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A Review on Stem Cell Therapy

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ABSTRACT

Hematopoietic Stem Cells (HSCs)

Hematopoietic Stem Cells (HSCs), the most primitive of the blood lineage cells, are predominantly found Stem cell therapy is now a highly promising and cutting-edge area of scientific study. There are high expectations for the advancement of treatment techniques. This article focuses on the identification of various stem cells and the possible treatments that could be developed with them. Controlled stem cell culturing and derivation are laboratory processes that come after stem cell genesis. Teratoma development tests and quality control are crucial steps in evaluating the characteristics of the tested stem cells. To create the ideal environmental conditions for regulated differentiation, derivation techniques and the use of culture media are essential. In the wide range of stem tissue applications, extracellular vesicle-based therapies and the use of graphene scaffolds are particularly noteworthy due to their versatility. The difficulties stem cell treatment has in gaining global acceptance serve as a summary of the review. This innovative treatment is a paradigm shift in contemporary medicine, offering hope for incurable illnesses due to its many potential applications. The benefits, opportunities, and drawbacks of stem cell-based cancer treatments are outlined in this study, which focuses on recent advancements in the field. It may also aid in improving future trials and easing the transition from experimental to clinical research.

Keywords: Stem cell, Teratoma development, Environmental condition, Potential application.

INTRODUCTION

Stem cell therapy

A major cause of death in both industrialized and developing nations, cancer is becoming a global health concern as the population ages and grows .Chemotherapy, fractionated radiation, and surgical resection are the main methods used to treat cancer. However, the effectiveness of many therapeutic alternatives is limited by drug

resistance, off-target effects, and side effects connected to treatment. Furthermore, recurrence is highly likely in cases when metastatic cancer cells cannot be eradicated by conventional therapy. As a result, scientists are trying to create novel, efficient treatments that are either non-toxic or very innocuous to healthy cells.

Certain characteristics of stem cells, like their migration toward cancer cells, production of bioactive substances, and immune suppression, facilitate tumor targeting and get around present barriers to gene therapy approaches.

Strategies based on preclinical stem cells have a lot of potential for use in targeted anti-cancer therapy applications. However, there are still scientific questions about the application of stem cell treatments, and more research is required to confirm preclinical results. This review highlights the benefits, opportunities, and possible drawbacks of contemporary research on anti-cancer stem cell therapy. This benefit of stem cell therapy, which focuses on recent developments in the field, describes the advantages, opportunities, and disadvantages of stem cell-based cancer therapy. It might also facilitate the shift from experimental to clinical research and help to improve studies in the future.

