Chapter 7

Stem Cell Based Therapies for Neurological Disorders

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A. Introduction

Stem cell therapy is the only potential regenerative treatment that provides complete treatment for neurodegenerative diseases. The currently available treatments, either neurosurgical or pharmacological, are not efficient in treating the progression of neurodegenerative diseases. Stem cell therapy aids neuronal regeneration which modifies aberrations occurring in neuronal circuitry. In this chapter, stem cells therapy for different neurodegenerative diseases with their uses and clinical applications are discussed.

B. Stem Cells

Stem cells were originally generated from the German word *Stammzelle*, which was coined by German biologist Ernst Haeckel.

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Stammzelle means a type of cell that produces other cells. One of Haeckel's theories describes a stem cell as a fertilized egg that generates many cells. Following that theory, embryonic cells and bone marrow cells are also named as stem cells by various researchers due to both differentiating into more specialized cells.

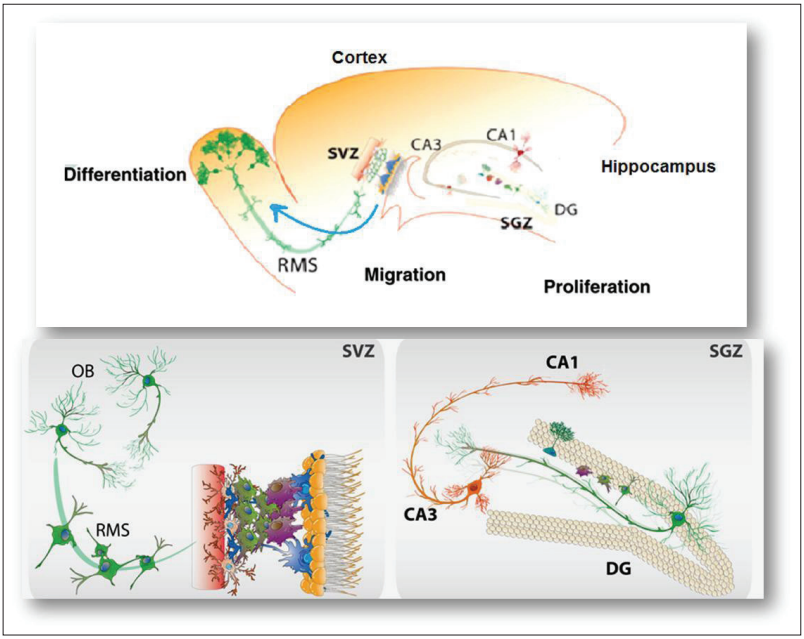
In recent research, stem cell has evolved as an extensive term and is defined as the cells having potency for regenerating and stimulating cells of various phenotypes. Stem cell biology has now been centralized in drug discovery for treatment of many diseases. Therapeutic approaches based on stem cells reflect a new pathway for management of chronic and persistent diseases. The definitive approach of stem cell-based therapy is to potentiate the body's regenerative capability through regulation of tissue homeostasis and regeneration.

On the basis of origin, stem cells are classified into mesenchymal, epithelial, hematopoietic, embryonic pluripotent, and neural stem cells. Human pluripotent stem cells, further include human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs), have been employed in preclinical studies of neurologic diseases.

Research advancements have shown great potentials of neural stem cell-based therapies as regenerative medicines for treating various neuronal disorders. Neural cells are differentiated into cells, namely oligodendrocytes and astrocytes. Meanwhile, progenitor cells are based on limited differentiation, just like neuroblasts which can only be differentiated into neurons. Similarly, glial or oligodendrocytes progenitor cells can be developed into either astrocytes or oligodendrocytes.

C. Neural Stem Cells Niche in Brain

The process of neurogenesis is conducted in the neurogenic region of the brain. The two neurogenic zones involved in this process are the subventricular zone (SVZ) and the dentate gyrus (DG) of the hippocampus (Figure 7.1). In addition to these areas, there are also



Source: Adapted from DeHamer et al. (1994)

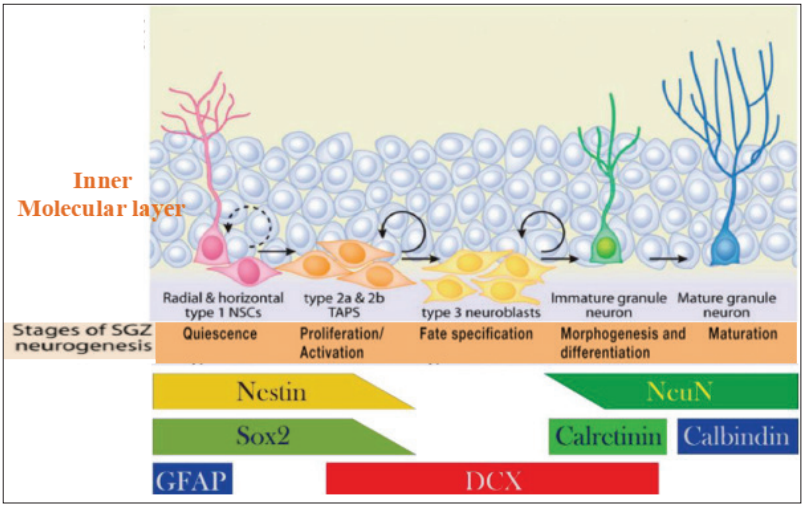
Figure 7.1 Neurogenic niches of the brain include the subventricular zone (SVZ) and the subgranular zone (SGZ) of the dentate gyrus (DG).

other distinct brain regions, such as hypothalamus, cerebellum, cortex, and striatum, where new neuronal cells are produced.

However, the highest proliferation of neurons has been observed in the SVZ area in the mammalian and human brains. An average of 40,000 cells per day are produced in the SVZ region of the brain. The new neuronal cells travel from the SVZ region to the olfactory bulb (OB), where they differentiate into interneurons.

