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Review Article

Stem Cell Therapy In Neurodegenerative Disease And Induced Pluripotent Stem Cells (iPSCs) In Disease Modelling

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ABSTRACT

The deprivation of medicinal curative therapies for neurodegenerative disease has high socio and economic impact to the society. neurogenerative disorder is characterized by progressive degeneration of neurons . stem cells based therapies offer promising avenue for disease modification , neuroprotection and neural repair. this comprehensive review examine the multifaceted involvement of stem cells in various neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis (ALS). Stem cells also involve in immunotherapy for cancer as well as for musculoskeletal disorders . In this review, we will summarize the recent concept in stem cell therapy for neurogenerative disorders and iPSCs in disease modelling and the current advancement in this field.

INTRODUCTION

Stem cells are undifferentiated cells found in multicellular organism that have the capacity to self renew and differentiate into specialized cell types. They can be classified into different categories based on their potency and origin . It includes Induced pluripotent stem cells ,Embryonic stem cells (ESC), Neural stem cells (NSC) .STEM CELLS THERAPY involves the transplantation or manipulation of stem cells to restore or replace damaged tissue or organs ,thereby promoting regeneration and functional recovery . One of the key advantages of stem cell therapy is its potential to address the underlying cause of disease and promote the tissue regeneration ,rather than simply managing symptoms . Stem cells can differentiate into specialized cell types relevant to the target tissue

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or organ ,integrate into existing tissue structure and release bioactive molecules that facillitate the tissue repair and regeneration.

TYPES OF STEM CELLS

1. **Embryonic stem cells (ESC)**

They are found in the inner cell mass of human blastocyst ,an early stage of developing embryo lasting from 4th to 7th day after fertilization. they disappear after 7th day and begin to form the three embryonic tissue layer . they are extracted from the inner cell mass during the blastocyst stage .ESC are pluripotent and having remarkable ability to divide and differentiate into any cell type in the body including cells of all three germ layer :ectoderm endoderm, mesoderm. The inner cell mass is isolated and cultured in laboratory to generate the embryonic stem cell lines. They are characterized by special markers that indicate there pluripotent state .these markers include transcription factor such as oct4,Nanog ,Sox 2 as well as surface antigent like SSEA-3, SSEA-4 and Tra-1-60. The expression of these markers help investigator and researchers to identify and maintain embryonic stem cells in an undifferentiated conditions.

2. **Induced pluripotent stem cells (iPSCs)**

Induced pluripotent stem cells are type of pluripotent stem cells derived from adult somatic cells .they are generated by reprogramming adult somatic cell like skin cells and blood cells back to pluripotent state. This reprogramming is typically achieved by introducing specific transcription factors into somatic cells ,which reset their gene expression patterns and cellular identity allowing them to regain pluripotency. The specific transcription factors used often are oct 4 ,sox2, klf4 and c-myc (referred as yamanaka factor) these factor reprogrammes the cell gene expression pattern leading to activation of pluripotency associated genes and suppression of lineage specific genes.

Characteristics:

iPSCs shares many characters with embryonic stem cells including self renewal capacity to differentiate into cell from all the 3 germ layers (ectoderm, endoderm, mesoderm)they form colonies with the morphology similar to ESCs and expresses pluripotency markers such as oct4, nanog, SSEA-4. They have a wide range of application in disease modelling allowing researchers to study disease mechanism in human cellular context. IPSCs derived cells are used for high throughput drug screening to identify the potential therapeutics and assess their efficacy and saftey.

3. **Neural Stem Cells (NSCs)**

NSCs are produced from fetal or adult central nervous tissue via the dissection of specific brain region such as hippocampus, subventricular zone and spinal cord . These cells have remarkable ability to self renew and differentiate into various type of neural cells including neurons , astrocytes, oligodendrocytes.

Key points :

self - renewal capacity – they can divide asymmetrically to produce one daughter cell that remain a stem cell and one daughter cell that differentiate into a neural progenitor or mature neural cell .the self renewal capacity allow NSCs to maintain their population throughout the life.