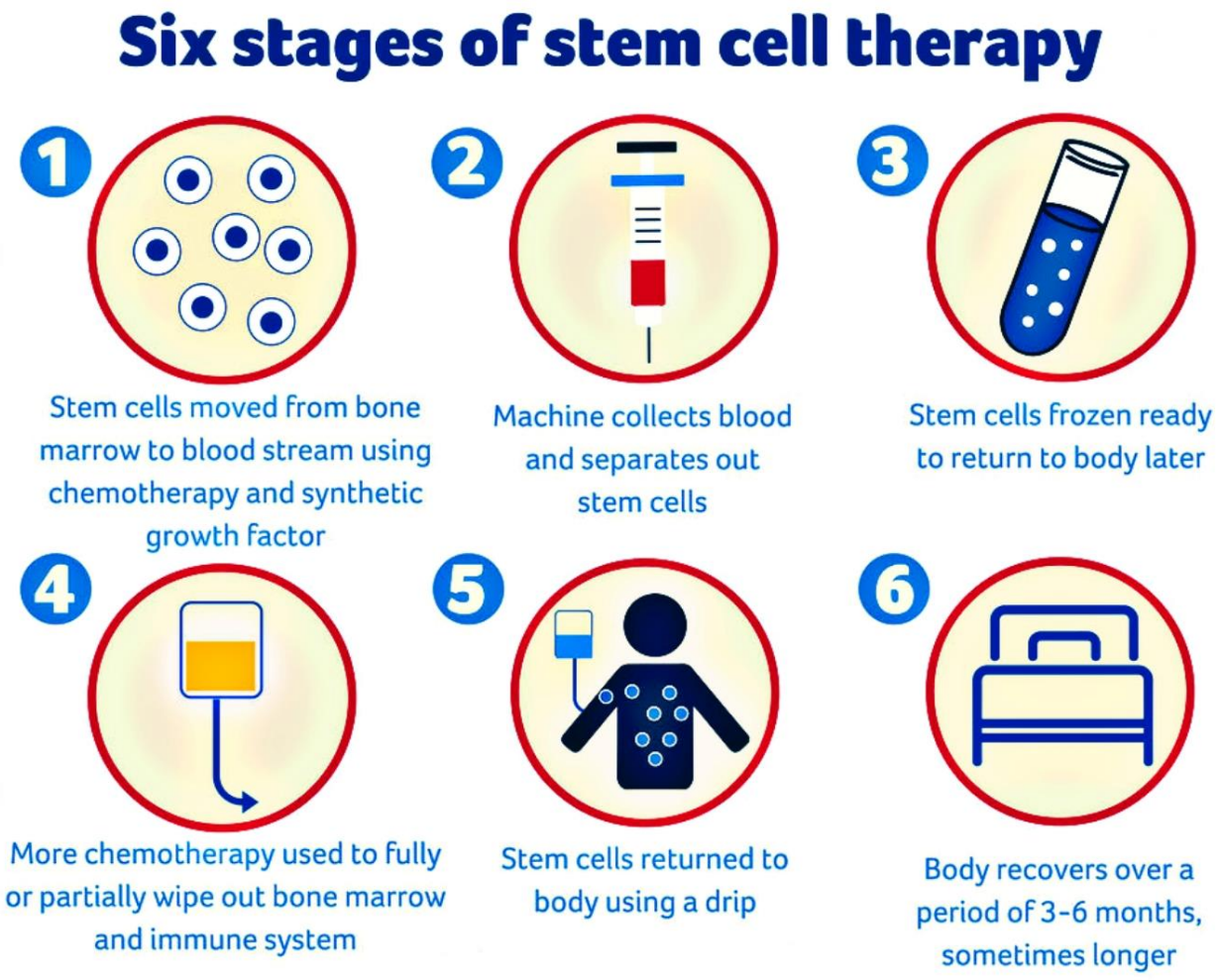


Fig.1 Stages of stem cell therapy

Stem Cell Classification

The human body contains unspecialized cells called stem cells. They have the capacity to self-renew and can differentiate into any type of organism's cell. Both adult cells and embryos contain stem cells. The process of specialization involves multiple steps. A unipotent stem cell cannot differentiate into as many different types of cells as a pluripotent one since developmental potency decreases with each stage. To help the reader understand the upcoming chapters, this chapter will concentrate on stem cell classification. The ability to divide and develop into cells of the entire organism is possessed by totipotent stem cells. With the greatest capacity for differentiation, totipotency enables cells to develop into both embryonic and extra-embryonic structures. A zygote, created when a sperm fertilizes an egg, is an example of a totipotent cell. These cells have the potential to grow into a placenta or any one of the three germ layers. The inner cell mass of the blastocyst turns pluripotent after around four days. The source of pluripotent cells is this structure. All germ layers' cells can be formed by pluripotent stem cells (PSCs), however extraembryonic tissues like the placenta cannot. One example is embryonic stem cells (ESCs). The inner cell mass of preimplantation embryos is the source of ESCs. Induced pluripotent stem cells (iPSCs), which are produced from the epiblast layer of implanted embryos, provide an additional illustration. From fully pluripotent cells like ESCs and iPSCs to representatives with lesser potency—multi-, oligo-, or unipotent cells—their

pluripotency is a continuum. The teratoma development assay is one way to evaluate their spectrum and activity. iPSCs work similarly to PSCs and are produced intentionally from somatic cells.Although multipotent stem cells can specialize in discrete cells of particular cell lineages, their range of differentiation is more limited than that of PSCs. A hematopoietic stem cell, which may differentiate into multiple blood cell types, is one example. A hematopoietic stem cell differentiates into an oligopotent cell. Then, it can only differentiate into cells that are related to it. But since some multipotent cells can differentiate into several cell types, it is suggested that they be called pluripotent cells. Numerous cell types can be differentiated from oligopotent stem cells. One type of stem cell that can differentiate into white blood cells but not red blood cells is a myeloid stem cell. These cells are only able to form one cell type, e.g. dermatocytes.

Biology of stem cell therapy

Following fertilization, sperm and ovum fuse to form a blastocyst. Short-lived stem cells, specifically embryonic stem cells, line its inner wall. The two different cell types that make up blastocysts are the trophectoderm (TE) and the inner cell mass (ICM), which differentiates into epiblasts and stimulates fetal development.ICM microenvironment control is the responsibility of blastocysts. The placenta and other extraembryonic support structures required for the embryo's successful origin are formed by the TE as it develops further. The ICM cells continue to be undifferentiated, totally pluripotent, and proliferative as the TE starts to develop a specific support structure **(Sukoyan MA *et al*., 1993)**. Because stem cells are pluripotent, they can differentiate into any type of cell in the body. The ICM is where human embryonic stem cells (hESCs) originate. Endoderm, mesoderm, and ectoderm are three cell aggregates known as germ layers that form during embryogenesis and eventually give rise to differentiated cells and tissues of the fetus and, subsequently, the adult organism **(Larijani B *et al*., 2012)**. hESCs become multipotent stem cells, whose potency is restricted to the germ layer cells, after differentiating into one of the germ layers. In terms of human growth, this procedure is brief. Following that, pluripotent stem cells are found throughout the body as undifferentiated cells. Their primary functions include proliferating by generating more stem cells and differentiating into specialized cells in response to specific physiological circumstances. There are two types of signals that affect the stem cell specialization process: internal signals, which are regulated by genes in DNA, and external signals, which include physical contact between cells or chemical secretion by surrounding tissue. Additionally, stem cells serve as the body's internal repair mechanisms. As long as an organism is alive, it can continue to produce new cells and replenish existing ones. The organ in which stem cells are found determines their activity; for instance, in bone marrow, they divide continuously, while in organs like the pancreas, this only happens under specific physiological circumstances.

