UNDER PEER REVIEW

CURRENT STATUS OF STEM CELL BASED THERAPY

3

Abstract

Stem cell therapy is an innovative and promising branch of medicine in research nowadays. The therapy uses stem cells, which are capable of developing into different types of cells, to treat injuries and diseases. Currently, scientists are using stem cells to regenerate tissues, treat autoimmune diseases, and create novel treatment strategies for cancer. Considerable progress has been achieved in stem cell research; however, there are still many ethical issues to solve, risks of tumor growth, and optimization of treatment procedures to be researched further. Although stem cell therapy has challenges to overcome, it will bound to enhance the quality of human health in the future.

➢ INTRODUCTION

Stem cell-based therapies are defined as any treatment for a disease or a medical condition that fundamentally involves the use of any type of viable human stem cells including embryonic stem cells (ESCs), iPSCs and adult stem cells for autologous and allogeneic therapies.(1)Stem cells provide an ideal answer for cases requiring tissue and organ transplants due to their capability to transform into the particular cell types necessary for healing damaged tissues.

Stem cells possess the remarkable ability to divide indefinitely and can differentiate into various cell types. Recently, they have become a primary resource in regenerative medicine, playing a crucial role in repairing tissue and organ abnormalities caused by congenital defects, diseases, and age-related changes.(2) Stem cells serve as the fundamental building blocks for all tissues and organ systems within the body, playing a crucial role in disease progression, development, and the processes of tissue repair. Based on their ability to transdifferentiate, stem cells can be classified into four categories: unipotent, multipotent, pluripotent, and totipotent.(3)

- **Classification of stem cells**

Stem cells can be categorized according to their ability to develop into various cell types, which include totipotent, pluripotent, multipotent, oligopotent, and unipotent stem cells.

Table 1. Types of stem cells and properties

Stem cells	Properties
Totipotent	These stem cells possess the ability to differentiate into any cell type. The cells generated during the initial divisions of the fertilized egg are referred to as totipotent. In contrast, embryonic stem cells are classified as pluripotent, as they lack the capacity to contribute to the extra-embryonic membranes or the placenta.(4)

Pluripotent	These cells originate from a pre-implantation embryo at an early developmental stage. The pluripotent cells possess the ability to differentiate into nearly all cell types.(5)
Multipotent	These cells possess the ability to develop into various types of cells within a closely associated family. For instance, mature hematopoietic stem cells can transform into red blood cells, white blood cells, or platelets.(6)
Oligopotent	These can transform into several distinct cell types. Mature lymphoid or myeloid stem cells have the ability to differentiate in this manner.(7)
Unipotent	Stem cells possess the unique ability to produce only their specific type of cells. Nonetheless, they are classified as stem cells due to their capacity for self-renewal. An example of this is the muscle stem cells found in adults.(8)

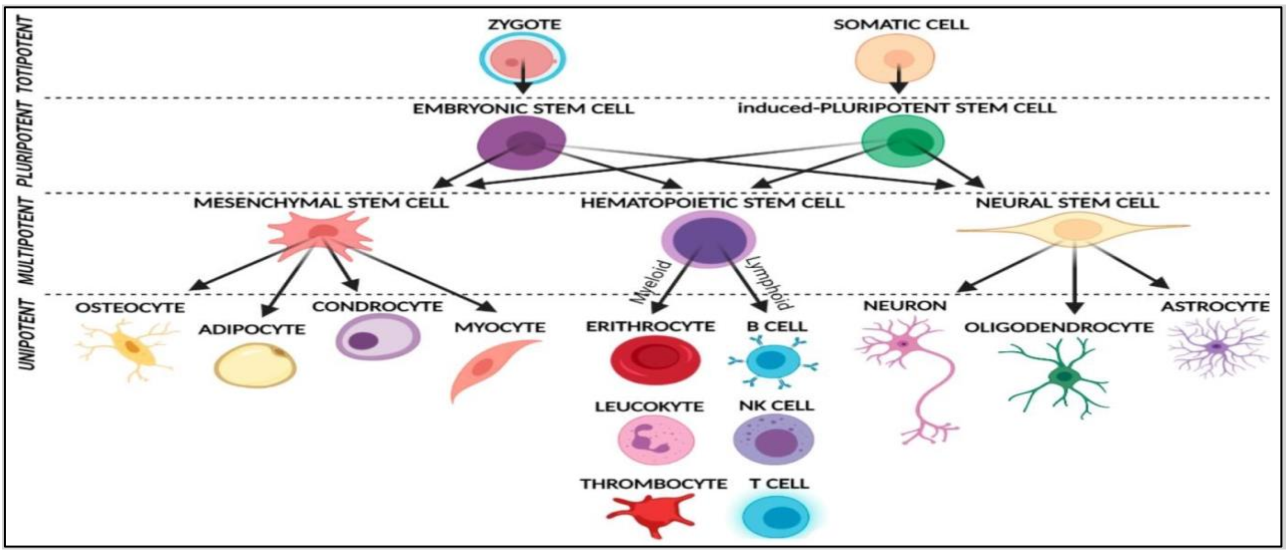

Fig.1: diagrammatic representation of stem cells.

- **Stem Cell Fates**

Four possible outcomes for stem cells are as follows:

A) Quiescence, where a stem cell remains inactive and preserves the stem cell population.

B) Symmetric self-renewal, in which a stem cell divides to produce two daughter stem cells, thereby enlarging the stem cell population.

