González CA, J Stem Cell Res Dev Ther 2021, 7: 080
DOI: 10.24966/SRDT-2060/100080

HSOA Journal of
Stem Cells Research, Development & Therapy

Short Review

Introducing New Neurons in the Alzheimer's Disease Brain

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Abstract

Alzheimer's disease is the most prevalent neurodegenerative disorder in the elderly population. The patients suffer cerebral atrophyas a consequence of extensive neuronal loss, especially in areas that play a role in memory and cognition. Cell therapies approaches have emerged as promising treatments to regenerate the brain tissue of the patients. Diverse cellular sources have been tested achieving their successful integration in the host brain, or a "bystander" effect, that reduce the pathology associated abnormalities or the activation of endogenous reparative mechanisms. Recent progress in reprogramming techniques shows that the direct conversion of glial cells into neurons *in vivo* is potentially possible in the near future, offering an interesting alternative to classic cell grafts. Regardless the technique used, the "new members" of the regenerated tissue must integrate in the pre-existing neuronal networks and survive in the toxic environment of the Alzheimer's disease brain. This is critical to achieve a long-lasting reversion of the clinical sings in the patients.

Keywords: Alzheimer's disease; Cell therapy; *In situ* reprogramming; Toxic protein aggregates

Alzheimer's Disease

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder highly prevalent in the advanced age population. The typical abnormalities observed in the brain of patients include a progressive cerebral atrophy, extensive neuronal loss (especially in areas implicated in memory and cognition), synaptic alterations, neuroinflammation and the presence of intra- and extracellular protein aggregates in the form of neurofibrillary tangles and senile plaques, respectively [1]. The affected individuals experiment a gradual cognitive decline, psychiatric symptoms and problems performing activities of daily living. The disease progresses from mild symptoms of memory loss to severe dementia [2,3]. The exact cause of AD is still a matter of debate. The "amyloid cascade hypothesis" holds the idea that its genesis is triggered by accumulation of the Amyloid Beta (Aβ) peptides in the brain, as a consequence of an imbalance between the secretion and clearance of this natural product of metabolis [4]. Nowadays, there is no effective therapy to treat this devastating illness since the current drugs are just palliative [5,6]. This is a very worrisome fact considering the quick aging of the word population. Another important problem is the lack of an early diagnosis method. The clinical signs associated to disease appear when the damage in the brain is already extensive. For this reason, the need to incorporate new neurons to replace the lost ones arises. To achieve this goal several strategies have been tested including the use of diverse cell types and the direct reprogramming of glial cells into neurons.

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Citation: González CA (2021) Introducing New Neurons in the Alzheimer's Disease Brain. J Stem Cell Res Dev Ther 7: 080.

Received: August 27, 2021; **Accepted:** September 07, 2021; **Published:** September 14, 2021

Cell Therapies

The neurons are postmitotic non-dividing cells that live many decades. Because the brain lack the capability to regenerate neurons lost because age or disease, cell therapies are appealing approaches to overcome this problem in AD treatment context. Several cell types have been tested including fetal neural stem cells, embryonic stem cell-derived neural stem cells, Mesenchymal Stem Cells (MSCs) and induced Pluripotent Stem Cells (iPSCs). Among all this alternatives, the MSCs and the iPSCs are the most promising options [7,8].

MSCs

MSCs of diverse origin have been tested in several preclinical studies. They are relatively simple to obtain, have little immunogenicity and form no tumors [9]. The graft of this cells has a positive effect in diverse AD associated abnormalities promoting the functional recovery as a consequence of a by-stander effect rather than a cell replacement phenomenon [9,10]. The graft of bone marrow MSCs in double transgenic AD mice (APP/PSN1 mice) reduces the levels of pro-inflammatory cytokines and Aβ-42 peptide [11]. In another study using a transgenic AD mice, Yokokawa and colleagues [12] reported that the transplantation of MSCs not only reduce neuroinflammation and Aβ-42 peptide levels but also Aβ plaque number in cortex and hippocampus. Additionally, in the same work, the authors show a reduction in oxidative stress, improvement of spatial memory and also evidence that soluble factors produced by MSCs improve the Aβ clearance by microglia. In another work, MSCs injected in the lateral ventricle in APP/PSN1 mice did not reduce the Aβ burden and neuronal cell loss but improved the cognitive impairment in the grafted transgenic animals which may be a consequence of an increased number of synapses in the grafted animals [13]. The same authors also found in these animals a decreased astrogliosis and microglial activation. Interesting, the aberrant activation of microglia in AD play a role in synapsis loss in AD [14]. Additionally, Nakano and co-workers [13] provide evidence that suggest that the reduction of neuroinflammation is provoked by the suppression of NF-kβ expression by the transference of miR-146a from the MSCs into astrocytes [13].