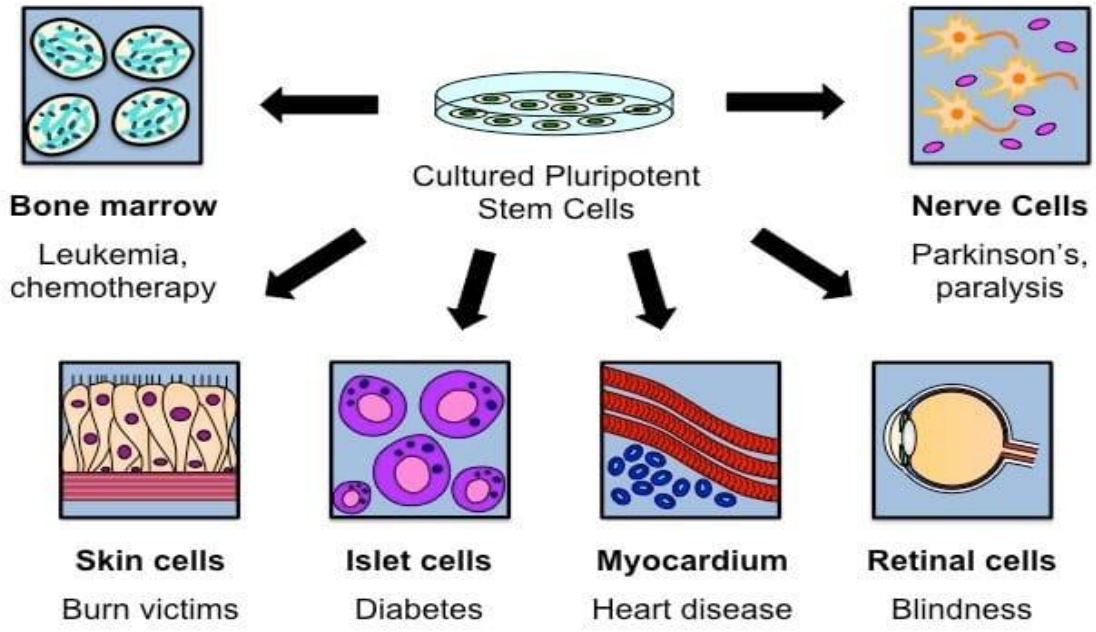


Fig.2 Biology of stem cell therapy

Definitions of STEM Cells and Their Sources

1) Self-renew indefinitely

2) Generate clonal cell populations generated from single cells

3) Specialize into diverse cell types distinguishes them as a distinct population **(Tran C *et* al.,2015)**.

In resident stem cell pools, self-renewal is essential for tissue repair and homeostasis **(Seita J et al., 2010)**. The two main categories of stem cells are "embryonic" (ESCs) and "somatic" (SSCs). Review www.impactjournals.com/oncotarget 75757 for SSCs. Adult stem cells, often referred to as oncotargets, are typically multipotent and have the ability to differentiate into any type of cell with a particular lineage, such as endothelial progenitor cells (EPCs), neural stem cells (NSCs), mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and others. Cancer stem cells (CSCs) have the potential to promote carcinogenesis and the advancement of illness in at least certain situations **(Xiao J *et al.*, 2015)**.

ESCs and iPSCs

ESCs are the gold standard for assessing all pluripotent cells cultivated in vitro since they are pluripotent cells that can develop into all cell types except those found in the placenta **(Lin HT *et al.*,2013)**. However, ESC applicability in research investigations and human clinical trials are limited because of ethical concerns. Because induced pluripotent stem cells (iPSCs) may be produced without destroying embryos, ESCs can be substituted with iPSCs that have been reprogrammed from adult somatic cells (such as skin fibroblasts) by forced expression

of pluripotency factors **(Takahashi K *et al*., 2006)** .Comparable to ESCs, iPSCs may have more therapeutic use than ESCs due to their absence of immunogenic or ethical restrictions.

NSCs

SCs are typified by expression of nestin, Sox2, and other classic markers, together with expansion in culture media rich in epidermal and fibroblast growth factors **(Bago JR *et al*., 2016)** .NSCs can self-renew and differentiate into astrocytes, neurons, or oligodendrocytes, and have been widely employed to treat brain, breast **(Kanojia D *et al*., 2015)** , prostate **(Lee HJ *et al.*, 2013)** , and lung **(Yi BR *et al*., 2014)** tumors.

MSCs

MSCs are derived from bone marrow and can differentiate into mesodermal cells, including cartilage, bone, adipose tissue, stroma, muscle, connective tissue, and tendon. MSCs are easily isolated and propagated in vitro and, like NSCs, are applied widely in the treatment of different cancers in bone marrow, and produce mature blood cells through proliferation and differentiation of increasingly lineage-restricted progenitors. Transplantation of HSCs has been employed clinically for over four decades.

EPCs

EPCs Vascular regeneration is mostly driven by EPCs **(Goligorsky MS *et al*., 2013).** According to Asahara et al., EPCs may be useful in cancer treatment after transfection or when combined with angiogenesis inhibitors or antitumor medications **(Asahara T *et al*., 1997)** .Recent developments, however, have brought attention to the functions of EPC in the etiology of illness and its possible advantages when used in therapeutic therapies **(Goligorsky MS *et al.*, 2013)**. EPCs in cancer treatment are seldom reported. CSCs CSCs are a stemlike subset of cancer cells that are identified from patient tissues and cell lines of various cancer types based on cell surface characteristics. In addition to self-renewing, expressing stemness genes, and differentiating into various non-stem cancer cells, CSCs also evade conventional cancer therapies **(Xiao J *et al*., 2017)**. Many kinds of cancer are probably started by CSCs. CSCs cannot be eradicated by conventional cancer treatments, yet they can kill non-stem cancer cells.

When the residual CSCs multiply and differentiate, tumors typically recur. Thus, focusing on CSCs might address clinical problems such recurrence and medication resistance **(Dawood S *et al*., 2014)**.