C) Asymmetric self-renewal, where a stem cell divides into one differentiated daughter cell and one stem cell, thus sustaining the stem cell population.

D) Symmetric division without self-renewal, resulting in a reduction of the stem cell population, while producing two differentiated daughter cells.(9)

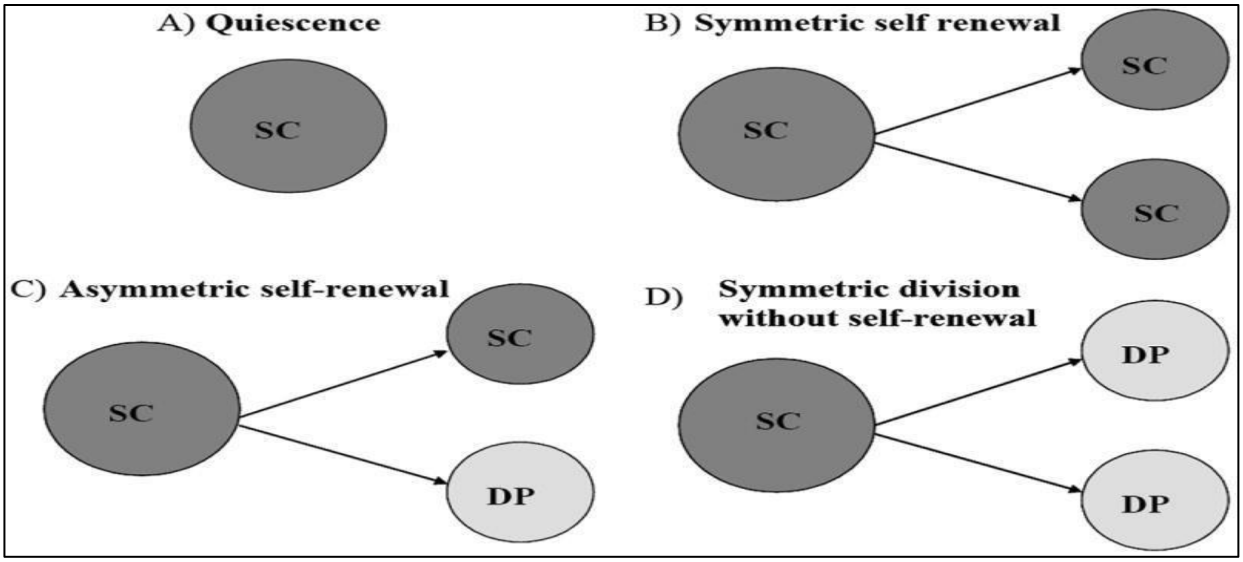

Fig.2: stem cell fate

• **Opportunities, Obstacles, and Risks of Cell Therapy**

Opportunities

• Promise for diseases with limited life expectancy: These therapies offer the ability to create treatments that can address numerous genes present in body.

Obstacles

•**Compatible donors**. Just like in human organ transplants, there are immune barriers that necessitate a careful "matching" of the HSC donor and recipient to prevent severe complications due to immune system incompatibility.

•**Precision needed**. Cell and gene therapies must ensure that the modified cells reach the appropriate tissue, at the correct dosage, and for the necessary duration.

•**Immune suppression**. Before administering cell therapy, chemotherapy and other preparatory treatments are commonly given to avoid triggering an immune response.

Risks

•**Obtaining informed consent**

•**Immune reactions**

•**Organ toxicities**.

TIME LINE OF STEM CELL BASED THERAPY

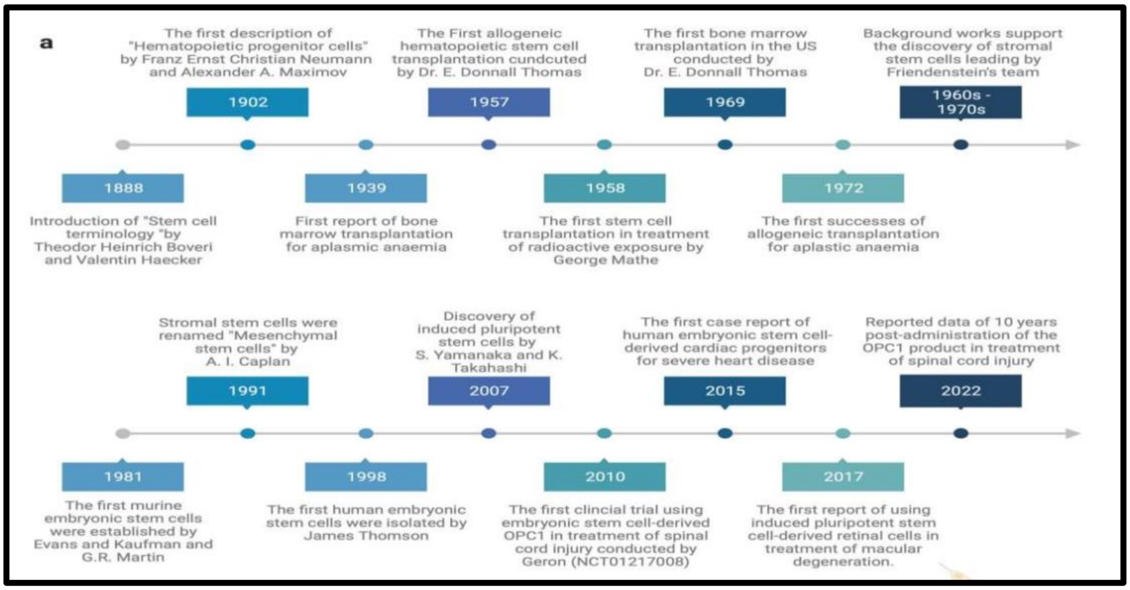

Fig.3: A chronological overview of significant breakthroughs and progress in fundamental research and clinical uses of stem cell therapy.

