Current Trends of Stem Cells in Neurodegenerative Diseases

14

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M. W. Qoronfleh et al. (eds.), *Proteins Associated with Neurodevelopmental Disorders*, Nutritional Neurosciences, https://doi.org/10.1007/978-981-15-9781-7_14

Abstract

Currently, there is extensive interest in stem cell technology. While the management of neurodegenerative diseases is still an open problem for the patients and the public health systems, this book chapter aims to provide information on neurodegeneration and their possible treatment by stem cells. The process of extension of stem cell research into translational and clinical therapies is the main aim of this book chapter. The authors have explained various neurodegenerative diseases and their burden on society with an emphasis on the usage of stem cells. Different types of stem cells used in therapy from bench to bedside have also been discussed. Finally, a descriptive account of the current applications of stem cell therapy in Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Huntington's disease (HD), and autism spectrum disorder (ASD) has been given. The book chapter is distinct in its compilation to provide updated and recent advances of stem cell therapy for the treatment of neurodegenerative diseases.

Keywords

Alzheimer's disease · Amyotrophic lateral sclerosis · Autism spectrum disorder · Clinical trials · Huntington's disease · Neurodegeneration · Parkinson's disease · Stem cells

Abbreviations

AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
ASDs	Autism spectrum disorders
BBB	Blood-brain barrier
CT	Computed tomography
ESCs	Embryonic stem cells
HD	Huntington's disease
iPSCs	Induced pluripotent stem cells
MRI	Magnetic resonance imaging
MSCs	Mesenchymal stem cells
NSCs	Neural stem cells
PD	Parkinson's disease
PET	Positron-emission tomography
SMA	Smooth-muscle antibody

14.1 Introduction

Neurodegenerative disease is a general term for several diseases that mainly affect neurons in the human brain. Neurons are the building blocks of the nervous system, which includes the brain and spinal cord. Neurons usually do not spontaneously reproduce and do not replace themselves, and therefore when they are damaged or die, they cannot be replaced by the body. Acute neurodegeneration can result from an immediate attack, such as a stroke or injury, leading to a loss of neurons in the lesion area. Chronic neurodegeneration can develop over a long period and results in a generalized loss of neuronal populations (Gitler et al. 2017). Examples of neurodegenerative diseases include Parkinson's, Alzheimer's, Huntington's, and amyotrophic lateral sclerosis (*Neurodegenerative Diseases | MedlinePlus* n.d., accessed in 2021; *Amyotrophic Lateral Sclerosis (ALS) Fact Sheet | National Institute of Neurological Disorders and Stroke* n.d., accessed in 2021; Winner et al. 2011). Neurodegenerative diseases are incurable and debilitating conditions that lead to progressive degeneration and/or eventually death of nerve cells. Degenerative nerve diseases can be severe or life-threatening, depending upon their type. Most of them however have no cure.

Treatment can help improve and slow the progression of symptoms, relieve pain, and increase mobility. As neurons deteriorate, a person may first experience relatively mild symptoms like problems with coordination or remembering names. But as vast numbers of neurons continue to die, the symptoms gradually get worse. In some cases, patients lose the ability to walk, think clearly, and generally function in the world. After all, many of these diseases are fatal. Degenerative nerve diseases affect many of your body's activities, such as balance, movement disorders, speech, mental function, respiration, and heart function. Dementias are responsible for the greater incidence of the disease, with Alzheimer's accounting for about 60–70% of cases (Roberts and Knopman 2013; Erkkinen et al. 2018).

This book chapter focuses on different neurodegenerative diseases and their prevention by stem cell therapy. The chapter is an elaborative description of the clinical studies using stem cells as a line of treatment for different neurodegenerative diseases.

14.1.1 Alzheimer's Disease (AD)

Alzheimer's disease (AD) is a progressive, neurodegenerative disease of the brain that slowly erodes memory and thinking skills and eventually causes an inability to perform simple tasks. It is the most common cause of dementia, accounting for about 50–70% of all dementia cases. Alzheimer's disease is a chronic neurodegenerative disease of the central nervous system (CNS). It is characterized in its mild form by gradual loss of memory and limitation of the brain's other mental functions. It is pathologically characterized by the deposition of two pathological proteins in the brain: the amyloid-beta protein (Aβ) and the tau protein. A buildup of these proteins leads to CNS dysfunction and subsequent death of nerve cells. The disease slowly

affects nerve cells in all areas of the cerebral cortex and some surrounding structures, making it difficult for a person to regulate emotions, recognize mistakes and patterns, coordinate movement, and remember (*Dementia Pathology: Dementia, Alzheimer Disease, Vascular Dementia* 2019; Mayeux and Stern 2012; Leyns and Holtzman 2017). The risk of developing AD increases exponentially with advanced age. It is a disease of the "elderly," although sporadic cases might occur under 65. The most significant risk for Alzheimer's disease is advanced age, with the risk continuing to increase as we age (Petersen et al. 2014; Edwards et al. 2019; Silva et al. 2019).

Although the main etiology of the disease is unknown, several risk factors are known to affect the development (Bekris et al. 2010). The condition can continue for many years without symptoms, referring to the preclinical or pre-symptomatic disease stage.

Genetic factors seem to play an important role. Simultaneously, environmental factors, including vascular disease (e.g., diabetes, hypertension, dyslipidemia) and lifestyle (e.g., education, occupation, mental, social activities, physical activity, diet), seem to influence the likelihood of developing the disease. Changes and lesions in the brain can take more than 20 years before symptoms develop (Ballard et al. 2011; Nazarko 2019). Eventually, a person with AD loses memory and many other mental functions. According to the World Health Organization, 10% of the population aged 65 years and over have AD, and over 14 million Americans will develop AD by 2060 (2020 Alzheimer's disease facts and figures 2020).

There is no etiological treatment for AD (Ballard et al. 2011; Alexiou et al. 2017). Drug therapy aims to slow the progression of the disease and treat the symptoms associated with the disease. The benefit of the drugs used to treat Alzheimer's disease is usually small. Therefore, patients and their families may not notice any benefit. Patients and their families should discuss with their physicians whether medication can help improve behavior or functional abilities. It should also be discussed whether medications should be prescribed early in the disease. Cholinesterase inhibitors and NMDA antagonists are often prescribed to treat Alzheimer's disease. The commonly used medicines include galantamine, donepezil, rivastigmine, and memantine (Giacobini and Gold 2013; Mendiola-Precoma et al. 2016).

