Breaking Boundaries: A Comprehensive Review on Stem Cell Therapies for Incurable Diseases

Short Title: Stem Cells as Regenerative Tool

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Abstract

Despite the remarkable progress and accomplishments in the fields of medicine and technology, several diseases remain highly fatal or incurable, even in the 21st century. The utilization of stem cells is a viable approach for treating such disorders. The regenerative capacity of stem cells has facilitated the development of treatments for various illnesses that result in organ damage. This review has examined the utility of stem cells in treating a wide range of medical conditions, including vascular disorders, neurological illnesses, autoimmune diseases, ophthalmologic diseases, renal diseases, hepatic diseases, cardiovascular diseases, skeletal diseases, Covid-19, and cancer. It has been determined that stem cells represent the next generation of weapons in the fight against illness and injury.

1. Introduction:

A human body repairs through stem cells employing an endogenous system of again generation of cells, although stem cells can be present in nearly every type of tissue. Evolution is highly appreciated in this process, and so it seems logical that recovery of function is best performed by these cells. Hence, the future of translational medicine greatly lies in stem cells. Aside from a strong interest in stem cell biology, there are few examples of clinical applications. Various reasons for this involve:

- Various problems are linked with the extensive expansion of cell in vitro.
- After implantation, occurrence of cell death.
- Hindrance in getting vascularization.

- Issues associated with biomaterials that are used as carrier.
- Ethical issues and moral concerns that obstruct clinical translation.
- Prices of extended cell culture.

Chronic degenerative diseases treatments are mostly relaxing, just decrease disease proliferation and complexities. Few scenarios, organ transplantation can be done like liver, heart, and kidney transplantation; although, that cannot be employed because of the limited availability of donor organs and long-term usage of immune suppressive agents. Regenerative medication involves repairing diseased or damaged organs and tissues, which were previously thought to be irremediable. Regenerative medicine uses different biomedical processes, involving utilization of biologically active substances to cause recreation of damaged organs or in-vitro remodeled useful tissues and organs implantation. Along with this, cell therapy approach also involves repairing the damaged mechanisms causing initiation of a disease, disease enhancement, and in the case of transplantation of organs preventing demand of donor organs and few scenarios need of use of immunosuppressive agents [1].

Cell therapy uses progenitor, stem, primary or stem cells derivatives (SC) for the replacement and repairing of tissues or organs. Cells could be introduced into veins, directly introduced in damaged areas, or obtained from one's own tissue. Stem cells include the most potential source for such kind of treatments because of their ineradicable renewing property and ability of differentiation. Various sources of cells can be used for cell therapy: which involve ASCs or adult primary cells derived from tissues, ESCs, FSCs, and iPSCs. After isolation of these cell types culturing, expansion, and differentiation or genetic changes are done to get the desired type of cell. Obtained cells can be again introduced to body of a diseased person in order to cure cardiovascular, nervous, musculoskeletal and other disorders [1].

Stem cells have the potential to restore function of a tissue either introduced as participant in the target tissues or as source that carries complex signals to a tissue which has to be cured without addition into the tissue itself [2].

2. Stem cell classification

Stem cells are undifferentiated human body cells. They have differentiation ability into any cell-type and have self-renewal capacity. They are present in both fetal and adult cells. Different specialization steps are as follows.

Totipotent stem cells have the greatest potential of differentiation and allow the formation of both embryo and extra-embryonic structures and can be differentiated into the cells of the whole organism. A source of pluripotent cells is the blastocyst taken from zygote.

Pluripotent stem cells (PSCs) makeup cells of germ layers except extra-embryonic structures formation (placenta) for example embryonic stem cells (ESCs). Induced pluripotent cells from embryos is an example. Culturing and utilizing iPSCs are very important for regenerative medicine's present and future.

Multipotent stem cells have finitely different potential than pluripotent stem cells, but they differentiate in different specific cell lineages like hematopoietic stem cell.

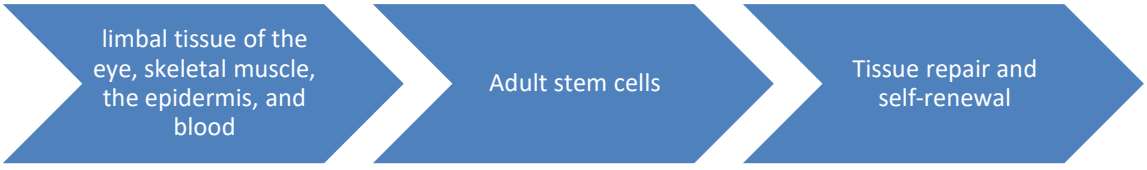
Oligopotent stem cells can diversify into different cell types, such as myeloid stem cells, which can be split into leukocytes rather than erythrocytes.

Unipotent stem cells checked by the narrowing differentiation abilities and a unique character of repeated division. These cells have only potential to form one cell type, for example dermatocytes [3].

Adult and fetal stem cells are derived from various specialized tissues like adipose, peripheral blood (PB), bone-marrow (BM), navel string blood, placenta and other that may serve as a mean of tissue specific Stem cells [4].

Table 1 Presents the basic kinds of adult and fetal SCs employed for therapy of untreatable diseases.

1. Mesenchymal stem cells (MSCs)	Used in treating brain, cardio-vascular diseases, stroke, spinal cord injury (SCI) and Crohn's disease (CD)
2. Hematopoietic stem cells (HSCs)	Used in therapy of autoimmune diseases.
3. Mononuclear cells (MNCs)	Used in treatment of critical limb ischemia, neurological disease, and cardiovascular disorders.
4. Endothelial progenitors' cells (EPCs)	Have beneficial results in ischemic diseases.
5. Neural stem cells (NSCs)	A promising candidate for the therapy of neurological diseases.