INVESTIGATIONS

Medical conditions and diseases for which the use of stem cell therapy is being explored include:

- Diabetes
- Androgenic Alopecia and hair loss
- Rheumatoid arthritis
- Parkinson's disease
- Alzheimer's disease
- Respiratory disease
- Osteoarthritis
- Spinal cord injury repair

➢ LEUKEMIA

A diverse group of hematologic cancers known as leukemia are caused by the aberrant proliferation of leukocytes during their development. The rapidity of proliferation determines whether it is acute or chronic, and the cell of origin determines whether it is myelocytic or lymphocytic.

The four primary subtypes of leukemia are as follows:

•**Acute lymphoblastic leukemia (ALL):** When B and T cells undergo a blastic transformation, ALL results. Approximately 80% of cases in this age group are of this form of leukemia, while only 20% of cases in adults are. It is the most common type of leukemia in children. Adolescent and young adult treatment regimens are mostly based on pediatric strategies because they have higher rates of success.

•**Acute myelogenous leukemia (AML):** The most common acute leukemia diagnosis in adults is acute myeloid leukemia (AML), which is characterized by the presence of more than 20% myeloid blasts. The prognosis for this most aggressive type of cancer varies depending on the molecular subtype.

•**Chronic lymphocytic leukemia (CLL):** CLL originates from the proliferation of monoclonal lymphoid cells. Most instances are diagnosed in individuals aged between 60 and 70. Generally, CLL is regarded as an indolent disease, meaning that not all patients will require immediate treatment until they develop symptoms related to the disease.

•**Chronic myelogenous leukemia (CML):** CML usually arises from a reciprocal translocation leading to the fusion of the BCR gene on chromosome 22 and the ABL1 gene on chromosome 9, which produces an abnormally active tyrosine kinase on chromosome 22 known as the Philadelphia (Ph) chromosome. This results in a monoclonal population of dysfunctional granulocytes, predominantly affecting neutrophils, basophils, and eosinophils.(10, 11, 12, 13)

Normal stem cells are essential in cancer treatment because of their regenerative capabilities, their potential to develop into specialized cell types, and their ability to influence the tumor microenvironment.(14, 15)These characteristics enable them to aid in tissue regeneration, boost immune responses, and function as carriers for anticancer drugs, positioning them as promising options for novel cancer therapies. (**Figure 4**).

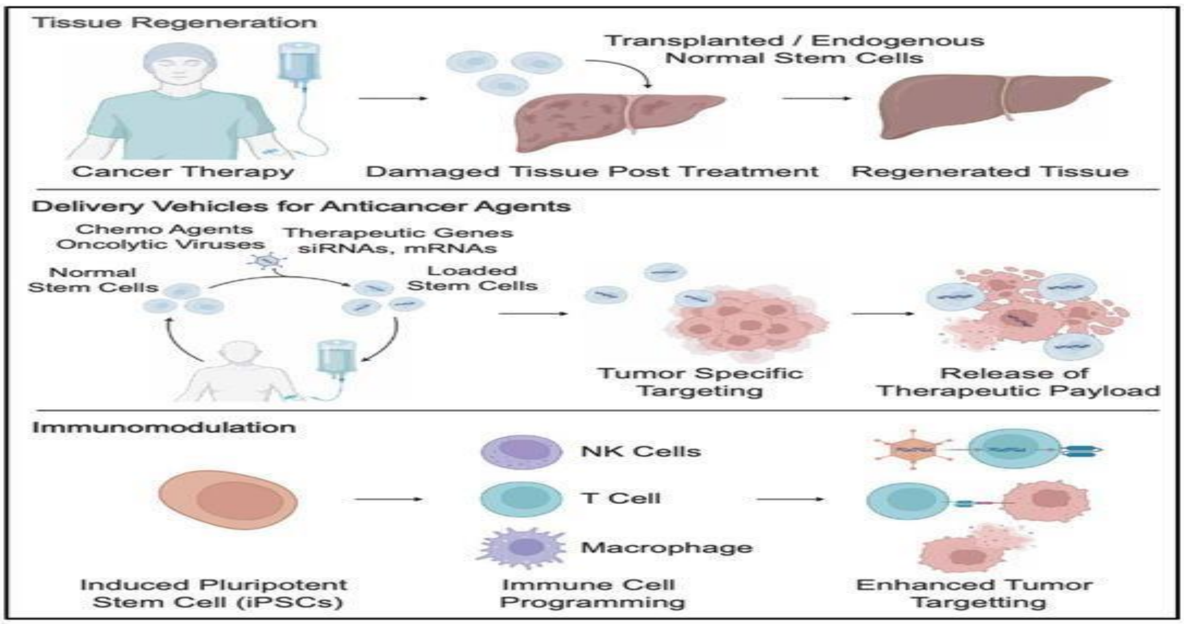

Fig.4: Normal stem cells in cancer therapy.