1. Neuronal Development and Survival of Stem Cells

The subgranular zone of the adult hippocampus possesses radial glial cells which act as the neuronal precursor cells (NPCs). These cells are further differentiated into Type-1, Type-2, and Type-3 cells (Figure 7.2).



Source: Adapted from Hsieh (2012)

Figure 7.2 Stages of neuronal development from neural stem or progenitor cells to mature neurons expressing biomarkers.

a. Type 1 Cells

Type 1 cells are uneven and triangular in shape, exhibit a long apical process raised from the granular cell layer. These are diffused into the inner molecular layer, where they develop numerous tiny processes. The type 1 cells express both *Nestin and Glail* fibrillary acidic protein (GFAP) biomarkers which will be further discussed later in this chapter.

b. Type 2 Cells

Asymmetrical division of neural progenitor cells gives rise to one neuronal stem cell (NSC) and one daughter type 2 cells. This daughter cell undergoes a frequent symmetric cell division and produces two differentiated or two symmetrical daughter cells, before acquiring its terminal fate and differentiation. These daughter cells are further termed as a "transit-amplifying cell". These cells are expressed by a protein biomarker namely nestin. They have distinct short processes

with dense nucleus and irregular shape. They have a swift and high proliferation rate.

The neural stem cells divide asymmetrically in constant manner, and produce differentiated astrocytes with self-renewing capacity. The NSCs are thought to be depleted after short span of time. However, recent research has shown that the NCSs can multiply and increase their population besides having self-renewing capability. It is an established fact through studies that NSC located in adult hippocampal niche have capability to generate various cellular lineages and resulting populations can survive for longer period of time. Additionally, the existence of an intermediate progenitor cell is capable to undergo several symmetric divisions and tends to produce transit-amplifying cell which are serving as NSCs or neurons. These pathways of lineage development can be influenced by functional alterations in the neurogenic and non-neurogenic niche in different animals.

c. Type 3 Cells

In most cases, transit-amplifying cells are differentiated and give rise to type-3 cells, which express doublecortin protein (doublecortin is found in differentiating and migrating neurons. It is a microtubular associated protein). These cells show negative expression for nestin. These cells also express a polysialylated form of neural cell adhesion molecule (PSA-NCAM). PSA-NCAM is a migrating and developing neuronal marker.

Type-3 cells can proliferate and amplify to the next phase, continuing to express a biomarker called as Distinct feature of double cortin (DCX) and convert to postmitotic immature granule neurons. DCX marks neurons in postmitotic stage, which are still having some neurons with characteristic of synaptic plasticity. Synaptic plasticity is described as the neuronal ability to strengthen their connections. It is an important process for brain development and regeneration.

Type 2 and type 3 cells are deficient in functional synapses, but are stimulated by GABA-nergic signals from surrounding interneurons.

A high proportion of stem cells reach type 2 and 3 neuronal phases after two to three days of division.

D. Progressions of the Adult Granule Neurons

Adult granule neurons transiently express a protein biomarker called Ca2+-binding protein calretinin in the early post-mitotic phase. They are also characterized by neuronal marker Neuronal Nuclei (NeuN) found in the postmitotic stage. At this stage, cells retain their round or triangular shape nucleus similar to the morphology of type 3 cells. This phase is followed by the rapid axonal extensions targeting CA-3 region, which is found in the hippocampus and regarded as a pacemaker of hippocampal region. The axonal connections become clearly visible, within three to five days of division.

The visibility of apical dendrites at initial division takes 48 hours and is retained in type 3 cells and early mitotic cells. The outgrowth and projections rise from newly born neurons, at the rate of 15 μm per day during first three days. However, the length of projections grows double approximately from four to five days. The release of inhibitory GABAergic signals from hilar cells, which is located in dentrate gyrus region of brain, facilitates synaptic networks towards immature granular neurons. These networks are further propagated from axonal projections of hilar cells adjoining dendrites and are located in deep molecular layer. A larger proportion of new born neurons are recruited for their functional integration or elimination following assortment processes.

The phases of stem cells development indicate that most of expansion processes takes place at the stage of precursor cells, although final differentiation and thereby the fate specification, for long term neuronal survival, occurs primarily in postmitotic phase. Majority of new cells of the population multiplies significantly during the early period of proliferation and amplification. Afterwards, these cells decline immensely—more than 50%—before acquiring stability within seven-fourteen days. This state continues over longer period of time, from several days to years.

E. Regenerative Role of Adult Neuronal Stem Cells

The main emphasis of modern stem cell research is to recognise the contribution of newly produced neurons in brain function and its efficient integration in brain circuit. Experimental approaches anticipate that progenitor or adult neuronal stem cells are not only produced throughout life, but also play an important role to develop the functional brain networking. The generation of adult NSCs and endogenous neurogenesis opens the new pathways to treat the neurological disorders.

Emergent understanding about the characterization of neural stem cell provides novel therapeutic targets based on stem cell therapy and are aimed to restore the functional deficit in CNS disorders. Comparable to adult stem cells, which are basically repairing various tissues and organs, the adult NSCs are likely to play an important role to replace the dead cell after injury and repairs the damage brain tissue. The capability of adult NSCs to regulate the brain homeostasis may protect the physiological functions against depression, trauma, and anxiety from neuronal defects.

F. Neuronal Stem Cell Generation in the Hippocampus

Hippocampus has a vital role in incorporating information into memory and generating new neurons. Moreover, it is also involved in pathophysiology of mood disorders. Hippocampal volume is being reduced in psychiatric conditions like depression. The production of neurons in the hippocampal region is termed as hippocampal neurogenesis. Stem cell generation in the hippocampus has been studied in non-human primates, rodents, and humans.

