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STEM CELL THERAPY AND NEUROGENESIS: A THERAPEUTIC VIABILITY IN ALZHEIMER'S DISEASE

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ABSTRACT

Neurodegenerative diseases result from a temporally discrete insult (stroke, trauma), aggregation of proteins, aging and any untoward injury leading to loss of a particular neuronal subtype or generalized loss of neuronal populations. Alzheimer's disease (AD) is a chronic, intricate, irreversible, dynamic neurodegenerative sickness which affects 5–7% of older adults globally, the number of AD cases currently estimated at 36 million and will triple by 2050. Currently, however, there is no cure for this condition as the approved and actively marketed drugs for AD, including cholinesterase inhibitors and N-Methyl-D-Aspartate antagonists, effectively improve daily functions to a certain degree, bur are not capable of modifying disease progression. AD has progressive loss of neurons and their synaptic connections, ultimately leading to a severe impairment of cognitive functions, dementia and neuropsychiatric abnormalities. The revival of lost cells and regenerative therapy thus could be a promising approach as the regeneration of lost cellular functions may reverse functional decline to an extent that raises the patient's survival rate and physiological functions. Stem cells hold immense potential to regenerate damaged tissues and may benefit the AD brain by modulating inflammation, stimulating re-myelination and supplying trophic support.

KEY WORDS

Alzheimer's disease, cognition, neurogenesis, stem cells

1. INTRODUCTION

Neurodegenerative disorders (NDD) involve brain atrophy, abnormal deposition of proteins and progressive decline in neuronal functions ultimately leading to cell death. The prevalence, complications and socioeconomic implications of these disorders are increasing with an aging population. [1]

Although there are immense efforts for the development of therapies for NDD yet, effective therapeutic agents are still not available as NDD involves (i) multiple cellular and molecular mechanisms, involved in the etiology of these diseases and the cause of neuronal death remains obscure (ii) no single molecular pathway has been shown to modulate disease progression (iii) for these disorders early diagnosis is impeded due to the absence of efficient biomarkers (iv) NDD often involves secondary effects such as neuropsychiatric changes, gliosis, neuronflammation etc. requiring adjustment of treatment and also (v) Drugs administered into the central nervous system should be able to cross the brain blood barrier and able to target specific cell types and regions.[1]

There has been an unparallel development during the last 2-3 decades in small molecules and biologics such as insulin, growth factors, antibodies, promoters and inhibitors of various metabolic pathways to modify the disease process. Currently stem cells including other types of therapeutic cells are sitting on the cusp of another revolution, emerging as the 3rd pillar of human

medicine [2] and emerging as an alternative treatment strategy. [3]

Stem cells are unspecialized basic cells in the body which perform special functions including self-renewal and can undergo indefinite cell cycles whilst maintaining the undifferentiated state. They have the potency and ability to differentiate into various specialized cell types and hence can be used in medical treatments of various conditions. Stem cell-based therapy takes advantage of multiple types of stem cells to modify disease pathophysiology, support neurons and non-neuronal cells, or directly replace cells. [3] Stem cell-based therapeutics hold a potential as NDD are characterized by gross loss of neurons, synapse, loss of tropical support and inflammation and loss of particular cell type.

2. STEM CELL THERAPY: STRATEGY

Stem cells are to be regarded as potential target as they all depict three unique but basic characteristic features that make them special for their use in therapeutics such as proliferation (divide rapidly), self-renewal (immortal) and differentiation to different cell types (pluripotent). There has been a significant progress to harness these potentials of stem cells so that they could be used potentially and effectively in human therapeutics. Generally there are two broad categories of stem cells (i) pluripotent stem cells (embryonic and induced pluripotent stem cells) that are derived from embryos or by changing fate of the somatic cells and (ii) adult stem cells that are derived from adult tissues and are by and large multi-potent.

