Jurnal Teknokes
International: Rapid Review: Open Access Journal **Vol. 15, No. 2, June 2022, pp. 58-68** **ISSN: 2407-896**

RESEARCH ARTICLE **OPEN ACCESS**

Manuscript received March 15, 2022; Revised April 17, 2022; accepted May 1, 2022; date of publication June 30, 2022
Digital Object Identifier (DOI): https://doi.org/10.35882/teknokes.v15i2.196

How to cite Sneha Chaklader and Shamayita Basu, "Therapeutic and Clinical Propositions of Mesenchymal Stem Cells(MSCs) Focusing on Recent Trial Updates", Jurnal Teknokes, vol. 15, no. 2, pp. 58–68, June. 2022.

Therapeutic and Clinical Propositions of Mesenchymal Stem Cells(MSCs) Focusing on Recent Trial Updates

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ABSTRACT The mesenchymal stroma harbours considerable population of stem cell-like cells with differentiation and self-renewal abilities that originate from several sources like amniotic fluid, Wharton's jelly, umbilical cord etc. Mesenchymal Stem Cells (MSCs) are most commonly found in the perivascular niche. This multipotent progenitor cells have the ability to differentiate into mesodermal cell types such as adipocytes, chondrocytes and osteocytes. MSCs can also exert significant immunosuppressive and anti-inflammatory effects by interacting with lymphocytes from both innate and adaptive immune system. MSCs of fetal origins can go through same processes as MSCs derived from elsewhere. Before senescence, they make more cell divisions than adult MSCs of bone marrow or adipose tissue. The propitious properties of mesenchymal stem cells (MSCs), such as their ability to differentiate into diverse cell lineages and their regenerative properties, have intrigued researchers, whose work has provided fascinating perspectives on cell-based therapies for wide range of diseases. MSCs have a high potential for replication in vitro. International Society for Cellular Therapy (ISCT)-based MSC isolation has resulted in heterogeneous, nonclonal stromal cell cultures containing stem cells with various multipotent characteristics, committed progenitors, and differentiated cells. Nonclonal stromal cultures which are derived from bone marrow and other tissues are presently used as sources of putative MSCs for therapeutic aims. Also, MSCs have potential to endogenously repair as well as reduce the inflammatory responses that may lead to decreased morbidity and mortality rate of COVID-19. MSCs and exosomes have been shown to be safe and effective in the treatment of COVID-19 symptoms in preliminary investigations. As a result of their potential to endogenously repair and diminish the inflammatory processes implicated in COVID-19 morbidity and mortality, they can be utilised on a compassionate basis. More preclinical and clinical research is needed to better understand their mechanism of action and confirm their safety and efficacy. Herein, the MSC-based clinical prospects, clarifies, the recent clinical findings, therapeutic effects of MSC and clinical trials. A systematic review was conducted to get an overall idea about therapeutic and clinical propositions of Mesenchymal Stem Cells(MSCs). Published research on this topic were searched using international databases (PubMed, Science Direct, and Scopus). Initially, keywords were used to select over fifty entire research publications. The papers were then further sorted by English language, title, and abstract, with duplicates and non-relevant studies being removed based on eligibility criteria. Finally, five study papers were included in this final article..

INDEX TERMS Wharton's jelly, clinical trial, senescence, cell-based therapies, COVID-19, mesodermal cell.

I. INTRODUCTION

Stem cell is a class of undifferentiated cells that are able to differentiate into specialized cell types and have capacity to self-renew. Embryonic stem cell and adult stem cells are two types of stem cell. It can also divide into groups according to their potency. Most common type of potency is being totipotent, pluripotent, multipotent and unipotent stem cells. In the stage of development of an embryo it comes across

