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Review Article

Biological Characteristics and Immunological Role of Mesenchymal Stem Cells for Improvement of Health

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Abstract

Mesenchymal stem cells (MSCs) are pluripotent progenitor cells that can be extended and controlled *in vitro*. These cells show different natural properties that make them eligible for cell therapy: separation potential, emission of nourishing components, and immunomodulatory properties. Core blood and bone marrow are the traditional source of MSC and research using MSC obtained from adult bone marrow has acquired numerous potential clinical applications. To perform cell therapy, MSCs should be extended *in vitro*. Notwithstanding, in some cases, the extension of the culture may lead to cytogenetic and molecular changes. The build-up of these changes during many entrances may prompt dangerous cell changes. Accordingly, it is essential to utilize various strategies for severe control to test the security and adequacy of MSC for cell therapy. Bone marrow MSC has possible clinical application in hematopoietic stem cell transplantation as a helper cell therapy. This review surveys the exploration progress of MSCs and the possible clinical utilization of MSCs in hematopoietic stem cell transplantation. We additionally portrayed the significance of measurable techniques to aid the investigation of the adequacy and security of the clinical utilization of MSCs for hematopoietic stem cell transplantation.

Keywords: Biological characteristics; Immunology; Mesenchymal stem cells

Introduction

The biology of stem cells is at the core of scientific interest, offering the supply of cells capable of tissue rebuilding after injury, infection and maturation. Based on the idea that tissue fixed relies upon cells flowing in blood in response to injury. Mesenchymal stem cells are pluripotent cells that can separate into mesenchymal cell ancestries *in vitro*, for example, adipocytes, bone cells and cartilage cells. MSC can be extended and controlled ex vivo. As per the base principles of the International Society for Cell Therapy, MSCs are controlled by their *in vitro* development mode (cultured plastic adherent cells) and explicit surface antigen articulation [CD73, CD90 and CD105] [without heredity responsibility markers like CD14, CD19, CD34, CD45) And HLA-DR] and multicellular potential (these cells should have the option to separate into bone cells, adipocytes and cartilage cells *in vitro*) (Conget and Minguell 1999; Dominici *et al.* 2006; Sotiropoulou and Papamichail 2007). MSC can be derived from grown-up bone marrow, fat tissue and some fetal tissues (like umbilical card). Bone marrow is viewed as a standard wellspring of MSC and a large portion of the information about potential clinical applications is acquired through examinations utilizing MSC obtained from grown-up bone marrow (Chan *et al.* 2014). MSC can be enhanced and controlled *ex vivo*, showing immunomodulatory works *in vivo* and *in vitro*. Hence, they address hopeful strategies for immunomodulation and regenerative cell treatment. As of late, numerous investigations have shown that the clinical utilizations of MSCs in the treatment of cardiovascular infections, neurodegenerative sicknesses, bone deformities and cracks, provocative joint inflammation and hematopoietic stem cell transplantation are arising (Stagg *et al.* 2006; Du-Rocher *et al.* 2020). Bone marrow mesenchymal stem cells represent about 0.01% of bone marrow mononuclear cells (Hoch and Leach 2014). This, for cell therapy, MSCs should be extended *in vitro* on tissue culture plastics. Without influencing the cell's genomic characteristics and differentiation characteristics, a lot of

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intensification must be carried out *in vitro*. However, the culture's expansion may sometimes deliver cytogenetic and molecular changes. The aggregation of these progressions during numerous entries may prompt dangerous cell transformation. Therefore, it is imperative to utilize various quality control strategies to test MSC's well-being and viability for cell therapy. MSC produces most of the stromal cells present in the bone marrow. They structure part of the specialty of hematopoietic stem cells and produce different factors that control hematopoiesis. It has been suggested that bone marrow-MSC can be utilized as a helper cell therapy to advance fast hematopoietic recovery in hematopoietic stem cell transplantation patients. This survey reviews the exploration progress of MSCs and the possible clinical utilization of MSCs in hematopoietic stem cell transplantation. We will likewise portray the significance of factual techniques to help analyze the efficacy and well-being of the clinical use of MSC for hematopoietic stem cell transplantation.

