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OVERVIEW OF STEM CELL THERAPY

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Abstract:

Stem cells are a distinct and versatile type of cell that can divide endlessly and have a special ability to regenerate. Additionally, it was capable of differentiating into various cell types and growing into adult cells with specialized functions and distinguishing features, like heart or skin cells (Wakitani *et al*., 1995), ligament (Altman *et al*., 2002), adipose tissue (Beresford *et al*., 1992), muscle, nerve cells ,cartilage (Johnstone *et al*., 1998; Yoo *et al*., 1998) . A stem cell is uncommitted and remained uncommitted until it received a signal to develop into a specialized cell.

Keywords: Stem cells, muscle, nerve cells

DEFINITION OF STEM CELLS

Stem cells are a distinct and versatile type of cell that can divide endlessly and have a special ability to regenerate. Additionally, it was capable of differentiating into various cell types and growing into adult cells with specialized functions and distinguishing features, like heart or skin cells (Wakitani *et al*., 1995), ligament (Altman *et al*., 2002), adipose tissue (Beresford *et al*., 1992), muscle, nerve cells ,cartilage (Johnstone *et al*., 1998; Yoo *et al*., 1998) . A stem cell is uncommitted and remained uncommitted until it received a signal to develop into a specialized cell. In contrast, the majority of the body's cells are committed to carrying out a specific function. (Chandross and Mezey , 2001; Slack , 2000). Stem cells were first studied by Becker *et al* in 1963, they injected bone marrow cells into irradiated mice and recognized that nodules advanced in the spleens of the mice in proportion to the amount of bone marrow cells injected, Each nodule was found to have originated from a single marrow cell, and later research revealed that these cells were capable of endless self-renewal. Stem cells were defined as having two essential properties., included the capacity to self-renew, producing more stem cells, and the capacity to differentiate into different cell lineages under suitable conditions. (Becker *et al*.,1963). It was discovered that pancreatic cells cultured on artificial capillaries and perfused with media released insulin in response to changes in the glucose concentration when the stem cells were placed inside the abdominal cavities of chick embryos. (Chick *et al*., 1975). In addition to other researchers, Friedenstein et al. (1987), Friedenstein, (1988), and Friedenstein, (1995) recorded the characteristics of these cells. Bone marrow-derived stem cells were first described and isolated by Owen and Friedenstein in 1960. Also the term of bone marrow stromal cell (BMSCs) was used to isolate bone marrow cells to compose a connective tissues (Owen, 1988). The'mesenchyme,' a mass of tissue developed from the embryo's mesoderm, was created by a subpopulation of these BMSCs known as mesenchymal stem cells, which are undifferentiated multipotent cells. This cell population was reported to be present in all postnatal tissues (Caplan , 2005). Finally, it was successfully accomplished to isolate these cells from a variety of mammals, including humans (Bruder *et al*., 1997; Ouyang *et al*., 2004).

STEM CELL CLASSIFICATION

Classification According To Their Sources Or Origin

1. Embryonic and Fetal Stem Cells

Embryonic stem (ES) cells, the first type of pluripotent stem cells to be discovered in mice, are produced in early, pre-implantation embryos. (Evans and Kaufman, 1981) and then in humans (Martin *et al.,*1981). Neonatal stem cells, fetal hematopoietic stem cells, fetus organs, and pancreatic islet progenitors are primitive cell types that have been isolated for use in abortions (Beattie *et al.,* 1997) . Fetal hematopoietic stem cells, which are abundant in the fetal brain, have been exposed to differentiation into fetal blood, glial cells, umbilical cord, placenta, and neurons. (Brustle *et al.,* 1998;Villa *et al.,* 2000), The ESCs are doubled in culture and have been kept in culture for various hundred folds. The benefit of keeping stem cells in culture was that it produced a lot of cells that were still immature. It was found that the ESCs, unlike the embryonic membranes, had a variety of characteristics and the ability to differentiate into cells from all germ layers.

2. Adult stem cells (ASCs)

There are two important populations of adult stem cells which have been recognized in the BM according to the following

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A. Hematopoietic stem cells (HSCs).