multiple cell divisions and in the process, gets different kind of potency. With each phase, the developmental potency of the stem cell decreases, implying that a unipotent stem cell cannot differentiate into all types of cells as pluripotent stem cell [1, 2]. A totipotent stem cell, also known as an omnipotent stem cell, is a type of stem cell that has ability to differentiate into a whole creature. A totipotent cell is a fertilized oocyte that consists of cells from the first two cell divisions. It is most potent and enables production of additional embryonic cells [3].When sperm and ovum unite, a blastocyst is produced. This blastocyst is made up of two types of cells: one inner cell mass(ICM) that develops into epiblast and then participates in the formation of the fetus, and other trophectoderm (TE) that aids in the formation of extra embryonic support structures like the placenta. Embryonic stem cells or pluripotent stem cell are the stem cell derived from the inner cell mass of blastocyst, it's a pre-implantation embryo in its early stage [2]. 4-5 days after conception, human embryo reaches the blastocyst, a 50-150 cell structure. This blastocyst gets differentiated into three types of germ layers: ectoderm, endoderm and mesoderm, each of which eventually gives rise to different types of cells and tissues [4]. When a human embryonic stem cell differentiates into each of the germ layers, it transforms into a multipotent stem cell. Multipotent stem cell has a limited spectrum of differentiation as compared to pluripotent stem cell, but these cells are specialized for specific cell lineages [5].This cell is found in tissues and differentiates into cell from a single germ layer [6]. One example is Mesenchymal stem cells (MSCs) which are most common multipotent cells, derived from bone, adipose tissue, bone marrow, Wharton's jelly, peripheral blood and umbilical cord blood [7]. MSC is differentiated into mesoderm- derived cells or tissue such as bone, cartilage etc. [8]. MSCs are differentiated into neural tissue, which is primarily derived from ectoderm, according to recent research. [9]. Mesenchymal stem cells (MSCs) are a type of adult stem cell that has self-renewing properties as well as multipotent lineages that differentiate into mesodermal cell types such chondrocytes, osteocytes, and adipocytes [10]. MSCs are most typically separated from bone marrow mononuclear cells [11], but they can also be extracted from adipose tissue [12, 13], amniotic fluid [14], placenta [15], and umbilical cord blood [16, 17]. The International Society for Cellular Therapy established the minimum criteria for being a multipotent mesenchymal stem cell, which include being plastic-adherent and expressing markers such as CD73, CD105, and CD90 but not Cd34, CD45, CD11b, CD14, CD19, CD79, or HLA-DR [18, 19], as well as analysing markers for chondrogenic and collagen gene expression confirmed by quantitative polymerase chain reaction and the results showed that the three sources of Mesenchymal stem cell(MSCs) such as umbilical cord(UC),bone and adipose tissues presented similar potency for chondrogenic and osteogenic differentiation, but differ from their adipogenic potential [20].

The goal of this review is to emphasise the available data on MSCs' prospective applications, which makes them appealing therapeutic agents for a variety of disorders. MSCs, for starters, can differentiate beyond the mesodermal lineage. MSCs are used in tissue repair and regenerative medicine because of their multipotency. According to a recent study, MSCs give therapeutic effect by secreting a soluble component that creates an immunomodulatory milieu. Third, MSCs have the ability to move to the microenvironment of damage and malignancy. These methods are unknown, however MSCs' unique characteristic permits them to act as a delivery vehicle for targeted therapy. The use of MSCs in clinical trials can aid with graft versus host illness after bone marrow transplantation, cardiovascular disease, orthopaedic injuries, and autoimmune disease[21]. There has never been a stem cell-based strategy for preventing or curing COVID-19 infection. However, a mesenchymal stem cell-based therapeutic therapy for COVID-19 has recently been introduced [22]. Because MSCs may fight viral infection due to the presence of particular cytokines, this property is primarily present in MSC intrinsic niches prior to differentiation, allowing MSCs to persist in the COVID-19 patients' bodies. This study focuses on the current clinical state of MSC therapy, as well as COVID-19 updates.

II. SOURCES OF MESENCHYMAL STEM CELL:

Different types of stem cells have been identified from various parts of the human body. The selection is based on the practical, logistical and in vitro characteristics.

A. BONE MARROW-DERIVED MESENCHYMAL STEM CELLS(BM-MSCS)

Friedenstein identified BM-MSCs in 1976. In 1987, they were first described as undifferentiated MSCs [24,25]. As a result, bone marrow is described as the primary source of multipotent stem cells. However, stem cell isolation from the bone marrow is very highly invasive and painful protocol with the involvement of high dose anesthesia; moreover, the cellular longevity, yield and potential for differentiation totally depends upon age of donor[26]. If compared with different sources of MSCs, BM-MSCs possess a prolonged duplication period, untimely cellular senescence, and contain 0.01% - 0.001% nucleated bone marrow cells [27]. Nevertheless, usage of BM-MSCs over other cell types is very advantageous because of its short culture time [28, 29].

B. PLACENTAL MESENCHYMAL STEM CELLS AND AMNIOTIC MESENCHYMAL STEM CELLS

According to immune-phenotypical analysis, the phenotypical characteristic of cultured cell type is obtained from the amniotic fluid (AF) which is similar to the BM-MSCs [30]. Isolated cells can be cultured and differentiated into mesenchymal lineage. Both tissue is fetal in origin and believed that it represents genetically identical MSCs, as proposed that the fact is amniotic MSCs express the pluripotent transcription factor Nanog, Oct 4(octamer-binding transcription factor 4) and SSER(stage-specific embryonic antigen-4) -human embryonic stem cell marker which is not found in mature MSCs. In addition, the AF-MSCs provoke that it has higher self renewal property (>300 cell divisions) and doubling time of 36h. Furthermore, AF-MSCs can differentiate into hepatocytes and neurons under specific condition[31]. While no report regarding human investigation using AF-MSCs has been reported, but several applications, including to treat nerve injuries, bladder formation, blood vessel and heart valve formation and regeneration of kidney, diaphragm, bone, heart, cartilage and lung [32-34].Moreover, AF-MSCs has successfully incorporated into the sciatic nerve , post- crush and transection animal model [35]. The placenta is another source of early stage of mesenchymal stem cell. These cells are produced from a portion of the mid-gestation placenta that expresses MSC markers as well as CD34 and CD49d, which are both expressed in other MSC sources (excluding Wharton's Jelly-derived MSC) [36]. Placenta-derived MSC (PL-MSC) express embryonic stem cell markers like OCT-4, SSEA-4, c-Kit, and the sex determining region Y-box 2 that aid in hepatic, neuronal, and pancreatic regeneration [37], as well as hematopoietic growth factor genes like SCF, LIF, and TPO that aid in the ex vivo expansion of