In the dentate gyrus (DG) of hippocampus, the subgranular zone (SGZ) possesses neural precursor cells which produces new-born neuronal cells. These cells move towards the granular layer and there they mature to granule neurons. The axons of these cells are projected to pyramidal cell layer of CA3 region, while the dendrites

are projected to molecular layer. In the following months, these cells are going to form further synaptic connections. Young neurons show distinctive properties like a lower threshold for excitation and longer period potentiation. Moreover, the new neurons are significant for hippocampal dependent learning and pattern separation. Neurogenesis in the dentate gyrus of hippocampus occurs in form of clusters linked with blood vessels.

1. Regulation of Hippocampal Neurons

Advance development of neuronal progenitor stem cells in hippocampus is influenced by various extrinsic and intrinsic behavioural, as well as molecular factors. These factors regulate all phases of neurogenesis. Enhancement factors of neurogenesis involves exercise, enriched environment, and learning. Mood-modulating antidepressant drugs, like fluoxetine, also increase the patterns of neurogenesis.

Factors which are likely to reduce hippocampal neurogenesis include different types stress, aging, and various other diseases such as Alzheimer's disease and Parkinson. In addition to these factors, numerous proteins, endogenous stimuli, hormones neurotransmitters, and epigenetic markers have an impactful role in regulating proliferation, differentiation, or fate determination of new born neurons.

The neural stem cells residing in SGZ are essential to modulate the hippocampal growth for memory formation and to maintain neural plasticity throughout life. Additionally, it has a substantial role in the regulation of mood. SVZ neural stem cells play a significant role in the maintenance of olfactory lobe (OB) structural morphology and conserves the high cellular turnover. Continuous addition of new neurons has promising roles in the development of olfactory circuits influencing sensory organs to adapt the behavioural alterations. Impaired memory and reduced ability to perform different tasks is a serious consequence of disruption in hippocampal neurogenesis.

2. Therapeutic Implications of Hippocampal Neurogenic Stem Cell Therapy

Neurogenesis in the hippocampus through neuronal stem cells differentiation supports hippocampal circuits repair. It also facilitates cognitive and emotional behavior patterns, regulated by the hippocampus. Distortions on adult hippocampal neurons are being associated with the dementia disorder called as Alzheimer's disease (AD). Stem cell therapy, including cell engraftment, reprogramming with glial neurons, and regenerating adult hippocampal neurons, has compensated degenerated neuronal circuits and emerged as potential treatments for recovering neuronal loss. Transplantation strategy of NSCs may also recover the neuronal loss by attenuating homeostasis of brain tissue and producing a synergistic effect with neuroprotective drugs and other therapies.

G. Potential Risks Associated with Stem Cell Therapy

Advanced clinical outcomes of stem cell therapy for neurological diseases are also associated with potential risk factors. These risk factors should be analyzed critically for better clinical treatment with stem cell products. These risk factors are dependent on stem cells types, in vitro culturing of cells, route of administration, intended location, proliferation, differentiation, treatment irreversibility, and survival time frame of engrafted cells. The potential identified risks in clinical and animal studies include allergic reactions, unwanted immune responses, and tumor formation.

The use of human embryonic stem cells (hESCs) are limited due to two major risk factors, including the risk of immunological rejection because hESCs are isolated from pre-implantation blastocysts, and ethical issues due to the human embryonic cells' destruction. The transplantation procedures with stem cells are often invasive and produce severe complications, especially in elderly and paediatric patients.

Human-induced pluripotent stem cells are also associated with potential risks of cardiac arrest to patients, arrhythmia, and risk of cancer formation. Bacterial infections and inflammation are also one of the crucial risk factors which cause mortality of patients undergoing stem cell-based therapy.

H. Safety Evidences Associated with the Administration of Stem Cells

Various clinical trials have established the results of efficacy and safety of mesenchymal stem cells for treatment of diseases, such as haematological malignancies, acute myocardial infarction, chronic heart failure, and acute respiratory distress syndrome. Large clinical trials with better outcomes are still needed to market stem cell-based products on large scale.

Safety and efficacy of mesenchymal stem cells (MSCs) treatment has been modulated at advanced stages through recent studies. These cells have demonstrated protective effects with no adverse effects in acute respiratory distress syndrome (ARDS) patients in small clinical trials

Diabetes is a serious medical health problem leading to various other diseases. Bone marrow-derived mesenchymal precursor cells (MPCs) have been evaluated for feasibility and tolerability, in type 2 diabetes patients. There were no serious adverse effects including serious hypoglycemia. There was no formation of donor-specific anti-HLA antibodies.

Stempeucel are allogeneic mesenchymal stromal cells (MSCs) derived from bone marrow of healthy, adult volunteers. Its safety and efficacy profile has been established through phase I/II randomized, double-blind, single-dose study in myocardial infarction patients. There was a great improvement in ejection fraction outcomes compared with the placebo group, with no serious adverse effects.

Intravenous administration of Cx611 which is a preparation of allogeneic expanded adipose-derived stem cells (eASCs) in patients

with refractory rheumatoid arthritis (RA) has proven to be safe and tolerable. The effects of eASCs were associated with none of the dose-related toxicity and have shown promising clinical efficacy.

Mesenchymal stem cells peripheral vein infusion has also emerged as a possible therapeutic approach for end-stage liver disease. The infusions of MSCs were effective with beneficial outcomes on liver synthetic functions and hepatic fibrosis. With better safety profile, they have also shown improved albumin, prothrombin, and alanine concentrations.

I. Limitations of Stem Cell Therapy

Remarkable investigations by various biologists, using transplantation techniques for inducing pluripotent cells (iPSCs) in neurodegenerative disease models, have aided in optimizing the current treatment protocols. Despite these advances and technical exploration, the approach of NSPCs or iPSCs transplantation may not be practically fruitful to cure neurodegenerative disorders due to inadequate knowledge of disease mechanisms and limitations in the treatment of brain diseases. Furthermore, transplantation of neuronal cells in the early stage of disorder can additionally complicate the therapy and result in greater risk than benefit.