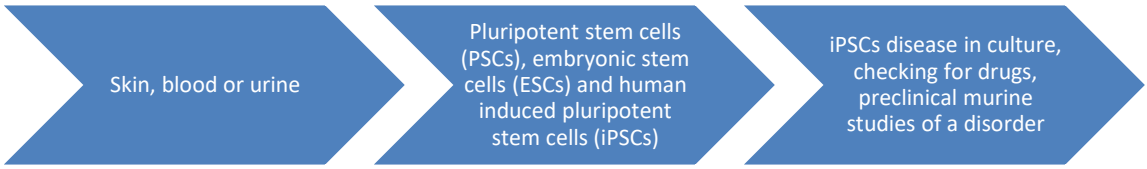


Fig. 1 Sources, types, and therapeutic role of basic stem cells

3. Stem cells treatment for vascular diseases:

Dysfunction/loss of endothelial cells is an event in incidence of vascular disorders, involving angioplasty-induced restenosis, and vein bypass graft atherosclerosis, native atherosclerosis, and transplant arteriosclerosis. Abnormality of the endothelium is believed to be one of the prior abnormalities. Long term effects of traditional medications cause death. Recent research has shown that stem cells found in artery walls and blood can regenerate endothelial cells after extended loss. According to the findings, stem cell treatment is an important alternative for treating vascular disorders and will most likely lead to tissue regeneration, that is, the regeneration of endothelium surrounding the arteries to repair the vascular system. in the future. ESCs can be characterized into both smooth muscle cells and vascular endothelial cells [5].

There are various origins of endothelial progenitor cell (EPC)**.** EPCs can be transferred from adipose tissues, bone marrow, vessel wall–especially adventitia–and spleen into the blood. Patients' own body cells were used to prevent rejection by the immune system. The thought of using stem cells to engineered vessels was also used at that time but those resulted to the generation of arteriosclerotic lesions. Stem cells used for the replacement of cells that have been dysfunction or lost after balloon angioplasty, therefore important for restoration the maintenance of the vessel and, most obviously, its quality [6]

To maintain transplantation of hESC-ECs for long time and observe full advantagess of hESC-EC treatments, changed procedure with pro-survival components [7] or addition of matrix [8] to avoid demise after engrafment. A combined strategy for enhancing transplantation of hESC-ECs by using growth factors and biomatrix were employed. Growth factors enhance cardiac stem cells (CSC) from bone marrow mononuclear cells (MNC) or peri-infarction region in the stream to move into the damaged zone to regenerate blood vessels or cardiomyocytes [9]

Cord blood-moving endothelial progenitors are also employed for the therapy of vascular disorders. Cord blood (CB) has more endothelial progenitor cells (EPCs) than peripheral blood (PB), and they are used for therapy after being expanded. After some passages, they can produce more than 10^7 cells. The number of endothelial cells extracted from one unit of cord blood is sufficient for analytical purposes. EPC colonies can be effectively generated, extended, and stored in culturing material and used for therapy in various *in vitro* and *in vivo* assays. Hence, endothelial cells from cryopreserved Cord blood contain identical observable and practical characteristics like newly obtained Cord blood. Possibility of utilizing CB for clinical purposes

proved effective in porcine models of ischaemia for characterizing their observable and practical characteristics compared from humans [10].

The characterization of multipotent vascular stem cells proved effective in various vasculopathies. The current type of stem cell found in blood artery walls, known as multipotent vascular stem cells, came to light. Multipotent vascular stem cells showed markers, involving Sox10, Sox17 and S100β can be cloned having activity of telomerase, and be permitted into neuronal cells and mesenchymal stem cells (MSC), like those eventually characterized into smooth muscle cells. Multipotent vascular stem cells begin to be expanded and characterized into mural cells and chondrogenic cells because of vascular abrasion. Hence take part to vascular remodelling and abnormalities [11]. Various methods employed to treat vascular disorders, and change cellular function through various micro-environmental hints [12]. Induced pluripotent stem cells (iPSC) provided effective method to gain one's own smooth muscle cell source (SMC) for patient-specific disease treatment.

Different important achievements and significant challenges are accomplished to precede endothelial cells (ECs) de novo from hPSCs. Different methodologies were acquired for summarizing the tissue specific and vessel useful diversity of endothelial cells in-vitro. Induced pluripotent stem cells (iPSCs), adult somatic cells and embryonic stem cells (ESCs) can be characterized into embryonic stem cells utilizing procedure of coculturing, embryoid body, monolayer, or transdifferentiation method. ECs obtained by these different methods can be employed for different therapeutic purposes [13].

Different methods are used to copy in-vivo endothelial sorroundings involve changing oxygen tension, allowing endothelial cells (ECs) to move, utilizing different growth components and small molecules, culturing ECs on substrates with various qualities, and cmbined culturing of embryonic stem cells with other cell types. Therefore, it was showed that hPSCs-ECs have quality to generate advanced treatments for vascular disorders [13].

The advancement of vascular grafts (TEVGs) developed from human induced pluripotent stem cells-derived vascular smooth muscle cells (hiPSC-VSMCs) provide innovator access for altering damaged blood vessels. To get hiPSC-VSMC-derived tissues not utilizing animal-derived reagents was necessary, accessed and showed equivalent mechanical power as from xenogeneic hiPSC-VSMCs. When generated onto biodegradable polyglycolic acid (PGA) extension, designed vascular tissues were obtained showing adequate deposition of collagen applicable for implanting into a mouse which was immunodeficient. This leads to reliable and virtuous therapy [14].

4. Stem cells therapies for Neurological diseases

Neurological abnormalities comprise of group of nervous system pathologies that include neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, brain ischemia, and Friedreich's ataxia. In recent years, Stem cell transplantation is getting consideration as a potential option for the possible treatment of neurodegenerative diseases.

4.1 Parkinson's disease

Parkinson's disease (PD) is the second most prevalent neurodegenerative ailment, characterised by the loss of dopaminergic neurons from the substantia nigra in the midbrain, resulting in a decrease in dopamine content. There is no definitive cure for Parkinson's disease. Recent drug therapeutics include DA agonists, subthalamic nucleus stimulation in brain, and anticholinergic drugs. These treatments can improve certain symptoms however, these they do not have enough capability to stop disease progression and they also cause serious side effects [15].

Cell therapy for Parkinson's disease using NSCs can significantly increase long-term neuronal cell survival and the presence of immunoreactive cells, and NSCs have been proposed as a trustworthy source of cells for therapies [16].

4.2 Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterised by neuronal cell death, synaptic failure, and extreme buildup of misfolded proteins in cerebral cortex. It is a common form of dementia [17].