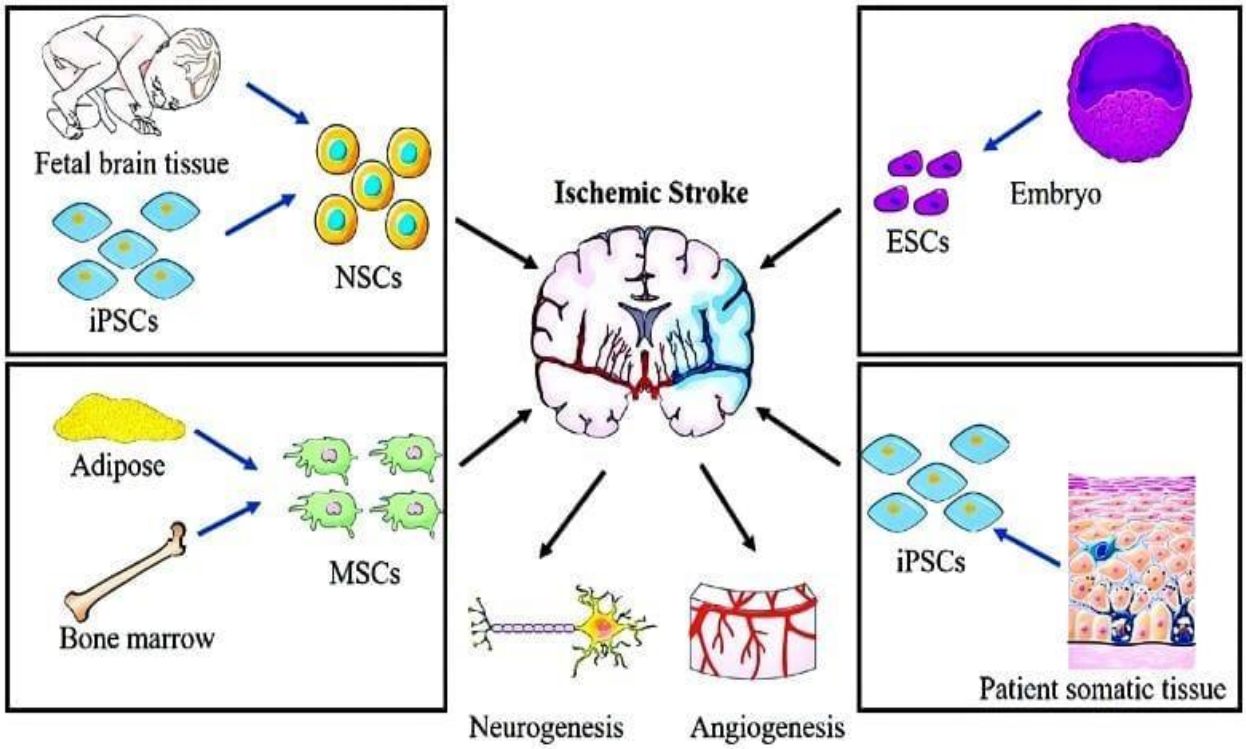


Fig.3 Stem cells and their sources

AN OVERVIEW OF CURRENT CLINICAL USES FOR STEM CELL-BASED THERAPY

CARDIOVASCULAR DISEASE

The subsequent portions of this study will elaborate on the therapeutic applications of stem cell-based therapy for cardiac disorders, which have recently been thoroughly reviewed in reviews (**Bolli, R *et al.*, 2014)**, **(Liu *et al.*, 2021)**. These talks will center on hPSCs and MSCs. A substantial amount of preclinical and clinical research generally supports the safety profiles of stem cell-based medicines, particularly adult stem cell therapy (such as MSC-based products).

Clinical trials, however, have not yet shown evidence of the treatment's effectiveness since, even in phase III trials, several studies have produced contradictory findings and no statistically significant variations in infarct size, cardiac function, or clinical outcomes. **(Zhang, J *et al.*, 2021)**.