NSCs have potential to generate and differentiate into different type of neural cells depending on signals they received from the microenvironment .under appropriate conditions ,NSCs can give rise to neurons which transmit the electric signals in brain ;astrocytes ,which provide the support and nutrition to neurons and oligodendrocytes, which produce myelin to insulate neuronal axons. During embryonic development NSCs play a crucial role in the formation of the nervous system. They give rise to a vast array of neural cell types that populate the brain and spinal cord, contributing to the intricate wiring and functional organization of the nervous system. Although neurogenesis is limited

in adult brain more than the embryonic development, certain regions of adult brain such as hippocampus and olfactory bulb retain neurogenic process such as learning and memory as well as olfactory functions and mood swings.

4. **Mesenchymal stem cells or mesenchymal stromal cells (MSCs)**

These cells are type of adult cell that can be found in different tissues throughout the body. including bone marrow, adipose tissues, umbilical cord tissues and dental pulp. MSCs are multipotent; have the ability to differentiate into a variety of cells type including bone cells (osteoblasts) cartilage cells (chondrocytes) fat cells (adipocytes) and connective tissue cell (fibroblasts). MSCs cells possess immunomodulatory properties that enable them to modulate the activity of immune cells and regulate the inflammatory response. they help to suppress the proliferation and functions of various immune cells, including T cells, B cells, natural killer cells and dendritic cells and promote the generation of regulatory immune cells. They have potential to enhance the success of organ transplantation. They have potential to promote neural repair and regeneration in neurological disorders such as stroke, traumatic brain injury, and spinal cord injury.

Neurodegenerative Disease

Parkinson's disease

It is the brain condition that causes problems with movements, mental health, sleep, pain and other health issues. That leads to decreased dopamine in the body.

Symptoms of PD includes

1. Slow movement
2. Tremor
3. Rigidity
4. Cognitive impairment
5. Sleep disorders and insomnia
6. Dyskinesias and dystonia's can cause problems like speaking and moving.
7. Sensory disturbance

ALZHEIMERS DISEASE

It is the progressive loss of memory and degeneration of brain cells that the cells themselves die, eventually destroying memory and other important mental functions. Level of neurotransmitter acetylcholine is particularly low in brains of people with Alzheimer's disease. over time the different areas of brain shrink. The disease is the most common cause of dementia among older adults. The disease is named after Dr. Alois Alzheimer. Dr. Alois notices changes in the brain tissue of woman who died after an unusual mental illness. He examined her brain and found many abnormal clumps (amyloid plaques) and tangled bundles of fibers (neurofibrillary). Another feature is the loss of connection between nerve cells in the brain. The damage uses to take place in parts of the brain involved in memory, including the entorhinal cortex and hippocampus. It later affects area in cerebral cortex, those responsible for speech, language, learning and social behavior. Mid cognitive impairment is the early sign of Alzheimer's ,but not everyone with MCI develops the disease.

Huntington's disease

- It is genetic disorder that affects the brain ,causing progressive deuteriation of physical and mental abilities. It is caused by mutation in the huntingtin gene .symptoms usually appear in adulthood and worsen with time leading to cognitive decline ,involuntary movements and emotional disturbances . There's currently no cure ,but treatment can help manage symptoms and improve quality of life.
- Also known as Huntington's chorea
- Symptoms include
- Movement disorder: involuntary movement such as jerking or twitching. These movements can progress to severe muscle rigidity and stiffness.
- **Cognitive decline:**

individuals with Huntington's disease may experience difficulties with thinking , reasoning and remembering. this can leads to problem with concentration , planning , and decision making.

- **Genetic inheritance:**

the disease is caused by genetic mutation in HTT genes. This disease follows an autosomal dominant pattern of inheritance, meaning that a person needs only one copy of the mutated genes from either parent to develop the disorder. each child of an affected parents has 50% chances of developing a disease.