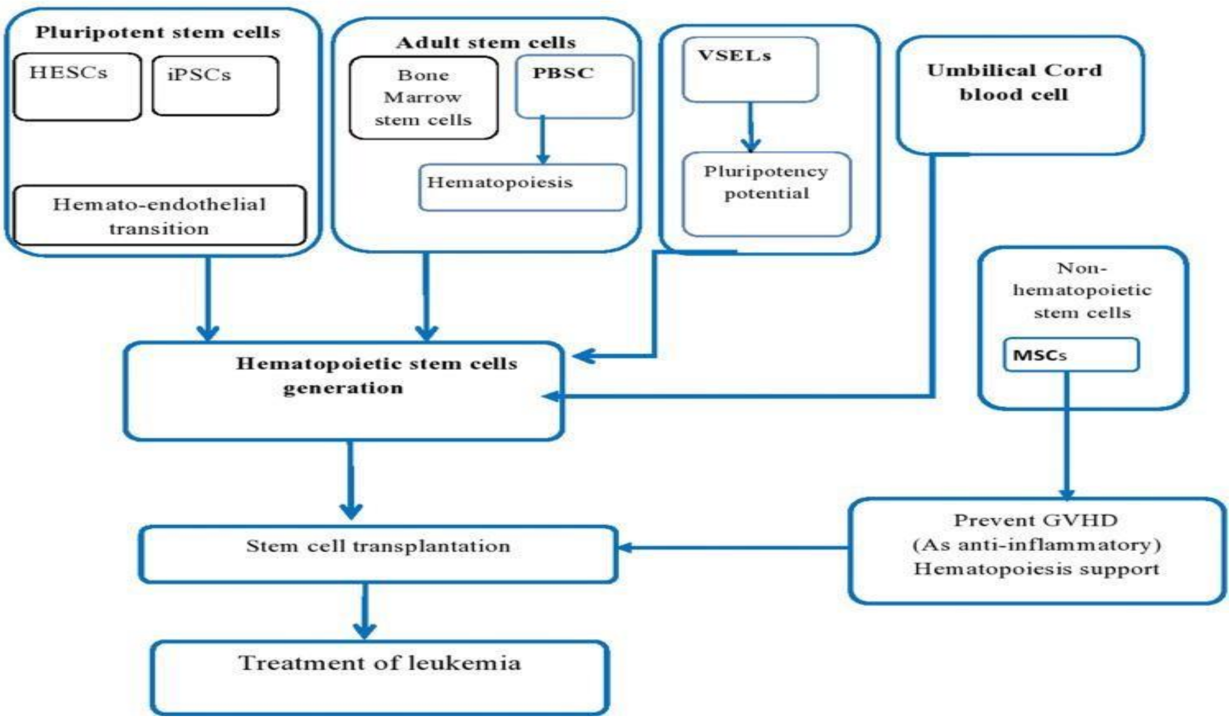

Fig.5: The function of various categories of SCs in SC transplantation.

Hematopoietic Stem-Cell Transplantation can be used to treat individuals with uncommon diseases, such as AML,(16)ALL,(17)CML, Burkitt's lymphoma, HL, and NHL,(18)and other hematologic malignancies.(19)While it is considered an alternative approach to treatment, HSCT still carries a relapse risk ranging from 40% to 80% for those who receive it.(20)Both autologous hematopoietic stem cell transplantation (auto-HSCT) and allogeneic hematopoietic stem cell transplantation (allo-HSCT) are key alternative cellular therapies for treating leukemia.

Autologous HSCT is a suitable and viable treatment option for multiple myeloma.(21, 22)

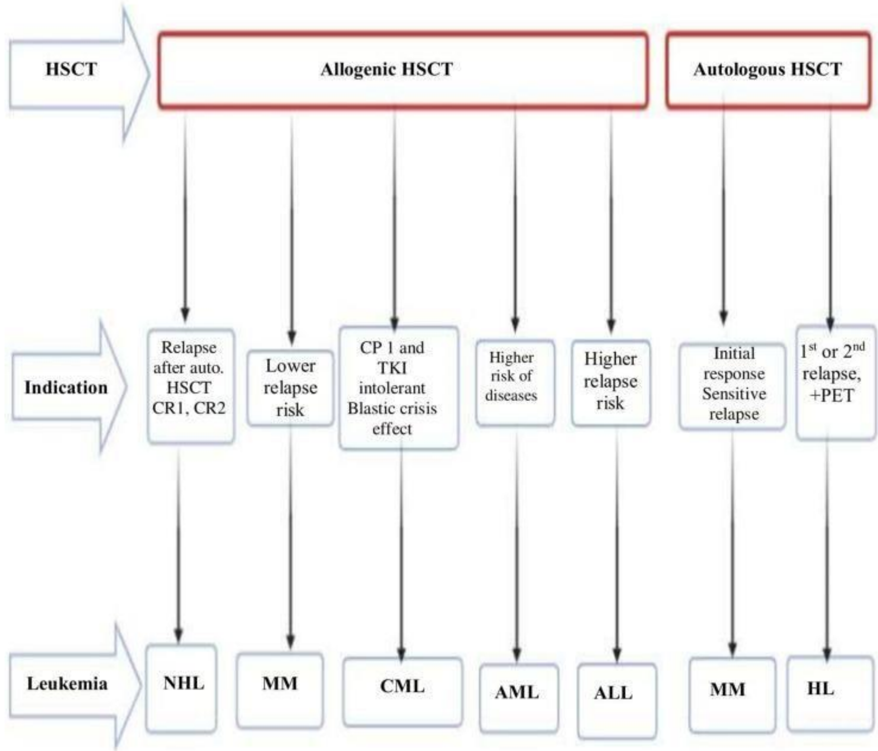

Fig.6: comparison between allogeneic and autologous stem cell transplantation in relation to hematologic conditions.