Both types of stem cells are progressing towards human therapeutics but adult stem cells have an edge over embryonic stem cells because of ethical and safety concerns with the latter. Another added advantage of adult stem cells is that since these can be derived from the same patient thus once transplanted back are less likely to be rejected because they will be autologous. The pluripotent stem cells will remain the analogous source of cells and will be likely to be rejected if transplanted. But since they are pluripotent, virtually every single cell in our body can be generated from them as supposed to in adult stem cells where they have restricted differentiation profiles. In literature a balance approach is being used for both kinds of stem cells in developing human therapeutics.[2] The stem cells have potential to cure rather treat human diseases particularly those that are characterized by loss of single cell type in the body as evidenced in NDD. [4]

There are two stem cell therapy strategies: cellular replacement and neuroprotection. Replacement of cells is grafting into a particular damaged neuronal subtype and transplanted cells may be integrated into host tissue, making synapses reconstitute neural networks like the original structure. Neuroprotection is to support residual neurons and that involves neuroprotective mechanism of stem cells, including their potent anti-inflammatory capacity, direct release of antiapoptotic and neurotrophic factors, and the ability to induce the proliferation of local neural progenitor cells. [5, 6]

The cell-based therapy has focus mostly on cellular replacement; however, because of problems associated with differentiation, the establishment of an appropriate neural network, and subsequent formation of a functional network, this approach has a limited effectiveness. Thus, neuroprotection has been indicated as a more practical application both in pre-clinical and clinical settings. [7] The replacement therapy may be appropriate for diseases where a particular neuronal subpopulation is damaged while neuroprotection using stem cells is preferred where support to remaining or viable neurons is required. [3]

3. STEM CELL TYPES

Stem cells are cells, capable of self-renewal and possess the ability to differentiate into multiple types of cells. On the basis of their differentiation abilities, stem cells can be classified as totipotnet, pluripotent or multipotent. Totipotent stem cells are capable of differentiating into any type of cell within the body, including extra-embryonic tissue, and can be isolated from only the four-cell stage of the embryo. Pluripotent stem cells are isolated from the blastocyst of the embryon, are capable of differentiation into any cell within the body, and are able to give rise to cells from any of the three major tissue lineages: ectoderm, mesoderm, and endoderm. Multipotent stem cells are capable of differentiation into only the select types of cells from which they are derived and can be isolated from various sources within the adult human body. As the human body develops, the margin of differentiation capability begins to be reduced from a totipotent state to a pluripotent state and lastly to a multipotent capability. [8]

Stem cells are further classified as embryonic stem cells (ESC), induced pluripotent stem cells (iPSC), adult stem cells (mesenchymal stem cells (MSCs) and neural progenitor cells (NPCs).

3.1 Embryonic Stem Cells (ESCs)

ESCs were first characterized in 1998 from the inner mass of the blastocyst. [9] If their pluripotency could be accurately controlled into the desired neural phenotypes, no other alternative cells would replace them as a better cell source for cell replacement strategies. In vitro attempts to differentiate ESCs into several specific neural cell types have been successful, including dopaminergic neurons. [10] Despite the ongoing preclinical studies, there are a number of issues that remain with the current technologies, including tumor formation, phenotype instability and low survival rate of transplanted cells.[11] Furthermore, there are ethical and immunogenic limitations that may preclude the clinical usage of ESCs. In fact, given the ethical policies and regulation, there are few clinical trials that have involved ESCs. [12]

3.2 Induced Pluripotent Stem Cells (iPSCs): iPSCs were first developed from mouse fibroblasts in 2006. These cells are reprogrammed into a state of pluripotency that is similar to that of ESCs. iPSCs are thought to be able to differentiate into a variety of cells, including neurons and neurospheres [13] and some neuronal subtypes can be generated and automated using iPSCs.[14] Despite many promising evidences, however, the following unresolved issues regarding iPSC usage constitute big hurdles to its clinical application that include teratoma formation, long term safety and efficacy, tumorigenicity, immunogenicity, patient-derived genetic defects and optimal reprogramming.[15] Unfortunately, prior studies have found that human iPSC lines have only a 10–50% differentiation potential for neurons, as compared to ESCs, which have a nearly 90% differentiation potential.[16]

3.3 Neural Stem Cells. In the adult brain, multipotent neural stem cells (NSCs) reside in the sub-granular zone (SGZ) and subventricular zone (SVZ). [17] They can differentiate into a variety of cell types, including neurons, astrocytes, and oligodendrocytes. NSCs can also be derived from fetal and postmortem neonatal brain tissues or differentiated from ESCs and iPSCs. [18] For successful neuronal replacement, the grafted cells should be distributed throughout the affected tissue (maintaining its original identity) and then integrated into the host brain's functional environment.[19] However, it is unknown if NSCs can generate into specific neural cell types. [20]