AD is a multifactorial disease, due to which determining the precise pathophysiological mechanism is extremely difficult. A growing body of evidence suggests that B-amyloid aggregates and tau accumulation in neurofibrillary tangles act as the major pathogenic drivers of neurodegeneration in AD [18]. However, there is no approved treatment for Alzheimer's disease, and stem cell therapy could be an avenue for regenerating damaged or lost neurons and thus improving patient's survival rate [19].

For the treatment of AD Cell therapy has not been studied widely. Few researches demonstrate that stem cell therapy could substantially reduce Ab accumulation [20], cognitive rescue problems [21], decrease ageing dependent neuronal atrophy and improve patients overall AD symptoms [22]. Moreover, mesenchymal stem cell therapy could also drastically lower Ab accumulation and cause resistance against neurotoxicity and degradation.

4.3 Spinal cord injury

Spinal cord injury (SCI) is a major cause of paralysis in more than 20 million individuals. This injury has inadequate regeneration capability to rebuild axonal linkagges, thus loss of myelin resulted in compromised autonomic functions. Moreover, there is no efficient treatment for SCI available yet [23].

Clinical trials using stem cells therapy for the treatment of SCI have not been widely conducted. however, NSCs excrete growth factors which significantly improves neural repair processes, improves function by reducing tissue loss and Neurological improvement without adverse effects, [24] and improved behavioral and locomotor recovery, increase in neuronal cell survival, decrease in glial scar development and generation of a functional synapse [25].

4.5 Huntington's disease

Huntington's disease (HD) is a foetal autosomal dominant brain ailment caused by repeat expansions of CAG nucleotide in the huntingtin gene on chromosome 4 [26]. This expansion produces the emergence of a polyglutamine domain within the protein's N-terminus [26]. Symptoms include dementia, depression and chorea (Frank, 2014). This disease is caused by the demise of nerve cells in the basal ganglia, motor dysfunction and subsequently death [27].

There is no effective treatment for this disease, and only a few medications that provide symptomatic relief are available after extensive research. NSC-based stem cell therapy for Huntington's disease can substantially improve motor impairment [27] and enhances anatomical and behavioral recovery. Moreover, by using ASCs for cell therapy can significantly slow down behavioral degeneration problem [28] and also delay further progression of disease [29]. Furthermore, By using MSCs for treatment greatly increases neurogenesis [30].

4.6 Friedreich's ataxia

Friedreich's ataxia is a genetic autosomal recessive disorder caused by GAA.TTC nucleotide repeats inside the first intron of the FXN gene which result in repression of frataxin [31]. Frataxin-deficient dysfunctional neurons contribute to the neuropathology of FA [32]. Substitution of these defective cells within the dorsal root ganglia may promote dorsal root ganglia neuron survival. There is no effective treatment to cure this disease, and existing treatments are unable to slow the progression of degeneration.

Cell therapy using bone-marrow-derived MSCs, drastically enhances motor functions and delay in the neurodegeneration, overturns neurological features of the disease and relieving of the motor impairments [33].

4.7 Brain ischemia

Brain ischemia is the most crucial cause of irreversible neurological impairments in neonates, with a global rate of 2 per 1000 term births [34]. This lesion lowers neuronal progenitor cells, resulting in decreased neurogenesis and oligodendrogenesis, which compromises motor and cognitive function. Furthermore, the disease has a limited progression capacity, and regeneration is necessary for the improvement of brain ischemia.

Cell therapy using NSCs significantly enhance functional recovery, neural generation, decreases functional deficits, and increases survival rate. Furthermore, BSC-based cell therapy greatly enhances cell proliferation, motor recovery, neurogenesis, and functional recovery [28].

5. Stem cells therapies for autoimmune diseases

In Autoimmune diseases, the immune system shows abnormal response against patient's own body tissues and are normally treated by immunosuppressive drugs and transformation of the abnormal immune system function is the main target of cell therapy.

5.1 Crohn's disease

Crohn's disease is an inflammatory bowel disease characterised by the patient's uncontrolled immunological responses and unusual T-cell activity. As conventional therapies frequently fails to produce satisfactory outcomes, a cell-based therapeutic approach was developed to heal damaged intestinal tissues while regulating auto-immune responses [35].

MSC and HSC-based transplantation are currently being under consideration in phase three clinical trials [36]. MSCs contribute to the healing of damaged epithelium caused by inflammatory processes which maintain mucosal repair processes and extracellular matrix deposition. MSCs also help in restoring epithelial tissues which induce the development of a new basement membrane. MSCs do not have only regenerative ability rather they can also regulate innate immune responses, promote expression of the antiinflammatory cytokine and repress dendritic cell development [21].

5.2 Type 1 diabetes mellitus

It is a chronic auto-immune disease exhibited by gradual annihilation of insulin secreting pancreatic beta-cells. Cell-based therapies for T1DM intend to attain at least substantial control at autoimmune reactions, to avoid subsequent beta-cell damage, conserve viable beta-cells, and produce transplantable insulin-producing cells that are glucose-responsive [37].

T1DM cell therapy for immune modulation uses MSCs, HSCs as well as T-regulatory cells. Most of clinical research studies have proved that by administering autologous HSCs to T1DM patients, followed by immune preconditioning, can cause a 'immunological reset', which improves beta-cell function [38]. Several clinical investigations have demonstrated that T-regs delivery can prevent onset of diabetes in an experimental lab. animal. Currently, it is being evaluated in a Phase one clinical research for safety and improvement of β cell function, modulation of autoimmune responses and to attain lifelong antigen specific tolerance [39]. MSCs can also be used to stimulate β-cell regeneration [37].

6. Stem cell therapy for Ophthalmologic diseases:

Many ophthalmologic diseases which are mainly due to injury or degeneracy of cells present in eyes can cause blindness. Eye is a well reachable and immuno specialized organ, therefore can be considered as a favorable target for cell based therapies [1].