HSC Transplantation has mainly been recognized as a conventional method for addressing multiple myeloma, leukemia, and lymphomas following cycles of intensive radiotherapy or chemotherapy.(23)

The administration of mesenchymal stem cells aids in preserving the homogeneous condition growth Hematopoietic Stem-Cell, which in turn improves the overall effectiveness of the treatment.(24, 25, 26)

➢ SPINAL CORD INJURY

Spinal cord injuries (SCIs) are the most debilitating and life-altering medical conditions,leading to a significant decline in the quality of life and imposing immense physical, psychological, and economic burdens on affected individuals and their families.(27)

Spinal cord injury (SCI) results in loss of nervous tissue and consequently loss of motor and sensory function.

Stem cell therapy offers hope for patients suffering from SCI by harnessing the unique regenerative capabilities of stem cells.(28)

These cells have the potential to differentiate into various cell types (29), thereby replacing lost neurons, promoting axonal growth, remyelinating damaged axons, modulating immune response, and creating a permissive environment for functional recovery.(30, 31, 32)

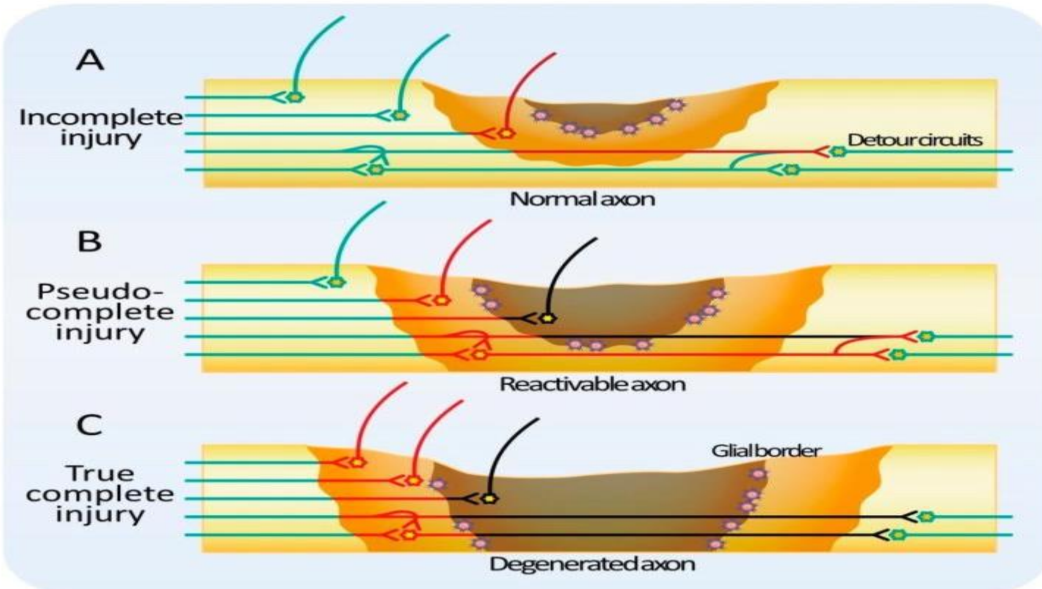

Fig.7: classification of SCI

The Potential of Different Stem Cell Types

Different categories of stem cells are currently investigated for spinal cord injuries. These cell types include embryonic stem cells, induced pluripotent stem cells, mesenchymal stem cells, and neural stem/progenitor cells, each presenting distinct benefits and obstacles within the realm of SCI therapy.

Table 2. Comparison of stem cell types for SCI treatment.

Stem Cell Type	Advantages
Embryonic Stem Cells (ESCs)	• Pluripotent • Can differentiate into all adult cell types
Induced Pluripotent Stem Cells (iPSCs)	• Pluripotent • Can differentiate into various cell types
Mesenchymal Stem Cells (MSCs)	• Multipotent • Immunomodulatory properties • Secrete growth factors

Neural Stem/Progenitor Cells (NSPCs)	Inherent ability to generate neural cells Promote functional recovery and reduce lesion size in preclinical studies