- Amyotrophic lateral sclerosis : (ALS)
- Also known as Lou Gehrig's disease.
- It is the progressive neurodegenerative disorder that affects nerve cell in the brain and spinal cord, leading to muscle weakness, paralysis and eventually respiratory failure. The exact cause of ALS is not known but it is believed to have a combination of genetic and environmental factors. In some cases, there may be a familial component where multiple members are affected (known as familial ALS),While in others, it occurs sporadically (known as sporadic ALS).
- Abbreviation
- PD – Parkinson's disease
- ESC- Embryonic stem cells
- NSC- Neural stem cells
- MSC- Mesenchymal stem cells
- IPSCs – Induced pluripotent stem cells
- ALS – Amyotrophic lateral sclerosis
- MCI – Mid cognitive impairment

STEM CELLS THERAPY EXPERIMENTS ON NEURODEGENERATIVE DISEASE.

1. PARKINSON'S DISEASE (PD)

PD is the disease of 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 . From the past 2 decades clinical and preclinical trials have been going on in PD patients .it demonstrated that the stem cell therapy for human embryonic mesencephalic tissue have the capacity to restore the lost nerve supply to a muscle or nerve by the surgery or regeneration of the striatum. The importance of stem cell therapy in PD is ability of stem cell to differentiate into dopaminergic neurons . Genetic engineering plays a vital role in the formation and differentiation of dopaminergic neurons . These neurons are obtained from rat neural stem cells, mouse fibroblast and human embryonic stem cells. Soldner and his colleagues found that fibroblast from the PD patient can be reprogrammed to differentiate into dopaminergic neurons was a turning point in clinical area of PD. Embryonic stem cells , neural stem cells and bone marrow stem cells (BMSCs) all successfully survived when grafted in animal model of PD. ESCs and NSCs derived from the embryonic ventral mesencephalon found to release significant amount of dopamine . The process involves growing these stem cells (ESCs or iPSCs) in the laboratory and then differentiating them into dopaminergic neurons . Once mature, these neurons are implanted into specific areas of the brain affected by Parkinson's disease such as substantia nigra where dopamine level has been depleted . despite the importance of stem cells in PD ,it carries the serious risk of graft induced dyskinesias , immune rejection and tumorigenicity.

HD (Huntington's disease)

HD is the fatal and progressive neurodegenerative disease of autosomal dominant inheritance due to expansion of cytosine – adenine –guanine repeats in huntingtin gene. The mutated genes of htt induces a preferential loss of medium spiny neurons of the striatum giving rise to motor , cognitive and emotional deficits. Stem cells therapy for Huntington's disease aims to replace the damaged neurons in the brain with the healthy

ones, potentially slowing or halting disease progression. ESCs, iPSCs, and adult stem cells such as mesenchymal stem cells (MSCs)have been investigated for HD treatment. IPSCs derived from HD patients cells can be used to create disease model in labs. These cells retain the genetic mutation associated with HD and can be differentiated into neurons allowing researchers to study disease mechanism and test potential treatments. Another approach to cure HD patient is replacement therapy that is transplanting healthy neural stem cells or precursor cells into the brain to replace the degenerating neurons . These cells can potentially integrate into the existing neural circuitry and restore functions. stem cells can also secrete factors that promote neuronal survival and protect existing neurons from further damage. This neuroprotective effect may help slow disease progression and alleviate symptoms. CRISPR/ Cas9 and other gene editing techniques are being explored to correct the genetic mutation responsible for HD in patient derived iPSCs. This approach aims to generate healthy neurons for transplantations, addressing the root cause of disease. Despite the potential benefits , there are several challenges such as immune rejection , graft survival, tumor formation, and ethical consideration surrounding the use of ESCs remains significant hurdles in the development of stem cell therapies for HD.

ALZHEIMERS DISEASE

Stem cell therapy for Alzheimer's disease aims to replace damaged or lost brain cells, particularly neurons with healthy ones derived from stem cells. Research in this area primarily focuses on the use of pluripotent cells such as embryonic stem cells or induced pluripotent cells. These cells have the ability to differentiate into various cell types including neurons .