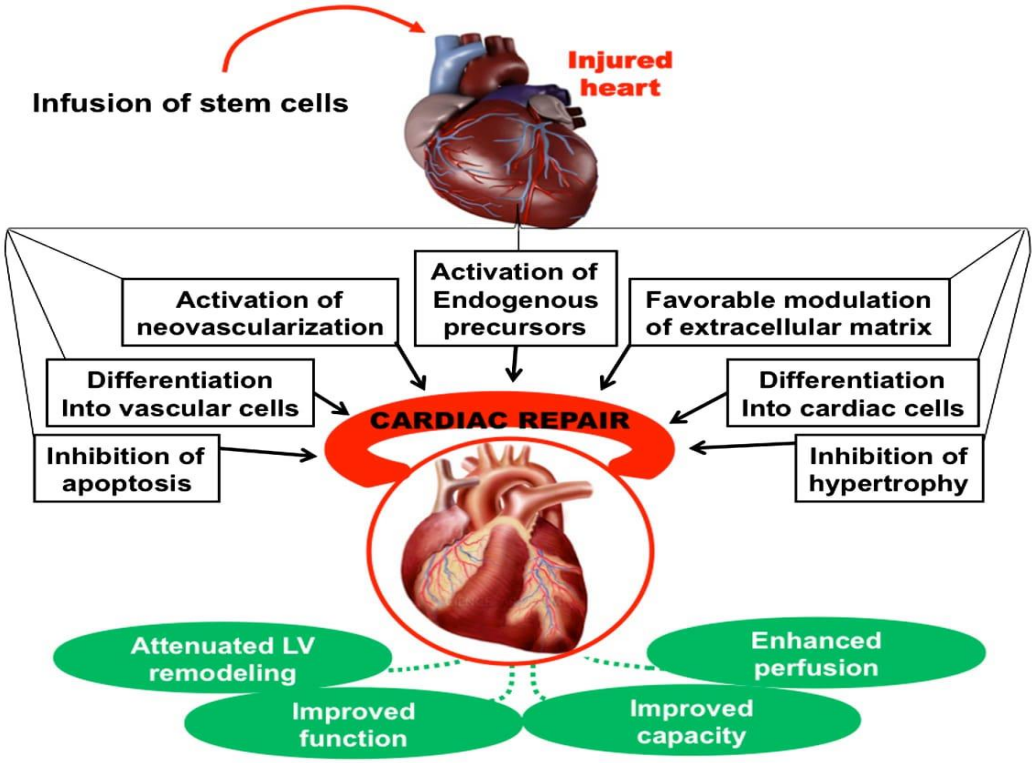


Fig.4 Stem cell therapy for cardiovascular disease

DIGESTIVE SYSTEM

Diseases Gastrointestinal diseases are among the most diagnosed conditions in the developed world, altering the life of one-third of individuals in Western countries. The gastrointestinal tract is protected from adverse substances in the gut environment by a single layer of epithelial cells that are known to have great regenerative ability in response to injuries and normal cell turnover **(Gyongyosi, M *et al.*, 2016)** .These epithelial cells have a rapid turnover rate of every 2–7 days under normal conditions and even more rapidly following tissue damage and inflammation. This rapid proliferation ability is possible owing to the presence of a specific stem cell population that is strictly compartmentalized in the intestinal crypts.**(Gehart, H *et al.*, 2019)** The gastrointestinal tract is highly vulnerable to damage, tissue inflammation and diseases once the degradation of the mucosal lining layer occurs. The exposure of intestinal stem cells to the surrounding environment of the gut might result in the direct destruction of the stem cell layer or disruption of intestinal functions and lead to overt clinical symptoms. **(Santos *et al., 2018*)** The two main types of inflammatory bowel disease (IBD) that affect the digestive tract and place a heavy strain on the healthcare system are Crohn's disease (CD) and ulcerative colitis. Segmental transmural mucosal inflammation and granulomatous alterations are hallmarks of the former, a persistent, uncontrollable inflammatory disorder of the intestinal mucosa**.(Roda *et al.*, 2020)**

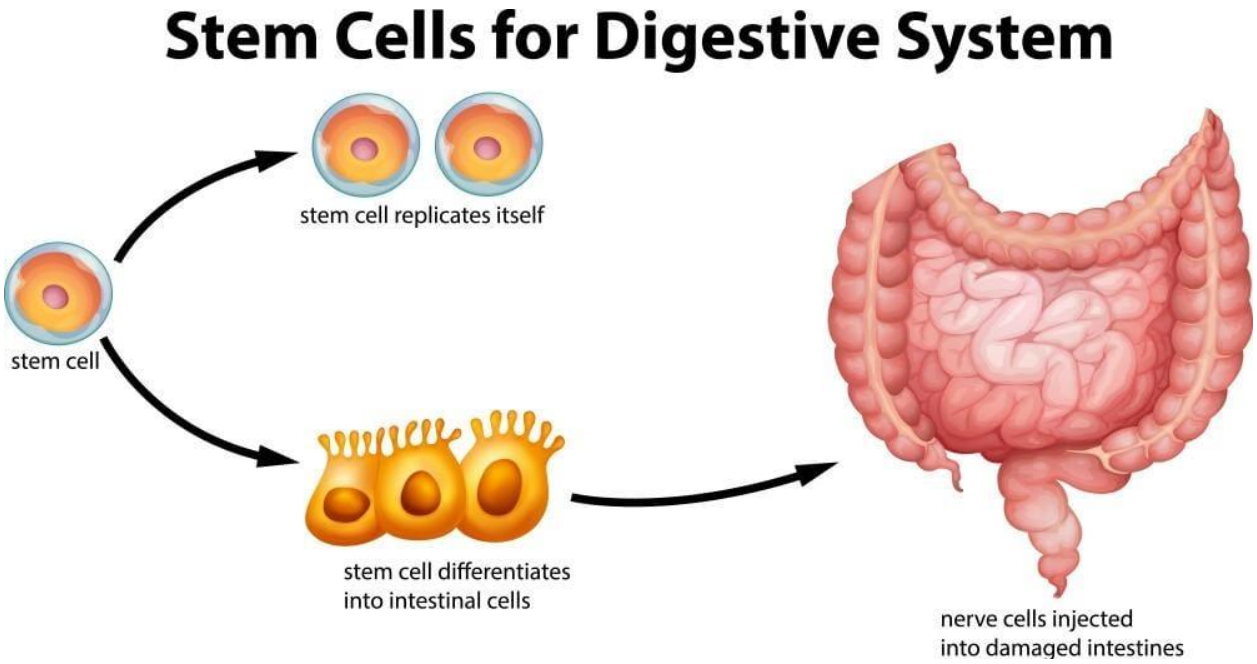


Fig. 5 Stem cell therapy for digestive system

LIVER DISEASE

The biggest critical organ in the human body, the liver supports digestion, aids in metabolism, stores vitamins, and detoxifies the body, among other vital biological processes. **(Si-Tayeb *et al.*, 210)** .Liver failure, cirrhosis, cancer, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), and autoimmune liver disease (ALD) are among the pathological diseases that may arise from a disturbance of liver homeostasis and function. The only effective treatment for severe liver illnesses is orthotropic liver transplantation, however there are extremely few appropriate and available donor organs. HSCs, MSCs, hPSCs, and liver progenitor cells are now linked to stem cell-based treatments for liver disease. With a comparatively high death rate, liver failure is a serious illness marked by severe liver dysfunctions or decompensation brought on by a variety of reasons. Since stem cell-based therapy is thought to contribute to the improvement of liver regeneration and recovery, it represents a fresh alternative strategy to the treatment of liver failure. According to the findings of a meta-analysis that included six nonrandomized controlled trials and four randomized controlled trials, stem cell therapy produced short-term clinical results for treating acute-on-chronic liver failure (ACLF), necessitating multiple doses of stem cells to extend the therapeutic effects. **(Xue *et al.*,2018)**, **(Shi *et al.*, 2012)** Curiously, while MSC-based treatments enhanced liver functions such as coagulation, albumin level, total bilirubin, and the model of end-stage liver disease score, positive impacts on survival rate and aminotransferase level were not noted**.(Liu *et al.*, 2012)**