3.4 Mesenchymal Stem Cells: Mesenchymal stem cells (MSCs) have received special interest in the treatment of NDD given their excellent accessibility, relative ease of handling, extensively studied characteristics, and broad range of differentiating potential (including neuronal cells). MSCs are additionally advantageous as cell-based therapies given that they can be administered intravenously, exhibit blood-brain barrier penetration, have low tumorigenicity and elicit less of an immune response (than do other cell-based therapies).[21] MSCs are adult multipotent progenitors derived from various adult tissues and are capable of self-renewal in vitro. MSCs are defined by their spindle-shaped morphology, their ability to adhere to tissue culture plastic, and their unique expression of cluster of differentiation cell surface molecules. [1]

MSCs, have been isolated from bone marrow, placenta, adipose tissue, cord blood, amniotic fluid, synovial fluid, dermal tissues and deciduous teeth. [22] MSCs can be differentiated not only into mesodermal cell lineages but also endodermal and ectodermal cell lineages via stimulation. MSCs have been vastly explored, considering their ability to secrete many cytokines and neurotrophic factors to control immune responses and enhance neuronal protection. [23] MSCs are widely used in clinical trials because MSCs avoid the ethical concerns of ESC and provide the possibility of autologous transplantation. iPSC- based cell therapy for human clinical applications remains controversial, given very limited preclinical data. [24]

4. Stem cells and neurodegenerative diseases

In neuroscience, the discovery of neural stem cells (NSCs) and subsequent research have nullified the previous idea that the adult CNS was not capable of neurogenesis. Indeed, neurogenesis occurs throughout life. NSCs are believed to reside in the sub-granular zone of the hippocampal dentate gyrus, where neurogenesis occurs. NSCs give rise to glial-restricted precursors and neuron restricted precursors, both of which differentiate into astrocytes, oligodendrocytes, or neurons. In a study it has been demonstrated that transplanted NSCs isolated from a 9-week-old human fetus have the ability to differentiate into neural cells and improve cognition in aged rats hence, the idea of using NSCs for neurodegeneration treatment is

intriguing. However, NSCs are not so easy to access as a source of stem cells for possible use to treat neurodegenerative diseases. [8] Many studies have suggested the use of bone marrow-derived MSCs for regeneration of neural cells since MSCs are present in bone marrow and are relatively easily accessible within the human body. The key factor for the development of stem cell for neurological diseases requires understanding of the pathology of the specific disease and each disease will need to be assessed individually and each treatment will need to be tailored accordingly. [8]

4.1 ALZHEIMER'S DISEASE (AD)

Neurogenesis in the hippocampus decreases as we age and is exacerbated in AD; therefore, cellular therapies that enhance neurogenesis or replace lost neurons may also delay the progression of AD.[25]

AD is characterized by progressive cognitive decline, dementia, memory dysfunction and other associated negative symptoms due to neuronal degeneration. Specific hallmarks of AD are neurofibrillary tangles caused by hyperphosphorylated tau proteins and Amyloid plaque deposition.[26] The Aβ plaque is formed by the generation of an Aβ peptide through enzymatic cleavages of the amyloid precursor protein (APP), whereas the neurofibrllary tangle is created by tau proteins.[27] AD shows a neuronal loss, especially cholinergic neurons and the destruction of synaptic networks throughout the whole brain cortex, hippo-campus, basal forebrain, amygdale and limbic system.

In addition to the progressive loss of neurons, the decrease of neurogenesis is exacerbated in AD. [28] A study using triple transgenic mice harboring three mutant genes (APP, presenilin 1, and tau) showed that the reduction in neurogenesis was directly associated with the presence of Aβ plaques in the hippocampus. [29] In addition, Aβ induced alterations in GABAergic neurotransmission or an imbalance between GABAergic and glutamatergic neurotransmission, both of which contributed to impaired neurogenesis in AD. [30]

The apolipoprotein E4 (apoE4) allele is the major genetic risk factor for sporadic AD due to the higher prevalence and earlier onset of AD in apoE4 carriers.[31] In response to central nervous system stress or injury, neurons can synthesize ApoE to protect against neuronal injury or to promote neuronal regeneration.[32] However, ApoE4 among the ApoE family uniquely undergoes neuron-specific proteolysis, resulting in bioactive toxic fragments that enter the cytosol, alter the cytoskeleton, disrupt mitochondrial energy balance, and cause cell death. Li et al. demonstrated that ApoE4 altered signaling that promoted glial differentiation leading to a detrimental effect on adult hippocampal neurogenesis. [33]