The aberrant neurogenesis has been reported in response to the disturbed CNS environment. Aging can significantly reduce the neurogenic capacity of neural stem or progenitor cells, leading to a much lower yield of sufficient neurons for replacing degenerated neurons or integrating into CNS.

Strategies to Overcome the Limitations of Using Stem Cells Safely and Effectively

To address these limited applications of transplanting NSPCs exogenously, one constructive approach would be the stimulation of endogenous neural stem cells, residing in the subventricular zone and subgranular zone of dentate gyrus. Alternatively, augmenting the neurogenesis in non-neurogenic niches can also be valuable such as

the continuous addition of new neurons in the spinal cord. The other useful endogenous stimulation advances are discussed as follows.

1. Stimulation of Ependymal Cells in The Spinal Cord

Ependymal cells are specialized ciliary cells of brain which arise from radial glia. NSCs can also be recruited from central canal surrounded by ependymal zone, serving as primary pool of stem cell. Further, the in vitro stem cell proliferation of ependymal cells is reported in comparison to astrocytes. The ependymal niche of spinal cord has shown rapid proliferation of ependymal cells after spinal cord injury. Although, more research is required to identify the exact role of ependymal zone of spinal cord in regard of proliferation and differentiation in to oligodendrocytes and astrocytes after injury. These findings can conclude that the subpopulation of ependymal cells of spinal cord can hold the underlying neural stem cells properties.

2. Neuronal Stem Cells Stimulation Through Endogenous Factors

The molecular signalling pathways which are involved in NSC proliferation and differentiation can be a biomarker of endogenous neuronal stimulation. Numerous factors are identified for modulating neurogenesis. Stimulation and migration of the neural stem cells at site of injury in response to neuronal deficit or trauma suggests that there are some endogenous factors which can affect proliferation and migration of precursor cells at the injury site. Moreover, intracerebral delivery of neurotrophic factors and stromal-derived factor -1 has influenced expansion and migration of intravenously administered NSCs into the brain.

These advances reveal that a well-synchronised anti-inflammatory response is also essential for tissue restoration processes. This should preferably be accomplished in presence of beneficial factors affecting proliferation, migration, and integration or replacement of neuronal cells. Conversely, a continuous and intensified response may initiate more exacerbated neuroinflammatory cascade, which may

accelerate the neurodegenerative signalling and result in worsening of disease. Considering this fact, the approach to augment endogenous neurogenic potential of NSPCs may achieve the therapeutic goals by recruiting and differentiating appropriate cell lineages.

3. Targeting Immature Neuroblasts

Adult-born NSPCs that are not damaged in early days of cell division retain unique morphology before undergoing physiological maturation in to granular neuron. There are new approaches to amplify endogenous neurogenic capacity that could target immature adult neuroblasts under critical period of maturation. Immature neuroblasts holds membrane resistance properties, reduce glutamatergic activity and distinct firing. These properties permit development of a maturation stage in which immature neuroblasts can be stimulated through several biological and environmental factors. The hyper excitable state of immature granular cells are important to concern in the perspective of neurodegeneration. The endogenous neurogenesis, stimulated by immature neurons, can also alter the behavioural patterns.

4. Enhancement of Neuronal Stem Cells Through Type 2 Amplifying Cells

There are certain specialized cells in hippocampus which are called as type 2 amplifying cells. These cells have shown rapid proliferation and yield the pool of many progenitor cells, presenting these cells as potential target for endogenous stimulation strategies. Neuronal proliferation can be activated through physiological as well as pharmacological pathways.

5. Endogenous Stimulation Through Neurogenic Compounds

Another captivating approach in modulation of endogenous neurogenesis is through screening and use of new molecules termed as neurogenic compounds. The development of certain synthetic compounds or natural molecules in recent research trends has shown promising results in stem cell-based therapies. These

molecules or compounds have advanced the therapeutic options for neurodegenerative disorders.

The neuroactive compounds have shown promising results in neurodegenerative animal models. Furthermore, neuroactive molecules have been explored as modulators of neurogenesis, which can also be implicated in stem cell based regenerative therapy. For example, isoxazole 9 (Isx-9) has been found to enhance adult hippocampal progenitor cell proliferation and differentiation into mature neuroblast without perturbing the number of neural stem cell. This compound also has role in enhancing spatial memory in mice. These small molecules have been identified to improve cognition by influencing the neuronal plasticity at various junctures of differentiation and maturity. Isx-9 also has neurogenic potential as it can induce neuronal genes to re-express and generate differentiated astrocytes *in vitro*. Therapies with such compounds can be an alternative strategy for recruitment of progenitor cells that may functionally be differentiated into neuronal lineage.

6. Targeting Adult-Born Neurons

One more approach is to target the different stages of adult-born neurons, for example by increasing synaptic connectivity, integrity into network, or maturation period. The phase of adult borne neurogenesis is also affected by physiological and pharmacological agents.

Endogenous neurogenesis for neurodegenerative treatment can also be achieved by initiating the migration of dividing and mature cells to desired region of brain. Various investigations have identified that NSPCs originating from, for example, SGZ and SVZ neurogenic niches are commonly reorganized to maintain their regular migratory tracks in the neuropathological state.

7. Applications of Endogenous Neurogenesis

It is possible that advance methodologies affecting endogenous neurogenesis will enable researchers to direct the migration of cells. For example, the lost neurons in Alzheimer's disease can be replaced

by dentate gyrus NPCs in cortical region. The spiny neuronal cells degenerated in Huntington's disease (HD) can be substituted from neurons of SVZ region into the striatum. Moreover, the exogenous transplantation of NSPCs in Parkinson's model of rat has shown to induce release of some trophic factors like stromal cell-derived factor-1α (SDF-1α) in local NSPCs, substantially promotes migration of endogenous neural progenitors to the grafted area.