14.1.2 Parkinson's Disease (PD)

Parkinson's disease (PD) is a progressive, degenerative disease of the central nervous system. As part of this degenerative process, some of the brain's nerve cells, primarily responsible for programming and coordination of movement, lose their functionality in adulthood (Winner et al. 2011; Erkkinen et al. 2018). This disturbance results in the gradual reduction of the individual's mobility. The programming and harmony in the execution of a movement are controlled by a complex system of structures in the brain (primary ganglia-cortex). The substance that plays a significant role in the communication of these structures is dopamine. This substance is produced by specialized nerve cells in an area at the brain's base, called a black

substance. Over the years and under the influence of genetic and environmental factors, these cells' functions may degenerate, reducing dopamine production levels in the brain. Low dopamine levels and disruption of the primary ganglia and cerebral cortex connections lead to decreased harmony of movement (Erkkinen et al. 2018; Tarakad and Jankovic 2020). Movement is controlled by neurons in the motor cortex and the basal ganglia, along with pyramidal and other afferent neuronal tracts. The initiation of movement is mediated by a dopamine-dependent neural circuit involving the basal ganglia, the cortex, and the substantia nigra. In healthy people, these messages are transmitted smoothly. However, in patients with PD, the messages are blocked and not transmitted correctly due to a lack of dopamine (Marino et al. 2019). In people with PD, 70–80% of dopamine-producing cells have degenerated and died. The degeneration mainly occurs in a small area of the brain called the substantia nigra. When there is dopamine deficiency, nerve cells do not function properly and cannot transmit messages to the brain, resulting in PD symptoms. Although dopamine is the primary neurotransmitter affected, PD can be disrupted by other neurotransmitters as well. The above mechanism partly explains why simple dopamine replacement therapy does not produce the expected results (Tysnes and Storstein 2017; Balestrino and Schapira 2020).

Disorders of other neurotransmitters might also explain the numerous non-motor symptoms in PD. It is unclear as to why dopamine-producing cells deplete so quickly. Multiple factors are generally thought to be involved, and modern research focuses on aging, viruses, and genetic and environmental factors (Balestrino and Schapira 2020).

It is also not clear why certain people develop Parkinson's disease and not others. The causes of the disease are still unknown. Systematic research is currently undertaken by many teams worldwide to determine the cause and possible association of the disease with environmental and genetic factors (Tysnes and Storstein 2017).

14.1.3 Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. ALS is the most common motor neuron disease in adults (Pupillo et al. 2014). Motor neuron diseases cause selective loss of nerve cells that connect the brain to the muscles. ALS affects both the upper and lower motor neurons throughout the brain and spinal cord. Motor neurons travel from the brain to the spinal cord, and from there, the spinal cord transmits neuronal signals to the muscles throughout the body. The progressive degeneration of motor neurons in ALS eventually leads to their death. When motor neurons die, the brain's ability to move and control muscle movement is lost. With the muscles' voluntary action being gradually affected, patients in the advanced stages of the disease can become paralyzed completely (Martin et al. 2017; Masrori and Van Damme 2020). ALS most often affects people between the ages of 40 and 60; however, persons

younger and older than the age range could also develop the disease. It is shown that men seem to become affected more often than women (Talbott et al. 2016).

The etiology of ALS is still unknown. An essential step in answering this question was made in 1993 when scientists from the National Institute of Neurological Disorders and Stroke (NINDS) discovered that mutations in the gene produced by the enzyme SOD1 were linked to some cases of familial ALS (Majoor-Krakauer et al. 2003). Although the mechanism behind the mutations in the SOD1 gene resulting in degeneration of motor neurons remains unclear, there is growing evidence that the mutated SOD1 protein might become toxic (Štětkářová and Ehler 2021).

14.1.4 Huntington's Disease (HD)

Huntington's disease (HD) is caused by neuronal degeneration at the basal ganglia, which is the area responsible for movement and coordination. The neural structures and circuits responsible for thought, perception, emotion, and memory are also affected, probably due to the connections of the basal ganglia with frontal lobes (Roos 2010; Erkkinen et al. 2018). HD is nowadays recognized as one of the most common genetic disorders. More than 1/4 of a million Americans suffer from HD or are at risk of inheriting the disease from an ailing parent. HD is characterized by substantial variability in its expression, even within the same families. The identification and localization of the responsible HTT gene facilitated the determination of the people who will develop the disease by DNA analysis. The documentation of family history is essential by means of genetic testing for HD (Nguyen and Weydt 2018). Brain imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), can detect atrophy in specific areas of the brain, especially in the caudate nucleus and putamen. Other studies have yielded generalized atrophy of the brain (Negi et al. 2014; Fazio et al. 2018). A DNA mutation analysis can be clinically valuable to predict HD in a person at risk, set a prenatal diagnosis in high-risk pregnancy, or confirm the disease after being suspected by relative symptoms. The symptoms include physical abnormalities (e.g., involuntary movements, anxiety, loss of balance, strange walking, poor coordination, dysarthria), cognitive changes (e.g., memory loss, miscalculation, disorganization), and emotional and behavioral disorders (e.g., depression, apathy, paranoia, anger, withdrawal, anxiety) (Nguyen and Weydt 2018).

HD is an inherited, fatal degenerative brain disorder. No treatment is available yet; however, Xenazine and Deutetrabenazine have been approved as symptomatic treatments for HD-associated chorea (Bachoud-Lévi et al. 2019). HD gradually reduces the affected person's ability to walk and talk. Eventually, the patient becomes entirely dependent on others for their care. HD profoundly affects the lives of the entire family emotionally, socially, and financially. The early symptoms of HD can affect the person's cognitive ability or mobility and include depression, mood swings, memory loss, awkwardness, involuntary contractions, and lack of coordination. Later on, as the disease progresses, the patient's concentration and

short-term memory decrease, while the head, torso, and involuntary movements of the limbs increase. Speech, walking ability, and swallowing coordination also continue to degenerate. Finally, the patients are not capable of taking care of themselves. Death occurs from complications such as drowning, infection, or heart failure (Mestre et al. 2009; Frank 2014).

HD becomes clinically apparent between 30 and 50 years, although it can begin from early childhood. Those children who develop the juvenile form of the disease rarely live to adulthood (Erkkinen et al. 2018). The prevalence of HD is similar between women and men and transcends all ethnic and racial boundaries. Every person who carries the HTT gene will develop the disease. Each child who suffers from HD has an inevitable 50% chance of fatally inheriting the gene. The HD gene was isolated in 1993. The genetic test, which was developed, can determine whether a person carries the HD gene accurately. The test, however, could not predict when the symptoms would start (Nopoulos 2016).