6.1 Retinal disorders:

The human retina consists of layers of cells that are made of specific neurons. The perfect coordination and positioning of neurons are provided by retinal pigmented epithelial (RPE) cells. Any injury in the eye can cause death of these neurons specially photoreceptors and RPE cells leading to irreversible visual defects and blindness. Recent studies therefore targeted the transformation of photoreceptors to make functional RPE layers [40]. Stem cell transplant studies intent to recover visual functions [41]. Pigment epithelium derived factor (PEDF) is secreted by RPE cells that can conserve photoreceptors in retinal degeneration models. When

MSCs were propagated in retinal degeneration mice, they interfere with apoptosis of photoreceptors due to influence of PEDF secreted by MSCs [42].

When neural cells that were obtained from ESCs were given to the rats via eye retina and vitreous humor, the rats showed maximum assimilation and neuro protective effect. IPSCs also showed improvement in the functioning of retina in rats [43]. MSCs could extricate into neurons of retina or could trigger tissue recovery by protecting them from cell death, adjusting inflammation and angiogenesis [40].

6.2 Retinitis pigmentosa:

It is a complex and partially understood disorder of retina that impede with normal visual cycle inducing deterioration of rod photoreceptor functions and causing visual loss [44]. MSCs destined to the network of trabeculae can cause reconstruction of ocular tissue via paracrine factors. The reduction in intra ocular pressure was related to improvement of TM cell, increased ocular outflow and enrollment of progenitor cells [45]. MSCs also display antimicrobial characteristics that are stimulated by excretion of human cathelicidin antimicrobial peptide-18 (HCAP18) to fight invading microorganisms [46].

Clinical practices showed useful results to treat a broad range of pathological complexities related to ocular degenerative diseases using MSCs [47]. Novel studies have found that maternal cord derived MSCs have important paracrine and immuno regulatory characteristics. They make several tropical factors that are comparable to those that are produced by RPE. They prohibit degeneracy of retina and protect photoreceptors. UC-MSCs can lessen the persistent inflammation and forbid cell death process [48].

6.3 Macular degeneration and glaucoma:

There are many kinds of stem cells that when implanted into damaged CNS could show innate neuro protective characteristics. Stem cells bring out neuro protective response by latent secretion of immense levels of neurotrophic factors [49]. Choroidal neovascularization pierced from neural retina cause leakage of fluid, fatty lipids and blood in neo vascular age-related macular degeneration leading to fibrous scarring [50]. When autologous bone marrow derived stem cells were given to patients with age related dry macular degeneration, 63% of patients showed better visual sense. Therefore this stem cell based therapy can enhance or normalize visual perception in dAMD patient [50, 51].

Glaucoma is referred to as damage of optic nerves which is a major contributor of non-reversible blindness all over the world [52]. Recent therapies struggle via lowering intra ocular pressure. Recent research has found that in a rat model of glaucoma, cells that secrete neurotrophin factors can protect RGCs from death. Therefore, stem cell transplant treatment seems to mitigate neuro degenerative problems in brain and spine via release of neurotrophic factors. When MSCs are transplanted, they form and secrete various neurotrophic factors and anti-inflammatory cytokines locally [53].

7. Stem cell therapy for renal diseases:

A kidney is an extraordinary, complicated organ, made up of more than 20 specific types of cells. When kidney is damaged, the renal tissues go through many different disease conditions like acute and chronic kidney failure [54]. Stem cells have capabilities in developing novel therapies to treat renal disorders. Stem cell therapy can help to recover injured nephrons both in acute and chronic kidney damage. They also play a substantial role in the advancement of gene-therapy for inborn kidney disorders. In patients with genomic deformities, HSCs can be used. HSCs are intrinsically transformed, differentiated, and assimilated into the recipient tissues to repair genomic deformities. Stem cells may also be developed to distribute therapeutics to specific targets such as hormones, cytokines etc. [55].

7.1 Acute kidney failure:

Various studies have demonstrated a few benefits for using MSCs on patients with acute kidney failure. When bone marrow MSCs were inculcated on NOD/SCID mice having immunodeficiency and acute kidney failure, the bone marrow MSCs became restricted chiefly in peritubular areas reducing the cell death of renal tissue and increasing its cell division. MSCs from bone marrow can also conserve the probity of peritubular blood vessels and tubular epithelium, extends survival in acute renal failure [56].

In cisplatin treated mice with acute renal failure, human iPSCs were administered to retinal progenitor cells and vigorously imparted into damaged tubuli. The iPSCs recovered the structure and function of kidney [57]. Human pluripotent stem cells have the potential to produce a new kidney or its part via organoid, blastocysts and scaffolds etc. [58]. When retinal progenitor cells were transplanted into a rat with ischemia-induced acute kidney injury, improvement in renal functions were observed [59]. mESCs transplantation into induced renal failure mice decreased the fatality, and evade histological degradation relevant to disease [60]. mESCs also have useful effects on acute kidney injury akin to the decrease in lipid peroxidation [61].

7.2 Chronic kidney failure:

In diabetic mice, MSCs have shown a good effect in the inhibition of hyperglycemia and halt kidney damage [53]. Human bone marrow derived MSC's were obtained and infused via heart into mice with immunodeficiency and type 2 diabetes induced by streptozotocin. The mice showed a decrease in interstitial fibrosis tubular degeneration [62]. In C57BL/6 mice with type 1 diabetes, beta-pancreatic islet is regenerated when a single dose of MSCs is infused intravenously thus impeding kidney damage, hyperglycemia and glycosuria [63]. When multiple doses of human bone marrow derived MSC's, maternal cord MSCs, and kPSCs were infused into athymic rats along with adriamycin-induced nephropathy, they exhibited finite podocyte and glomerular endothelial cell destruction. They also constrict the development of podocytes and PEC bridges resulting in lowering of glomerulosclerosis and fibrosis [64].

MSCs can divide into a number of lineages and can drift toward damaged tissue and their capability to secrete various factors is crucial in tissue rehabilitation [65]. When an intravenous

dose of RPCs was given to renal damaged mouse, RPCs assimilate into kidney tissue after 24 hours and resulted in lowering the levels of blood urea nitrogen thus enhancing renal tissue functions [63].

8. Stem cell therapy for liver disorders:

Liver failure is a severe clinical disorder marked by huge necrosis of liver cells that occur due to different types of acute and chronic damages [64].