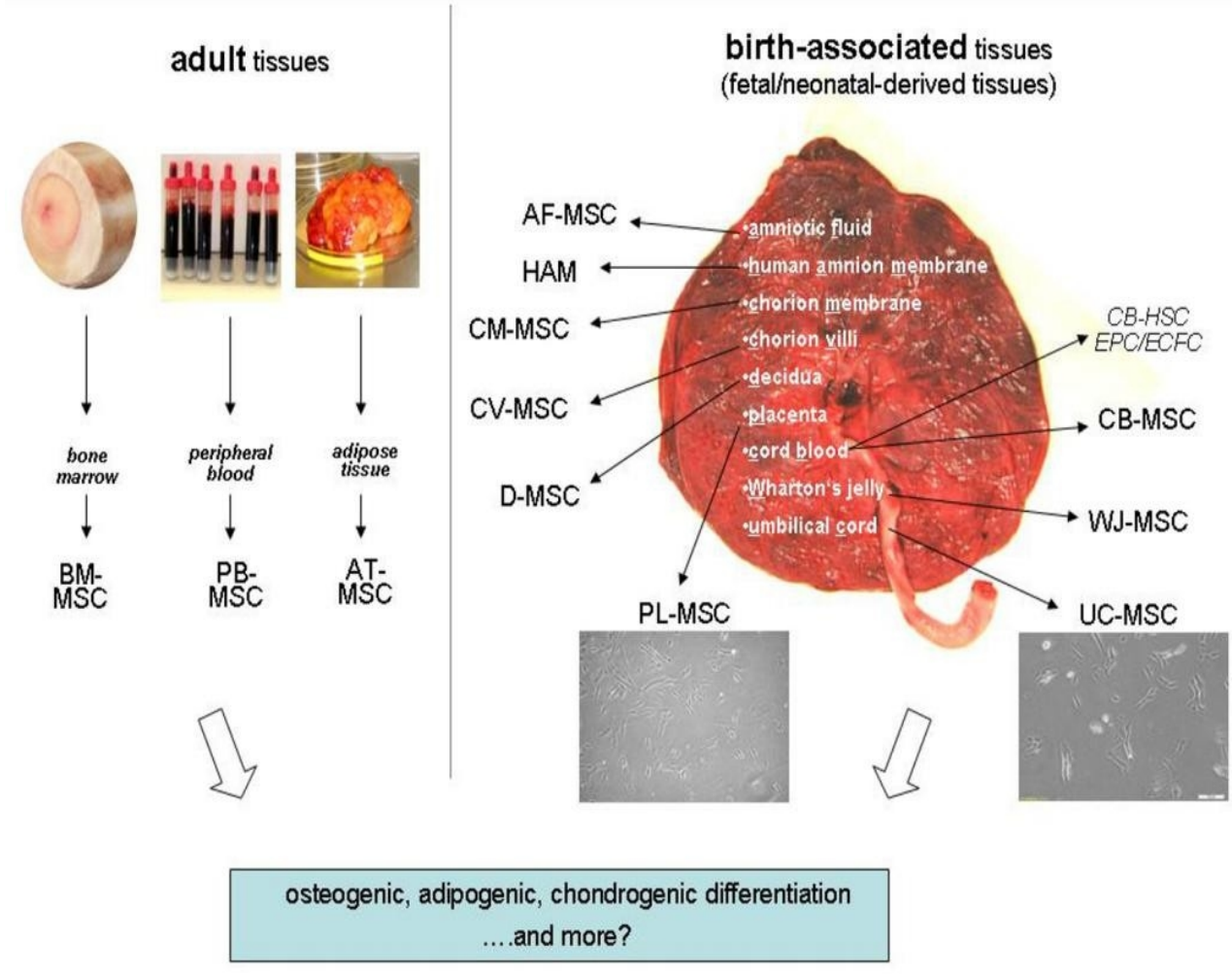

FIGURE 1. Human mesenchymal stem cells (MSC) come from a variety of places. Adult tissues, such as bone marrow (BM), peripheral blood (PB), and adipose tissue (AT), and neonatal birth-associated tissues, such as placenta (PL), umbilical cord (UC), and cord blood, can be separated (CB). Other stem/progenitor cell types from cord blood include hematopoietic stem cells (CB-HSC) and two endothelial populations, endothelial progenitor cells (EPC) and endothelial colony forming cells (ECFC) (ECFC) [23].

animal model is being studied till now for various clinical hematopoietic stem cell (HSC In an animal model, placental

MSCs aid to enhance lung function and pulmonary fibrosis, as well as treat eye and skin illness [39, 40]. Moreover, this cell is able to create artificial amnion with the collagen scaffold [41]. Other clinical prospects of PL-MSC in the animal model include inflammation, Duchenne muscular dystrophy, ischemic stroke etc. Among all of that the more benefit regarding PL-MSC is that isolation during delivery need not require specific protocol for derivation and advantages in the terms of proliferation and plasticity [42].