1. **Neural replacement:**

stem cells can be differentiated into neurons in the laboratory and then implanted into brain to replace the lost or damaged neurons. These newly integrated neurons may help restore neural circulatory and improve cognitive functions.

2. **Beta amyloid clearance:**

some studies explore the potential of stem cells to clear beta amyloid plaques which are characteristics of Alzheimer's disease and contribute to neuronal damage. Stem cells engineered to produce enzymes or factors that break down beta amyloid could potentially reduce its accumulations in the brain.

3. **Anti–inflammatory**

effects of stem cell help to reduce the neuroinflammation associated with Alzheimer's disease. Stem cells can interact with the immune response by modulating the activity of immune cells such as T cells, B cells, macrophages and dendritic cells. They can promote the shift from proinflammatory to anti- inflammatory phenotypes in macrophages, reducing the overall immune responses. Stem cells could potentially mitigate neuronal damage and cognitive decline.

4. The challenges include optimizing transplantation methods, ensuring long term survival and integration of transplanted cells, minimizing immune rejection and addressing ethical considerations.

Amyotrophic lateral sclerosis(ALS)

Stem cell therapy for amyotrophic lateral sclerosis involves using stem cells to replace damaged neurons in central nervous system, particularly motor neurons. There are different types of stem cells used in ALS therapy including embryonic stem cells, induced pluripotent stem cells and mesenchymal stem cells. Embryonic stem cell therapy in ALS involves the use of pluripotent cells derived from embryo . These cells have the potential to divide into various cell types, including motor neurons, which are progressively lost in ALS. The idea behind embryonic stem cell therapy is to replace damaged motor neurons with healthy ones derived from these pluripotent stem

cells. By replenishing the motor neuron population , it is hoped that the progression of ALS can be slowed or even halted. However the use of embryonic stem cells in therapy raises ethical concerns due to need to harvest cells from human embryos. This had lead to strict regulation and limitation on research involving embryonic stem cells in many countries.

INDUCED PLURIPOTENT STEM CELL (iPSCs) IN DISEASE MODELLING.

IPSCs derived from patients with genetic disease retain the genetic mutations present in the patient's cells. Scientists can then differentiate these iPSCs into specific cell type affected by the disease, such as neurons for neurodegenerative disorders or cardiomyocytes for heart disease. By studying these cells in the lab, researchers can observe disease mechanisms, identify potential drug targets and test new therapies. IPSCs based drug models are valuable for drug discovery and development. Researchers can use them to screen large libraries of compounds to identify molecules that elevate disease symptoms or target underlying pathological processes. This personalized approach can lead to more effective and safer treatment for patients. Disease modelling using iPSCs involves creating cell cultures that mimic the characteristics of a specific disease.

Platform for drug discovery using human iPSCs disease modeling. The development of organoids for disease modelling has emerged as a cutting edge approach in biomedical research . Organoids are 3 dimensional cell cultures derived from stem cells, including iPSCs or adult tissue specific stem cells, that self-organize and mimic the structure and function of specific organs.

USE OF ORGANOIDS TO MODEL DISEASE.

Recreating organ complexity:

Organoids replicate the intricate architecture and cellular diversity of organs, allowing researchers to study disease mechanism in a more physiologically relevant context compared to traditional two dimension cell culture.

Patient specific modelling:

Organoids can be developed from patient derived cells, enabling personalized disease modelling. This approach captures individual variability and facilitate the study of patient specific disease characteristics and response to treatment.

Multicellular interactions:

Organoids contain multiple cell type found in the organ they mimic, allowing for the study of complex multicellular interaction involved in disease development and progression. For eg. Intestinal organoids can be the model interaction between epithelial cells and microbiota in gastrointestinal disease.