8.1 Role of MSCs:

Stem cell therapies comprising IPSCs, MSCs and HSCs appeared to be an excellent source to treat hepatic disorders [66]. MSCs secrete different types of cytokines which play an important role in treating liver failure alternative to differentiation into working liver cells and restoration of damaged parenchyma [67]. MSCs also have capability to divide into liver cells, thus they can repress inflammatory responses, decreased liver cell death and increase the formation of new liver cells thus enhance the liver functions [68].

MSCs can also suppress and repair the immune system in patients with immune-mediated liver failure [69]. MSC's have the potential to enhance tissue growth and rehabilitation, to decrease apoptosis, to increase formation of new blood vessels and to suppress immune system [70]. Extracellular vesicles that are obtained from MSCs have various benefits in treating liver disorders via reducing fibrosis, enhancing production of liver cells and improving immune activity [65]. New research has discovered that if MSCs were treated with some chemical agents such as hypoxia, microenvironment and undergo genetic modification, they can protect liver cells from injury. These modified MSCs can increase hepatogenic differentiation, lifespan of liver cells and paracrine effects both in vivo and in laboratories to cure liver diseases [66].

8.2 Role of ESCs:

In vitro, embryonic stem cells can be differentiated into cells similar to hepatocytes or hepatoblast progenitor cells [71]. Mouse derived embryonic stem cells when grown under pre-determined conditions are differentiated into a pool containing liver precursor cells. When such precursor cells are expanded for a long time, they can form liver cells without formation of any tumor when induced into fuylmaracetoacetate hydrolase deficient mice [72]. Differentiation of human ESC-derived hepatoctes can be increased if we suppress MicroRNA-199a-5p. When such ESC-derived HLCs are induced into the liver of an immuno-compromised mice, they enhance the production of human albumin [73].

8.3 Role of iPSCs and HLCs:

When differentiation of human derived iPSCs into liver cells occurred, they explicit several liver markers such as albumin, alpha fetoprotein and were able to perform liver cell functions (Song et al., 2009). hiPSC-HLCs can enhance serum albumin level after 7 days of induction into carbon tetrachloride infected mice liver [74].

Human iPSCs can be cultured in vitro to produce liver buds that can transform and develop into a functional human liver. It is regarded as first, comprehensive human functional tissue that have been produced from IPSCs [75]. Induced multipotent progenitor cells can differentiate to form liver cells when implanted into immuno-compromised and fuylmaracetoacetate hydrolase deficient mouse via injection into spleen. This therapy can be used to manage liver damage caused by type-1 hereditary tyrosinemia [76]. Hepatocytes derived PSCs have been diagnosed to treat liver failure and increased the improvement of xenogenic free 3D culture procedures [66].

9. Stem cell therapies for cardiovascular diseases

Over time, cardiovascular diseases become a common reason of death around the globe. The number of these patients is increasing day by day. Infectious and non-infectious factors are causes of myocardial infraction, stroke, and ischemic heart diseases. As a result, the function and elasticity of myocardial cells are lost and even death [77].

Developments in surgical intervention, medication and surgical therapies have been only able to slow the progression of disease, not to regain the viability of affected cardiac myocytes. The recruitment of lymphocytes to the ischemic part can initiate the inflammatory reaction, is facilitated by myocardial infraction. The onset of signal transduction pathways modulates the heart functionality. Increase in load and myocyte necrosis results in cardiac failure by continuously damage to heart tissues. Heart transplant is the only treatment for cardiac patients. In past few years, the requisition of stem-cells for the remedy of heart diseases has revolutionized the world [78].

9.1 Therapeutic potential of Mesenchymal stem cells

Mesenchymal stem cells are potent therapy for cardiovascular disease due to their unique features [78].

1. Differentiation into Cardiomyocyte-like cells.
2. Immunomodulatory property.
3. Antifibrotic activity.
4. Neovasculogenesis.

9.2 Differentiation into cardiomyocyte-like cells

MSCs differentiate into cardiomyocyte-like cells upon transplantation. This is confirmed through an increase in myocardial specific marker proteins, like troponin T. Within one-week, perivascular cells from the human umbilical cord form contracting cell clusters on cardiomyocyte's feeder layers. These are the one of the type of MSCs [79]. Graft transplantation and cardiac cells formation from mesenchymal stem cell can be promoted by perfusion of Retrograde pivotal fibroblast growth factor and that helps to regain activity of heart [80].

9.3 Immunomodulatory properties

By utilizing innate and adoptive immune system, mesenchymal stem cells have immunoregulatory activity. MSCs helps in the prevention of myopathy and lessens the amount of

proinflammatory monocytes producing Ly6C levels in the blood ranges from moderate to high, cardiac and spleen tissues of CVB3 mice treated with MSC [81]. Guo et al. discovered that MSC implantation minimized TNF-, IL-1, and IL-6 expression as well as Ischemia, resulting in a considerable improvement in cardiovascular output in MI mice [78].

9.4 Antifibrotic effect

MSCs can suppress actions of fibroblasts, decrease extracellular matrix deposition, minimize left ventricular remodeling, and promote heart output through controlling matrix metalloproteinase. According to study, HGF produced by MSCs is an effective fibrosis inhibitor, and HGF is the crucial element necessary for MSCs' antifibrotic function in vitro [82]. In a myocardial infracted mouse model, direct cell contact method was used for the perfusion of mesenchymal stem cells in the nearby cells of myocardial infracted zone having released human growth factor. This enhanced the remodeling of left ventricular and minimized the signalling cascades. Studies have shown that mesenchymal cells can suppress the activity of fibroblast by controlling the matrix metalloproteinase and decreasing the accumulation of this extracellular matrix which recovers the activity of cardiomyocyetes. Human growth factor(HGF) acts as important regulator and have antifibrotic action [82]. In the mouse MI model, Mesenchymal stem cells inserted at the place of infraction have shown the antifibrotic function in the presence of HGF by reducing miR-155-mediated profibrotic signaling to improve the left ventricular of heart [78].

9.5 Neovascularization capacity of MSCs

Bone marrow derived pluripotent stem cells promotes the angiogenesis [83] and MSCs cells at the site of infraction helps in restoration of ischemic tissues but we have still some hurdles like low rate of transfer at infraction area and less survival rate [78].