C. MESENCHYMAL STEM CELLS FROM CORD BLOOD AND UMBILICAL CORD MESENCHYMAL STEM CELLS

According to most studies, roughly 10-30% of umbilical cord blood can be used to culture MSCs when plated on plastic for adherent culture[43-45]. When the dish is precoated with foetal calf serum, the culture size will rise (FCS). UCB-MSCs can be cryopreserved in great quantities for future research, however it appears that culture of umbilical cord (CB-MSC) is more difficult[46]. Cord blood MSCs require 2-4 weeks to cultivate after plating, which is significantly longer than other MSC sources. Although the pace of recovery in culture is slow, and plated cells typically experience early cellular senescence, many CB-MSC colonies have a longer life span. Moreover, UCB-MSC has differential potential to osteogenic, adipogenic, chondrogenic and myogenic lineage. In humans, UCB-MSCs have been successfully employed to treat graft versus host disease (GVHD) and SLE through intravenous delivery [48] and the MSC which is derived from CB has some beneficiary affects seen after infusion in certain medical aspect such as diabetes, sciatic nerve defect etc. in the animal models with superior result [49]. Currently umbilical cord blood is not used universally as the source of MSCs but Wharton's jelly (WJ) has taken attention as a potential source of MSCs. In the field of clinical applications, WJ-MSCs show to be advantageous and secure treatment of myocardial infarction and LV functions [50]. In a study, human WJ-MSC is placed on a 3D scaffold in a specific medium which is taken from the culture of human articular chondrocytes [51]. Afterwards the WJ-MSCs undergo chondrogenic differentiation without involvement of growth factors, but high accumulation of cartilage-related genes and glycosaminoglycans can accelerate the differentiation. These examination shows that the WJ- MSCs may be the good weapon for regeneration of articular cartilage [51].

D. ADIPOSE TISSUE MESENCHYMAL STEM CELL

Adipose tissue (AT) is another convenient source for mesenchymal stem cell. After liposuction procedure approximately 98-100% of cells are isolated from the adipose tissue and those are viable cells [52,53]. Furthermore, phenotypic, morphological, and functional characteristics are similar to those of BM-MSCs [54], with positive expression of CD49d and negative expression of CD106 and STO-1 on the one hand and BM-MSC on the other. [55]. So, AT represents autologous source for MSCs in the tissue engineering than BM-MSCs but it has certain limitation regarding characteristic of donor, such as age, it affect the proliferation and differentiation of AT-MSCs, particularly in the osteogenic and chondrogenic lineages but it does not affect the adipogenic lineages because it is not able to express the BMP-2 and dlx5 transcription factors which regulate the osteogenic genes. The name suggest that it is a stem cell so it also have the self renewal property, furthermore it is capable of secreting multiple number of growth factors with anti-inflammatory, cytokines and it has anti-apoptotic and immunomodulatory properties. Some examples of growth factors are hepatocytes growth factor, vascular endothelial growth factors and insulin like growth factors, all of these growth factors are required for the tissue repair and angiogenesis and besides this characteristic helps to treat ischaemic diseases [56]. Additionally, due to the presence of immunomodulatory property in the human AT-MSCs, AT is the most important source of allogenic mesenchymal stem cells, and the benefits of employing AT-MSCs include the fact that they do not express the major histocompatibility complex type II antigen, resulting in a very low rejection rate. [57]. AT-MSCs mostly regulate the T cell functions by promoting the induction of T cell suppressor and inhibit the production of natural killer cells, cytotoxic T cells and proinflammatory cytokines (including interferon-ϒ, tumour necrosis factor-α and interleukin [IL]-12). Moreover, cell sometime secretes soluble factors, like IL-10, prostaglandin E2 and transforming growth factor-β [58,59]. Furthermore, in the rat model AT-MSCs have stimulated the skeletal muscle regeneration. Interestingly, it expresses some Schwann cell and neuronal markers, such as myelin basic protein, myelin protein zero and peripheral myelin 22 so, expression of this marker suggest that it may have capability for myelin-generation [60].