The genetic manipulation of MSCs before the graft procedure is an interesting possibility to over-express soluble factors in the grafted cells. The signaling molecules wnt3a and CXCL1 have been over expressed in MSCs using adenoviruses before their inoculation in a

double transgenic APP/PS1 mice [15]. These authors show, using this experimental strategy, a reduction of neuroinflammation and a significant alleviation of cognitive impairment in the grafted animals. They show evidence that this phenomenon is due to a better synaptic integrity and increased hippocampal neurogenesis reflected by the high number of proliferating $Sox2^{+}$/$Ki67^{+}$ neuronal precursors and DCX^{+} neuroblasts [15]. This strategy shows that the cells used in the cell therapy approach can become a source of secreted factors that may reduce disease associated abnormalities and/or promote endogenous reparative mechanisms in the receptor patients.

iPSCs

The iPSCs were first created by viral transduction of somatic cells (skin fibroblasts) with a set of transcription factors expressed in pluripotent cells [16,17]. Like Embryonic Stem Cells (ESCs), iPSCs have the ability to generate any cell type of the body including neuronal precursors [18]. Working with iPSCs not only avoid the ethical issues associated with fetal tissue or embryonic stem cells, but also have the advantage that can be generated from somatic cells of the same patient avoiding the immunological rejection upon their transplantation. The potential of these cells has been tested using neuronal precursors derived from human iPSCs (hiPSC-NPs) grafted in the lateral ventricle of neonatal mice. The transplanted cells are able to survive and migrate extensively in the mouse brain including cortex and hippocampus. Most of the cells differentiate in excitatory neurons [19]. The same authors show morphological evidence that the human neurons form synapsis with the host cells suggesting their functional integration. This evidence highlights the potential of hiPSC-NPs to be considered in cell therapies strategies. Real and coworkers [20] show additional data in experiments wherein hiPSC-NPs were inoculated in adult mouse somatosensory cortex. Besides the survival and differentiation of the grafted human cells in neurons and glia, these authors show a long-distance projection of human axons and electrophysiological data that demonstrate functional synapses between human and mouse neurons.

It has been reported that iPSC-derived neurons hold a promise to treat neurodegenerative disorders. Dopaminergic neurons derived from iPSCs have been tested in rodent and primate models of Parkinson disease. The grafted animals show better dopamine levels and an improvement of neurological deficits associated to this pathology [21]. In a rat model of Huntington disease, intracerebral transplantation of hiPSC-NPs recover behavioral defects at least in part as a result of restauration of the neuron density [22]. The transplantation of iPSCs in the brain of a transgenic mice with five familial AD mutations (5XFAD) ameliorate the AD associated pathology [23]. Besides the reduction of cognitive deficits, these authors found that the iPSC treated 5XFAD animals show a reduced plaque number, lower levels of Aβ40 and Aβ42 and a reduction of β- and γ- secretase activities. On the other hand, the transplantation did not reduce the neuronal loss. It is interesting to mention that in this work the iPSCs were produced with a novel method: treating mouse fibroblasts with an embryonic stem cell protein extract. Upon transplantation, these cells were able to differentiate in glial cells and not in neurons suggesting that the iPSCs used in this study have a positive bystander effect on the AD pathology rather than a cell replacement phenomenon [23]. The transplantation of hiPSC-NPs in the hippocampus of a double transgenic mouse carrying two mutations in the APP precursor protein associated to familial cases of AD restored the spatial memory deficits in the animals [24]. These authors found that the grafted human cells differentiated in cholinergic and GABAergic neurons. They suggest that the recovery of the grafted animals is a combination of a cell replacement phenomenon and a bystander effect by the human cells that stimulate the differentiation of endogenous mouse neuronal precursor in cholinergic neurons [24]. Armijo and co-workers [25], in a very recent work, grafted neuronal precursors generated from mouse iPSCs in the hippocampus of a transgenic AD mouse model carrying three mutations associated to familial AD (3XTg-AD). The grafted cells differentiate into neurons and glia. Importantly, the treated transgenic animals show, and improved learning and memory as assessed by the object location task and Barnes maze tests. This research group show evidence that this phenomenon was a consequence of the amelioration of several aspects linked to AD pathology including improved brain activity and synaptic plasticity, reduction of neuroinflammation, reduction of Aβ plaques, reduction of insoluble Aβ protein and a decreased phosphorylated tau protein level. By the other side, this work does not show strong evidence that all these beneficial effects are a consequence of the integration of transplanted cells. They claimed that the most likely mechanism involved is an indirect or "bystander" effect [25].