Biological characteristics of mesenchymal stem cells

MSC was first defined in 1966 (Friedenstein *et al.* 1966). After the discovery, several studies were conducted using human mesenchymal stem cells. They revealed the presence of fibroblasts, which can be obtained from the bone marrow of mice, and when relocated subcutaneously, they can differentiate into osteoblasts. After the disclosure, several examinations were led utilizing human mesenchymal stem cells. These examinations affirmed that the entire bone marrow could be subcultured and put in a plastic petri dish and following a couple of long periods of disposing of non-adherent cells, the cells adherent to the plastic can form colonies. It is seen that MSC has two significant qualities. First, they can differentiate pluripotent stem cells from the lab to clinic 496 into extraordinary terminal cell types, including bones, ligament, muscle, bone marrow stroma, ligaments/tendons, dermis and other connective supporting tissues. Second, MSC secretes a variety of biologically active macromolecules with immunomodulatory effects and can build a re-generable microenvironment in injured tissues (Caplan 2007). MSC isn't just present in the bone marrow. MSC has been detached from a variety of tissues, like skeletal muscle, fat tissue, synovium, dental mash, periodontal layer, cervical tissue, umbilical cord, amniotic liquid and placenta. However, a lot of knowledge about biology characteristics and clinical experience has been gained from exploring grown-up bone marrow-derived MSCs. MSCs, also called multipotent cells, exist in adult tissues from various sources. They are self-renewable, flexible, simple to obtain, and culturally scalable *in vitro* (Ball *et al.* 2007). When cultured *in vitro*, MSCs have different biological properties that make them qualified for cell treatment: (1) Differentiation potential, (2) emission of dietary factors that add to tissue rebuilding and (3) immunomodulatory properties (Chan *et al.* 2014).

The therapeutic advantage of MSC depends on its ability to go about as a supply of nutritional factors. After MSC enters the infected tissue site for healing, it will communicate with nearby upgrades, like inflammatory cytokines, Toll-like receptors ligands and hypoxia. They can animate MSC to create countless development factors with various capacities and recover numerous elements of the association. Many of these variables are key mediators of angiogenesis and apoptosis anticipation, for example, vascular endothelial growth factors, insulin-like growth factors and inter-Lukin-6 (Wei *et al.* 2013). Numerous investigations have demonstrated the immunomodulatory properties of MSC. These cells influence the safe reaction by connecting with the cell parts of the resistant framework (T and B lymphocytes, natural killer cells and dendritic cells). MSC immunomodulation can happen through cell contact or potentially the discharge of various factors. Because of these attributes, mesenchymal stem cells can forestall unseemly actuation of T lymphocytes and produce a resistance-initiating environment during the maintenance interaction or stop the safe reaction during the healing process, thereby helping to maintain immune homeostasis (Wang *et al.* 2012; Castro-Manrreza and Montesinos 2015). The immunomodulatory properties of MSC can be divided into three classes: low immunogenicity, regulating T cell aggregate and local immunosuppressive environment (Atoui and Chiu 2012; Faiella and Atoui 2016). MSC decreased the outflow of surface molecules, including low levels of MHC class I and co-stimulatory CD40, CD80 and CD86 and yet no major histocompatibility complex class II particles. This appropriation of surface markers empowers MSCs to avoid identification by certain immune cells and adds to their low immunogenicity. MSCs can additionally immunosuppress the local environment, which can be credited to their effect on the discharge attributes of cytokines. In co-culture with resistant cells, MSC can, by implication, influence T cells by up-managing the emission of inhibitory cytokines (IL-4 and IL-10) to decrease the discharge of pro-inflammatory cytokines (TNF-α) Maturation and multiplication α and IFN-γ) come from dendritic cells, T helper cells and macrophages. MSC can initiate administrative T cells, which eventually hinders the multiplication and capacity of B and T cells and normal executioner cells. A few dissolvable middle people, for example, changing development factor β1, prostaglandin E2 (PGE2), human leukocyte antigen G5, blood oxygenase I, nitric oxide, IL-6 and indoleamine 2, 3-dioxygenase this interaction is vital (Castro-Manrreza and Montesinos 2015). IFN-γ-actuated indoleamine 2, 3-dioxygenase catalyzes the change of tryptophan to kynurenine and represses T-cell reactions (Potula *et al.* 2005; Hurley *et al.* 2006). As we have noticed, the immunomodulatory properties of MSC are significant for cell therapy. In any case, the clinical utilization of MSCs requires around 2 × 106 cells/kg (Du-Rocher *et al.* 2020). Hence, for cell therapy, it is important to utilize culture strategies to extend MSCs.