III. PROPERTIES OF MESENCHYMAL STEM CELLS

A. DIFFERENTIATION

Human 1st and 2nd trimester foetal blood, spleen, liver, and BM have all been used to isolate MSC. Although MSCs differ in their ability to differentiate in different tissues, the relationship between typical BM-derived MSCs and MSCs produced from other populations of cells is also heterogeneous. As a result, MSCs from various origins, such as human adipose tissue-derived multipotent stem cells known as lipoaspirate (PLA) cells, which are identical to BM-MSCs, can differentiate into many lineages of mesenchymal cells in vitro. However, there are some differences in the expression of particular markers, such as CD49d, which is found on the surface of PLA cells but not MSCs, and CD106, which is expressed on the surface of MSCs but not PLA cells. However, Adult human Mesenchymal stem cells reported that it secret moderate levels of major histocompatibility complex (MHC) class I

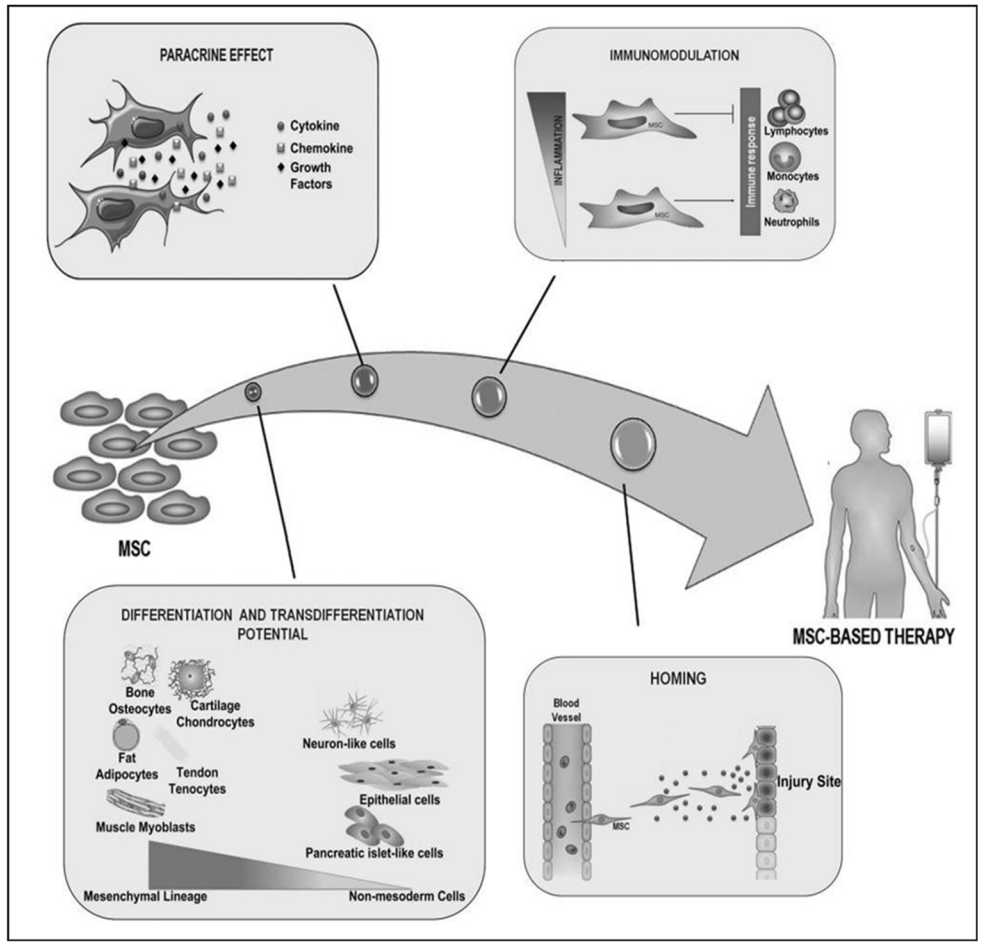

FIGURE 2. MSC clinical usage is supported by biological characteristics. MSCs' therapeutic potential is based on their unique properties, which include the ability to differentiate into various cell lineages (bottom, left), the ability to secrete soluble factors that are critical for cell survival and proliferation (top, left), the ability to modulate immune response (top, right), and the ability to migrate to the exact site of injury (bottom, right).[61]

but not able to express human leukocyte antigen (HLA) class II antigen on the cell surface. It is the major source of immunosuppressive drug compared to other sources [62].

1) DIFFERENTIATION INTO ADIPOCYTES

In cells that contain lipid droplets, adipogenic differentiation appears. UG-MSCs and AT-MSCs (ASC) both have the ability to develop into adipocytes [63,64]. T-MSC (ASC) differentiation requires high cellular density and growth arrest in the G0/G1 phase [65,66]. Furthermore, thiazolidiones such as troglitazone, FGF2, pioglitazone, 17-estradiol, and rosiglitazone are required for AT-MSC (ASC) adipogenic differentiation[67,68]. With the use of a specific medium containing insulin and dexamethasone, Hu et al were able to successfully differentiate UC-MSC into adipocytes. [69]. Commonly oil red staining is used for verifying adipogenic differentiation. [70].