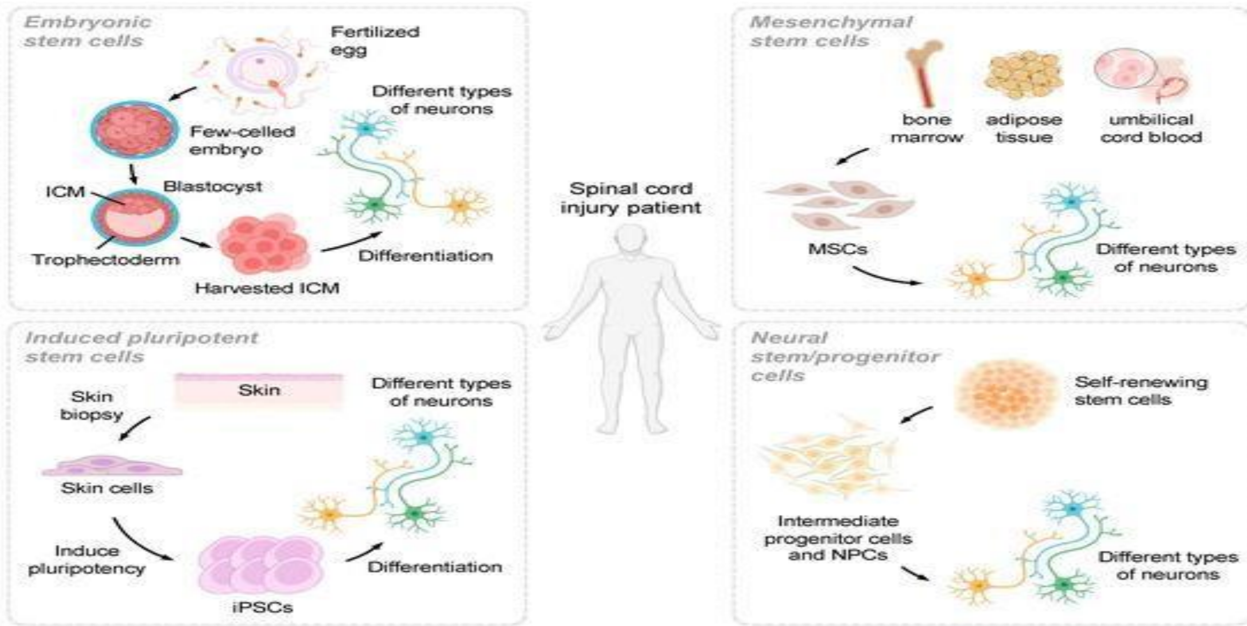

Fig.8: Overview of various stem cell types explored for their potential in SCI treatment.

➢ NEURODEGENERATIVE DISEASES

Neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, and frontotemporal dementia, are characterized by disruptions in protein balance, leading to the degeneration of particular groups of neurons and the formation of inclusion bodies made up of insoluble and misfolded proteins. So it results in the gradual deterioration of sensory perception, cognitive abilities, motor neurons, and an eventual onset of paralysis.

The "R3" strategies (Rejuvenation, Regeneration, and Replacement) can be utilized to address cellular senescence and assist in managing neurodegenerative diseases.

We particularly emphasize stem cell therapy and cellular reprogramming as key R3 approaches. These techniques are designed to counteract the impacts of cellular aging by

(1) Revitalizing current cells

(2) Regenerating neural tissues by activating or introducing stem cells, or (3) Replacing lost neuronal groups with fresh, functional cells.

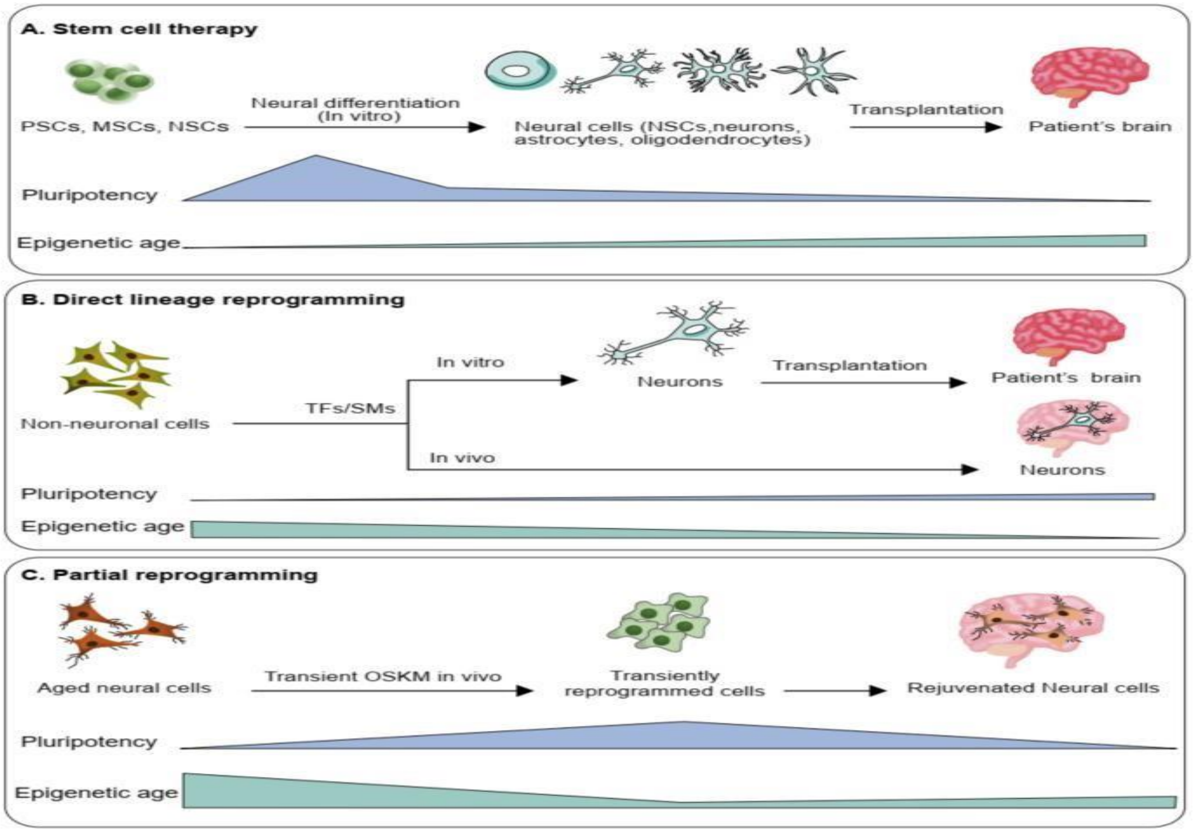

Fig.9: Summary of cell-oriented approaches for addressing neurodegenerative disorders.