Hematopoietic stem cells (HSCs), also known as adult hemocytoblasts, are the stem cells that develop into all other blood cells during the hematopoiesis process. They originate from mesoderm and are found in the red bone marrow, which makes up the bulk of human bones. *(Birbrair et al., 2016).* HSCs could develop alongside the lymphoid and myeloid blood cell lineages, Natural killer (NK) cells, B cells, and T cells are found in lymphoid cells, whereas macrophages, monocytes, neutrophils, basophils, erythrocytes, dendritic cells, and megakaryocytes or plates are found in myeloid cells. (*Till and Mcculloch, 1961) .*

B. Mesenchymal Stem Cells

The stromal source are mesenchymal stem cells (MSCs), which may develop into a range of tissues. MSCs have been extracted from blood, fat, cartilage, placenta, muscle, adipose tissue, tendon, ligament, lung, and bone due to their ability to develop into a number of cell types, including hepatocytes, adipocytes, chondroblasts, neuroectodermal cells, and osteoblasts (*Phinney and Prockop, 2007).* MSCs may have been created in the bone marrow, Additionally, non-hematopoietic bone marrow stroma can be found after birth. Adipocytes, macrophages, reticular cells, estrogenic cells, and smooth muscle cells are among the cells that make up marrow stromal tissue. (Bianco and Riminucci , 1998 Also one of the important issue for isolated mesenchymal stem cells was adipose tissues (ADSCs) that had an osteogenic ability together in vitro and in vivo. (Halvorsen *et al*., 2001), Furthermore, ADSCs could be induced to differentiate in vitro into a variety of new cell lines, including neurogenic lineages. (Mizuno *et al* .,2002)**.** (Safford *et al*., 2002; Ashjian *et al* .,2003), hepatic, adipogenic (Seo *et al*.,2005) and chondrogenic .(Erickson *et al*., 2002; Huang *et al*., 2004).

Furthermore, MSCs may be extracted from the skin; these cells were present in the skin throughout development but only in trace levels after adolescence..(Fernandes *et al* ., 2004 ; Shih *et al*., 2005;Toma *et al* ., 2005). Because of their capacity to develop into Schwann cells, skin-derived mesenchymal stem cells presented a readily accessible alternative autologous source (McKenzie et al., 2006) These cells effectively myelinated and connected with regenerated axons..(Marchesi *et al* 2007) . Single pigmentary ciliary border cells proliferate clonally in vitro to form spherical colonies of cells that can be differentiated into cell types specific to the retina, such as rod photoreceptors, bipolar neurons, and Muller glia. Instead of the central and periphery of the retinal pigmented epithelium, adult retinal stem cells are concentrated close to the pigmentary ciliary edge (Tropepe *et al.,* 2000) **.** Furthermore, The endocrine cells of the rat pancreatic islets of Langerhans, including insulin-producing beta-cells, reportedly underwent turnover every 40–50 days through apoptosis and the proliferation and differentiation of new islet cells (neogensis) from progenitor epithelial cells situated in the pancreatic ducts. The pancreas contained true stem cells (Zulewski *et al.* 2001) . Furthermore, MSCs can be found in umbilical cord, Wharton's jelly, and the placenta. (Lee *et al*. 2016) .

APPLICATIONS OF MESENCHYMAL STEM CELLS

MSCs for Liver Disease

In cases of intrinsic liver disease, the liver's amazing regeneration capacity may be hampered, in which mesenchymal stem cells are promised for liver transplantation, or in liver metabolic diseases. Stem cell-based therapy, which has generated a lot of interest, offers support (Lagasse *et al* ., 2000). In vitro, mesenchymal stem cells could differentiate into hepatocytes, and they were successfully transplanted into the acutely injured liver, improving its functionality. (Yamamoto *et al* ., 2003; Agarwal *et al.,* 2008). MSC treatment significantly improved liver functions, suggesting that MSC therapy was applicable in end-stage liver disease, practical, and safe. .(Dormandy *et al.,* 1999) .

Mesenchymal Stem Cell Therapy For Autoimmune Diseases

Management of an autoimmune conditions may be safer and more practical with the use of MSCs. Inflammatory bowel disease, also known as Crohn's disease, has been studied in animals to determine how MSCs behave therapeutically. In Crohn's disease, the immune system attacks the digestive tract, causing a chronic inflammatory illness. Animals with Crohn's disease who received autologous MSCs derived from adipose tissue displayed typical healing and signs of repair. (Khuu *et al.,* 2007 ; Najimi *et al.,* 2007). There have been other reported clinical studies on the therapeutic impact of MSCs in the treatment of multiple sclerosis and chronic inflammatory demyelinating CNS diseases (Mohyeddin , 2007). MSCs have also been linked to systemic lupus erythematosus (SLE), an autoimmune inflammatory disease that affects several organs, including the lung, brain, and kidney. Corticosteroid administration is the most often used immunosuppressive therapy, although these steroid-based medications are associated with significant adverse effects. (Cintron *et al.,* 1993 ; Orlic *et al* ., 2001). MSCs generated from the umbilical cord have also been found to have therapeutic promise in SLE. (Murry *et al* ., 2004 ; Adler and Maddox, 2007) .