In situ reprogramming

Besides conversion of somatic cells into a pluripotent state as described by Yamanaka's group [16,17] differentiated somatic cells can be converted directly into another differentiated phenotypesuch as cardiomyocytes, hepatocytes, endothelial cells and neurons [26,27]. Neurons have been generated *in vitro* and *in vivo* from fibroblasts and glial cells using specific transcription factors, microRNAs and small molecules [28,29]. The forced expression of three transcriptions factors, Ascl1, Brn2 and Myt1l (ABM) in mouse fibroblasts using lentiviral vectors, convert these cells into neurons able to generate action potentials and functional synapses [30]. Human astrocytes expressing the same transcription factors under the control of doxycycline promoter were transplanted in the striatum and hippocampus of adult rats. After the administration of doxycycline in the drinking water, the grafted cells differentiated into neurons [31]. Additionally, lentiviral vectors carrying the cDNA for ABM were injected in the striatum of GFAP-Cre transgenic mice that allow the expression of the transgene only in Cre-expressing cells. This experiment show that is possible to convert resident GFAP-expressing astrocytes in Neu-N+ neurons [31]. Niu and co-workers [32] provide additional evidence of this phenomenon. Using a lentiviral expression system and just a single transcription factor, SOX2, they achieve the conversion of mature astrocytes of the mouse striatum in proliferating neuroblasts. The co-expression of SOX2 with BDNF and noggin or the expression of SOX2 plus the treatment of the animals with valproic acid, a histone deacetylase inhibitor, promote the differentiation of the induced neuroblasts into functional neurons integrated in the host brain [32]the process by which this reprogramming occurs is unclear. Here, we show that a distinct cellular sequence is involved in SOX2-driven in situ conversion of adult astrocytes to neurons. This includes ASCL1(+. These works provide evidence that the direct neuronal conversion of somatic cells *in vivo* is possible and highlight the potential of direct conversion of resident glial cells into neurons as a neuronal replacement strategy to treat neurodegenerative disorders like AD [29,33]. In an AD model, induced by intracerebral injection of streptozotocin, the inoculation in the hippocampus of lentiviral particles expressing the MicroRNA-302/367 plus the i.p. administration of valproic acid induced the conversion of reactive astrocytes into NeuN+ functional neurons [34]. In a very interesting work, Guo and colleagues [35] show the conversion of reactive glial cells into

functional neurons *in vivo* in a model of AD. In this work, the authors generated neurons from reactive astrocytes using a retroviral vector to express a single neural transcription factor, NeuroD1, under the control of GFAP promoter. The rationale behind the use of this type of vector is because retroviruses infect only proliferating cells and not dividing cells such as neurons. The AD model they used was a transgenic mice 5XFAD that have many cortical reactive astrocytes. The injection of GFAP::NeuroD1-GFP viral vector in the cortex of the transgenic animals induce the generation of NeuN+ neurons from resident reactive astrocytes. Electrophysiology tests demonstrated that these neurons are functional and integrated in the brain [35]. It is important to highlight that reactive astrogliosis is a hallmark of AD pathology and is associated with brain damaged areas [1]. The conversion of reactive astrocytes into neurons aloud the generation of new neurons just in the areas where they are needed.

It has been reported that the direct conversion of one phenotype into another is possible using small molecules. Mouse fibroblasts can be converted in functional neurons *in vitro* using a cocktail of small molecules [36]. A recent work, using genetically modified mice that aloud to follow astrocyte fate over the time, show convincing evidence that the astrocytes can be converted into functional neurons integrated in brain circuitry using a combination of small molecules applied with a mini-osmotic pump [37]. Overall, the conversion of glial cells into neurons by genetic or chemical methods have the potential to re-stablish the brain neuronal population when the clinical sings of the disease became evident, holding a promise to treat AD, a neurodegenerative disorder with an increasing prevalence in the world population.

The New Neurons Must Survive in A "Toxic" Environment

The grafted or reprogrammed cells must face a diseased environment in the brain of the patients. In this scenario, those cells became exposed to neurotoxic protein aggregates. These structures are generated from Aβ peptides and hyperphosphorylated tau proteins that undergo a conformational change from a native and functional conformation, that is water-soluble and rich in α-helix domains, to a hydrophobic pathological β-sheet enriched conformation, that have a high tendency to aggregate. This misfolded conformation is acquired spontaneously and can be transmitted from one misfolded molecule to a native one. This template recruitment of additional native proteins generate protein aggregates of diverse size, from small oligomers to large amyloid fibers [38]. During this phenomenon, the native protein loss its normal physiological function and gain a toxic role that triggers neurodegeneration. The intervening mechanisms in this protein toxicity are still a matter of debate [39].