9.6 Exosomes for Cardiovascular Diseases

The another potential and valuable method for cardiovascular diseases is application of exosomes [84]. Most cells in the body can secrete exosomes, which are small extracellular vesicles with phospholipid bilayers. The exosomes can be derived from any type of stem cells like ESCs, IPSCs, and MSCs [85]. ESC-derived exosomes having anticardiomyocyte apoptosis and antimyocardial fibrosis properties can enhance cardiac restoration by stimulating cardiomyocyte proliferation and enhancing cardiac cell formation [86].

- iPSC-derived exosomes can reduce myocardial fibrosis [87]. Exosomes derived from iPSCs have been shown to minimise apoptosis in H9C2 cells exposed to H2O2 induced oxidative stress by lowering caspase 3/7 activity [88].
- MSC-derived exosomes were shown to reduce ischemic area and improve cardiac function in a pig myocardial ischemia reperfusion paradigm. Exosomes derived from human MSCs have been shown in earlier studies to significantly improve myocardial regeneration and cardiac output in rats [88].

9.6.1 Exosomes as Biomarker

Recent research suggests that plasma levels of exosome associated miRNAs could be used as novel biomarkers for the diagnosis of myocardial infarction [88].

• A substantial rise in miR-499 and miR-208b in plasma from induviduals with acute myocardial infraction has been confirmed [89]

• miR-208a could be a marker for myocardial infarction in its early stages.

• After acute myocardial infraction in the early stages of HF, the expression of small RNAs linked with p53 genes (miR-192, miR-194, and miR-34a) was considerably enhanced [90]

8.2.4 Exosomes and Myocardial Ischemia-Reperfusion Injury

Exosomes, which are a key component of stem cells' paracrine impact, can deliver miRNAs, mRNAs, and proteins to target cells, promoting cell proliferation, differentiation, survival, and angiogenesis while inhibiting apoptosis and inflammation. As a result, cell-free exosomes appear to be a viable CVD treatment option [88].

10. Stem cell therapies for degenerative skeletal diseases

Stem cells, especially mesenchymal stem cells, have revolutionized the Science for regeneration of bones in degenerative skeletal diseases like osteoporosis and osteoarthritis.

10.1 MSCs and Osteoporosis

Osteoporosis is a metabolic disorder in which there is an imbalance between the bone resorption and formation of new bone. In this condition, the remodeling of bones which shape the bones during any injury or accidental event has reduced. The diminishing of bone formation and more resorption activity causes the fracture among the individuals [91]. Osteoporosis is intimated due to any pathological condition, any nutrient deficiency, hormone imbalance in the body, aging or usually after menopause among women [92]. The lifespan of osteoblasts is linked to the start and progression of osteoporosis. Nuclear estrogen receptors and androgen receptors are involved in the remodeling of bone and control of interleukin-6 levels. Estrogen has a significant function in the suppression in the expression of apoptotic gene in osteoblasts [93].

There is another better method to treat osteoporosis is the application of autologous mesenchymal stromal cells/mesenchymal stem cells [94]. In vitro, three-dimensional cell culture allows for better physiological development and stem cell modification, in comparison to growth on typical round platforms, with more Osterix expression, enhanced ALP activity, and higher mineralization levels. Rampichová et al. (2013) found that 3Dcultivating minipig MSCs in electrospun 3D polycaprolactone increased their proliferation and vitality [95].

The rational design of 3D cell culture conditions might boost MCSs' bone regeneration performance even further. Furthermore, the rigidity of the scaffold, its topography, and the possible retention and release of paracrine substances must all be considered. Finally, because electrical stimulation of MSCs has a significance to increase their osteogenic potential, and

conductivity may be a key factor in the expansion of appropriate osteoinductive biomaterials [94]. In rat model, Osteoporotic rats were injected with MScs for 4-8 weeks and upon diagnosis, there was increase in calcium deposition, and calcium phosphatase activity in the serum and joint regions. After continuous exposure there was formation of fatty bone marrow and uniformity in the trabeculae. It was like normal red bone marrow. Scientists are thinking to apply it on human model in near future [96].

10.2 Osteoarthritis and stem cell therapies

Osteoarthritis is characterised by the deterioration of articular cartilage and subchondral bone. Knees and hips are weight-bearing joints that are impacted [97]. Cell transplantation and medication treatment are two techniques with risks and adverse effects. The chondrogenic potential of iPSCs and hESCs has been established both in laboratory as well as in animal model. However, their capacity to produce ECM and the duration they can retain their chondrogenic potential are still unknown [1].

Studies have proved that synovial-derived MSCs had the highest chondrogenic capacity. Their implantation resulted in complete cartilage repair, either in conjunction with collagen or ECM derived from their in vitro cell cultures. It demonstrates the usage of MSCs in osteoarthritis cell treatments [1].

Human adipose derived mesenchymal stem cell exosomes have been found to attenuate inflammation and oxidative stress, perhaps mediating antisenescence in osteoarthritis [98]

11. Stem cell therapies for Covid-19

11.1 Mesenchymal stem cells and COVID-19

Mesenchymal stem cells may be instrumental in preventing critical lung infection and inhibiting the SARS-CoV-2-induced cell mediated inflammatory response. Furthermore, Because mesenchymal stem cells lack the angiotensin-converting enzyme 2 (ACE2) receptor required for SARS-CoV-2 to penetrate cells and are resistant to infection [99, 100].

11.2 MSCs prevent the cytokines storm

Covid-19 may trigger reactions that result in destruction of the immune system. Patients suffering from covid-19 have over production of immune cells and inflammatory factors causing flux of cytokines. Here the concepts of MSC therapy for cure of coronavirus first emerges. MSC therapy may be able to prevent the immune system from producing a massive influx of growth factors and boost endogenous owing to repairative capabilities of mesenchymal stem cells. After intravenous injection, MSCs become trapped in the lungs, that are commonly recognized as a restriction in systemic infusion. Furthermore, These cells may aid in the restoration of the pulmonary milieu, sustaining the health of alveolar epithelial cells, the prevention of pulmonary fibrosis, and the treatment of lung dysfunction and COVID-19 associated Pneumonia [101]. The major limitation of this therapy is the availability of clinical-grade MSCs which are obtained

from different human adult tissues. One type of MSCs or mixture of various MSCs is the suitable option for clinical trial in COVID-19 patients [101].