Mesenchymal Stem Cell Therapy For Cancer

As a result of their innate propensity to move in the direction of malignancies, MSCs are used as a chariot for cancer gene therapy. (Valentine *et al.,* 1996). It is

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currently debated whether MSCs have anticancer effects, as some research has demonstrated that even unmodified MSCs decrease tumor development and angiogenesis. (Esato *et al* .,2002). Others have reported that MSCs induce metastasis and cancer. (Higashi *et al.,* 2004). MSCs have been hereditarily modified to over expressed different anticancer genes, for example IFNs, Prodrugs , ILs, oncolytic viruses, antiangiogenic agents (, proapoptotic proteins, and growth factor antagonists (Payne *et al* .,2007).

Mesenchymal Stem Cell Therapy For Cardiovascular diseases

Research on cardiac stem cells has recently focused on fetal and bone marrow-derived stem cells, with the goal of treating heart failure and myocardial infarction. (Passier *et al*., 2008). The first studies demonstrated the development of cardiomyocytes from bone marrow stem cells and the recovery of cardiac function in mice after myocardial infarction. (Orlic *et al*., 2001). MSCs possessed a cellular repressor of E1A-stimulated genes (CREG), and they also played a function in activating HIF-1, other than HIF-1, by insulting a critical protein that insulted HIF-1 (Das *et al.,* 2010). This in turn modified paracrine signaling, resulting in the upregulation of angiogenic molecules such as hepatocyte growth factor (HGF) stromal cell-derived factor-1α (*SDF-1α*) and vascular endothelial growth factor (*VEGF*). (*Kim et al., 2011*). Furthermore, CREG causes a decrease in cardiomyocyte proliferation and fibrotic tissue. (MSCs have also been studied for their ability to release extracellular vesicles under hypoxic conditions, which has been linked to improved heart function and neoangiogenesis. (*Bian et al., 2014*) . In vitro, guinea pigs and pigs with atrioventricular blockages were effectively treated with cardiomyocytes that could be generated from embryonic stem cells to restore atrioventricular conduction. (Xue *et al.,* 2005). Even though it is frequently insufficient to allow for damage repair, normal angiogenesis happens. Contrarily, progenitor stem cells are thought to initiate the denovo process of vasculogenesis, which leads to the development of a new vascular network. (Velazquez ,2007). In order to conduct numerous clinical studies and deliver endothelial progenitor stem cells for the treatment of critical limb ischemia, endothelial progenitor cells have now been identified in adult peripheral blood and have been extracted from bone marrow or peripheral blood. Vasculogenesis was previously believed to only happen during embryonic development. (Velazquez *et al* .,2007) .

Mesenchymal Stem Cell Therapy For Neurologic Diseases

Acute traumatic brain injury, Alzheimer's disease, Parkinson's disease, and stroke (which causes damage to the cord) have all been treated using stem cells (Mendez *et al*., 2007). Researchers have looked into human mesenchymal stem cells and bone umbilical cord blood stem cells produced for potential stroke treatments Intracerebral, intravenous, or intraarterial stem cell therapy has been shown in numerous animal studies to improve functional outcomes. thirty days following the ischemic lesion (Shen *et al* ., 2007). Surprisingly, stem cell injection results in the augmentation of neurogenesis, angiogenesis, and synaptogenesis rather than stem cells transdifferentiating into efficient neurons, which has a neurorestorative effect. (Chen *et al* .,2003). Astroglial cells have been identified as in vivo progenitor and neural stem cells. (Hess and Borlongan , 2008). Following a middle cerebral artery infarction, mesenchymal stem cells were administered intravenously in another clinical trial, and the results showed improved angiogenesis, neurogenesis, and synaptogenesis enhancements that facilitated increased functional recovery (Bang *et al* ., 2005).