However, the effectual migration of NSPCs to injured or deficit areas is needed to be discovered, for the said purpose of extensive exploration of NSPCs. In addition, the extracellular pathways and transcriptional regulation of migrating cells should also be investigated.

J. Biomarkers for Neuronal Progenitor Stem Cells

Development of stem cells into neurons and astrocytes require working of certain protein biomarkers which are expressed at various stages of differentiation processes. These include nestin, glial fibrillary acidic protein (GFAP), and bromodeoxyuridine (BrdU). However, it is unknown at which stage the progeny is limited to the neuronal fate, either in the subgranular zone of the hippocampus or subventricular zone. Moreover, the number of cells incorporating into the existent neural network is also unclear.

1. Nestin

Nestin is a protein belonging to the sixth class of intermediate filament proteins. The expression of nestin occurs in adult neural stem cells (NSCs) and immature progenitor cells. However, it disappears as cell differentiation occurs. This protein has also been recognized as a marker of neural stem cells in both adult brain and embryo. Nestin is involved in self-renewal and proper survival of NSCs. Most nestin-positive cells, in the early stages of embryonic development, work as progenitor stem cells that can proliferate and differentiate in certain brain regions. As the cell division and differentiation of these cells terminate, the expression of nestin is also downregulated.

2. GFAP

Glial fibrillary acidic protein (GFAP) is a known marker for astrocytes (the specialized glial cells). It is an intermediate filament that is responsible for maintaining the mechanical strength of the astrocytes. During neurogenesis, the cells possessing astrocytic properties can function as an origin for new neurons. GFAP-positive progenitor cells are able to produce distinct neuronal cell types during the process of neurogenesis. Studies have shown that radial astrocytes also function as DG neuronal stem cells (NSC).

3. BrdU

Bromodeoxyuridine (BrdU) is a synthetic structural analogue of thymidine nucleoside. It has been used as an efficient source to label cells involved in the s-phase of the cell cycle, in both perinatal and adult proliferating cells. BrdU labelling is a prevalent technique used for studying neurogenesis. BrdU targets the proliferating cells at distinct stages of neurogenesis. Although these techniques are considered as valuable tool for monitoring adult neurogenesis, they have limited application in the analysis of stem cells. When exposed to proteins like BrdU, the expression of stem cell markers is reduced or they exhibit transient labelling.

K. Transcriptional Regulators for Neuronal Development: From Stem Cells to Neurons

Neuronal cell differentiation is regulated by one of the super families of transcriptional factors called basic Helix-Loop-Helix (bHLH). These neuronal factors are responsible for adequate production of glial and neuronal cells. The conversion of somatic stem cells or pluripotent stem cells into neuronal cells also requires bHLH genes functioning. The aberrations and mutations in bHLH factors are related to development of various cancers and neurological disorders. Two most important bHLH genes are NeuroD and Neurogenin.

1. NeuroD

The family of transcription factors that possess a fundamental role in tissue development and maintenance is the bHLH superfamily. The neural lineage bHLH factors, a subgroup belonging to this family, have a great importance in the development of the central nervous system (CNS). The NeuroD is the subset of neural lineage bHLH factors that are involved in neuronal development and progression. As neuronal differentiation is a complex process, the NeuroD gene also serves as a marker for differentiation of adult hippocampal neurogenesis. It is also classified as an indicator of adult cells in the sub-granular zone and the inner granular layer. In the adult brain, NeuroD is also responsible for neuronal cell proliferation. Moreover, the polysialylated neural cell adhesion molecules (PSA-NCAM) are also positive for NeuroD simultaneously, therefore the NeuroD expression can also be detected in these molecules.

2. Neurogenin

Neurogenin is another transcription factor belonging to the bHLH family and it plays a fundamental role in neurogenesis. This proneural gene can initiate a neurogenic program, both in vitro and in vivo, in distinct progenitor cells. Various studies have reported that these factors are involved in cell-type-specific neurogenesis. The importance of neurogenins can also be seen through gene mutations. Neurogenin 1 (Ngn1) or Neurogenin 2 (Ngn2) single or double mutant mice have shown a loss of spinal cord neurons, as well as spinal and cranial sensory ganglia. Apart from inducing neurogenesis, Neurogenin 1 inhibits NSCs differentiation into astrocytes by restraining CBP-Smad1 complex away from genes that are responsible for astrocyte differentiation.

3. Signaling Mechanisms Involved in Differentiation Processes of Neuronal Stem Cells

Beside transcriptional activation, the stimulation of signalling pathways, such as epidermal growth factor (EGF), fibroblast growth

factor (FGF), notch and bone morphogenetic proteins (BMP) have been well recognized for their role in neural progenitor, astrocytes, and neural stem cell proliferation, differentiation and fate decision. Several pathways that stimulate neural differentiation can effectively generate different types of neurons using in vitro methods. These cell types include dopaminergic neurons, cholinergic neurons, spinal motor neuron, and oligodendrocytes.

The in vitro differentiation protocols of producing neurons has great importance, such as functional spinal neurons are produced from NSCs through induction of Sonic Hedgehog signalling and retinoic acid treatment. One of the clinical approaches for Parkinson's disease (PD) therapy is to generate dopaminergic neurons from NSCs after exposure with fibroblast growth factor 8 (FGF8) and stimulation of Sonic Hedgehog activity. The inhibition of transforming growth factor beta (TGF beta) and BMP signalling also induce differentiation of NSCs towards dopaminergic neurons. Following differentiation, the subtype specification of dopaminergic neurons is influenced by various transcription factors, including Nurr1, Lmx1a, Pitx3 and FoxA.

Identification of cellular features in developmental brain can introduce effective differentiation approaches of desired and appropriate neural identity, such as obtaining neuronal midbrain dopaminergic cell groups from induced pluripotent stem cells (iPSCs) or mesenchymal stem cells (MSCs) in in vitro methods. Additionally, differentiation can be improved using co-culture of neural progenitor stem cells with bone marrow stromal cells (BMSCs) or neonatal cortical astrocytes.

