INTRODUCTION

Alzheimer’s disease (AD) is a debilitating neuropsychiatric disorder characterized by the multifaceted decline in cognitive and behavioral functions. Since its discovery by Dr. Alois Alzheimer in 1906, AD has become the most common neurodegenerative form of dementia that is responsible for 50 to 70% of all dementia cases worldwide. Over decades of research, many hypotheses on the etiology of AD have been proposed. Early models focused on the functional decline of specific neuronal systems (e.g., cholinergic and GABAergic neurons) in the prefrontal lobe and hippocampus. Today, an established hallmark neuropathologic feature of AD is neuronal death caused by plaques of extracellular amyloid-β (Aβ) peptides and intracellular neurofibrillary tangles (NFTs) of abnormally hyperphosphorylated tau proteins. In the past two and half decades, the amyloid cascade hypothesis has received the most support in the field of AD research. But after years of clinical examination, existing hypotheses and pharmacological treatments fail to capture the whole picture behind AD.7 With increasing human longevity and growth of the older populations in the society, AD without cure remains as one of the greatest obstacles in modern medicine. Novel stem cell techniques that target neurogenesis hold potential for treating AD patients. This review will discuss the characteristics of AD, current progress in stem cell therapy and remaining challenges and promises in its development.

AD PATHOGENESIS AND CURRENT TREATMENTS

The two key biochemical features of AD are 1) extracellular Aβ plaques and 2) intracellular NFTs. The formation of Aβ plaques are a consequence of misguided production of the amyloid peptide. In unaffected individuals, amyloid precursor protein (APP) is cleaved by α-secretase or β-secretase to yield soluble sAPPα or sAPPβ peptides, both of which promote neural survival and growth. In AD, another pathway occurs where APP is sequentially cut by β-secretase and γ-secretase to produce insoluble Aβ peptides. These aberrant proteins are rich in β-sheets in contrast to α-helices as in healthy amyloid peptides. Aβ travels through the bloodstream to stimulate additional production of Aβ in other cells and its neurotoxicity causes death of neurons widely across the cen-
Intracellular NFTs, on the other hand, are formed by atypical hyperphosphorylation of the tau protein, a microtubule-associated protein (MAP) that supports other cytoskeletal structures and regulates various functions in neurons. Hyperphosphorylation of intracellular tau is caused by atypical hyperactivation of protein kinases (e.g., PKC and PKA) and leads to cellular apoptosis and neuronal loss. The amyloid cascade hypothesis puts Aβ formation at the pathologic center of AD progression.

Based on available biochemical and genetic data, physicians generally categorize AD into two types: early-onset or familial AD (FAD) and late-onset or sporadic AD (SAD). FAD is a rare form of AD that affects patients under the age of 65. Three genes involved in the production of Aβ—amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2)—have been strongly implicated in this type of AD. Mutations or overexpression of PS1 (chromosome 14) or PS2 (chromosome 1), which comprise the γ-secretase complex, or APP (chromosome 21) have led to widespread neurodegeneration in AD patients. SAD in contrast occurs in older individuals and accounts for almost 90% of AD instances. Apolipoprotein E (APOE), triggering receptor expressed on myeloid cells 2 (TREM2) and CD33 that are related to tau modification and microglial phagocytosis of Aβ, are the most significantly associated genes to SAD as discovered in genome-wide association studies (GWAS).

In addition to such biochemical changes in the brain, dysfunctions in the metabolism and processing of biomolecules including protein, cholesterol and glucose are also commonly observed in AD patients. Proteostasis failure such as the breakdown of the ubiquitin-proteasome pathway triggers uncontrolled cell death and higher formation of NFTs. Inability to process gangliosides aggravates the conversion of non-toxic APP precursors to insoluble, toxic Aβ. Furthermore, disrupted glucose metabolism has been shown to cause aberrant synthesis and modification of tau proteins. Metabolic dysfunctions lead to increased levels of cytokines and reactive oxygen species (ROS) and produce deteriorating chronic neuroinflammation in patients with AD.