Mesenchymal Stem Cell Therapy For Diabetes Mellitus

A clinical issue has been the development of pancreatic transplantation as a treatment option for diabetes mellitus that is resistant to standard therapy. There are many drawbacks to pancreas transplantation, including high costs, a shortage of donors, severe morbidity, and long-term immune suppression (Casey *et al* .,2002). Animal trials have been carried out to investigate the therapeutic potential of mesenchymal stem cells., (Rajagopal *et al*., 2003) Furthermore, Mesenchymal stem cells have been employed effectively in mice to cure or alleviate diabetes.. (Tropepe *et al.,* 2000). Rodents have also revealed bone marrow's potential. Mesenchymal stem cells will develop into functional islet cells. (Hess *et al* .,2003).

Mesenchymal Stem Cell Therapy For Ovarian Failure

There are numerous forms of stem cells that have been studied in POF therapy; the recovery of ovarian function is mentioned in follicles derived from embryonic and stimulated (PSCs) pluripotent stem cells that can be induced into oocytes. (Hübner *et al*., 2003). Transplantation of mesenchymal stem cells could be found in ovarian tissue and restored ovarian function; moreover, multiple studies have shown that mesenchymal stem cells may suppress stromal cell death during the production of several paracrine factors like stanniocalcin-1. (Nicholas *et al*., 2009 ;). MSC transplantation was employed in the reconstruction of oogenesis and preparation for fertilization, which not only has enormous implications for both human and animal reproduction, but also had relevant applications in basic biology. (Hayashi and Saitou, 2013). Mesenchymal stem cells (MSCs) have

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been examined for their ability to correct ovarian dysfunction caused by chemotherapy. (Kilic *et al.*, 2014) . Animal studies revealed that MSCs infusion or implantation had a beneficial effect on repairing tissues and organs; additionally, MSCs were located to sites of tissue damage when given intravenously and intraperitoneally, after which they either engrafted to damaged tissue or secreted bioactive molecules that promoted tissue repairing. (Ranganath *et al.*,2012). Transplantation of umbilical cord mesenchymal stem cells (UCMSCs) might restore mouse ovarian function via the paracrine route. UCMSCs, For example, by modifying its G-protein coupled receptor protein signaling and MAPK pathways, which are both needed for follicle and oocyte development, might be protected from GC apoptosis. Another form of MSC, adipose-derived stem cells (ADSCs), could be differentiated into several cell types; the ADSCs had a protective role in POF in mice. (Sun *et al.*, 2013). The effect of BMSCs occurred by regulation of GC apoptosis led to decrease in FSH hormone and regulation in production of AMH hormones led to increase the number of follicles. Ovarian failure and hormone disorders induced by chemotherapy drug which was caused over apoptosis in granulose cell (GC) resulted in an increase the receptor of FSH lead to accelerated follicles storage depletion, decreased E2 and AMH hormones levels. (Lee *et al.*, 2016), Additionally, it has been demonstrated that BMSCs released VEGF, which repaired endometrial injury and reduced ovarian granulosa cell death. Additionally, MSCs' ability to control the inflammatory response to injuries indicated their beneficial impact on the therapeutic response. The antioxidant activity of marrow-derived MSCs was assessed, and MSCs encouraged an increase in glutathione peroxidase (GPx) and superoxide dismutase production, which facilitated effective wound healing. Additionally, it has been demonstrated that vascular endothelial growth factor (VEGF) is upregulated in wounds due to GPx-mediated detoxification of hydrogen peroxide, indicating a pro-angiogenic action.. (Lee *et al.*, 2016). These findings suggested that BMSCs may have the ability to restore ovarian structure and enhance ovarian endocrine function. In addition, BMSCs may be encouraged to differentiate into ovarian tissue-like cells, which may aid in repairing damaged ovarian niches.(Fu *et al* ., 2008). The MSCs may have a possible role in tissue repair and may also be an effective tool in reestablishing pregnancy and fertility, since they produce bioactive mediators that encourage cell development and have anti-inflammatory unique effects on the constrained microenvironment.(Augello *et al.*, 2007).

CONCLUSION

We discussed the most recent research results from clinical studies on cardiovascular diseases, pulmonary dysplasia, skin regeneration, and endocrine and reproductive issues.With regard to the use of MSCs from various sources in the treatment of human illnesses, the ramifications of the conclusions and discussions described in this review, as well as a sizeable body of well-written, in-depth reviews as well as methodical analyses in the literature, offer a unique viewpoint and perspective. We believe that the ongoing discussion will significantly deepen our understanding of MSCs and advance the fields of regenerative medicine and MSC-based therapy.

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