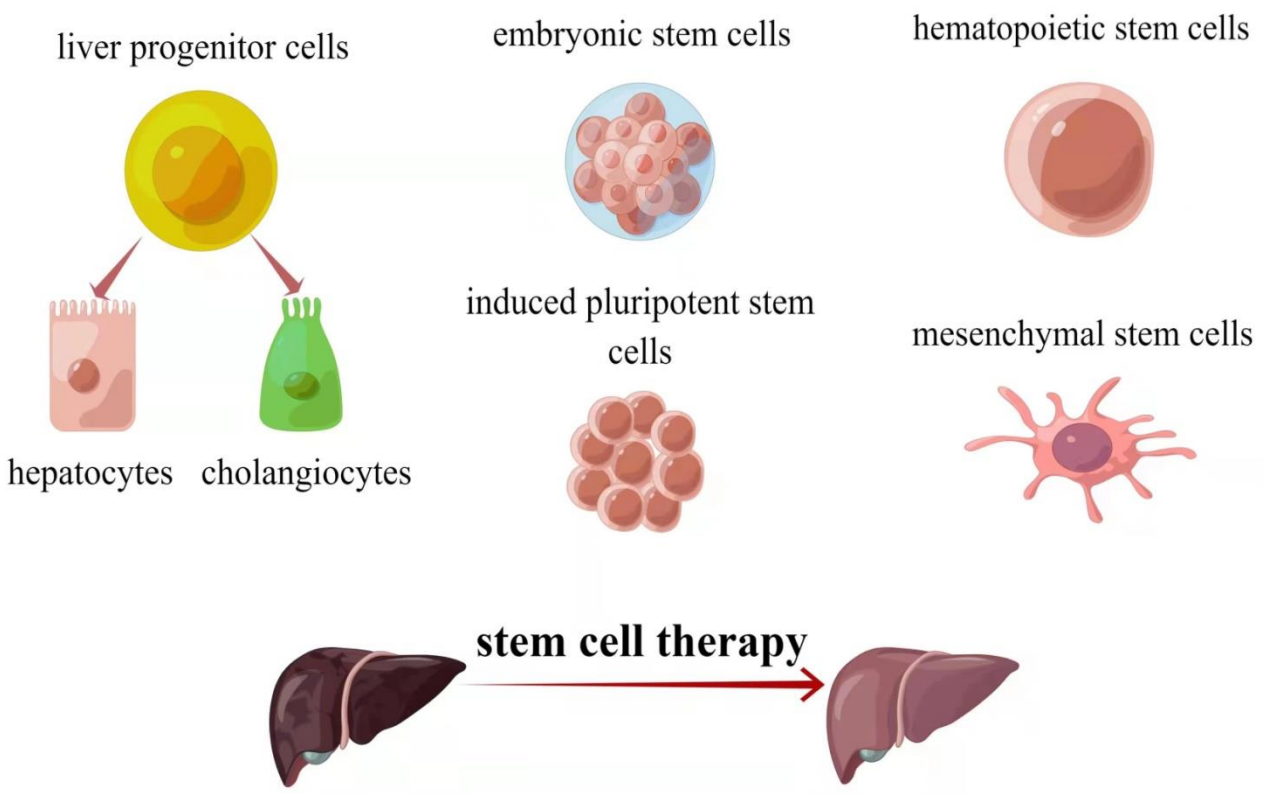


Fig.6 Stem cell therapy for liver disease

ARTHRITIS

The broad term for cartilage disorders that result in joint discomfort and inflammation is arthritis. The most prevalent kind of arthritis is osteoarthritis (OA), which is brought on by articular cartilage that is degenerating and not recovering well. **(Martel-Pelletier *et al.*, 2016)** OA affects one or more diarthrodial joints, including major knee and hip joints and minor hand joints, resulting in excruciating pain and a consequent decrease in patients' mobility. Primary OA, also known as idiopathic OA, and secondary OA, which are brought on by trauma, surgery, and aberrant joint development from birth, are the two forms of OA**. (Olsson *et al.*, 2021)** There is a need for a more dependable, less painful, and curative therapy that targets the underlying cause of OA because traditional therapies for the condition are inconsistent in their efficacy and may result in excruciating pain and long-term rehabilitation (in the case of joint replacement). **(Mahmoudian *et al.*, 2021)** .As a result, stem cell therapy has gained a lot of interest in the regeneration sector and has lately surfaced as an alternate treatment for OA. It has been demonstrated that administering HSCs can lessen bone lesions, promote bone regeneration, and accelerate the vascularization process in degenerative cartilage. Ten OA patients received three intraarticular injections in an attempt to test the effectiveness of peripheral blood stem cells. Analysis conducted after injection showed a substantial decrease in all parameters and a decrease in the WOMAC score. Every patient finished a 6-minute walk test with a greater than 54-meter gain.