Despite the long years of research and therapeutic trials in AD, an effective treatment is yet to be developed. Current FDA-approved treatments can temporarily delay the progression of AD by inhibiting neuronal death related proteins and restoring the functions of cholinergic neuronal systems. But even cocktail treatments present insufficient efficacies to handle the rising number AD patients in the older populations. Pharmaceutical companies around the world shared efforts to develop novel treatment regimes that use passive anti-amyloid immunotherapy or Aβ-targeted protein chaperones and they are currently under clinical trial phases. However, a growing consensus in the field is that current pharmaceuticals are introduced too late in the progression of AD and that new treatments should target earlier stages in the progression of the disease before widespread neurodegeneration and overt dementia occur. Stem cell therapy, with its capacity to generate various types of neurons and glial cells, has lately received considerable attention as a potential therapeutic option for reversing neuronal loss in AD, and studies using animal models show promising results. Although long-term investigations are necessary to comprehend its safety and efficacy before human clinical trials, stem cell based therapy holds potential as a next generation treatment for AD.

STEM CELL THERAPY FOR AD

Treatment of AD with stem cell technology depends on the neurogenesis capacities of stem cells. The strategy is to utilize stem cells to physically replace the neurons that are lost in the neurodegenerative stages in AD. In recent findings, the importance of glial cells and intercellular binding proteins in shaping the external environments of neurons have been suggested. The decline of microglia, astrocytes and oligodendrocytes that support the neuronal networks in the CNS through immune, nutritional and homeostatic mechanisms are correlated with the neuroinflammatory biochemistry of AD. Additionally, the deterioration of central binding proteins between neurons such as Slitrk and LAR-RPTP contributes to the widespread neuronal loss. Through transplantation or in situ regeneration of lost neurons and key proteins that support them, there is hope to rebuild the integrity of the CNS and to alleviate the decline in cognitive functions in AD patients. The four types of stem cells that can be generated from the human body—neural stem cells (NSCs), mesenchymal stem cells (MSCs), embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs)—each holds unique properties that could be utilized in the stem cell therapy regime in a variety of ways (Figure 1). NSCs

Found in small amounts in the mammalian brain, NSCs are multipotent stem cells that can be differentiated into all types of cells found in the CNS. The self-renewal and differentiation potentials of NSCs have been established both in vitro and in vivo. Although limited in their differentiation capacities compared to ESCs and iPSCs, NSCs are the ideal candidates for replacing neurons in the human brain due to their relatively low risks in tumorigenesis and immunogenicity. Potential treatment methods with NSCs involve the induced differentiation of neurons or glial cells through the exposure of specific morphogens followed by overexpression of...
the healthy cells in patients. In rodent models, the overexpression of NSC-derived cholinergic neurons and choline acetyltransferase (ChAT) restored cognitive performance and synaptic integrity. A limitation of this type of stem cells, however, is their small number in human brain tissue. If their proliferation could be induced and controlled through growth factor exposure, genetic or epigenetic manipulations, NSCs could be developed into an effective addition to current AD treatments.

**MSCs**

MSCs are another multipotent line of stem cells found in the human body (Lanza and Atala, 2014). They generate diverse cell types at the bone marrow, lungs, umbilical cord, blood, adipose tissue and muscle tissue. Given their greater availability compared to NSCs, MSCs may be a promising source for therapeutic stem cell treatments. But a drawback is that they can only give rise to a limited number of lineages and display limited survival and short half-lives post-transplantation, particularly depending on the donor cell population and harvest and culture locations. In rodent studies, bone marrow MSCs (BMSCs) and umbilical cord blood MSCs (UCB-MSCs) could be used to generate cholinergic neurons. Treatment using MSCs in mice also contributed to the clearance of abnormal Aβ plaques via microglial activation, prevented neuronal death and increased neuronal differentiation. In addition, MSCs safely restored cognitive functions such as memory in rodent analyses. MSCs have been shown to further play roles in activating proinflammatory cytokines that are beneficial to the recovery of damaged neuronal environments. Identifying morphogens in differentiating MSCs to a larger range of neural cells would be key in developing MSCs as effective therapeutic treatments.

**ESCs**

Extracted from the inner cell mass (ICM) of blastocysts, ESCs are pluripotent stem cells that innately give rise to all cell types in the development of an embryo. Given their potential differentiation capacities, direct transplantation of ESCs has high risks of teratoma formation and thus strict control and maintenance of stability in differentiation are main areas for improvement with ESC techniques. Several rodent studies suggest that ESC-derived NSCs can be safely transplanted without tumorigenesis, but further research is needed to confirm these results. Moreover, unlike NSCs and MSCs, ESCs carry the added risk of transplantation rejection and immune responses. Although the brain is immune-privileged, the human leukocyte antigen (HLA) profile of donor cells must be considered in transplantation to avoid immune rejection. Experimentation with human ESCs (hESCs) have so far have been able to successfully produce dopaminergic neurons, spinal motor neurons and astroglial cells.