Drug screening and discovery:

Organoids serve as valuable platforms for drug screening and discovery. Researchers can test the efficacy and safety of potential therapeutic in organoids models, providing more accurate prediction of drug response compared to traditional cell culture systems. Cerebral organoids, also known as mini brains, reproduce fetal brain development and thereafter serve as powerful platform to study human development and disease related to central nervous system. The development of blood-brain barrier (BBB) organoids for disease modeling represents a significant advancement in neurobiology and drug development. The BBB is a highly specialized barrier that regulates the passage of molecules between the bloodstream and the brain, protecting the brain from toxins and pathogens while maintaining homeostasis. Here's how BBB organoids are created and utilized for disease modeling:

1. **Generation of BBB Organoids:**

BBB organoids are typically derived from human iPSCs or brain-specific progenitor cells. These cells are cultured in conditions that promote their differentiation into various cell types found in the

BBB, including endothelial cells, pericytes, and astrocytes. By carefully controlling the culture environment and signaling cues, researchers can coax these cells to self-organize into structures that resemble the architecture and function of the BBB.

2. **Modeling Neurological Disorders:**

BBB organoids provide a platform to study the pathophysiology of neurological disorders that involve BBB dysfunction, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and certain types of brain tumors. By incorporating patient-derived cells or disease-specific genetic mutations, researchers can mimic disease conditions and investigate how BBB dysfunction contributes to disease progression.

3. **Drug Screening and Delivery:**

BBB organoids offer a valuable tool for evaluating the permeability of drugs and potential therapeutics across the BBB. Researchers can assess how drugs penetrate the barrier, interact with BBB components, and affect brain function. This information is critical for identifying promising drug candidates and optimizing drug delivery strategies for neurological disorders.

4. **Investigating Neuroinflammation and Neurodegeneration:**

BBB dysfunction is often associated with neuroinflammatory processes and neurodegeneration. BBB organoids enable researchers to study how inflammatory mediators, immune cells, and neuronal factors interact at the BBB interface, contributing to neuroinflammation and neuronal damage. This insight could lead to the development of novel therapeutic approaches targeting BBB dysfunction in neurodegenerative diseases.

5. **Personalized Medicine:**

BBB organoids derived from patient-specific iPSCs allow for personalized disease modeling and drug testing. By using cells from individual patients, researchers can assess how genetic variations and disease-specific factors influence BBB integrity and drug responses, paving the way for personalized treatment strategies.

While organoid models offer many advantages for disease modeling and drug discovery, they also have several limitations:

1. **Complexity:**

Organoids, while more physiologically relevant than traditional cell culture models, still lack the complexity of whole organs. They may not fully recapitulate all aspects of organ structure, function, and cellular diversity, limiting their ability to model certain diseases or responses to drugs accurately.

2. **Variability:**

Organoid cultures can exhibit variability in terms of size, shape, cell composition, and functionality, even when derived from the same source material. This variability can affect the reproducibility and reliability of experimental results.

3. **Maturation:**

Organoids often require extended culture periods to mature and develop organ-like characteristics, which can take weeks to months. During this time, cells may undergo genetic and phenotypic changes, affecting the fidelity of disease modeling and drug screening assays.

4. **Vascularization:**

Many organoids lack a functional vascular network, which is essential for nutrient and oxygen exchange, waste removal, and mimicking physiological responses to drugs. Without proper vascularization, organoids may not accurately replicate tissue-specific microenvironments or drug distribution patterns.

5. **Modeling Complexity:**

While organoids can mimic certain aspects of organ development and function, they may struggle to model complex physiological processes, such as organ-organ interactions, systemic responses to drugs, or long-term tissue remodeling.

6. **Ethical Considerations:**

The generation of organoids often requires the use of human embryonic stem cells or induced pluripotent stem cells, which raises ethical concerns regarding the source of the cells and their potential for misuse or exploitation.

7. Standardization:

There is a lack of standardized protocols and quality control measures for organoid generation and characterization, leading to variability between different research groups and hindering the comparison of results across studies. Addressing these limitations will require ongoing technological advancements, such as improved culture systems, better characterization techniques, enhanced vascularization methods, and increased standardization of protocols. Despite these challenges, organoid models remain valuable tools for studying human development, disease mechanisms, and drug responses, with the potential to revolutionize personalized medicine and drug discovery.

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