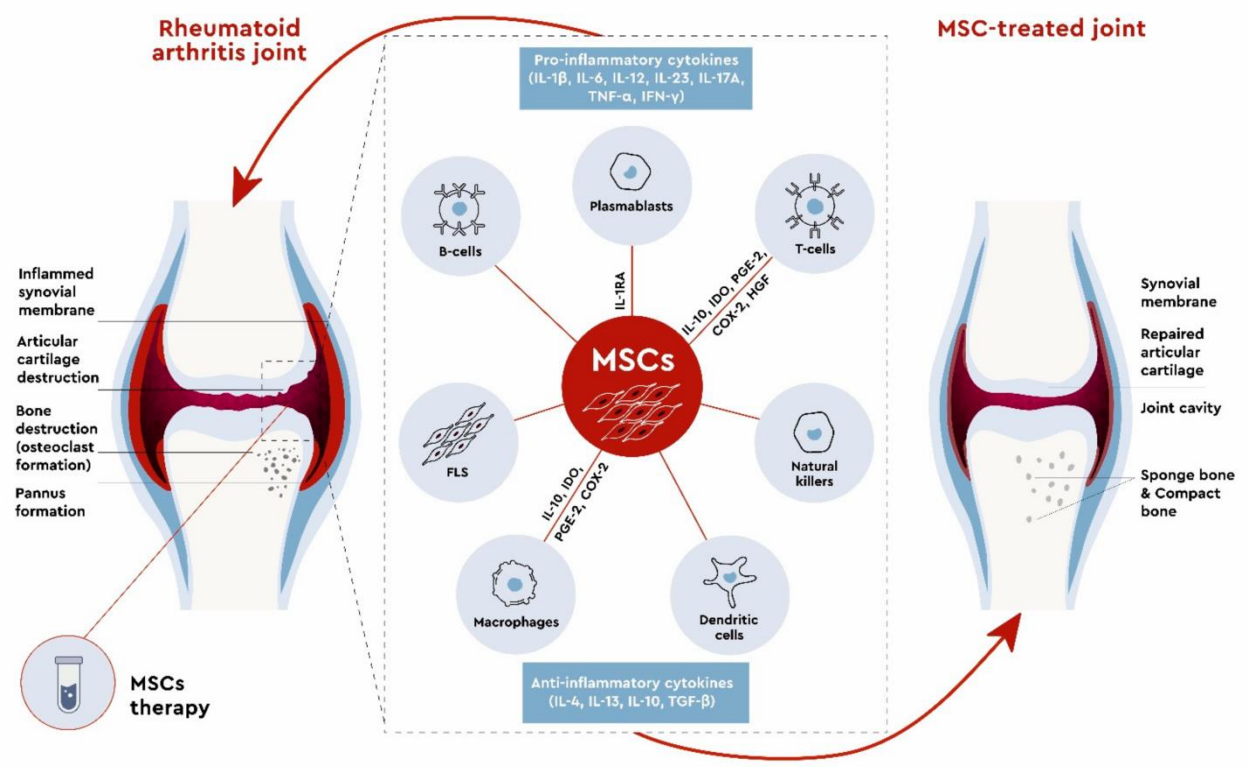


Fig.7 Stem cell therapy for arthritis

CANCER TREATMENT

The use of stem cell therapy in the treatment of cancer is a delicate topic that requires careful consideration. Patients without a cancer diagnosis should be shielded from the risk of developing cancer by clinicians and researchers, as well as cancer patients from costly, possibly harmful, or inefficient stem cell-based therapy. Three cell-based therapies—autologous HSCTs, stromal vascular fraction (SVF), and multipotent stem cells like MSCs—were generally used in untested stem cell clinics to treat cancer. Allogeneic HSCTs provide the capacity to produce donor lymphocytes, a phenomenon known as "graft-versus-tumor effects," which aid in the suppression and regression of some solid tumors and hematological malignancies. **(Barisic *et al.*, 2022)**. Furthermore, there was no discernible difference in the survival advantages between patients who had HSCTs after high-dose chemotherapy and those who received conventional treatment, according to a research including over 41,000 patients with breast cancer. **(Mello *et al.*, 2001)** Therefore, it is necessary to warn cancer patients about the use of autologous T-cell transplants as monotherapy and the promotion of stem cell-based treatments as the preferred or medically authorized treatment for solid tumors. **(Sissung *et al.*, 2019)** Because of their special qualities, several preclinical studies conducted over the last few decades have shown the promise of MSC-based therapy in the treatment of cancer. Their innate tropism, which is regulated by growth hormones, chemokines, and cytokines, allows them to travel toward injured regions. In order to react to external cues, MSCs express particular C–X–C chemokine receptor type 4 (CXCR4) as well as other chemokine receptors (such as CCR1, CCR2, CCR4, CCR7, etc.).

Furthermore, the MSC surface expresses certain adhesion proteins, including as CD49d, CD44, CD54, CD102, and CD106, which enable the cells to adhere, rotate, migrate, and enter the blood vessel lumen in order to reach the injured tissue. (**Zachar *et al*., 2016)** Tumors release a variety of chemoattractants that, like damaged tissues, draw MSC migration through the CXCL12/CXCR4 axis. Diffusible cytokines like interleukin 8 (IL-8) and growth factors like transforming growth factor-beta 1 (TGF-β1), platelet-derived growth factor (PDGF), fibroblast growth factor 2 (FGF-2), vascular endothelial growth factor (VEGF), and extracellular matrix molecules like matrix metalloproteinase 2 (MMP-2) have also been shown in earlier research to tightly regulate MSC migration toward the cancer site. The main issues with MSC-based treatment are the protumor and antitumor effects that arise from the interaction between MSCs and cancer cells once they have effectively migrated to malignant tissue. MSCs are renowned for their regenerative properties, which control tissue healing and repair. The tumor activities of these cells are also responsible for this special capability. According to a prior research, MSCs secrete chemokine (C–C motif) ligand 5 (CCL-5) in response to breast cancer cells, which controls the tumor invasionprocess. **(Aldinucci *et al*., 2020), (Karnoub *et al*., 2007)** According to other research, MSCs release a variety of growth factors that prevent cancer cells from dying, including VEGF, basic FGF, HGF, PDGF, and others. **(Kucerova *et al*., 2010)** About 25 clinical studies utilizing MSCs as a therapeutic therapy for cancer have been registered on ClinicalTrials.gov thus far. **(Hmadcha *et al*., 2020)** The majority of these trials are phase 1 and 2 investigations that assess the treatment's effectiveness and safety.