14.1.5 Autism Spectrum and Neurodevelopmental Disorders

Autism spectrum disorders (ASDs) consist of a heterogeneous group of neurodevelopmental disorders. The principal features are stereotypical behaviors and problematic social communication and reciprocal interaction (Sharma et al. 2018). ASDs have become more prevalent over the past two decades, although their increasing prevalence could be partly attributed to the elevated level of awareness among physicians, educators, and parents. In the United States, ASDs affect up to 1 in 88 children (1 in 54 males and 1 in 252 females) older than 8 years (*2020 Community Report on Autism* 2020). Globally, it is estimated that 1 in 160 children suffer from ASDs. Up to 75% of patients with ASDs have psychiatric comorbidities, including but not limited to depression, bipolar disorder, and attention-deficit–hyperactivity disorder (ADHD) (Antshel et al. 2013).

ASDs are multifactorial disorders in terms of etiology. Risk factors implicated in their pathogenesis include impaired immune responses, neuroinflammation, neurotransmission abnormalities, dysfunction of the mitochondria, oxidative stress, and environmental stressors/toxins. Associated genetic deficits and disorders include fragile X syndrome, tuberous sclerosis, epilepsy, and Down syndrome (Lacivita et al. 2017; Eissa et al. 2018).

The International Classification of Diseases (ICD-10) has reserved the F.84.0 code for ASDs, classifying them as "pervasive developmental disorders" (*F84.0—Autistic disorder | ICD-10-CM* n.d., accessed in 2021). The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) of the American Psychiatric Association has set the major criteria for the diagnosis of ASDs: persistent deficits in social interaction, restricted stereotype behavioral patterns, symptoms with an onset in the early developmental age, considerable functional impairment of everyday activity, and failure to better interpret these symptoms using other intellectual deficits (*Autism Diagnosis Criteria: DSM-5 | Autism Speaks* n.d., accessed in 2021). Disorders of the autism spectrum include but are not limited to autistic disorder, Rett's and

Asperger's syndromes, disintegrative childhood disorder, and pervasive developmental disorder (PDD). Despite the common perception, individuals without significant intellectual disability (high-functioning autism) are usually capable of attending college, graduating, and living independently, although they typically struggle with social interaction. In many cases, the failure of individuals with autism to live independently or graduate is due to increased social demands and lack of adequate psychosocial support (Eissa et al. 2018; Sharma et al. 2018).

The treatment of ASDs is mainly symptomatic and includes various pharmacological and non-pharmacological modalities. Approved pharmacological agents such as serotonin reuptake inhibitors (fluoxetine), tricyclic antidepressants (imipramine), anticonvulsants (lamotrigine), atypical antipsychotics (clozapine), and inhibitors of acetylcholinesterase (rivastigmine) are used to mitigate the behavioral symptoms of ASDs (Leskovec et al. 2008; Accordino et al. 2016). Educational enhancement therapies with a focus on speech, language, auditory ability, and social integration are used in combination with various models of psychotherapy. Ongoing research for curative treatments focuses on anti-inflammatory agents, novel psychotropic agents, and food supplementation (Eissa et al. 2018).

14.2 Stem Cells

Stem cells constitute primate cells which are precursors of all the cells in the human body and, under suitable conditions, can be transformed into each human cell. Stem cells could potentially heal all organs that contain cells into which they can be transformed (Imamura and Inoue 2012).

14.2.1 Stem Cell Sources

The primary sources of stem cells are umbilical cord blood and tissue, placenta, deciduous teeth, adipose tissue, and bone marrow (Wislet-Gendebien et al. 2012a).

The **embryonic stem cells (ESC)**, as their name implies, are derived from embryos. They are developed from eggs that have been fertilized in vitro at fertilization clinics and then made available for research purposes with donors' consent (Girlovanu et al. 2015). Embryonic stem cells are not derived from fertilized eggs in a woman's body. Adult stem cells are thought to be undifferentiated cells found among differentiated cells in tissues or organs. Adult stem cells can be renewed and differentiated, while they can generate some of the most important cells of a tissue, too. An adult stem cell's primary role in a living organism is to maintain and repair the tissue in which it is located. Adult stem cells usually produce the cell types of the tissue in which they live. For example, the bone marrow's hematopoietic adult stem cells usually give rise to many types of blood cells (Goya et al. 2018; Zakrzewski et al. 2019).

Moreover, in recent years, experiments have shown that stem cells originating from one tissue could generate a completely different tissue type (Liu et al. 2020).

The issue remains an area of significant discussion within the research community. The above controversy underlines adult stem cell studies' challenges, and it seems that additional research is needed to understand their potential as future therapies entirely (Lim et al. 2013). In contrast with embryonic stem cells, which are defined by their origin, the origin of adult stem cells in specific mature tissues is still under investigation. Stem cells are distinguished from other cell types by two characteristics. First, they are undifferentiated cells capable of regenerating themselves through cell division (sometimes after long periods of inactivity). Second, under certain physiological or experimental conditions, they could be stimulated to generate specific organ or tissue cells with specific functions. They are characterized by the remarkable ability to evolve into many different cell types of the body during early life and growth. When a stem cell is divided, each new cell that occurs has the potential to either remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell. Besides, stem cells can serve as a kind of internal repair system in many tissues, being continuously divided for the reconstitution of other cells, as long as the person or animal is still alive (Sivakumar et al. 2015; Liu and Deng 2016).

Another possible application of stem cells is their usage in medical treatments. Nowadays, there is an increasing demand for donated organs, which are needed to replace diseased or damaged organs. Unfortunately, the number of people who require a transplant far exceeds the number of organs available for transplantation (Sivakumar et al. 2015).

The **multipotent stem cells** are a renewable source of replacement cells or tissues to treat many diseases, conditions, and disabilities, including PD, spinal cord injury, burns, heart disease, stroke, and ALS (Hermann and Storch 2013). In some specific organs, such as the intestine and the bone marrow, stem cells undergo continuous division to repair and replace degenerated or damaged tissue. However, in other organs like the pancreas and the heart, stem cells divide only under specific conditions (Kurtzberg 2017).

The hematopoietic stem cells (HSC) are responsible for creating blood cells: red blood cells, B-lymphocytes, T-lymphocytes, neutrophils, basophils, eosinophils, monocytes, and macrophages (Lim et al. 2013).

The mesenchymal stem cells (MSC) can create various cell types: bone cells, cartilage cells, fat cells, and other types of connective tissue cells, such as those in tendons (Table 14.1).

Neural stem cells (NSC) can create three main cell types: nerve cells and two classes of non-neuronal cells, astrocytes, and oligodendrocytes, as presented in Table 14.2.

The epithelial stem cells differentiate into many types of cells, including but not limited to absorptive cells, goblet cells, and Paneth cells (Girlovanu et al. 2015).

The epidermal stem cells are located in the basal layer of the skin and at the base of hair follicles. Epidermal stem cells create keratinocytes, which eventually migrate towards the skin's surface to form a protective layer (and eventually shed off) (Lenkiewicz 2019) (Fig. 14.1).