2) CHONDROGENIC DIFFERENTIATION

In pellet culture, the production of glossy cell-spheres that express type II collagen indicates chondrogenic differentiation. Medium supplements such as ascorbate-2-phosphate, transforming growth factor 1, and dexamethasone are required for chondrogenic development [71,72]. By supplementing AT-MSC (ASC) with growth and differentiation factor-5 (GDF5), Feng et al promote chondrogenic differentiation [73], and stimulation with FGF-2 or BMP-6 has also been documented [74,75]. Extracellular matrix component glycosaminoglycans (GAG) and immune-histological staining, such as aggrecan and collagen II, or PCR verification of chondrogenic lineage genes, are used to detect chondrogenic differentiation. [75].

3) OSTEOGENIC DIFFERENTIATION

Expression of high amount of alkaline phosphates and mineralization assay by the alizarin red and von Kossa indicates the presences of osteogenic differentiation. Different group of researchers reported differentiation

methods by the using of supplement such as ascorbic acid, β-glycerophosphate and dexamethasone [76,77,78]. This same medium composition was also used for UC-MSCs' osteogenic differentiation [74]. For enhancement of osteogenic differentiation some more medium supplement is added such as BMPs [79, 80, 81] or 1,25-dihydroxyvitmin D3 [82,83].

B. IMMUNE MODULATION

Immunosuppression or immunoprivilege are two terms used to describe MSCs' ability to suppress the function of numerous immune cells such as T cells, B cells, and natural killer (NK) cells, implying that MSCs are immune to immunological effects. MSCs' therapeutic importance as an immunosuppressive and anti-inflammatory drug is linked to the adaptive and innate immune systems' interplay inside lymphocytes. MSCs inhibit B cell functions, T cell proliferation, natural killer cell proliferation, and cytokine generation while also preventing dendritic cell differentiation, maturation, and activation.Most importantly, MSC can apply immunosuppressive affect directly from cell to cell contact, this mechanism is achieved by the production of certain soluble factors like hepatocytes growth factor (HGF), transforming growth factor-β, nitric oxide and indolemine 2,3-dioxygenase (IDO) [84-86].

C. MIGRATORY CAPACITY

Researchers reported that MSCs are able to migrate towards the tumor microenvironments. Although the exact mechanism governing MSC migration is unknown, some studies claim that MSC migration is influenced by chemokine and receptor interactions such as stem cell factor/c-kit, HGF/c-Met [87], stromal cell-derived factor 1 (SDF-1)/C-X-C chemokine receptor type 4 (CXCR4) [88,89], monocyte chemoattractant protein-1 (MCP-1)/C-C chemokine receptor type 2 [90 These chemokines and cytokines are extremely important in leukocytes that are involved in inflammation and damage. Furthermore, because the tumour microenvironment is akin to an unhealed lesion, inflammatory mediators such as chemokines, cytokines, and other chemoattractant molecules are produced. [94]. MSC migration is aided by this communication. CXCR4 and SDF-1 are key mediators of stem cell attraction to tumour microenvironment among all chemokines [92]. Furthermore, hypoxia induces the production of proangiogenic molecules in some tumour microenvironments. Several variables are induced by the hypoxic environment, including tumour necrosis factors, transcription factor HIF-1, VEGF, macrophage migration inhibitor factor, and a slew of proinflammatory cytokines. [95], including several chemokines, e.g. MCP-1, which enhance the migration of MSCs toward tumors [94]. Many studies say that interaction between chemokine/receptors play an important role in MSC therapies to tumor and inflammatory sites.

IV. MESENCHYMAL STEM CELL BASED THERAPY: CLINICAL TRIALS

A. MESENCHYMAL STEM CELL IN CHRONIC DISEASES

*Considering the property such as multilineage potency, anti-inflammatory molecule, migrating ability and immunoregulatory effects, it gives promising area for treatment of inflammatory, autoimmune and degenerative diseases. Some role of mesenchymal stem cells is there for the treatment of chronic diseases in animal model. MSCs implication in therapeutics has a promising future worldwide for clinical regeneration medicine and numerous clinical trials have been going on since last decade. According to the US National Institute of Health's official data, 493 MSC-based clinical trials have been reported as of June 15, 2015; mostly governed on the biomedical potential of MSCs areas like GVHD, diabetes, hematological diseases, liver diseases, inflammatory diseases, kidney disease, lung disease, as well as bone and cartilage, cardiovascular, autoimmune, neurological disease.

1) PARKINSON'S DISEASE

Parkinson's disease (PD) is a neurodegenerative condition characterised by the death of dopaminergic neurons in the brain. As a result, after transplanting MSCs into mice, the amount of tyrosine hydroxylase is increased. [96]. MSCs by excretion of trophic factors such as FGF-2, neurotrophin-3 (NT3), vascular endothelial growth factor (VEGF), BDNF and HGF helps in neuroprotection without differentiating into neurocytes [97,98].