L. Stem Cell-Based Therapies for Neuronal Degenerative Disorders

Every organ and tissue of the body has a replacement and repair system for organizing new cells and replacing the older and dead cells. Regeneration of neuronal cells is the most crucial phase for restoring

neuronal functions. This is because of the fact that CNS has weaker aptitudes for developing proper cell repair and cell replacement.

Various therapeutic approaches have been designed for neuronal cells repair therapy. These include neuroprotective drug therapies for enhancing neurogenesis, neural stem cells transplantation and targeting inflammatory pathways for repairing neuronal distortion.

1. Neuroprotective Drug Therapy for Enhancing Neurogenesis

Neuroprotective drug approaches are in investigational stages for revitalizing brain cells. Certain examples include the use of neurotrophic agents, free radical scavangers, metal ion chelator, neuronal gene modulators, and neuronal apoptosis inhibitors.

The potential stimulations of neural stem cells endogenously, for regenerating new neurons in adult CNS, is less invasive technique than cell transplantation. Such an advancement in neuronal cell research has been successful for treatment of complex CNS diseases, for example Alzheimer's disease. Use of mitotic trophic factors has been associated with amplified neurogenic response. Also, Olanzapine, which is used for treatment of schizophrenia, nitric oxide (NO), and 5-phosphodiesterase inhibitors have been screened ex vivo for potential ability for inducing neurogenesis.

2. Neural Stem Cells Transplantation

Neural stem cells transplantation is considered as the most advantageous for reconstructing neuronal cells connections. This requires an appropriate selection of neuronal cells with specificity, possessing proliferative potential, and should be phenotypically plastic. Successful exogenous transplantation of NSCs has upregulated regulatory processes like angiogenesis and neurogenesis after stroke. SVZ-derived neural stem cells have been used for intracerebral transplantation in experimental models of various brain disorders including Parkinson's disease, Huntington's disease, and multiple

sclerosis. Clinical trials have shown successful therapeutic advantages of spinal cord injection of NSCs in treatment for amyotrophic lateral sclerosis (ALS).

3. Neuronal Stem Cells Modification by Anti-Inflammatory Agents

Inflammation has a deleterious impact on neurogenesis, as it affects generation of new neural cells endogenously from brain's cells or by exogenous transplantation of neural cells. Neural cell repair therapy could be modified by use of anti-inflammatory drugs. Neural cell proliferation has been associated by moderating inflammatory pathways. Therefore, optimizing the potential neural inflammatory markers can increase differentiation of neurons and promote recreation of new cells in lesioned areas. In this context, potential treatment with natural or synthetic drugs, possessing anti neural-inflammatory property, should be used. Specifically, this treatment strategy should be specified towards the activation of microglial cells in cumulative neural stem cell proliferation and differentiation into neuronal cells.

Here are some examples of medical treatments utilizing stem cells.

a. Neuronal Stem Cells and Their Relation o Alzheimer's Disease Management

Alzheimer's disease (AD), also known for years as short-term memory loss, is being identified for weaker cognitive functions. The underlying pathology is based on declined cholinergic neurons. This ultimately progresses towards distorted behavioral patterns of learning and emotions. Available drug therapies for treatment of Alzheimer's disease are associated with serious adverse effects that leads to incomplete cure.

Neural stem cells have demonstrated a better portrait of advanced therapeutic approach providing effective behavioral responses. Transplantation with these cells has developed boosted neuronal networks, replacing degenerated neurons. This provides neuronal regeneration backup for AD where neuronal connection is incessantly

disturbed. Transplanted cells have capability to differentiate into cells in damaged area for nurturing cells giving prompt recovery.

Neuronal stem cells are found in hippocampus and sub-ventricular zone in adults. NSCs are genetically redesigned after being differentiated from brain tissues or embryonic stem cells. Development of zebrafish model of AD by Bhattarai et al. (2017) is one of the most advantageous applications of NSCs transplantation. The amyloid toxicity, induced by human Aβ42, enhanced inflammatory markers causing synaptic loss, leading to cell death and lack of behavioral responses. Interleukin-4 mediated NSCs transplantation produced significant outcomes for regenerating neuronal cells.

The population of cholinergic neurons are mostly affected in Alzheimer's disease (AD) and resulted in cognitive decline. Basal forebrain cholinergic neurons have been generated by application of two methods which include transplantation of neuronal stem cells with transcription factors Gbx1 and Lhx8 and controlled differentiation of NSCs to cholinergic neurons by using diffusible ligand Bone Morphogenetic Protein 9 (BMP9). The obtained cholinergic neurons also successfully engrafted into hippocampal slices and they expressed functional properties of cholinergic neurons in electrophysiological experiments. These differentiated forebrain cholinergic neurons can be an effective therapeutic alternative for AD treatment.

Neuronal stem cells have also been transplanted in 3xTg (triple transgenic) AD model of mice. The transplanted NSCs differentiated into glial cells, enhancing synaptic density. Improved behavioral responses are the key results in novel object recognition and Morris-water-maze tests while Tau and Aβ protein levels remain unchanged.

b. Parkinson's Disease Treatment with Neuronal Stem Cells

The most common neurodegenerative diseases include Parkinson's disease (PD), a prevailing disorder which has been increased to 4% in aged people over 80. It is diagnosed with presence of aggregates of α-synuclein. Genetic mutations in genes such as parkin (PRKN) and alpha-synuclein (SNCA) are associated with progression of PD.

Basic treatment of PD includes restoration of dopamine levels through monoamine oxidase-B inhibitors and L-Dopa. Deep brain stimulation (DBS) is also in current strategies for PD treatment. All these treatment protocols have failed in reversing neuronal degeneration. Therefore, a compliant treatment protocol should be developed for recuing motor and non-motor symptoms of PD.