Table 14.1 An overview of the literature related to mesenchymal stem cells in neurodegenerative disease research

Albani et al. (2013)	Literature review	Hydrogel-based nanocomposites and mesenchymal stem cells: a promising synergistic strategy for neurodegenerative disorder therapy
Chen et al. (2018)	Literature review	Mesenchymal stem cell-mediated immunomodulation in cell therapy of neurodegenerative diseases
Fričová et al. (2020)	Literature review	Challenges and translational considerations of mesenchymal stem/stromal cell therapy for Parkinson's disease
Huang et al. (2012)	Literature review	Mesenchymal stem cells as therapeutic agents and potential targeted gene delivery vehicles for brain diseases
Lo Furno et al. (2018)	Literature review	Functional role of mesenchymal stem cells in the treatment of chronic neurodegenerative diseases
Nery et al. (2013)	Classification, flow cytometry	Human mesenchymal stem cells: From immunophenotyping by flow cytometry to clinical applications
Ng (2014)	Literature review	Progress of mesenchymal stem cell therapy for neural and retinal diseases
Olson et al. (2012)	Literature review, develop a siRNA delivery system	Genetically engineered mesenchymal stem cells as a proposed therapeutic for Huntington's disease
Peng et al. (2013)	Literature review	Mesenchymal stem cells: a revolution in therapeutic strategies of age-related diseases
Shariati et al. (2020)	Literature review	Mesenchymal stromal cells (MSCs) for neurodegenerative disease: A promising frontier
Staff et al. (2019)	Literature review	Mesenchymal stromal cell therapies for neurodegenerative diseases

Recently, cell replacement therapy was proven to help relieve symptoms or even reverse the progression of neurological disorders, where neither pharmacological interventions nor other treatments were sufficient or available (Shin et al. 2011; Abdullah et al. 2012). Thus, various stem cells have been transplanted into the injured brain, including mesenchymal stem cells (MSCs), to release or stimulate the release of nutrients (Huang et al. 2012). MSCs are of utmost importance for treatment strategies because of the simplicity in their isolation process (Lescaudron et al. 2012). MSCs are defined by their surface marker expression pattern and can be easily extracted from the patient's bone marrow or adipose tissue. They can also be replanted into the same patient to repair injured or degenerated tissues (Kan et al. 2007).

It has been shown that the MSCs and genetically modified MSCs offer therapeutic benefits in brain diseases, such as strokes, neurodegenerative diseases, and brain stem gliomas (Tanna and Sachan 2014). They are considered a promising treatment for PD due to their neuro-rehabilitation properties and constitute a promising

Table 14.2 An overview of the regenerative medicine for neurodegenerative diseases and relevant research

Ahani-Nahayati et al. (2021)	Literature review	Stem cell in neurodegenerative disorders; an emerging strategy
De Filippis and Binda (2012)	Literature review	Concise review: Self-renewal in the central nervous system: Neural stem cells from an embryo to adult
Díaz (2019)	Literature review	Regenerative medicine: Could Parkinson's be the first neurodegenerative disease to be cured?
Harris et al. (2020)	Literature review	Emerging regenerative medicine and tissue engineering strategies for Parkinson's disease
Hermann and Storch (2013)	Literature review	Induced neural stem cells (iNSCs) in neurodegenerative diseases
Kim et al. (2013)	Cell culture experiments	Neural stem cell-based treatment for neurodegenerative diseases
Kittappa et al. (2012)	Literature review	The role of eNSCs in neurodegenerative disease
Relaño-Ginés et al. (2014)	Literature review	Prion diseases and adult neurogenesis: How do prions counteract the brain's endogenous repair machinery?
Struzyna et al. (2017)	Original research report	Anatomically Inspired Three-dimensional Micro-tissue Engineered Neural Networks for Nervous System Reconstruction, Modulation, and Modeling
Van Den Berge et al. (2013)	Literature review	Resident adult neural stem cells in Parkinson's disease—The brain's own repair system?
Wislet-Gendebien et al. (2012a)	Literature review	Adult bone marrow: Which stem cells for cellular therapy protocols in neurodegenerative disorders?
Ziemka-Nalecz (2012)	Literature review	Endogenous neurogenesis induced by ischemic brain injury or neurodegenerative diseases in adults

therapeutic tool for reducing Aβ deposits in patients with AD (Kim et al. 2013). The application on transferring agents provides benefits over other methods. Emerging evidence suggests that the implantation of MSCs in the corpus striatum might delay the loss of median neurons in HD.

MSCs have also been proven to be superior to NSCs, as their isolation and application are well established and could be received from various adult tissues (Lescaudron et al. 2012). In addition, they are highly interactive with their microenvironment and can share proteins, RNA, and even mitochondria with damaged tissue (Wislet-Gendebien et al. 2012b). Viral vectors have been used to construct MSCs, which overexpress cell receptors on their cell surface. On the other hand, nonviral vectors might be more suitable for the controlled release of genes into cells or tissues. A significant obstacle to the effective implementation of MSC therapy is the inability to deliver these cells under minimally invasive conditions (Dey et al. 2010).

Magnetic resonance imaging (MRI) is mainly used to detect stem cells, and when correlated with positron-emission tomography (PET) imaging, it can visualize metabolic events. Several cytometry techniques are being developed to visualize stem cell transplantation into damaged tissue (Nery et al. 2013). In chronic neuronal