- ***Underlying mechanisms of stem cell treatments***

The mechanisms that underlie stem cell therapy are intricate and multi-dimensional, including neuronal replacement, paracrine functions, immune system modulation, neurotrophic support, and mitochondrial transfer.(33, 34)

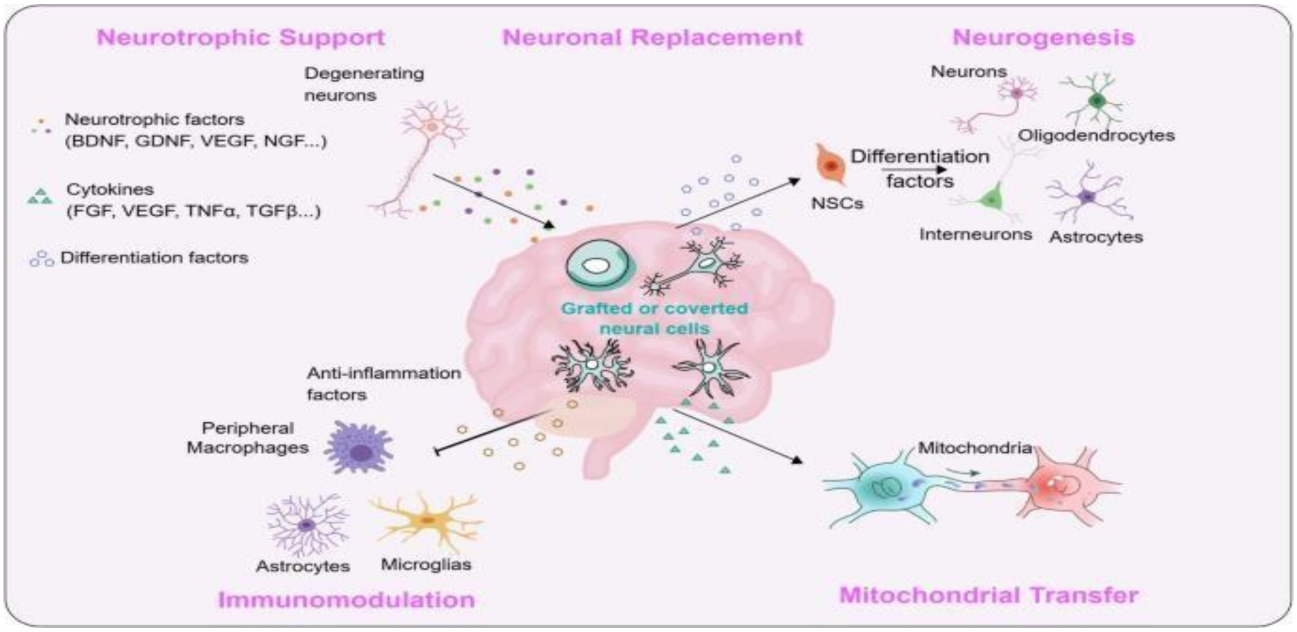

Fig.10: Possible mechanisms that support stem cell treatments.

Table 3. Overview of stem cell treatment for managing neurodegenerative disorders.

Disease	Therapy	Mechanism	Rejuvenation mechanism
PD	1.PSCs-based	• Restores motor function, reinnervates host brain	• Neuronal replacement
	2.MSCs-based	• Enhance motor function	• Neuronal replacement, Neurotrophic Support
	3. NSCs-based	• Improved motor and non-motor functions and preserved dopaminergic neurons	• Neurotrophic Support, Neurogenesis

AD	1.PSCs-based	• Reduced pathology, improved cognitive function • Increased synaptic strength, improved memory	• Neuronal replacement, Neurogenesis
	2.MSCs-based	• Aβ degrading and anti-inflammatory, increase in hippocampal synaptic density, enhances endogenous neurogenesis	• Neurogenesis, AntiNeuroinflammation
	3. NSCs-based	• Enhance neuronal connectivity and metabolic activity	• Neurogenesis
ALS	1.PSCs-based	• improved neuromuscular function	• Neuronal replacement, Neurotrophic Support
	2.MSCs-based	• improvements in motor abilities	• NA
	3. NSCs-based	• Delay disease onset	• Anti-Neuroinflammation, Neurotrophic Support
HD	1.MSCs-based	Decrease in the severity of motor and non-motor symptoms	• NA
CA	1.MSCs-based	Decrease in the severity of motor and non-motor symptoms	• NA
MS	1.MSCs-based	Decrease inflammation and enhance remyelination, leading to improved neurological function	• Anti-Neuroinflammation
	2. NSCs-based	slow the disease's progression	• NA

➢ OSTEOARTHRITIS (OA)

Osteoarthritis (OA) is a chronic degenerative joint disease. The articular cartilage damage could be induced by biomechanical, metabolic, biochemical, or genetic factors. Increased risk factors of OA are obesity, aging, direct joint injury, and/or a genetic predisposition. OA is a complex disease that activates all aspects of the immune system response.