11.3 Clinical Data for COVID-19

Emerging and re-emerging viral diseases have been recognised as the greatest hazard to humanity worldwide. Several viral infections have grown pandemic-style; the most recent example is the coronavirus-19 outbreak [102]. Applications of mesenchymal stem cells to cure of SARS-CoV-2 infection have been reported in different but limited case studies and open label trials.

11.4 Treatment with human maternal cord mesenchymal stem cell (hUC-MSC)

Ten verified COVID-19 patients who were classified as critical, severe, or common type by the National Health Commission of China were participated in a pilot research of intravenous mesenchymal stem cell perfusion. Mesenchymal stem cells were administered into three test groups of seven patients of which one with critical conditions, four severe patients and two with common type disease three out of four patients with severe illness got placebo. Four patients that underwent mesenchymal stem cells therapy recovered completely. Among the three very unwell placebo-treated patients, one died, one was diagnosed with acute respiratory distress syndrome (ARDS), and one remained stable with severe sickness [103].

In this study, human maternal cord mesenchymal stem cells were administrated in the patients suffering from severe COVID-19. These patients had no improvement by care after 7-10 days of treatment. Supplemental oxygen, umifenovir/oseltamivir, antibiotics, and glucocorticoids were among standard-of-care treatments. The trial was intended to be a randomised, controlled experiment but due to hUC-MSC limitations, it was not practicable to randomize the people as planned. Twelve of the 41 patients who were eligible for the research got hUC-MSC infusions, whereas the other 29 received just routine treatments. In terms of demographic features, laboratory test findings, and illness severity, the research arms were well balanced. The 12 people who received hUC-MSC infusions all healed without the need for artificial ventilator and were discharged to home. Four patients who received only standard-of-care therapy developed severe illness and required mechanical breathing; three of them died. These findings are not statistically significant, and The lack of randomization and limited sample size in the study limit interpretation of the findings. [104].

A double-blind randomised controlled trial was conducted to investigate the effectiveness and safety of hUC-MSC administrations in patients with COVID-19 ARDS. On Day 0 and Day 3, Twenty-four patients were randomly assigned to receive either two infusions of hUC-MSC (made at a single site) or placebo. The primary endpoints were the occurrence of predefined infusion-related serious side effects within a period of six hours of each hUC-MSC infusion, cardiac stroke, or death within a single day of each infusion, and the incidence of adverse events. Survival after 31 days of hUC-MSC infusion and time to recover were secondary goals [105].

There were no differences between the arms in the first safety analysis; however, by Day 31, the group receiving placebo (7 fatalities) had more deaths than the hUC-MSC group (2 deaths). The data for one hUC-MSC participant who died owing to a botched incubation was omitted from the study. The hUC-MSC group recovered quicker than the placebo arm (HR 0.29; 95% CI, 0.09-0.95). The small number of participants and a modification in inclusion conditions from solely those on invasive mechanical breathing to those on high-flow oxygen or noninvasive ventilation restrict the interpretation of these findings [106].

11.5 Treatment with human umbilical cord Wharton's jelly derived MSCs (hWJCs)

On February 24, 2020, in Liaocheng People's Hospital in China, A severe COVID-19 patient underwent treatment with MSCs derived from Wharton's jelly (hWJCs) from a healthy donor. The patient with COVID-19 pneumonia had a considerable improvement in pulmonary function and symptoms after two days receiving hWJC transfusion and recovered and was discharged seven days later. After hWJC therapy, the proportion, and numbers of lymphocyte subsets (CD3+, CD4+, and CD8+ T cells) increased, whereas IL-6, TNF-, and C-reactive protein levels were considerably reduced. Thus, intravenous transplantation of hWJCs is the appropriate therapy method for pneumonia patients, particularly those in severe condition [107].

11.6 Treatment with MSCs derived from Cord blood

A recent case study of a 65-year-old female patient identified in critical condition with COVID-19 discovered the identical 2019nCoV variant now known as SARS-CoV-2 [108]. Antiviral drugs such as ritonavir/lopinavir, oseltamivir and IFN-, as well as intravenous injections of moxifloxacin, methylprednisolone, Xuebijing, and immunoglobulin, were used to treat the patient, who had an >85 percent increase in neutrophils and a 9.8% decrease in lymphocytes. The patient was also supplied noninvasive mechanical ventilation to help with breathing and to alleviate muscular tiredness caused by low oxygen levels. The patient was administered three times with cord MSCs alone and 1 thymosin 5x107 cells as his vital signs deteriorated. The study's findings revealed that blood albumin, CRP, and ALT/AST levels steadily reduced after the second injection, while other vital signs improved. Following that, the patient was taken off the ventilator and allowed to walk again, and the patient's white blood cell and neutrophil counts went back to normal. Most significantly, the number of CD3+, CD4+, and CD8+ T cells increased considerably [101].

Furthermore, the qualitative results gathered through computed tomography (CT) scans after the second and third infusions of cord stem cells revealed that the pneumonia had been greatly relieved, and the patient was discharged from the intensive care unit (ICU) two days later, with most vital signs and clinical laboratory parameters returning to normal. The data suggested that the umbilical cord's mesenchymal stem cells, either alone or in combination with other immune modulators, could be an excellent therapy preference for acute COVID-19 patients[108].

12. Role of stem cells in treatment of cancer

Cancer is a leading cause fatality across developed and developing countries, and it is becoming a greater healthcare burden globally as of increasing population and age [109]. The most used cancer therapies are surgical removal, fractionated doses of radiation, and chemotherapy. Many therapeutic options, however, are restricted by treatment related side effects, drug resistance and off target consequences. Furthermore, conventional therapies usually fail to eradicate metastatic cancer cells, making recurrence very likely. As a result, researchers are working hard to develop new, effective drugs that pose minimal or no toxic effect to normal cells [110, 111].

Stem cells have unique characteristics, including mobility towards cancerous cells, the formation of bioactive compounds, and immunosuppression, which aid in targeting tumours and overcoming barriers to gene therapy. The employment of preclinical stem cell-based techniques in targeted anti-cancer therapeutic applications shows a lot of potential. Nonetheless, there are scientific concerns about stem-cell therapies, and advanced research is required to confirm preclinical findings [111].