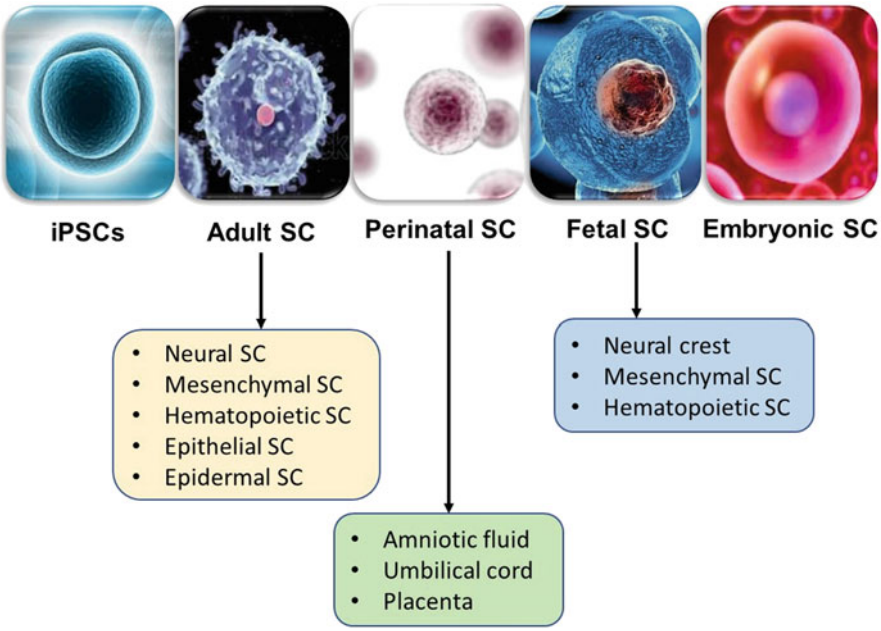

Fig. 14.1 Classification of stem cells based on the source of origin

degeneration, nanocomposite gels might be a powerful tool for achieving a controlled and long-lasting drug delivery in close contact with affected areas (Albani et al. 2013). Severe side effects were not observed or reported in the use of MSCs. Few studies have shown contradictory results on the immunomodulatory properties of MSCs, which can be explained by the heterogeneous stem cell population (Lo Furno et al. 2018).

Significant challenges need to be overcome before MSC treatment can be adopted in everyday clinical practice. These include (1) poor MSC in vivo retention; (2) poor MSC implantation, viability, and in vivo function; (3) unclear mechanisms of action; and (4) lack of standardized, controlled studies. MSCs do not seem to be a viable alternative to NSCs as a strategy for neural tissue replacement. There is no precise definition of the mechanisms behind stem cell therapies for brain diseases yet (Peng et al. 2013).

Nevertheless, MSCs provide a promising platform able to produce neural regulation agents. The importance of enhancing MSCs' targeting capacity for future treatment of brain diseases has been highlighted (Joyce et al. 2010). It is also imperative that the surgical and transport strategies need to be improved, and safety issues should be thoroughly studied. It has been noted that rodent MSC cultures are often contaminated with hematopoietic elements and do not sufficiently reflect human stem cell biology (Ramakrishnan et al. 2013). Further investigation is needed to study the details of cell therapy. Additional clinical studies, combined with genetic and pharmacological approaches for increasing cell survival and uptake of

endogenous repair mechanisms, would reveal the stem cell source's potential. It is expected that the infusion and transplantation of preserved, genetically allogenic, or homologous MSCs for the treatment of multiple human neurological diseases would be improved in the upcoming years. Therefore, future research should focus on neurodegenerative diseases.

Cell replacement therapy and gene transfer in the diseased, degenerated, or injured brain provide the basis for developing new therapeutic strategies for human neurological diseases (De Filippis and Binda 2012). The endogenous neural stem cells (eNSCs) can allow therapeutic interventions in neurodegenerative diseases, especially in cases where the damaged brain tissue is located close to the NSC niches, such as the striatum in PD, close to the subventricular zone (SVZ). The NSCs are present in the SVZ of patients suffering from PD. The mobilization of the SVZ endogenous NSCs to reconstitute the dopamine striatum constitutes an attractive approach strategy for treating motor symptoms in patients with PD without the ethical and immune problems of NSCs and fatal brain transplantation (Alexiou et al. 2020). It has been observed that the proliferation of NSCs in SVZ was not statistically significantly different between patients and controls.

In conclusion, dopamine deficiency reported to be caused by various toxins in different animal models had a variable effect on the proliferation of NSCs in SVZ (De Filippis and Binda 2012; Yuan and Shaner 2013).

Immortalized NSCs have emerged as a highly effective tool for genetic manipulation and ex vivo gene transfer to the central nervous system. The cells were genetically modified in vitro, survived, integrated into host tissues, and differentiated into neurons and glial cells after transplantation into the intact or damaged brain in vivo. Clonally generated immortalized cell lines of human NSCs, as produced by introduction of oncogenes, have advantages for cell therapy and gene therapy. The advantages include (1) homogeneity of NSCs since they are produced from a single clone, (2) potential to be extended to a large number of cells in vitro, and (3) stabilization of the expression of therapeutic genes to be easily achieved (Ramakrishnan et al. 2013).

The development of innovative methods for creating NSCs in vitro has been one of the main goals of researchers after discovering active neurogenesis in the central nervous system of mammals (Compagnucci et al. 2014). The new technology for production of the induced NSCs (iNSCs) from easily accessible cell sources, such as skin fibroblasts, opens up a new field in personalized medicine for neurodegenerative diseases. iNSCs appear to provide some advantages over induced neurons (iNS) and possibly iPSCs in replacing and modeling neurodegenerative disease cells (Hermann and Storch 2013). Although the available studies convincingly showed the similarities between iNSCs and primary NSCs, many open debates and questions remain regarding the following aspects: (1) Are retroviral vectors completely silent in iNSCs? (2) Does the iNSC conversion process lead to genetic changes? (3) Are the iNSC conversion states stable, and does it lead to a stable change of the epigenome to NSC?

There is no doubt that the replacement of endangered or damaged cells can alleviate the symptoms of the disease. However, it does not necessarily stop the

progression of the disease itself (Kittappa et al. 2012; Ziemka-Nalecz 2012). Evidence from several research groups has underlined that extensive eNSCs are present throughout the adult brain and across the whole spinal cord (Wislet-Gendebien et al. 2012b). Hence, as reported in the models of degenerative disease and acute attacks, the treatments that increase the numbers of cells in living tissues also provide neuroprotection and rescue of neurons from death. The determination of the presence of eNSCs depends mainly on two experimental approaches. The first is the identification of biomarkers for the immediate detection of eNSCs. The second approach is to extract the cells from the primary tissue and grow them under conditions that support survival and self-renewal (Lescaudron et al. 2012).

Regarding cell therapies, the most obvious question is the source utilized for cell replacement (Kittappa et al. 2012). Should the emphasis be kept on embryonic or adult stem cells? What is the optimal source to avoid immunocompatibility, inefficient cell proliferation, and cancer induction and minimize ethical issues? Understanding the endogenous configuration of the neurogenesis system is expected to bolster the development of effective therapies based on nerve stem cells (Relaño-Ginés et al. 2014) (Table 14.3).

