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Stem Cells: Potential Role in Management of Neurodegenerative Diseases: The Dental Aspect

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Abstract

Neurodegenerative disease is a chronic, progressive nervous system disease characterized by neuron degeneration. Current treatments which are available in the market do not provide an appropriate cure. Possible alternative treatment, which is under investigation includes cell therapy, especially with the use of mesenchymal stem cells (MSCs). Dental stem cells offer many advantages over other types of stem cells. Thus, the aim of this article was to briefly review various therapeutic mechanisms of dental stem cells and their potential role in the treatments of neurodegenerative diseases.

Introduction

Stem cells are undifferentiated or partially differentiated cells that can differentiate into various types of cells and proliferate indefinitely to produce similar types of cells. These are the earliest type of cells in cell lineage [1]. These are found in both embryonic stages and adults but have slightly different properties. These are usually distinguished from progenitor cells, which cannot divide indefinitely and are usually committed to differentiating into one cell type. Two criteria for a cell to be classified as a stem cell are:-

Self-renewal: It is the ability to go through numerous cycles of cell growth and cell division, known as cell proliferation while maintaining the undifferentiated state.

Potency: It is capacity to differentiate into specialized cell types. To have this property cell requires either to be totipotent or pluripotent—to be able to give rise to any mature cell type, although multipotent or unipotent progenitor cells are sometimes referred to as stem cells.

Mesenchymal stem cells

Mesenchymal stem cells (MSC) are known to be multipotent, can be found in adult tissues such as in the muscle, liver, bone marrow. These usually provide structural support in various organs and control the movement of cell substances. MSC has the capacity to differentiate into numerous cell categories [2]. The term “meso” means middle, infusion originated from the Greek, signifying mesenchymal cells are able to range and travel in early embryonic growth among the ectodermal and endodermal layers. This mechanism act with space-filling, hence a key for repairing wounds in the dermis (skin), bone, or muscle of adult organisms[3]. Thus, mesenchymal stem cells are considered essential for regenerative medicine. These are broadly studied in clinical trials. Since these are easily isolated and obtain a high yield, high plasticity, which makes them able to facilitate inflammation and encourage cell growth, cell differentiation, and restoring tissue by influencing immunomodulation and immunosuppression. MSC comes from the bone marrow, which requires an aggressive procedure when it comes to isolating the quantity and quality of the cells, which is also affected by the age and condition of the donor tissues. MSCs are known to be heterogeneous, and they express a high level of pluripotent markers when compared to other types of stem cells, such as embryonic stem cells [3].

MSC has been widely studied for the management of various systemic diseases. Some of the clinical trials have given promising results for the treatment of neurodegenerative diseases. For cell therapy, various types of stem cells such as embryonic, fetal, adult, and induced pluripotent cells can be obtained from various sources e.g., heart, skin, liver and hair. Regardless of their types and source, all stem cells possess self-renewal properties and can differentiate into other types of cells. In the following section, dental stem cells and their role in the management of neurodegenerative diseases have been discussed.

Dental Stem Cells

These were first isolated from dental pulp tissue in the year 2002. These cells can differentiate in vitro into tissues that have similar characteristics to mesoderm, endoderm and ectoderm layers.

Sources of Dental Stem Cells:

These can be obtained from postnatal teeth, wisdom teeth and deciduous teeth, thus provide a non-invasive technique of extracting stem cells. This is one of the biggest advantages of dental stem cells. As a result, dental stem cells have been thought of as an extremely promising source of stem cells used in tissue engineering [4]. Similar to other stem cells, dental stem cells have the potential to induce neurorestorative processes and thus could be utilized for the treatment of neurodegenerative diseases. Following advantages of dental stem cells over other types make them a promising cell therapy candidate in the management of such diseases:-

1.The proliferation rate of these cells is 30% higher than in other stem cells, such as bone marrow stem cells.

2.These have lower immunogenicity reactions as compared to others.

3.Easy to harvest.

4.Easy accessibility and strong therapeutic ability.

5.No associated ethical concerns.

6.Non-invasive isolation of cells.

7.Ability to differentiate into brain cells in presence of specific stimuli.[5]

Neurodegenerative diseases are common neurological diseases that arise from the loss or destruction of specific neurons. Some examples of diseases resulting from damage of neurons are Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS) etc. The primary pathology in these diseases is the accumulation of misfolded proteins in the brain, which leads to neurological dysfunction and disease. Although the etiology of these diseases has been proven to be related to a variety of cellular and molecular mechanisms, the pathogenesis remains unclear, and the pathogenic factors are complex. For most patients, early diagnosis is not possible due to the lack of effective biomarkers or the absence of diagnostic tools to rule out the diseases [6]. Neuronal degeneration is accompanied by secondary effects which impair the quality of life. Although some treatment options are available which can delay the development of the disease when diagnosed, satiable results are often difficult to achieve, and thus overall prognosis remains poor.

