. Studies on 8- and 9-month-old double transgenic mouse model for APP_{Swe}/PS-1 also suggest defective neurogenesis [147] (Figure 1). However, they did not observe any significant reduction of either NSPCs (MCM2-positive) or neuroblasts (DCX-positive) in an APP_{Swe} knock-in line alone. The reduction of both cell types was slightly higher for PS-1 knock-in and much higher for the double mutant mouse models. This can be explained by the fact that presenilins are expressed in NSPCs and are crucial during both developmental and adult neurogenesis [148-151]. The adverse effect of amyloid deposition was considered long-lasting and persistent up to age 18 months in mice [147]. Interestingly, one study reports a different observation: In this study, the mutant APP is overexpressed exclusively in the mature neurons, thus ensuring the release of Aβ by mature granule neurons into the neurogenic niche. Surprisingly, neither a positive nor a negative effect was seen in terms of adult hippocampal neurogenesis [152]. However, the comparison with previous mouse models is not valid since in former studies, the APP overexpression was driven under NSPCs' specific promoters. This may indicate that the effects of Aβ deposition on stem cell proliferation might not be due to neuronal Aβ accumulation, but at the stem cell level, possibly at an earlier stage of the disease. Alternatively, AD neuropathology in mature neurons could follow distinct molecular programs and etiology compared to the effects of Aβ42 on neurogenic potential. However, not much is known about the effect of amyloid deposition prior to the onset of the disease phenotype. One study reports hampered neurogenesis in a 2-month-old transgenic mouse co-expressing a chimeric mouse-human APP_{swe} and mutant human PS1dE9. These animals were shown to express decreased numbers of proliferating NSPCs in the SVZ, as well as the hippocampus together with a lower number of newborn neurons [153]. This observation might indicate that the decreased neurogenesis itself contributes to the progression of AD. In addition to the neuronal loss, production of neurons into the circuitry by reduced NSPC proliferation could also be an effect on cognitive decline and other pathologies of AD.

In addition to NSPCs and neurons, another cell type that is affected by Aβ pathology is parenchymal astrocytes. These are the cells distributed in the parenchymal mass, and have been shown to bear neurogenic potential under certain circumstances in vitro

[154-158]. Additionally, *in vivo*, these cells can be converted to become neurogenic in various injury and disease conditions [157,159-162]. Therefore, as discussed in the previous sections, these cells can also be potential targets of therapies to bring back neurons and relevant studies are awaited.

ZEBRAFISH AS A MODEL ORGANISM TO STUDY NEURODEGENERATION

In the last two decades, different animal models of AD have been generated with an aim to dissect the pathology, dynamics, and molecular mechanisms of the disease [42,43]. More recently, the iPSC technology complemented the existing vertebrate models and provided the community with an excellent in vitro model to test the key questions directly on AD patient-derived cultures. However, in order to elucidate the regenerative capacities of CNS, such model organisms as zebrafish, salamander, or frog came into play [87]. While anuran amphibians (e.g. Xenopus) lose their ability to regenerate the CNS after the larval stage and the urodele amphibians (salamanders) regenerate only some parts of the brain [87-89], zebrafish keeps this widespread neurogenic and regenerative ability to replenish the lost neurons in the CNS throughout adult life [81,82,163-169]. Moreover, the extensive use of zebrafish for various studies led to a deep understanding of zebrafish genetics and a development of reverse genetic tools.

With the advance of such genome editing tools as TALENs, Zinc-finger nucleases, and CRISPR/Cas9, it became plausible to model a wide spectrum of neurodegenerative diseases in zebrafish. Recently, several studies aimed to understand the molecular pathways underlying the regenerative response in adult zebrafish brain suggest that zebrafish might use "induced molecular programs" to endow its NSPCs with a regenerative ability [163,164,170-173]. Attempts to model neurodegeneration in zebrafish have established tools to examine the pathology [169,174-185]. Nevertheless, most of these studies are performed in embryonic or larval stages of early development or ceased to generate a progressing neurodegeneration model that could be assessed in adult stages. Thus, the programs in zebrafish brain might underlie the disparity between the neurogenic abilities of NSPCs and, in turn, the regenerative capacities of zebrafish brains and mammalian brains. This property of zebrafish brain offers enormous opportunities to understand how vertebrates could efficiently form neurons after neuronal loss (e.g. neurodegeneration), and what we might learn from fish could be applied to humans for imposing a regenerative capacity to mammalian NSPCs, which would be useful for designing regenerative therapies. Thus, the modulation of adult zebrafish NSPCs to produce more neurons to compensate the damaged neuronal cells by AD-like mechanisms might open up new avenues in regenerative medicine. Also, high-throughput drug screening opportunities [186] make zebrafish an excellent model to study the neurodegenerative mechanisms as well as the regenerative potential for future therapeutic purposes in AD patients.

This goal definitely demands currently nonexistent tools for efficient analysis of gene function in adult zebrafish brain. However, although zebrafish brain has a highly conserved phylogenetic similarity to humans in terms of development, neuronal types, and brain structure [187,188], it does not reflect the exact same physiological and neurochemical complexity of the human brain (just as rodent brains do not). Thus, there is a definite need to combine all possible lines of experimental approaches and findings (in zebrafish, mouse, iPSCs, and human) to reach a consolidated molecular understanding of stem cell plasticity upon neurodegenerative conditions. These molecular programs will be extremely useful and informative because they could be the direct clinical targets to turn on in human brains to treat many neurodegenerative diseases, including AD.

CONCLUSION

Neurodegenerative diseases are complex disorders where various cell types are involved in the overall pathology. Regeneration in such diseases, the causes of which are not fully elucidated, may seem a far dream; however, findings in model organisms may herald a promise for advancement toward cellular therapies. The field requires novel approaches and new model organisms to tackle the hurdles of reverting neuronal death, preventing synaptic degeneration, ameliorating cognitive decline, and inducing the plasticity of neural stem/progenitor cells.

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