4.1.1 Stem cells, AD & Neurogenesis

In early development neurons are rapidly produced to form the intricate complexity of the brain and peripheral nervous system. Postnatally, the role of neurogenesis is shifted from brain development into brain plasticity. The neurogenesis takes place only in specific niches in the adult brain, in the sub granularzone (SGZ) of the dentate gyrus (DG) of the hippocampus and the subventricular zone. [34] Recent evidence suggests substantial levels of hippocampal neurogenesis in the human brain, estimating about 700 new neurons a day in the DG. [35] Humans replace ~35% of the DG, while rodents are estimated to replace only 10%. [36] The existence of adult neurogenesis in the human brain supports the notion that neurogenesis has important functional significance and implications for cognitive disorders and their therapy.[35,36] The circuitry of the DG, of which new neurons are part, promote several important functions, namely, pattern separation, conjunctive encoding of multiple sensory output, facilitation of encoding of spatial information and encoding of time in new memories.[37] In support of the role of hippocampal neurogenesis in plasticity, learning and memory, increasing evidence suggests that cognitive deficits, difficulty learning new information and memory loss, as occurs in Alzheimer's disease (AD), may be, at least in part, due to impairments in adult neurogenesis.[38,39] Some of the foundation for the association between impairments in adult hippocampal neurogenesis and cognitive deficits leading to AD might be due to the fact that several key signals implicated in AD play a role in regulation of hippocampal neurogenesis. [37]

Considering the destructive nature of AD and no curative treatment, stem cell therapy for AD, which protects neurons, increases neurogenesis or replaces lost neurons, may slow the progression of the disease thoroughly or halt it completely. [3]

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. [40-42]

Transplanted stem cells elevate the levels of various factors, including BDNF, glial cell line-derived neurotrophic factor (GDNF), insulin-like growth factor 1 (IGF-1), Glucagon-like peptide-1 (GLP-1), vascular endothelial growth factor (VEGF) to exert a paracrine effect. Stem cells have been recognized to improve various cellular functions in animal models of AD, including synaptic strength, neurogenesis, microglial activity, angiogenesis, mitochondrial function, autophagy and apoptosis. [40-42] Stem cell transplantation influences AD via multiple mechanisms; therefore, it is promising compared with conventional treatments that target a single pathology. [43]

Neurotrophic factors as discussed are secreted proteins that regulate multiple aspects of neural cell functions and are widely known to play central roles during brain development, homeostasis, and neurodegeneration. [44] These multiple neurotrophic factors have been implicated in induction of neurogenesis in the adult SVZ. BDNF and VEGF administration into the lateral ventricles of adult rats was shown to increase the generation of new neurons. [45,46] Also glial cell line-derived GDNF, fibroblast growth factor 2 (FGF2), and neurotrophin-3 (NT-3) were shown to have roles in enhancing adult neurogenesis. [1, 47] The trophic support provided by transplanted stem cells improves the microenvironment and promotes the survival of affected/ remaining nerve cells. [48] Using this strategy, the primary target to stimulate hippocampal neoneurogenesis (in order to compensate for neurodegeneration) is the upregulation of resident neural stem cell niches. [21]

Further, the Basal forebrain cholinergic neurons play essential roles in various aspects of cognitive function, such as learning, memory and attention, and the cholinergic blockade disrupts the cognitive function of normal humans. There is severe devastation of basal forebrain cholinergic innervations and resultant declined cholinergic neurotransmission in the brains of AD patients. A number of endogenous neurotrophic factors, such as nerve growth factor NGF, BDNF, basic fibroblast growth factor (bFGF) and bone morphogenetic protein 9 (BMP9), have been reported to participate and promote the survival, growth, and differentiation of cholinergic neuron in the brain. [49,50] In rodent models, the overexpression of NSC-derived cholinergic neurons and choline acetyltransferase (ChAT) restored cognitive performance and synaptic integrity [51] and stable generation of cholinergic neuronal populations from human ESCs following transplantation, were able to functionally integrate into hippocampal neuronal circuitry. [52]

CONCLUSION

Alzheimer's disease involves complex interplay of multiple cell types and a large variety of cellular activities. The key molecules involved in the modulation of endogenous neurogenesis and intervening with them might be a preliminary, but fascinating, strategy to prevent or even reverse AD. Various neurotrophic factors involved in modulating multiple cellular functions that promote the amelioration of pathological features and cognition in animal models have been recognized. Although the 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.

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