Due to the lack of appropriate disease models and a sufficient number of brain biopsy specimens, the true etiology and pathology of many neurological diseases remain unknown (Kunkanjanawan et al. 2011). It has been proposed that the induced pluripotent stem cells (iPSCs) could become a new tool for the production of patient-specific multipotent stem cells to be used as a model of genetic neurological diseases (Mohamet 2014). Human PSCs, including iPSCs and embryonic stem cells (ESCs), can renew themselves, grow indefinitely, and retain the ability to form all kinds of cells in the body. The iPSCs are induced pluripotent stem cells derived from fibroblasts through forced expression of critical multivalent transcription factors of human embryonic stem cells (hESCs) (Oct4, c-myc, SOX2, and KLF4) (Abdullah et al. 2012). The two types of multivalent cells exhibit quite similar properties, such as self-renewal, differentiation, and same cell surface antigens and gene expression profile. However, studies comparing hESCs with iPSCs have indicated that they are genetically and epigenetically similar but not identical (Schwartz et al. 2012). Modeling neurodegenerative diseases requires a differentiation process of iPSCs into specific neuronal cell types (Compagnucci et al. 2014). One of the limitations of the iPSCs' human technologies is that it is time consuming to generate neurons from multivalent stem cells. Both the formation of iPSCs and the subsequent differentiation into neuronal cells require 1–2 months. Although iPSC technology is still in its infancy and faces several problems and obstacles, it has a great potential for identifying therapeutic targets for treating neurodegenerative diseases (Gao et al. 2013). Compared to ESCs, the therapeutic use of iPSCs is considered to be ethically more profitable because it does not involve the destruction of human embryos. The iPSCs seem to be potential sources for cell therapy because they can be differentiated into NSCs and MSCs to replace damaged cells. The unlimited possibilities of iPSCs to differentiate might allow us to model AD and ALS and provide possible treatment without HD. The iPSC technology has emerged as a revolutionary tool in medical research and clinical therapy (De Filippis and Binda 2012; Schwartz et al. 2015).

Table 14.3 Pluripotent stem cells in neurodegenerative disease—an overview of the available literature

Abdullah et al. (2012)	Literature review	The path from skin to brain: generation of functional neurons from fibroblasts
Chang et al. (2017)	Original research report	Combining Induced Pluripotent Stem Cells and Genome Editing Technologies for Clinical Applications
Chang et al. (2018)	Literature review	Induced Pluripotent Stem Cells: A Powerful Neurodegenerative Disease Modeling Tool for Mechanism Study and Drug Discovery
Compagnucci et al. (2014)	Literature review	In vitro neurogenesis: Development and functional implications of iPSC technology
Gao et al. (2013)	Literature review	Potential therapeutic applications of differentiated induced pluripotent stem cells (iPSCs) in the treatment of neurodegenerative diseases
Imaizumi and Okano (2014)	Literature review, electron microscopic observation, analysis of postmortem brain tissue, expression analysis	Modeling human neurological disorders with induced pluripotent stem cells
Imamura and Inoue (2012)	Literature review	Research on neurodegenerative diseases using induced pluripotent stem cells
Jongkamonwiwat and Noisa (2013)	Reports review	Biomedical and clinical promises of human pluripotent stem cells for neurological disorders
Jung et al. (2012)	Literature review	Human-induced pluripotent stem cells and neurodegenerative disease: Prospects for novel therapies
Kunkanjanawan et al. (2011)	Literature review	Modeling neurological disorders by human induced pluripotent stem cells
Liu and Deng (2016)	Original research report	Reverse Engineering Human Neurodegenerative Disease Using Pluripotent Stem Cell Technology
Mohamet (2014)	Literature review, cluster analysis	Familial Alzheimer's disease modeling using induced pluripotent stem cell technology
Pen and Jensen (2017)	Literature review	Current status of treating neurodegenerative disease with induced pluripotent stem cells
Siller et al. (2013)	Literature review	Modelling human disease with pluripotent stem cells
Yuan and Shaner (2013)	Method	Bioengineered stem cells in neural development and neurodegeneration research

Nowadays, scientists can isolate a patient biopsy and, through iPSC technology, grow cells, stimulate pluripotency, and differentiate the resulting iPSCs into the specific cell type affected by the disease (Siller et al. 2013). iPSC technology could also be applied to understand the molecular mechanisms involved in cancer and oncogenicity (Siller et al. 2013). iPSC technology has potential applications in (1) disease modeling, (2) drug screening, and (3) stem cell transplantation therapy (Compagnucci et al. 2014). The first and most crucial step in building cellular models is to create iPSC-derived patient cell lines (Jung et al. 2012). Smooth-muscle antibody (SMA) is one of the first human neurodegenerative diseases characterized by the iPSC in vitro model of the disease.

Furthermore, PD is one of the diseases in which cell therapy with iPSCs is effectively applied. It is also possible to create iPSC models of patients and study how each individual could develop the disease (Yuan and Shaner 2013; Payne et al. 2015). The use of iPSCs offers improved clinical cell models that are expected to significantly reduce the time and costs needed to develop new therapies, thereby increasing the number of new drugs available on the market for neurodegenerative diseases. Nowadays, there are multiple methods to derive the cell types that researchers are interested in; the method of selection depends mainly on the research question and its effectiveness. Current research shows that disease-specific iPSC technology can accurately reflect and image conditions before the onset of clinical disease, or in many cases, during the early stages of the disease (Imaizumi and Okano 2014). Dramatic progress in elucidating pathogenetic mechanisms is expected in the following years, with the assistance of iPSC technology, whole-genome analysis, and noninvasive imaging technology. Although hPSCs have been proven to be functional in vitro and have been able to treat phenotypes in diseased mice, there are still several issues which are needed to be resolved before this technology is applied to everyday clinical practice, such as the purity of the transplanted cells, the transplant sites, and the oncogenesis (Shin et al. 2011; *Transplantation of Neural Stem Cell-Derived Neurons for Parkinson's Disease* 2017). There is an imperative need to improve our knowledge of the mechanisms that control neurogenesis in vivo to effectively guide cell modeling and possible therapeutic applications of iPSC technology. While iPSC technology is a powerful technique that allows scientists to investigate the process and stratification of degeneration in neurological diseases and discover new drug therapies and strategies (Kunkanjanawan et al. 2011), researchers should examine the following (Siller et al. 2013): (1) what should be defined as a high-quality iPSC, (2) the standardization of methods necessary to confirm pluripotency, and (3) the determination of the minimum number of clones, subjects, and controls that are needed for genetic variation.

14.3 Clinical Trials for Stem Cell Therapies

In the following part of the chapter, the authors provide a twofold account of clinical trials for stem cell therapies in neurodegenerative diseases. First, an overview of stem cells investigated in clinical trials is provided. In addition, the ongoing and

projected clinical trials in the context of particular neurodegenerative diseases, such as AD, PD, and HD, are discussed.