Cell therapy:

This approach employed a blend of surgical and cell culture techniques necessitate binary phases of processes.(35)

A cartilage biopsy was first obtained from the healthy area of the patient's articular cartilage. Following this, chondrocytes were extracted from the cartilage tissue through the use of collagenase. These chondrocytes were then cultured in a monolayer prior to their transplantation into the cartilage defect during the subsequent phase of the procedure. This transplantation was performed either in suspension beneath a periosteal flap or synthetic membranes, or within threedimensional matrices.(36)

MSCs based therapy:

MSCs are multipotent cells having ability to differentiate into cell types, such as chondrocytes, adipocytes, osteoblasts, as well as myogenic and neuronal cells. (37, 38, 39, 40, 41)

Mesenchymal stem cells can be obtained from multiple sources, mainly including bone marrow, adipose tissue, dental pulp, placenta, and umbilical cord, as well as from skeletal tissues.(42)

Alongside their remarkable tissue regeneration capabilities, the immunomodulatory effects of mesenchymal stem cells stand out as another significant attribute. This positions MSCs as a promising source of cells for repairing cartilage damage while simultaneously providing an immunomodulatory effect that helps alleviate inflammation associated with osteoarthritis (OA). Extensive research has focused on the role of MSCs in inflammation. MSCs react to inflammation by migrating injured tissues, modulating immune and inflammatory responses in affected areas, aiding in the fixing damaged tissues.

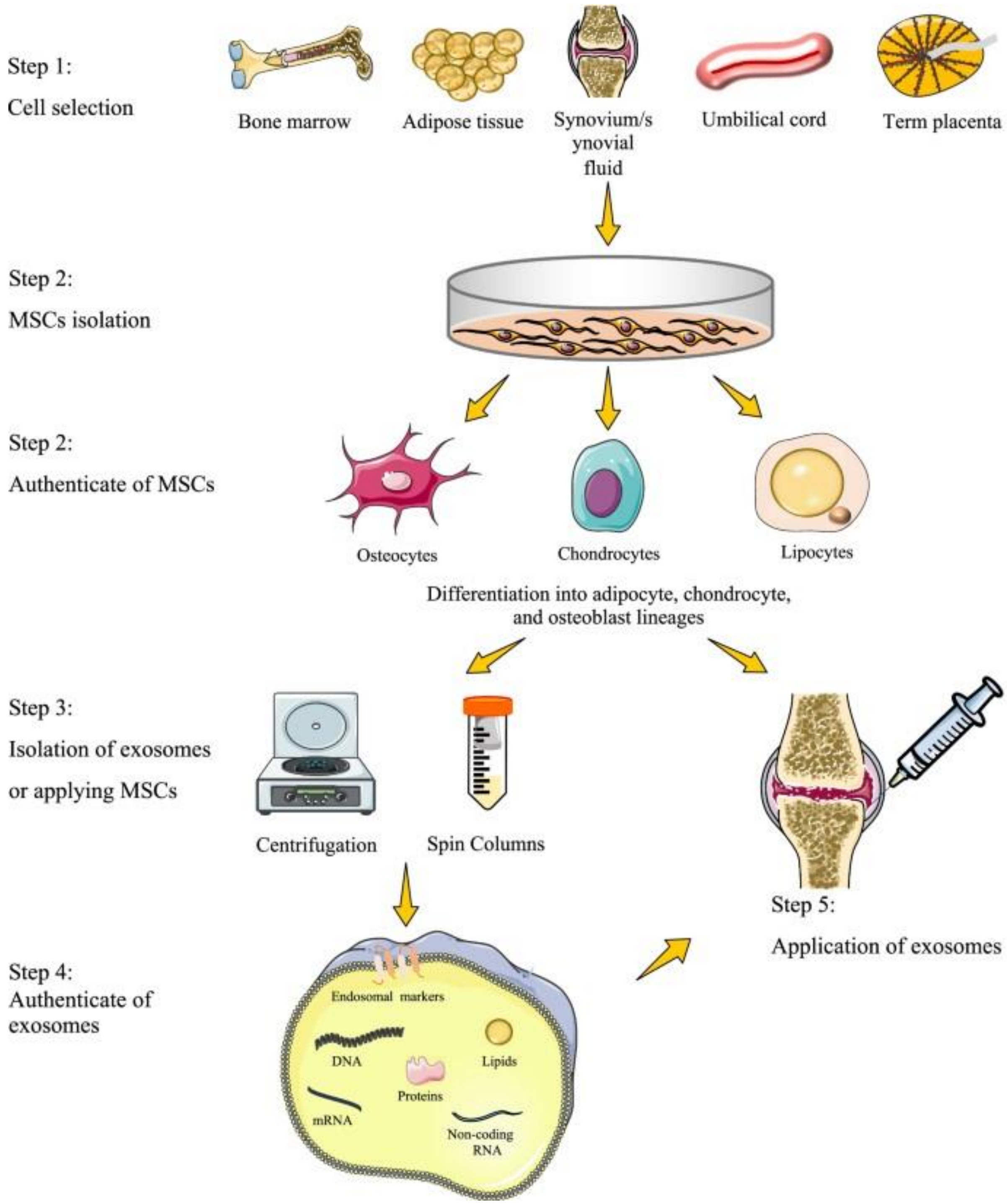

Fig.11: Flow chart of MSC therapy Mesenchymal stem cells are significant in this field and are essential for maintaining tissue balance, as well as for repair and regeneration. These cells are defined by their ability to selfrenew, their versatility, capacity to distinguish into specific categories of tissue cells, such as those found in cartilage and bone.(43)

CONCLUSION:

Stem cell therapy is a fast-developing field with great promise for treating various illnesses and injuries. Although it is still in the preliminary phases, it has demonstrated positive outcomes for specific conditions, and ongoing studies are investigating its capacity to tackle more intricate diseases.

Nevertheless, ethical issues and potential dangers continue to be subjects of active discussion and examination. As advancements in research occur and regulations change, stem cell therapy could transform healthcare.

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