Innervation of undifferentiated stem cells in brain areas with decreased dopaminergic neurons are having inclination for producing better effects in in vivo PD models. Effective transplantation therapy with neuronal cells depends on brains recognition process of donor cells. This is also involved in reducing dyskinetic side effects associated with PD in clinical trials. Effective protocols must be programmed for reducing chances of immune rejection.

Transplantation treatment of PD primates along with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) have produced significant effects of cellular survival and also moderate behavioral patterns. The neural cells are not capable of being pre-differentiated into dopamine containing cells. However, investigations are still in process for transplanting dopaminergic neuronal stem cells in PD models. Neural stem cells may provide a repaired system within the brain through creating anti-inflammatory and neurogenic factors. Neural stem cells have the functional capability to be transformed into dopamine neurons but their quantity is insufficient to produce significant effects. Neural stem cells are usually differentiated into astrocytes. These astrocytes released glial cell line-derived neurotrophic factor (GDNF), which is responsible for neuronal homeostasis.

c. Functional Responses of Neural Stem Cells in Ischemia

Recent in vitro NPSCs transplantation have produced successful outcomes in ischemia-induced rat model. Oligodendrocytes have been originated from subventricular zone (SVZ) cells of neonatal rats. Findings of in vivo experiments also supports the positive effects of neural stem cells in stroke. An Increase in neuronal protein biomarker BrDU is also associated after neuronal stem cells transplantation

in hypoxia-induced neuronal cells. Neuroblast and mature cells proliferation also increases after neuronal stem cells treatment after ischemia.

d. Neural Stem Cells as Effective Treatment for Gliomas

The administration of human glioma (U251) cell lines with NSCs increases the animal's survival rate in nude mice model. The neuronal cells treatment can decrease extracellular-regulated kinase (ERK1/2), tumor suppressor gene (p53), and phosphorylation of protein kinase B (AKT) genetic markers. Following administration of NSCs, there is also a substantial upregulation in apoptotic markers known as caspase-3. This suggests that NSCs have potential antiapoptotic activity. The coculturing of NSCs conditioned medium with U87 glioma stem-like cells has shown decreased viability of glioma cells. Endogenous stimulation of stem cells in the subventricular zone also targets glioma cells and decreases.

Neural stem cells after genetic modulations can stimulate endogenous secretion of anti-cancer compounds near tumor zone. These endogenous antitumor compounds are also called as immunomodulators, include interleukin-4 (IL-4) and interleukin-12(IL-12). IL-4 is extensively involved in recruiting precursor T-cells. This is advantageous to kill cancer cells through increased immune response. IL-4 is also regraded as tumor combating cytokine, which improves survival rate of neurons. IL-4 can also be transmitted through retroviral transfer, which in turn can improves survival rate. IL-12, a potentiator of T-cells, enhances differentiation of T cells into CD4+ and CD8+ T-cells. IL-12 also induces natural killer cells activation. Both immunomodulatory approaches of interleukin production by NSCs have successful implications in enhancing survival rate and decreasing tumor burden.

e. Neural Stem Cells Induction in Spinal Cord Injury

In spinal cord injury (SCI), various factors affect the regeneration of neurons. These factors include cell loss, neutrophins deficiency, and glial scar. Therapeutic strategies of using neural stem cells are

more effective in recovering cellular loss after SCI. Neural stem cells are considered as potent candidate for SCI therapy for improving neuronal functional distortions.

Nogo66 receptor (NgR) vaccine is a nucleic acid vaccine, which targets Nogo66 receptors found in central nervous system. Combination of Nogo66 receptor vaccine with neuronal stem cells transplantation increases recovery phase of SCI in preclinical testings. NgR+ NSCs vaccine could promote better functional recovery than when NgR vaccine or NSCs are used alone. This vaccine also prevents motor neuronal entry in the injured tissues of spinal cord. Also, this therapy enhances neuronal cells differentiation into oligodendrocytes and neurons.

M. Effects of Neurotrophic Factors Secreting Mesenchymal Cells in Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder in which there is a progressive motor neurons degeneration. This eventually affects muscles of whole body. Muscular paralysis affects movement, speech, and ultimately leads to respiratory failure and death.

An average of 4–7 per 100,000 people is affected by ALS worldwide, with survival of 3–4 years. Rilizole and Edaravone are two medications for ALS treatment, approved by the US Food and Drug Administration. These drugs are moderately treating ALS by slowing the functional decline of each organ system affected by ALS.

Clinical trials are in advancements for using neurotrophic factors, released by mesenchymal stem cells, in treatment of muscular degeneration of ALS. A multi-step approach is in progress in current clinical trials. This is initiated by removing patient's own bone marrow and then extracting undifferentiated MSCs from a bone marrow cell.

The MSCs are then cultured further in ex vivo cell culture techniques and allowed to differentiate. The differentiated MSCs are

now releasing essential neurotrophic factors, required for phases of neuronal cells development, growth, proliferation and survival. These cells are then transplanted back in the patient.

The neurotropic factors involve vascular endothelial growth factor (VEGF) for angiogenesis and nourishment of neuronal cells, glial-derived neurotrophic factor (GDNF) for promoting neuronal survival, hepatocyte growth factor for promoting angiogenesis, and morphogenesis in various organs and brain-derived neurotrophic factor (BDNF) for neuronal plasticity. Neuronal plasticity is one of many important neuronal functions to change cellular structural and functional responses accordingly to certain stimuli or injuries. The functional importance of neurotrophic factors in modifying neuronal plasticity and survival makes them useful in treating progressive degeneration in ALS.

The differentiated transplanted MSCs have achieved favourable results in Phase II clinical trials for 48 ALS patients in United States in 2017. The transplanted cells are found to be well tolerated and safe. The cells have also improved ALS functional rating responder score (ALSFRS-R). Additionally, inflammatory markers have been downregulated alternatively with increase in neurotrophic factors, improving cerebrospinal fluid biomarker profiles. However, Phase III clinical trials in 2019 did not produce the required responses to meet primary endpoints.