14.3.1 Human Embryonic Stem Cells

Even though scientists were able to extract ESCs from mice in the 1980s, it was not until 1998 when a research team from the University of Wisconsin-Madison isolated and kept the human fetal embryonic stem cells alive in cell cultures (Kim et al. 2013). This time interval was necessary to develop the required techniques for tracing embryonic stem cells. This can be partly attributed to the fact that adult stem cells are inherent, indistinguishable in shape, size, and function. They also reside deeply in tissues in countable populations, hence complicating their tracing and isolation. Despite the common belief that human fetal stem cells could contribute as treatment options in many catastrophic diseases, basic and clinical research is still in its infancy. The first clinical trials have just started to be published. The National Institutes of Health (USA) funded the first ESC research study in 2002 (*Embryonic Stem Cells* n.d. | *stemcells.nih.gov*, accessed in 2021). From then onwards, biotechnology companies rely on these foundations to develop human stem cell therapies. There are currently two active clinical trials utilizing human embryonic stem cell-based therapies conducted by a biotechnology company called ACT (*Sub-retinal Transplantation of hESC Derived RPE(MA09-hRPE)Cells in Patients With Stargardt's Macular Dystrophy* 2020). The company has started enrolling patients for Phase I as follows: (1) The first clinical trial was conducted to document the safety of human fetal ESCs isolated from the retina for the treatment of Stargardt disease (SMD), an inherited form of macular degeneration. (2) The second clinical trial was concerned with the safety of human fetal retinal-derived ESCs to treat patients with age-related macular degeneration. In January 2012, researchers published a preliminary report about the first two patients treated with human-derived embryonic stem cells (Schwartz et al. 2012).

Pfizer has launched a study in collaboration with the University College London to test the treatment of human embryonic germinal cell-derived stem cells for acute wet age-related macular degeneration. The results of this study are expected to be announced in due time (Coffey 2019). A third clinical trial with hESCs was stopped on November 14, 2011. The trial was conducted by the biotechnology company Geron. Four patients with a spinal cord injury were included in the clinical trial treated with hESCs (Scott and Magnus 2014). Oligodendrocyte precursor cells derived from hESCs were injected directly at the site of spinal cord injury. On November 14, Geron announced that it was shutting down its stem cell programs to focus on cancer programs. The vulnerability of patients, in combination with the complexity of the transplantation procedure, has contributed to its continuation (Scott and Magnus 2014).

14.3.2 Induced Pluripotent Stem Cells

In late 2007, scientists reported that they could reprogram adult human skin cell iPSCs to behave like ESCs (Baker 2007). From the first reports until now, researchers have rapidly improved the iPSC creation techniques, providing a valuable way to differentiate cells whose developmental fate has been determined. In July 2013, Japan's health minister approved the first clinical trial with iPSCs, in an attempt to cure age-related macular degeneration, a form of blindness (Sipp 2013).

14.3.3 Bone Marrow and Umbilical Cord Stem Cells

Bone marrow contains hematopoietic stem cells that have been used for decades to treat blood cancers and other blood disorders (Tigue et al. 2007). Umbilical cord blood is another source of hematopoietic stem cells used in therapeutics (Lo Furno et al. 2018). Such stem cells are either deposited to a global hematopoietic stem cell blood or stored in private blood banks. The therapeutic potential of the latter practice is controversial and limited, although private banks make stem cells constantly available to the owners (Gluckman et al. 2011; Iriberri 2011). More than 2100 clinical studies are currently investigating the therapeutic potential of these cells (Chivu-Economescu and Rubach 2016). About 42 trials registered in Clinicaltrials.gov are currently investigating bone marrow stem cells in neurodegenerative disorders, particularly AD, PD, and ALS (*Search of: Bone Marrow Stem Cells | Neurodegenerative Diseases* 2021), while 19 registered trials are studying umbilical cord stem cells in this context (*Search of: Umbilical cord stem cells | Neurodegenerative Diseases* 2021). The majority of the latter studies also focus on AD, PD, and ALS, although fewer are related to juvenile and hereditary neurogenerative disorders such as hereditary cerebellar ataxia.

14.3.4 Human Spinal Cord Stem Cells

A biotechnology company called Neuralstem is conducting a clinical trial using human stem cells to treat spinal ALS. The company received FDA approval to conduct a Phase I trial and began enrolling patients in January 2010. About 12 participants received transplants in the lumbar region, and in March 2012, a second group of participants received microinjections in the cervical region (Feldman et al. 2014; Riley et al. 2014). Results are expected to be announced in due time.

14.3.5 Human Mesenchymal Stem Cells

Osiris Therapeutics conducts three separate Phase II clinical trials with derivatives of adult mesenchymal cells. These clinical trials are concerned with (1) protection of

islet pancreatic β-cells in children and adults diagnosed with type 1 diabetes, (2) repair of heart tissue after a heart attack, (3) repair of lung tissue in patients with chronic obstructive pulmonary disease (COPD) and particularly with regard to neurodegenerative diseases, and (4) use of MSCs for the generation of brain-derived neurotrophic factor (BDNF) in patients with HD (Nolta 2016). The main challenges regarding the latter consist of the safety of MSC transplantation, in terms of procedures and in terms of immune compromising and histocompatibility.

14.4 Clinical Trials in the Context of Neurodegenerative Diseases

14.4.1 Clinical Trials for Alzheimer's Disease

Going back in time, efforts to utilize stem cells in the therapy of Alzheimer's disease have been done from the 2000s decade. The first attempts were aiming at the mobilization of endogenous bone marrow-derived stem cells. Tsai KJ et al. using the granulocyte colony-stimulating factor (G-CSF), a therapeutic regimen widely prescribed in medical oncology to reverse the neutropenia caused by chemotherapy, documented a positive effect on treated mice model. Their mental status did not deteriorate and the neuronal loss was reversed by hematopoietic stem cells (Tsai et al. 2007). These results have been verified by several studies in the course of time (Guo et al. 2020). Some researchers taking a few steps further enlighten the cellular processes of chemotaxis of BM-SC in the damaged area. Wu CC et al. reported that BM-MSCs are recruited in the brain with CXCR4/SDF-1-depended chemotaxis (Wu et al. 2017), which can give more specific treatments (Shin et al. 2011). From the RADAR, a systematic review in order to record the side effects of G-CSF, a causal link between the drug and carcinogenesis, was not established (Tigue et al. 2007). Given all the above, a Phase II clinical trial of filgrastim has been completed, but their results are pending (*To Evaluate the Efficacy and Safety/Tolerability Profiles of G-CSF in Subjects With Mild to Moderate Alzheimer's Disease—Full Text View—ClinicalTrials.gov* 2018). Researchers from Nature Cell Co. Ltd explore in a Phase IIB clinical trial the role of mesenchymal stem cells derived from the patient's adipose tissue in the treatment of Alzheimer's (*Study to Evaluate the Safety and Efficacy of AstroStem in Treatment of Alzheimer's Disease—Full Text View—ClinicalTrials.gov* 2020). Researchers from John Wayne Cancer Institute still recruit patients with mild Alzheimer's dementia in Phase II clinical trial with allogenic mesenchymal stem cells (*Allogeneic Human Mesenchymal Stem Cells for Alzheimer's Disease* 2016). Finally, researchers from the University of Miami have designed a Phase I clinical study to certify the safety of manifold infusions of allogenic mesenchymal stem cells (*Alzheimer's Disease Stem Cells Multiple Infusions* 2019).