12.1 Modification of Stem Cells

Multiple techniques can be used to modify stem cells, especially noteworthy to use MSCs and NSCs in cancer therapy. Common adaptations include therapeutic enzyme or prodrug system, as well as oncolytic virus or nanoparticle administration at the tumor site.

12.2 Enzyme/prodrug therapy

It is possible to design NSCs and MSCs to express enzymes that transform non-toxic prodrugs into cytotoxic compounds. When transformed stem cells are implanted into tumor-bearing mice, the foreign enzyme transforms the prodrug into a deadly compound, causing the tumour cells to die. As a result, medicine release can be carefully controlled in terms of time, quantity, and place. Suicide gene therapy, also known as enzyme/prodrug treatment, was the first NSC therapeutic application to enter clinical trials [112].

Cytosine deaminase (CD) is a commonly used enzyme in enzymatic/prodrug therapy. The prodrug 5-fluorocytosine (5-FC) is converted to hazardous form 5-fluorouracil by CD. Glioblastoma (GBM) cell development was suppressed by a combination of CD-bearing mouse NSCs and 5-FC, according to Aboody et al [113]. Administrating CD-expressing MSCs with 5-FC into the brain minimized tumor development [114]. Human HB1.F3 cells are modified to express CD (HB1.F3.CD) in one of the most regularly utilised cytotoxic treatments [115]. HB1.F3.CD/5-FC therapy was recently employed in the first human clinical study, with exceptional success and safety (clinicaltrials.gov identifier: NCT01172964), in which HB1.F3.CD cells were introduced into the cavity wall followed by GBM resection, and patients underwent oral 5-FC therapy [112](K. S. Aboody et al., 2013). The research was finished, but the results have not yet been made public. Another study using modified NSCs for the treatment of glioma has been completed in October 2018 (ClinicalTrials.gov identifier: NCT02015819).

MartinezQuintanilla et al. (2013) employed suicide gene therapy with the herpes simplex virus-thymidine kinase (HSV-TK). HSV-TK phosphorylates monophosphorylate ganciclovir (GCV) to form cytotoxic triphosphate ganciclovir (GCV-TP). GCV-TP integrates into the DNA of neighbouring cells during cell division, inducing cell death by blocking DNA polymerase [116]. Li et al. showed that intraperitoneal GCV injection followed by intratumoral HSV-TK transduced NSC (NSC-TK) administration daily for a period of ten days (two 15 mg/kg each day) successfully cured C6 gliomas in mice. Six of the nine rats survived 100 days after the treatment with no symptoms of tumour growth [117].

12.3 Secreted agents

Stem cells serves as in-situ drug factories, secreting anticancer drugs for extended periods of time and overcoming some of cancer therapy's boundaries, such as higher systemic toxicity and shorter drug half-life. TNF-related apoptosis-inducing ligand (TRAIL) is a commonly utilized, secreted therapeutic drug that promotes apoptosis in tumor cells [118]. Its short half-life, however, reduces its in vivo therapeutic efficiency [119]. This might be minimized by encasing TRAIL-expressing stem cells in a synthetic extracellular matrix (sECM) that is injected into the GBM resection cavity following surgical debulking [120]. At the resection margins, the encapsulated cells might continuously release therapeutic chemicals. In mice, this method reduces the regrowth of malignant and invasive brain tumours and improves survival.

Growth inhibitory proteins (e.g., IFN-) have been secreted by modification in the stem cells, rendering the tumour microenvironment hostile. Ling et al. investigated the migration and engraftment of IFN-expressing MSCs into primary breast tumour locations and discovered reduction in the tumour cell proliferation, as well as hepatic and pulmonary metastases. In the tumour microenvironment, MSCs released large quantities of IFN. In situ IFN-expression of MSCs decrease or stop proliferating cancer cells by inactivating the signal transducer activator transcription factor 3 (Stat3) [121].

13. Other applications of stem cell in cancer therapy

13.1 Regenerative medicine

Healthy iPSCs derived from patient tissues might theoretically be employed to regenerate tumour or treatment-damaged tissues. In regenerative medicine, iPSCs can be used to generate various kinds of tissues. iPSC therapy could be used for replacing or restoring iPSCs damaged by radiation, chemotherapy, or surgery in cancer patients. On the other hand, human iPSC-mediated regeneration requires a high level of iPSC-derived tissue engraftment in vivo. Currently, only a few types of human iPSC-derived cells (e.g., hepatocytes) have been successfully transplanted in experimental animals [122].

13.2 Targeting CSCs

CSCs are multipotent, self-renewing, and proliferative, all of which lead to rapid tumour metastatic activation and invasion. As a result, targeting CSCs is crucial for improving therapeutic efficacy and minimising cancer recurrence [123]. CSCs are attracted to normal stem

cells; hence normal stem cells could be used to target CSCs in cancer therapy. Normal stem cell interactions with CSCs suppress cancer progression, metastasis, angiogenesis, inflammation, and mortality. examined the potential of NSCs and HSCs in anti-glioblastoma therapy and reported that HSCs may be excellent for developing technologies for controlling glioblastoma CSC activity as HSCs are less susceptible to neoplastic transformation in neuronal tumors than NSCs [124]. Engineered HSCs may also make it easy to develop cell systems capable of inducing targeted CSC death [125].

13.3 Anticancer drug screening

iPSCs may be employed to assess potential anticancer drugs as well as directly cure cancer. Differentiating patient cancer tissue-derived iPSCs results in cell types that are more physiologically analogous to human tumors than current drug screening methodologies, such as conventional cancer cell lines, mouse tumours and mice xenograft models [126]. Hepatotoxicity is another barrier that prevents many promising anticancer drugs from reaching the clinic, and it might be investigated using hepatocytes derived from human iPSCs that have distinct genetic origins [127].

Conclusion

Stem cell technology is a powerful and promising method for treatment of diseases which are till date thought to be uncurable. Mesenchymal stem cells are especially the major role player. But this technology or technique is still lagging because of some ethical issues. These issues must be resolved at a rapid pace. More and better research should be conducted on the production and medicinal use of stem cells. More about the signaling and mode of action should be explored. It has a high potential, but a lot of fruitful efforts are needed to exploit its complete potential.

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