Separation and culture development of MSCs for cell therapy

The clinical protocol utilizes cell culture innovation, which utilizes the little part of essential MSCs secluded from chosen tissue sources and extended through various entries to deliver clinically pertinent quantities of cells. Therefore, when the tissue source of MSCs for explicit clinical applications is resolved, cell bioprocessing conventions may fundamentally influence safety and adequacy (Hurley *et al.* 2006; Horwitz *et al.* 2011). There is no standard culture protocol for MSC isolation and development. In this way, the method of refining these cells *in vitro* fluctuates extraordinarily between various examination gatherings. Consequently, it is hard to analyze the consequences of various investigations (Penfornis and Pochampally 2011; Jung *et al.* 2012). In any case, the mesenchymal and tissue stem cell committee of the international society for cell therapy has proposed the base principles for characterizing MSC *in vitro*: (1) MSC should stick to plastic under standard tissue culture conditions; (2) MSC should communicate certain cell surfaces markers, like CD105, CD90 and CD73, however, don't have the declaration of different markers, including CD1, CD34, CD45 or CD11b, CD79alpha Or CD19 and HLA-DR surface atoms; (3) MSC should separate into osteoblasts, adipocytes and chondroblasts under *in vitro* conditions (Dominici *et al.* 2006). The technique used to isolate MSCs from bone marrow generally utilizes thickness centrifugation (utilizing Ficoll™, Lymphoprep™ or Percoll™ thickness medium) to isolate the monocyte portion with other bone marrow segments like red platelets, plasma and lipids. This monocyte portion contains Abundant B and T cells, Monocytes, hematopoietic foundational microorganisms, endothelial begetter cells and MSCs. After being vaccinated on the tissue culture carafe, the MSC addressed the disciple cell populace framed states. Follower cells stay in the way of life medium, and other non-disciple cells are disposed of while changing the medium (Bara *et al.* 2014). MSCs harbor subordinate cells that swell when kept up under culture conditions (for instance, DMEN medium enhanced with 10% PBS). The arrangement of single cell-inferred states portrays the underlying development of MSCs in essential BM cell societies on plastic surfaces. The proficiency of their state development is yet a significant proportion of the nature of cell readiness. When all is said in done, even though their multiplication potential is a profound factor, MSCs have extraordinary development potential in culture; for the most part, among youthful and more seasoned contributors, their expansion potential is decreased (Kassem 2006). The cultivating thickness of MSC is somewhere between 2.000 and 5.000/cm^2; in any case, there is proof that a lower cultivating thickness can advance multiplication, which is believed to be because of a lessening in contact restraint. A few examinations have shown that by plating cells at a low thickness of 10–100 cells/cm^2, MSCs multiply more quickly when sub-cultured (Sekiya *et al.* 2002; Both *et al.* 2007). MSC is most of the pluripotent undifferentiated cells from the research facility to the center 498, generally extended in a fundamental medium, for example, Dulbecco's changed Eagle medium (DMEM)/DMEM F-12 or alpha-containing 10% fetal bovine serum (Zhuang *et al.* 2014). All current conventions for MSC culture *in vitro* incorporate FBS as a dietary enhancement (Shahdadfar *et al.* 2005). Nonetheless, the utilization of FBS can bring a few issues, for instance, the danger of pollution with unsafe microbes (for example, infections, mycoplasma, infections, or unidentified zoonotic microorganisms). The possibility of pollution or safe reaction to heterogeneous mixtures should likewise be considered (Tonti and Mannello 2002). Hence, for the utilization of FBS, tests should be performed to give the best development conditions (Zhuang *et al.* 2014). The effective development strategy intends to advance a huge expansion in the number of cells without bargaining the restorative capability of MSCs. MSC can be refined *in vitro* for 8–15 ages, which is identical to roughly 25–40 times the populace multiplying and 80–120 days. MSCs showed a critical decline in expansion with the increment of culture time and section number, in this way maturing and halting multiplication (Banfi *et al.* 2000; Bonab *et al.* 2006; Hoch and Leach 2014). MSCs may lose their capacity to separate during society, making it difficult to evaluate their multi-ancestry potential. The viability of MSC is quickly declining with the 2D extension work, which shows the requirement for elective development innovation. Bone is a 3D substrate made from water, natural collagen, and inorganic hydroxyapatite. MSCs are situated in the hole of bones inundated in blood and interface with various cell types to associate with complex crosstalk groups. Numerous parts of the bone marrow specialty that manage the conduct of MSCs are absent in 2D culture. In this manner, it is important to grow new advances to reconstruct the attributes of the refined specialty to protect the power of MSC forebear cells through 3D extension (Kornberg *et al.* 1992; Zhao *et al.* 2007; Frith *et al.* 2010). A few examinations have shown that a platform or a framework free technique can for the most part be utilized in blend with a bioreactor to grow MSC. 3D MSC intensification has been performed on hydroxyapatite, chitosan gelatin and HA/chitosan gelatin and gelatin microcarriers (Braccini *et al.* 2007). A bioreactor is a gadget that advances the improvement of natural or potentially biochemical cycles through working boundaries like pH, temperature, supplement supply and waste expulsion. The bioreactor framework is an essential device to accomplish objectives in clinical scale extension and tissue designing applications (Hoch and Leach 2014). They keep up the base standards for characterizing MSCs, including plastic attachment, the declaration of a bunch of explicit surface markers, and the capacity to separate along the osteogenic, adipogenic, and ligament heredities (Dominici *et al.* 2006). MSC additionally has a wide scope