14.4.2 Clinical Trials for Parkinson's Disease

The body of clinical trials has just started to grow. There is only one clinical trial which has finished patient recruitment. Researchers give increasing doses of allogenic bone marrow-derived mesenchymal stem cells in order to certify the safety of the method (*Allogeneic Bone Marrow-Derived Mesenchymal Stem Cell Therapy for Idiopathic Parkinson's Disease* 2015). At the same center, the University of Texas Health Science Center at Houston, the next stage of the aforementioned study is conducted, a Phase IIb clinical trial. It still recruits participants (*Phase IIa Randomized Placebo Controlled Trial: Mesenchymal Stem Cells as a Disease-modifying Therapy for iPD* 2020). Two trials grasp the attention of the scientific community. Independent researchers from two centers, the NeuroGeneration which is a biotechnology corporation and the Shanghai East Hospital, have planned to stereotactically implant progenitor cells. The first team will implant neural progenitor cells and the other will transplant human amniotic epithelial stem cells (hAESCs). Both trials are designed as Phase I (*Transplantation of Neural Stem Cell-Derived Neurons for Parkinson's Disease* 2017; *Stereotactic Transplantation of hAESCs for Parkinson's Disease* 2018).

14.4.3 Clinical Trials for Amyotrophic Lateral Sclerosis (ALS)

There is a multitude of different treatment approaches that are being investigated with clinical trials. Since 2007, researchers from Peking University have conducted a Phase II clinical trial about the effect of granulocyte colony-stimulating factor (G-CSF) on the natural history of ALS. Preliminary results have been published, but no further update has come to the attention of the authors to date *[Basic and clinical researches on amyotrophic lateral sclerosis/motor neuron disease]—PubMed* 2009). Nabavi SM et al. documented that both intravenous administration and injection of mesenchymal cell derived from the patient's bone marrow in the spinal canal are safe (Nabavi et al. 2019). Researchers from the University Hospital "Dr. José Eleuterio González" in Mexico conducted a Phase II/III with bone marrow-derived hematopoietic stem cells injected through lumbar puncture directly in cerebrospinal fluid. Data are not published yet (*Effect of Intrathecal Administration of Hematopoietic Stem Cells in Patients With Amyotrophic Lateral Sclerosis (ALS)* 2013). Another clinical trial enrolled patients in Phase II study with autologous adipose tissue-derived mesenchymal cells injected intrathecally (*Intrathecal Autologous Adipose-derived Mesenchymal Stromal Cells for Amyotrophic Lateral Sclerosis (ALS)* 2017). A more straightforward approach is designed by Q Therapeutics, Inc. In a Phase I/II study, the researchers would check the safety and efficacy of progenitor glial cells implanted surgically in the patients' spinal cord. The study is not enrolling patients at the moment (*Study to Investigate the Safety of the Transplantation (by Injection) of Human Glial Restricted Progenitor Cells (hGRPs; Q-Cells®) Into Subjects With Amyotrophic Lateral Sclerosis (ALS)* 2015). A hallmark trial for the study of stem cell-based therapies in neurodegenerative diseases is

the Neurologic Stem Cell Treatment Study (NEST). Researchers estimate to enroll 300 patients to applicate bone marrow stem cell-derived treatments locally through the nasal canal and systemically (*Neurologic Stem Cell Treatment Study* 2016).

14.4.4 Clinical Trials for Huntington's Disease

There are only a few clinical trials on HD. The most mature trial is a Phase II/III clinical trial designed to inject the subjects with Cellavita-HD, a stem cell-based biologic therapy, intravenously (*Clinical Extension Study for Safety and Efficacy Evaluation of Cellavita-HD Administration in Huntington's Patients* 2020). Encouraging perspectives are emerging from the basic research. It is easily perceived that transplantation of allogenic tissues raises serious concerns, as these biologic products become immunogenic when they are injected into the circulation or implanted locally in tissues. Immunosuppression should be implemented to achieve successful implantation, which comes with severe complications. Difficult-to-treat infections such as bacterial meningitis and encephalitis are common adverse events of lumbar puncture, especially in immunocompromised patients, and the need for regular infusions exacerbates those risks. To address those concerns, Wu Z. et al. succeeded to transform stromal cells of the brain parenchyma into functional neurons. Researchers infected glial cells with a genetically manipulated adenovirus vector, inducing the coexpression of NeuroD1 and Dlx2, two critical transcription factors (Wu et al. 2020). Clinical trials in humans are expected.

14.4.5 Clinical Trials for Autism Spectrum Neurodevelopmental Disorders

According to the Clinicaltrials.gov records, 19 clinical trials are investigating the use of stem cells in the context of autism spectrum disorders, of which 6 studies have been completed. Of the six completed studies, one is a Phase I trial, and five are Phase II trials. Out of the ongoing ten studies, only two are Phase II trials. Most of the studies investigate autologous transplantation of bone marrow or umbilical stem cells (*Stem cells | Autism Spectrum Disorder* n.d., accessed in 2021).

One Phase I trial has been completed in 2012, and its results have been published. In this study, 15 participants with autism spectrum disorders underwent infusion of autologous umbilical cord blood. The principal outcome measure was the improvement of language ability and behavioral improvement over 55 weeks. The most encouraging results were related to motor capacity within 6 months, which was significantly improved compared to the placebo group (Mauron 2012).

Clinical trials for autism spectrum disorders face several challenges, given the high cost of autologous stem cell storage and its controversial efficacy. The use of stem cells from global umbilical cord banks or bone marrow donors appears quite intricate. Future directions for research include mesenchymal, neural, and fetal stem cells. Moreover, research focused on particular ASDs might yield more encouraging

disease-specific results (Siniscalco et al. 2012, 2014; Yuan and Shaner 2013; Bradstreet et al. 2014).

14.5 Conclusions

There is a tremendous societal burden due to neurodegenerative disorders owing to their devastating sequelae and lack of effective therapies. Till date, only stem cell is the potential therapy which can offer "cure" for neurodegenerative disorders. The capability of stem cells to cross BBB and migrate to brain has made them a versatile treatment modality. The usage of stem cells in clinical trials has showed promising effects on people suffering from these dreaded diseases. Further, more research is needed to understand the mechanisms of action underlying the efficacy of stem cells in the context of neurodegeneration.

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