![Figure 1. Schematic diagram showing the potential applications of stem cell therapy in Alzheimer's disease.](image-url)
stem with hESCs in FDA-approved clinical trials, however, is ethically controversial and must be approached more carefully than other types of stem cells.39,99

iPSCs

iPSCs are an intriguing line of stem cells that are reprogrammed from adult fibroblasts.80 In iPSC technology, new stem cells that possess pluripotency comparable to that of hESCs are created through the overexpression of four transcription factors (TFs)—Oct3/4, Sox2, Klf4 and c-Myc.81 In 2006, Professor Shinya Yamanaka’s research team generated the first iPSCs through retrovirus induced overexpression of these four TFs, but this initial formula exhibited low success rates.82 So far, novel methods such as inducing serum starvation and aligning cell cycle rhythms or inducing gene expression through plasmids and adenoviruses have significantly improved the reprogramming techniques.83-85 Screening methods for successful reprogramming such as tetraploid complementation have also been developed.86,87 Early iPSC protocols solely relied on the complete reprogramming of somatic cells to pluripotent stem cells, but recently developed methods also capture somatic intermediates and transdifferentiate them into induced neural precursor colonies (iNPCs), which are similar in their differentiation potential to NSCs.88 In regards to immune reactions, research with iPSCs have shown inconsistent results. Some rodent studies found little or no immune recognition against transplanted iPSCs while others found major histocompatibility complex (MHC) incompatibility of donor and acceptor to elicit immune rejection reactions.22,69,89

The unresolved question of immunogenicity with iPSCs must be unraveled before any clinical trials can be started.

Challenges and promises

Despite the excitement for cell replacement therapy for AD, several challenges remain in its development. An overarching issue in all stem cell based treatments is donor-to-donor variation. Data from transplantation experiments strongly indicate the importance of considering genetic and epigenetic backgrounds of donor cells. In generating neurons and glial cells for transplantation, the genetic defects that cause biochemical symptoms of AD (e.g., APP, PS1, and PS2 in SAD) must be corrected in the donor cells.90 This could be achieved by DNA editing with molecular scissors such as CRISPR. Epigenetic memory of donor cells was shown to affect gene expression and cellular stability following transplantation and reprogramming, posing unexpected risks for tumorigenesis.91,92 Selecting for purity of donor cells in some studies could reduce heterogeneity and improve functional integrity in the iPSC products.93 For this purpose, genome-wide reference maps on epigenetic prints such as DNA methylation are under development.94 Another question in stem cell treatment is determining the target for transplantation. Given the widespread neurodegeneration throughout the CNS in AD, it is difficult to determine the ideal location for introducing the new population of neurons while minimizing stability and rejection risks. The hippocampus and lateral ventricles which are known to contain NSCs in the human brain are possible candidates.95 Additional setbacks pertaining to ESCs and iPSCs are possibilities of transplantation rejection tumor development. In iPSC research, in vivo or in situ reprogramming have been proposed as solutions.96 By reprogramming cells within their endogenous locations, immune responses and risk factors introduced in the in vitro processes could altogether be avoided.

Stem cell technology could also be utilized to model AD to further extend our understanding of the complex disease and to identify potential pharmaceutical agents. Through GWAS and meta-analysis studies, some risk factors and gene candidates in the pathogenesis of AD have been discovered.97,98 But given the multifaceted nature of neurodegenerative disorders and the lack of effective pharmaceuticals, our knowledge on AD progression appears to be inadequate. The amyloid cascade hypothesis is currently the most dominant theory on AD pathophysiology, but certain cases of AD patients without Aβ deposition suggest the possibility of a AD mechanism not related to Aβ such as the suspected non-amyloid (or Alzheimer’s disease) pathophysiology (SNAP).99 Operating on cultured populations from stem cells could be useful in identifying defects responsible for Aβ and NFTs that current medications fail to target as well as examine the possibility of other modes of pathogenesis.100 Cultured neurons from patients’ stem cells could also be implemented in screening for drug efficacies and the development of personalized treatment.

CONCLUDING REMARKS

Stem cell therapy is an expanding area of research that holds vast potential for treating a variety of illnesses such as neurodegenerative disorders. Up to date, stem cell technology is only at its developmental stages but rapid developments and advances indicate its potential uses in direct as well as indirect treatments of AD. Combined with the knowledge from past decades of research on AD, stem cell therapy is a prospective next generation treatment for AD.

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