of regenerative and wholesome exercises, including the emission of an extracellular network (ECM), mitogenic and angiogenic factors, calming and immunomodulatory factors and other organically dynamic particles that animate tissue recovery by reconstructing the recovery advancing microenvironment. What's more, by controlling the invulnerable and provocative reaction? Consequently, these special attributes assume a critical part in the accomplishment of MSC-based remedial applications (Bianco *et al.* 2013; Sart *et al.* 2016).

MSC has the capability of multi-line separation. This property has been examined to create MSC transplantation as a regenerative treatment. The multi-genealogy potential is the rule for characterizing MSC *in vitro*. Multi-ancestry potential can be seen under culture conditions that initiate cell separation into three ancestries: osteogenic, adipogenic and ligament (Shi 2012). Numerous *in vitro* tests can be utilized to evaluate the pluripotency of these cell arrangements. Dexamethasone, 2-phosphate ascorbic corrosive and *β*-glycerophosphate can prompt osteogenic separation of MSCs. Osteoblasts can be distinguished utilizing Alizarin Red S staining. The medium containing dexamethasone, indomethacin, isobutyl methyl xanthine and insulin can initiate adipogenic separation. The accumulation of lipids inside the cell is determined through Oil red O staining (ORO). Chondrogenesis can be separated by dexamethasone, ascorbyl 2-phosphate, insulin, Selenite, transferrin, sodium pyruvate and changing development factor-*β* (Bobis *et al.* 2006). The capacity of MSCs to separate along these ancestries is firmly identified with their pluripotency and immature microorganism properties. Although, MSCs can't keep up with these attributes inconclusively and MSCs will age after an enormous number of subcultures *in vitro*, subsequently losing their expansion and separation potential (Solchaga *et al.* 2011). This social extension may likewise deliver hereditary and epigenetic flimsiness, including chromosomal changes. The collection of hereditary changes during cell culture and the danger of resulting cell change are other significant parts of undifferentiated organism treatment (Kim *et al.* 2015a).