Considerable neurological research is focused on methods for regenerating and replacing the degenerated nerve cells, stem cell therapy may be a suitable clinical intervention for neurodegenerative disorders. In recent decades, scientists have made great efforts in the treatment of neurodegenerative diseases. As brain cells have limited ability of self-repair and regeneration, conventional treatments of neurodegenerative diseases have not achieved ideal results. Stem cells, which have strong differentiation capacity, are considered the best potential therapy for brain tissue damage or degeneration caused by injury, aging, or disease. In recent years, with advances in the understanding and development of stem cells and related technologies, the treatment of neurodegenerative diseases has ushered in new opportunities. Because of the advantages offered by dental stem cells over other types, these have been widely studied in clinical models and studies. Various possible mechanisms of action of dental stem cells proposed based on previous research have been discussed in the following section.

Mechanism of Action of Dental Stem Cells

The mechanism of action of dental stem cells in the treatment of neurodegenerative conditions is still under investigation but some of the possible pathways which have been proposed in previous studies and clinical trials are discussed below:-

1.Homing Phenomenon: It is based on the property of stem cells to migrate into the injured sites rapidly. This characteristic is significant and can be used in diseases treatment [7]. Dental stem cells have the capacity to migrate into inflammatory and injured sites and these get converted into other types of cells such as glial cells and neurons which can result in improvement of motor functioning. Thus, this mechanism can be utilized for the management of neurodegenerative diseases treatment. One drawback of this process is that stem cells are home to an exceptionally low proportion of tissues in the body, so a full cure can't be obtained. In order to attain desired results, it is really important to improve the efficiency of this mechanism.

2.Paracrine Mechanism: Dental stem cells play an important role in cell migration and immune regulation by secreting various chemical mediators such as chemokines, growth factors and enzymes [8]. These also secrete endosomal derived components and bioactive molecules such as proteins, lipids, different types of RNAs, collectively known as exosomes. These molecules are anti-inflammatory, play an indispensable role in immune responses and antigen presentation, cell migration and differentiation. These exosomes have a unique quality of repairing damaged tissues. Studies have shown that these mediators have a direct therapeutic effect on injured sites. These are capable of stimulating neurogenesis [9]. Thus, this mechanism has futuristic possibilities of the usage of stem cells for the treatment of neurodegenerative diseases.

3.Immunoregulation: Stem cells also interact with T cells, B cells and Natural killer cells. These can regulate the immune function in the following ways

a. Activation of T cells,

b. Inhibition of T cell proliferation

c. Suppressing the production of antibodies by B cells,

d. Suppressing B cell proliferation

e. Secretion of Cytokines by Natural Killer cells.[10]

Some studies have reported that dental stem cells can inhibit the release of inflammatory cytokines and other mediators and increase the survival rate of neurons and nerve regeneration [11]. The investigations and clinical trials are in the early stages, but these outcomes have given researchers a ray of light to keep going.

4.Vasculogenesis: Stem cells are considered to establish therapeutic angiogenesis either through differentiation into vascular cells or through paracrine angiogenic growth factor secretion. Dental Stem cells are highly innervated and vascularized, contains blood vessels and neuron precursor cells. These can differentiate into vascular and neuronal cells. These are also capable of releasing angiogenic factors and cytokines which are critical for vascular network remodeling. Moreover, these can induce migration and tube formation in vascular smooth muscle cells indicating that stem cells can produce vessel-like structures [12, 13]. These properties can be utilized for healing tissues and the management of neurodegenerative diseases.

5.Apoptosis: It is programmed cell death. The primary aim of stem cell therapy is to prevent secondary cell death. Stem cell therapy can reduce cell loss through apoptosis attenuation, thus preserve tissues and neurons. Stem cells secrete anti-inflammatory cytokines which participate in restorative processes and neutralize the effects of apoptosis. Dental stem cells are also capable of producing apoptosis inhibitor proteins such as Bcl2 [14]. Thus, dental stem cells may have therapeutic potential specifically as a stimulator and modulator for the local repair response in the nervous system.