N. Clinical and Biological Applications of Stem Cells in Neurological Disorders

It is important to take into consideration that all the applications of stem cells are either in the animal modelling stage or in the initial phases of clinical trials. Some of these are elaborated as follows.

1) Treatment with mesencephalic tissue in Parkinson's disease

   A project namely TRANSEURO in the United Kingdom has been investigating the advantages of transplanating fetal ventral mesencephalic tissue derived allogeneic dopaminergic neuroblasts

in to PD patients. It was useful in targeting areas which regulates normal neuronal function within the brain.

2) Multiple sclerosis therapy with mesenchymal stem cells

   The therapeutic effects of human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) have been evaluated in patients with multiplesclerosis. Symptoms of the hUC-MSC-treated patients were improved compared to patients in the control group.

3) Neural stem cell therapy approach for amyotrophic lateral sclerosis

   A cell therapy approach has been developed for the treatment of later-phase ALS patients. This clinical trial has used fetal human neural stem cells (hNSCs) into the anterior horns of the spinal cord to test for the safety of both cells.

4) Treatment of spinal cord injury with human embryonic stem cells

   Human embryonic stem cells have been utilized in the treatment of spinal cord injury. All patients have shown significant power and movement of limbs, improvement in their control and sensation of bowel and bladder and sitting balance.

5) Bone marrow-derived cells in treatment of brain injury

   Transplantation with bone marrow-derived cells is a good alternative and valid strategy to treat a focal brain injury.

6) GABAergic interneurons in treatment of epilepsy

   Transplantation of GABAergic interneurons (INs) differentiated from embryonic stem cells can provide long-term functional benefits in animal models of epilepsy and other neurological disorders.

7) Autism spectrum disorder treatment with pluripotent stem cells

   Three-dimensional neural cultures (organoids) derived from induced pluripotent stem cells (iPSCs) have been investigated

neurodevelopmental alterations in individuals with severe idiopathic autism spectrum disorder (ASD).

O. Evidences for Safety and Effectiveness of Stem Cell-Based Therapy for Neurological Disorders

Promising outcomes of human umbilical cord mesenchymal stem cells (hUC-MSCs) have been found in the treatment of ischemic neurological disease. The safety profile and therapeutic effects of hUC-MSCs have been successfully evaluated in clinical trials. The intravenous administration of hUC-MSCs in ischemic patients has markedly improved neurological outcomes such as emotional reaction, extrapyramidal function, and cognition ability.

One of the most serious neurological disorders are intracerebral haemorrhage. Treatment with conventional strategies have been associated with greater risks. MSCs have been found safe and efficacious for treatment of intracerebral haemorrhage. MSC therapy has been associated with neuro-restoration and clinical improvement. Patients treated with this stem cell-based approach have not been associated with any serious adverse effects including de novo tumor development.

Treatment of progressive neurological disorders has been associated with limited safety and efficacy issues. Complicated diseases such as multiple sclerosis is of greater concern as its treatment is highly linked with conventional drugs toxicities. Adipose-mesenchymal derived stem cells (AdMSCs) show a better therapeutic option with minimal invasive procedures. There are improved safety outcomes in treating patients with multiple sclerosis and measures of treatment have shown recovering effects with AdMSCs infusions. PDA-001, human placenta-derived cells have been emerged as well tolerated and efficacious in treating progressive multiple sclerosis patients. There were no signs of paradoxical worsening of lesions with doses of PDA-001.

Cordstem-ST, an IV transplantation of umbilical cord-derived mesenchymal stem cells, has been found to be safe and has greater therapeutic potential in the treatment of acute cerebral infarction. Patients treated with Cordstem-ST experienced no serious adverse effects.

Differentiation of mesenchymal stromal cells into neuron-like cells has also attenuated recovery in cerebral oedema and acute stroke patients. The intravenous infusions of differentiated stem cells have accelerated recovery and improvement with no clinical adverse effects in these patients.

The regenerative therapy, also known as stem cell therapy, is now a part of the treatment regimen of various neuronal diseases. The basic concept behind this advanced therapy is improving the repair response of dysfunctional neuronal cells by transplanting stem cells. This is a revolutionary therapy approach for treating PD, AD, ALS, etc. All these diseases are characterized by the loss of specific neuronal cells and deposition of insoluble and unfolded proteins. Cognitive impairment, motor neuronal dysfunction and paralysis are serious manifestations of these diseases.

The critical pathology of these diseases and involvement of multiple molecular signalling proteins makes treatment more difficult. Also, serious adverse effects associated with conventional therapy makes the patient to leave therapies prior to the completion of treatment. Therefore, there is still a need for efficacious treatment with lower consequences of adverse events. Stem cell therapy has emerged as a safe and beneficial strategy in treating neurodegenerative diseases. It involves isolation of specific neuronal subtypes and reviving a neural network in replacement of the damaged and lost neurons in the disease. Although more research work is still required especially preclinical and clinical studies.

The recent clinical trials have set the stage to continue progress in stem cell-based therapy. Moreover, technological developments using hydrogels and nanoparticles are being in evaluation processes to make stem cell-based treatments more effective. In the future, regenerative

therapies involving stem cell-based treatments for neuronal diseases are expected to be used successfully in clinical settings, making an impossible cure to a better and more effective remedy.

P. Conclusion

Neurodegenerative diseases have disturbing adverse effects profile with conventional pharmacological therapies. To date, therapy with stem cells is probably the most efficacious and preferred treatment option for patients suffering from neurodegenerative diseases. From in vitro studies to animal model, now stem cells have been extensively evaluated in clinical settings in the treatment of various neurological diseases, such as PD, AD, etc. The cost, manpower requirement, and post-transplant monitoring are some of the concerns that are still under investigation for making this therapy more effective and advantageous.

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