Molecular characteristics of MSCs

The MSC usage for cell therapy requires huge scope of *in vitro* development, which builds the chance of cytogenetic and molecular stability (Kim *et al.* 2015b). The development of MSCs in culture can produce chromosomal irregularities, like aneuploidy (an unusual chromosome in the cell) or primary chromosomal changes, reflecting chromosomal insecurity. Be that as it may, the number of sections that can be performed isn't clear before these cells obtain chromosomal precariousness or lose pluripotency (Zhang *et al.* 2007; Nikitina *et al.* 2011). A few examinations have shown that the in vitro culture of MSC from bone marrow and fat tissue holds the typical karyotype between entries 1 and 5 (Bochkov *et al.* 2007). In ensuing subcultures, MSCs started to show chromosomal anomalies, like aneuploidy. Nonetheless, different investigations have discovered that MSC societies obtained from bone marrow and fat tissue have an ordinary karyotype before entry 20 (Bernardo *et al.* 2007; Izadpanah *et al.* 2008). Although these outcomes deserve conversation, they demonstrate that cytogenetic investigation should be performed to guarantee security before treatment with mesenchymal stromal cells. The sub-atomic examination likewise assumes a significant part in deciding appropriate MSCs for cell treatment. In cell senescence interaction, all crude human cells (counting MSC) go through just a set number of cell divisions under standard culture conditions. Maturing is viewed as a pressure reaction brought about by the actuation of systems like telomere disintegration and aggregation of DNA damage (Collado *et al.* 2007; Estrada *et al.* 2013). *In vitro*, culture brought about critical telomere shortening. Telomeres are the closures of eukaryotic chromosomes and their primary capacity is to shield chromosomes from unlawful combination and recombination, along these lines keeping up genome honesty (Zimmermann *et al.* 2003). Since MSC has the capacity of self-reestablishment like most physical cells, the recognition of telomere length in the MSC can give key data about cell replication capacity, which is a significant measure for cell determination. MSC is utilized for treatment. Telomere length is typically evaluated by Southern smudging, and fluorescent pluripotent undifferentiated cells 500% in situ hybridization from the lab seat to the center, and as of late, performed by a polymerase chain response-based technique (Samsonraj *et al.* 2013). The pluripotency of MSC has prompted significant advances in our comprehension of the separation pathways of different genealogies for tissue designing and helpful purposes (Rastegar *et al.* 2010). Deficiency-related record factor 2 (Runx2) is viewed as the principle administrative quality liable for early osteogenic separation (Fujita *et al.* 2004). Although Runx2 assumes a part in advancing osteoblast separation, another significant osteoinductive specialist, osterix, restrains ligament arrangement and advances osteoblast separation at a later stage. A low degree of osterix is adequate to hinder ligament development, while an undeniable degree of articulation is fundamental for osteogenic separation (Tominaga *et al.* 2009). What's more, separated MSCs have effectively separated into osteoblasts in osteogenic media enhanced with dexamethasone and ascorbic corrosive. The specific capacity to advance osteogenic separation has expected clinical importance in bone fix and recovery (Griffin *et al.* 2011). Through openness to development factors, co-culture with ligament and overexpression of explicit qualities (like SRYbox9 (Sox9)) to advance chondrocyte separation, the separation of MSCs into chondrogenic ancestries *in vitro* was considered. Sox9 and its downstream proteins Sox5 and Sox6 act synergistically to advance the multiplication and development of chondrocytes and grid arrangement (Akiyama 2008). MSC likewise can separate into the lipid