2) ALZHEIMER DISEASE

Alzheimer's disease (AD) is a well-known neurological illness. Memory loss, dementia, and intellectual deficiencies are common signs and symptoms. There is currently no way to reduce or stop the progression of Alzheimer's disease. [99]. Nowadays researchers are trying to reduce the neuro-pathological defect by involvement of stem cell therapy in mice model. In another way AD-MSCs has efficiency to modulate inflammatory environment, specifically activating the microglial cell which decrease the expression of proinflammatory cytokines and increase the activity of Aβ-degradation enzymes [100] and also take part in regulation of T-cells (Tregs) [101] while side by side modulating microglial activation [102]. Moreover, working with UCB-MSC shows that it modulates the microglial activity leading to neuronal survival in Alzheimer disease affected mice model [103]. Most recently, it has been discovered that MSCs activate the autophagy pathway, which prevents amyloid plaque formation and increases survivability both in vitro and in vivo. [104].

3) CARDIOVASCULAR DISEASE

Despite advancement in medical and surgical area, cardiovascular diseases such as ischemic heart disease and congestive heart failure is considered as a major cause of high morbidity and mortality rate worldwide [105]. Cardiac

muscle has little ability of differentiation and current medication and surgical procedure are not able to raise the contraction ability of cardiac muscle. For this limitation stem cell therapy plays a remarkable role, so MSCs therapy is key for therapeutic application for cardiovascular repair due to its immunomodulatory and cardiomyocyte differentiation is aided by this source. MSC transplantation improves heart muscle activity in a preclinical investigation [106]. Furthermore, in vivo cardiomyocyte development is uncommon, whereas in vitro cardiomyocyte differentiation is prevalent primarily in young cell culture sources [107]. MSCs transdifferentiated into cardiomyocytes in the presence of growth medium [108], which are utilised to treat heart failure caused by left ventricular injury and myocardial infarction. [107].

4) RHEUMATOID ARTHRITIS

It's an inflammatory condition of the joints brought on by a loss of immunological self-tolerance.. Preclinical studies reveal that injection of human AD-MSCs in mice model DBA/1 result in increase of level of inflammatory response [109]. Moreover, injection of AD-MSCs helps in expansion of Th17/Th1 antigen specific cells for reduction of inflammatory cytokines and chemokines level, side by side increases the secretion IL-10 [110]. In vivo, IL-10 is an important factor for Treg cell activation because it helps to control self-reactive T-cells and raise peripheral tolerance. And in the other hand BM derived MSCs introduced into the collagen-induced arthritis mice model DBA/1, gives same result as previous one. However, several inconsistencies have been noted, such as the fact that MSCs are only effective when injected at the outset of sickness; MSC loses its immunoregulatory capacity when exposed to an inflammatory microenvironment, according to an adjuvant-induced and spontaneous arthritis paradigm. [110].

5) SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Previously SLE was treated based on the high dose of cyclophosphamides, corticosteroids and other biological and immunosuppressive agent, though these drugs helped to improve its outcome in SLE patients [110]. In other hand some patient suffered from adverse effect such as ovarian failure, secondary malignancy and infection [111] which was one of the main cause for mortality in SLE. So, MSC treatment is more modern technique to fight against SLE. Clinical studies based on the refractory and severe SLE patients interpreted that improvement in serological marker of organ dysfunction [112]. Till date there is two clinical trials going on for SLE treatment but status is unknown.

6) CANCER

MSC has migratory capability toward tumor, hence it's a very good carrier for cancer gene therapy. Some study says MSCs have anti tumor activity but not yet clear [113] and in other hand some group says MSCs is good source of metastasis and tumorigenesis [114]. Moreover, genetically modified MSCs can induce over expression of anticancer genes like IFN [114], ILs, oncolytic virus, prodrugs and growth factor antagonists [113] for the treatment of different types of cancer. So, genetically modified MSCs are well studied, clinical trials have not reported yet. Although the genetically edited MSC has been delayed in clinical trials due to a lack of safety, MSC administration has been postponed due to a lack of safety.

A novel safety mechanism is currently being developed, namely a suicide system that relies on the inducible caspase-9 protein activating a specific chemical inducer of dimerization (CID) [115]. So, CID directly kills MSCs within 24 hours. Lastly the progression of safety mechanism enhances genetically engineered MSCs for the treatment of different types of cancer.

B. COVID-19 UPDATES

At the end of 2019, the novel corona virus disease (COVID-19) caused by severe respiratory infection was first reported in Wuhan, China which grew up to be a global public health emergency. The name corona virus or SARS-COV-2 was given by World Health Organization(WHO).