It has been proposed that the pathogenic aggregation of proteins can be transmitted from one cell to another, leading to the spreading of neurodegenerative process through the brain [38,39]. The first evidence that this phenomenon may be possibly came from the post-mortem analysis of brains of patients with Parkinson's disease that were grafted with human fetal mesencephalic dopaminergic neurons in the putamen and caudate nucleus. The grafted neurons display Lewy bodies and Lewy neurites, intracellular amyloid structures composed by aggregated α-synuclein, a protein that play a central role in the pathogenesis of this disease [40]. Additional evidence is provided by a work wherein cultured cells and grafted neurons in mouse brain capture exogenous α-synuclein aggregates [41] and that this phenomenon can induce the misfolding and aggregation ("seeding" effect) of the endogenous protein [42]. Espuny-Camacho and colleagues, in a very interesting work, grafted human neuronal precursors, derived from human embryonic stem cells, in a transgenic mouse model of AD that display Aβ deposition and neuroinflammation. The grafted cells differentiated into neurons that survive and integrate in the host, but later on suffer neurodegeneration and death [43]. Before this event, the human neurons show AD associated abnormalities only when they are grafted in transgenic mice and not in wild type animals. Among these alterations they found dystrophic neurites with abnormal accumulation of presynaptic proteins in close association with Aβ plaques, immunoreactivity to specific antibodies that recognize hyperphosphorylated tau protein and transcriptional changes found in human patients [43]. The question that arises is: is it really worth the introduction of new neurons in the brain of patients if they will die over the time anyway? There are some potential strategies that may confer to the new neurons a more resistant "phenotype" and/or convert them into a source of protective molecules. This is discussed in the next section.

How to Survive in the Diseased Brain?

Monolayer neuronal cultures produced from human iPSCs derived from sporadic or familial cases of AD display AD associated abnormalities such as higher levels of Aβ peptide and phosphorylated tau (p-tau), endoplasmic reticulum and oxidative stress, down regulation of synaptic proteins and increased apoptosis [44-49]. These findings reveal that neurons derived from AD-specific iPSCs can reproduce AD traits spontaneously *in vitro*. Furthermore, the neurons differentiated from iPSCs produced from somatic cells obtained from familial cases of AD are more vulnerable when they are exposed to Aβ aggregates *in vitro* [50].

In the case of evaluation of performing a graft of hiPSC-NPs in a patient with a familial form of AD, which have an earlier onset and a more aggressive clinical outcome, there is a higher need that the grafted cells survive longer time. One exciting possible solution of this problem is the use of gene edition tools such as CRISPR/Cas9 [51]. This technique has been used in iPSCs with mutations associated to familial cases of AD to create isogenic cell lines without the mutations. Remarkably, neurons differentiated from cells with the edited genome lack the AD pathological phenotype [51]. It looks that the graft of hiPSC-NPs with the corrected mutations will increase their survival chance considering that these cells develop spontaneously a diseased phenotype that is more susceptible to suffer the toxic effect of protein aggregates. But the evidence presented by Espuny-Camacho and colleagues [43] suggests that the genome edition is not enough to confer full protection because human cells with normal genotype get AD related alterations after grafting them in the brain of AD Tg mice probably because a seeding mechanism as described before. So, the question is: how the grafted cells can avoid the seeding from diseased cells in the AD brain?

Considering that the protein aggregates, conformed by misfolded Aβ and tau proteins in the case of AD, are toxic to neurons, a strategy to interfere with the aggregation process seem plausible to fight against the cell-to-cell propagation of the disease. Short synthetic peptides know as β-Sheet Breakers (BSBs) prevent the aggregation of Aβ protein *in vitro* and inhibit the amyloidogenesis *in vivo* in a rat model of Aβ deposition [52]. After this first pioneering work, improved BSBs has been created with higher efficiency and increased solubility and stability [53]. Interesting, some specific Aβ-derived synthetic peptides not only inhibit Aβ aggregation but also tau aggregation as well [54] having the potential to prevent the spreading of Aβ and tau

pathology over the brain. The genetic manipulation of hiPSC-NPs in order they express anti-aggregation peptides is an appealing option. Using this strategy, the grafted cell may become a source of proteins that will protect themselves and the neighboring cells from the toxic effect of protein aggregates.

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