Taken together, cancer research and therapy have entered an innovative and fascinating era with advancements in traditional therapies such as chemotherapy, radiotherapy, and surgery on one hand and stem cell-based therapy on the other hand. Although stem cell-based therapy has been considered a novel and attractive therapeutic approach for cancer treatment, it has been hampered by contradictory results describing the protumour and antitumour effects in preclinical studies. Despite this contradictory reality, the use of stem cell-based therapy, especially MSCs, offers new hope to cancer patients by providing a new and more effective tool in personalized medicine. The authors support the use of MSC-based therapy as a Trojan horse to deliver specific anticancer functions toward cancer cells to suppress their proliferation, eradicate cancer cells, or limit the vascularization process of cancerous tissue to improve the clinical safety and efficacy of the treatment.

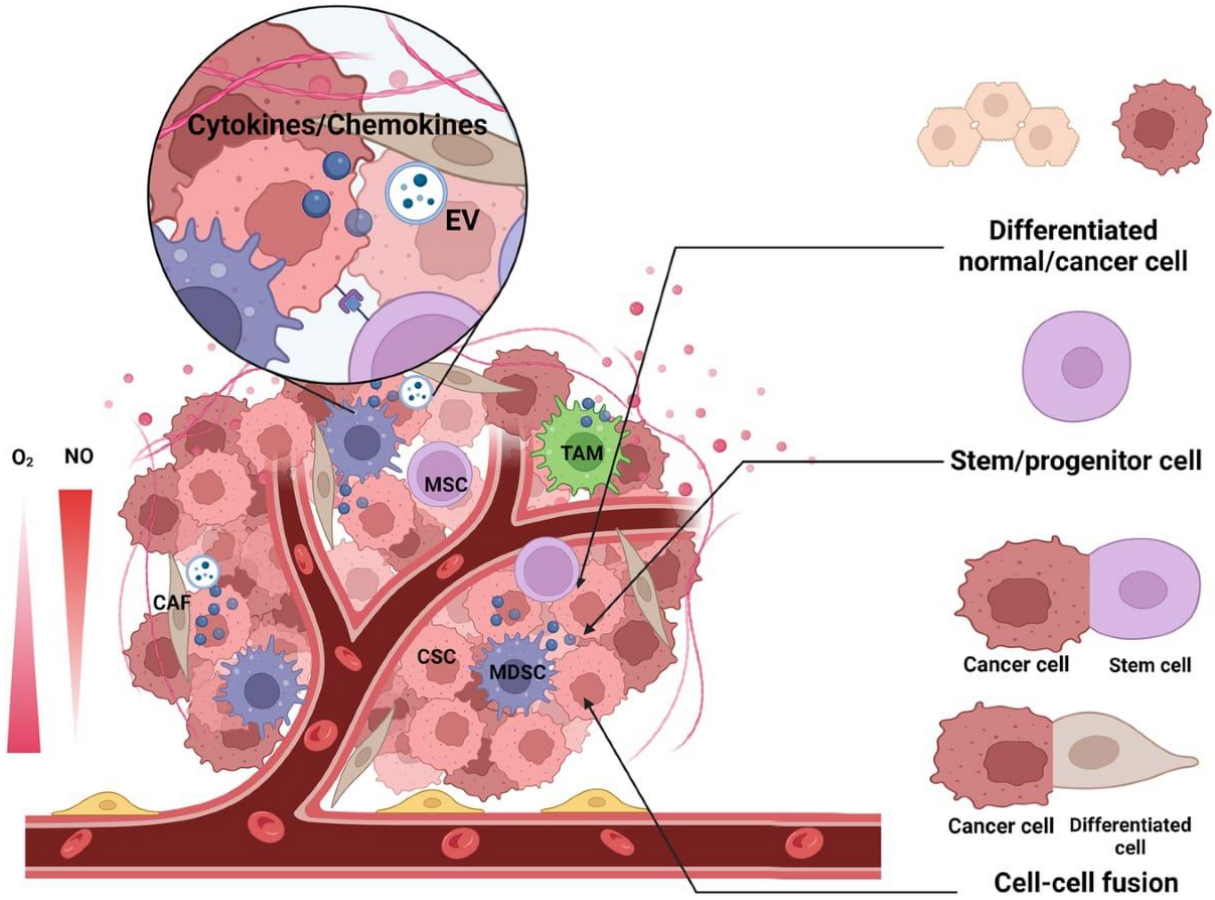


Fig.7 Stem cell therapy for cancer tratment

CONCLUSION

According to our own experience in a clinical trial setting as well as cellular and molecular analysis, AD-, BM-, and UC-MSCs display distinct functional activities and therapeutic efficacy across a broad spectrum of human disorders. We have presented current information from the most recent clinical trials that have been published in the following areas: cardiovascular diseases, pulmonary dysplasia, skin regeneration, endocrine and reproductive abnormalities, and neurological diseases. A distinct viewpoint on the application of MSCs from various sources in the treatment of human diseases is offered by the implications of the findings and discussions in this review as well as in a vast body of thorough and excellent reviews and systematic analyses in the literature. Our understanding of MSCs will be greatly advanced by active conversation, which we firmly believe will aid the fields of regenerative medicine and MSC-based therapies. . Based on the proposed mechanisms presented in this review, we suggest several key mechanistic issues and questions that need to be addressed in the future .It is evident from the mechanism of action's confirmation and proof that tissue origin is important for the MSCs' downstream uses.

From our clinical perspective, the underlying proposal in our review is to no longer use MSCs for applications

while disregarding their sources but rather to match the MSC tissue source to the application, shifting from one cell type for the treatment of all diseases to cell source-specific disease treatments. The transplantation of MSCs derived from various sources for each specific disease requires more research and the establishment of protocols through multicenter, randomized, placebo-controlled phase II and III clinical trials, regardless of whether the application of MSCs from various sources still demonstrates their effectiveness to some extent in the treatment of diseases.

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