Role of Dental Stem Cells in Treatment of Neurodegenerative Diseases

1.Parkinson's disease (PD): It is typically a disease of the basal ganglia characterized by progressive degeneration of dopaminergic neurons in the substantia nigra. The depletion of dopamine in the nigrostriatal pathway leads to motor dysfunction characterized by tremors, myotonia, and reduced movements. The currently available therapies for PD address symptoms but do not cure this illness [15]. Over the past two decades, preclinical and clinical trials in PD patients have demonstrated that stem cell therapy of human embryonic mesencephalic tissue has the capacity to reinnervate the striatum. PD, in fact, has emerged as the best-suited neurodegenerative disease for stem cell therapy [16,17]. The essence of stem cell therapy in PD is the ability of stem cells to differentiate into dopaminergic neurons.

Additionally, stem cells can inhibit the polarization of microglia cells, minimize the levels of alpha-synuclein and promote the survival of neurons. Data reported that stem cells may play a vital role in cell replacement, anti-inflammatory, and immune regulation in Parkinson's disease treatment. Many clinical trials have supported this data, but further studies are warranted to better explore these results.

2.Alzheimer’s disease (AD): It is the most common form of dementia accounting for more than half of all dementias. It is characterized by the insidious onset of dementia and histologically by senile plaques and neurofibrillary tangles. Clinical signs and symptoms include cognitive decline, memory impairment, behavioral disorders, and aphasia [18]. As the etiology and pathogenesis of this disease are not known so no effective preventive or treatment modalities are available. Stem cell-based therapy may support nerve growth by reconstructing the neural microenvironment and minimizing the factors that damage the nerve structure. Some studies have reported that stem cells can improve spatial learning and memory functions, differentiate into neural cells in the aging brain, enhance physical and cognitive functions by increasing brain-derived neurotrophic factors and nerve growth factors. Further research is required to confirm and explore the findings of these studies.

3.Amyotrophic Lateral Sclerosis (ALS): It is a complex progressive neurodegenerative disease related to many pathological mechanisms, including mitochondrial dysfunction, oxidative stress, and axonal injury [19], which lead to degeneration and death of nerve cells. It is characterized by degeneration of both upper and lower motor neurons in the brain and spinal cord, leading to progressive muscle atrophy and weakness in the limbs. Available drugs can only relieve symptoms. ALS can be effectively treated if the survival time of motor neurons can be prolonged. Therapies based on stem cells may lead to more effective treatments for ALS. Studies have shown that stem cells can migrate to the spinal cord and suppress the activation of microglia and tissue glial proliferation, thus increasing the number of motor neurons and having neuroprotective effects. Moreover, it has also been reported that stem cells can reduce oxidative stresses and increase cell survival rates.

4.Spinal Cord Injury (SCI): It is a debilitating neurological disorder causing a severe clinical and socioeconomic burden on the patient. Stem cell transplantation techniques hold great potential in the management of this condition. Studies have reported the improvement in motor neuronal survival with the grafting of stem cells [20]. Improvements in locomotion have been observed along with the preservation of neural elements [21]. Overall improvement in the functioning of the spinal cord has also been reported in rat studies.

5.Stroke: Primary aim of stroke treatment is to better the functional recovery at the cellular, molecular, and organismal levels. Recent studies and trials have used stem cell therapy in stroke recovery models, but limited success has been achieved. It has been reported that transplantation of cells accelerated neovascularization of the ischemic zone and enhanced neuronal regeneration.

Futuristics Approaches

Neuro-restoration is a concept which is evolving at an accelerated pace over the past decade. Stem cell therapy has set off both interests and alarms in the scientific community. Despite all the elegant studies in this area, there are still more questions than answers. In the future, researchers should attempt to identify the ideal stem cell type and route of administration for each neurodegenerative disease. Clearly, a tailored approach is required for each neurodegenerative disease to effectively salvage the neuronal networks.

Conclusion

Stem cells have important clinical application value in nutrition, immunoregulation, and neuroprotection and can effectively avoid immune rejection and improve a patient's quality of life. Stem cells are being explored as a new treatment modality for the treatment of neurodegenerative diseases. Many studies have reported the potential role of stem cells in the management of neurodegenerative diseases. However, a comprehensive understanding of the healing processes in the nervous system triggered by stem cell therapies has not yet been achieved. There needs to be further elucidation of the fundamental biological mechanism responsible for molecular recovery and functional recovery. But further studies are warranted to better explore the findings of previous studies and attempts should be made to find the best possible solution which could be cost-effective and clinically feasible for the management of these diseases.

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