Researchers and physicians from several sectors of biomedicine were enlisted to find effective treatments for the epidemic. There is no approved stem cell-based therapy to treat COVID-19 infection, according to the International Society for Stem Cell Research (ISSCR), yet current updates suggest that the participation of mesenchymal stem cells may pave the way for COVID-19 treatment. By spontaneously healing, mending, and regenerating damaged or diseased tissue and organs, this cell-based therapy can heal injuries and diseases. [116]. A recent experiment conducted by Beijing You'an Hospital, Capital Medical University in China demonstrate meaningful therapeutic approach of Mesenchymal stem cell for the treatment of COVID-19 pneumonia and the result says that symptoms like fever, low oxygen saturation level and shortness of breath improve in status after 2-4 days post treatment [117]. The immune regulatory property of MSCs regulate the stimulation and effector function of immune cell, increase the resolution of pulmonary edema and reduce lung infiltrated cells but it does not have clear evidence yet. On the other hand, anti-inflammatory role of MSCs plays a potential therapy for severe COVID-19 outbreak. Moreover, acute lung infection (ALI)/ acute respiration distress syndrome (ARDS) can be cured efficiently by MSCs (both infectious and noninfectious form) due to production of specific cytokine. This property is present in the intrinsic niche of MSCs.

In the search of proper treatment, some scientist working with vaccination for COVID-19, mesenchymal stem cell opens a promising path for therapeutics without adverse affect [118].

1) MESENCHYMAL STEM CELL THERAPY FOR COVID-19

Recently, cell based therapy especially stem cell based therapy shows many opportunities to prevent incurable diseases [119]. Working with stem cells arise ethical issues which are not solved yet. Among all this limitation MSCs draw attention for its high proliferation rate, very less invasive and mainly because it is free from ethical issues [120]. MSCs are also immunological privileged due to low levels of co-stimulatory molecules on the cell surface and class II major Histocompatibility Complex (MHC-II) expression [119]. MSCs have a strong immunoregulatory capacity, which is mediated via regulatory T cells, on B cells, T cells, and natural killer cells. Through numerous soluble factors such as PCE-2, IDO, TGF-, HCF, HLA-G5, and NO, MSCs can decrease T cell proliferation in vitro, which is stimulated by mitogenic stimuli. This characteristic aids in the reduction of TNF- and IL-6, two crucial anti-inflammatory proteins [120]. MSCs with monocytes or dendritic cells, on the other hand, help to promote the anti-inflammatory cytokine IL-10, which helps to downregulate the human leukocyte antigen (HLA) and provides protection. Direct regeneration and the creation of various paracrine components, including antimicrobial peptides, are examples of these effects [122]. While regulatory dendritic cells (DC) play a crucial role in immunological homeostasis and have immunosuppressive abilities to reduce Th2 type inflammation, MSC also induce specific immune tolerance and mature dendritic cells (DC) in the unique Jagged-2 dependent regulatory dendritic cell population. So, all of this interaction of MSC and dendritic cells lead to changes in immune system from Th1 response toward an anti-inflammatory Th2 response [121]. Furthermore, stem cell therapy can protect against influenza A/h5N1 infection by reversing lung harm. [122]. So, all the property of MSCs such as immunomodulatory, anti-inflammatory and homing property and regenerative potential attract attention of scientist for the treatment of COVID-19 [123].

V. CONCLUSION

Therapeutic use of MSCs and MSC based product for treatment of tissue injury and some incurable disease like diabetes, Alzheimer, cancer has brought a new ray of hope and its success will bring a radical change in the modern medical science. Encouraging results has been shown in animal models and also in some kinds of patients. A lot of research is needed to ensure the safe and convenient procurement of these cells. Stem cell therapy has opened up a new dimension in the field of treatment and the goal is not far from us. But the safety and efficacy of different types of MSCs, particularly BM-MSCs should be given top priority. It is the most promising option of treatment in medical science. MSCs' therapeutic promise, however, has yet to be translated into solid clinical efficacy proof. We believe that more money should not be spent on premature clinical trials that have no obvious reason. Rather, we advocate that resources be committed in clinical studies that are built around a scientifically established mechanism of action and that use molecular markers to identify human participants and track therapy responses. In the absence of these criteria, we believe money would be better spent funding fundamental mechanistic studies on MSCs, which are projected to lead to more impactful clinical trials in the future. To improve MSCs' therapeutic efficacy in diverse diseases, more study is needed to establish their mechanism and biological features. The study focuses on a variety of issues, including the heterogeneity of MSC populations. As a result, a standardized finding is critical. Multiple clinical trials with MSCs have been promising, but they also highlight the important problems that must be addressed. MSCs have the ability to endogenously repair and minimize inflammatory reactions that cause COVID 19 morbidity and death, and they can be used on a compassionate basis. A standardized method of MSCs isolation, characterization and clinical administration is absolutely necessary for effectiveness of therapeutic use of MSCs. COVID-19 is one of the most serious socioeconomic and public health threats we've ever seen. With the development of a vaccine to eradicate the viral infection still a long way off, there is a pressing need for treatments that are both effective and safe. MSCs and exosomes have been shown to be safe and effective in treating COVID-19 symptoms in preliminary investigations. Because of their ability to endogenously repair and reduce the inflammatory reactions that cause COVID-19 morbidity and mortality, they can be used on a compassionate basis, but more preclinical and clinical studies are needed to understand their mechanism of action and establish their safety and efficacy.

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