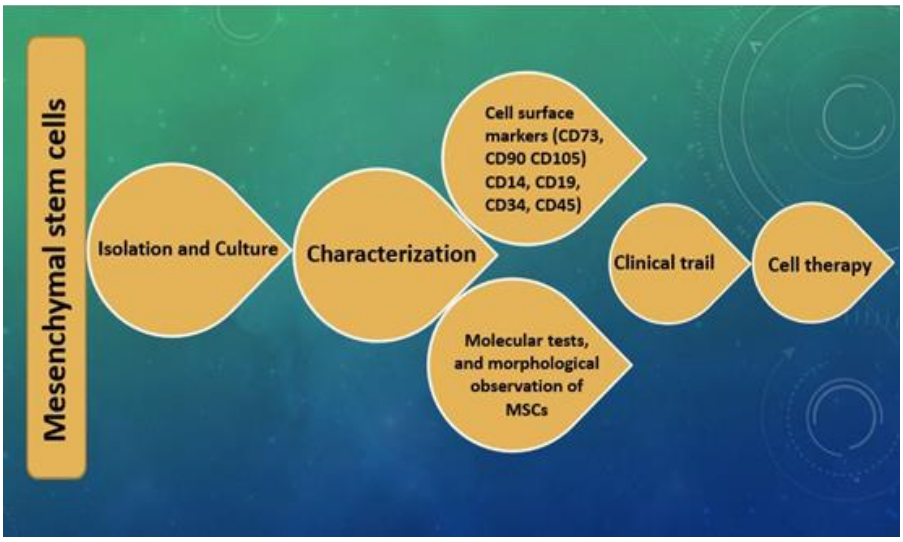

Fig. 1: Some traits and evaluations that might be used as a quality check for the application of MSCs in cell therapy

genealogy. PPAR-γ assumes an essential part in this interaction by directing the elements of numerous adipocyte-explicit qualities. Also, PPARγ collaborates with individuals from the CCAAT/enhancer-restricting protein (C/EBP) family to control adipogenesis. Adipogenesis can likewise be prompted by openness to exogenous variables or by refining the cells in an adipogenic medium containing insulin and dexamethasone (Farmer 2005). As per the International Society for Cell Therapy (Horwitz *et al.* 2005), since the multi-heredity potential is one of the three measures for characterizing MSC *in vitro*, atomic tests are utilized to dissect the declaration of qualities identified with osteogenic, chondrogenesis, and separation. Adipogenesis is vital for connecting the natural capacity of MSC with its clinical application. The *in vitro* extension of MSCs is identified with hereditary unsteadiness. Along these lines, atomic examinations that analyze sub-atomic profiles during society are critical to acquire information about sub-atomic adjustments and the possible dangers of cell treatment. In this sense, proteomics and transcriptomics strategies have been utilized to confirm the atomic alteration of MSCs from various societies. Prior to utilizing BM-MSC in clinical applications, we should be cautious. A few changes might be Analysis like expanded morphology, diminished number of cell divisions, arbitrary loss of genomic locales and abbreviated telomeres. These alteration cycles may prompt a lessening in the pluripotency of MSCs and may prompt the development of tumors under specific conditions. It is vital to describe the cytogenetic and sub-atomic qualities of BM-MSCs during *in vitro* extension. Hence, suitable tests ought to be performed to guarantee the uprightness of the genome and epigenome (Redaelli *et al.* 2012).

Quality control of cell therapy

Numerous challenges exist in characterizing and measuring cells for cell and tissue-based medicines. From an administrative point of view, these high-level medicines should not exclusively be protected and viable yet should likewise be fabricated through excellent assembling measures (Rayment and Williams 2010). Drawn-out openness to unpleasant conditions during cell enhancement and separation has raised worries about the security of undifferentiated organism treatment. The international society for stem cell research has defined the "Rules for Clinical Translation of Stem Cells" (Lovell-Badge *et al.* 2021). To guarantee the well-being of foundational microorganisms, some cytogenetic tests can be performed, including G-banding, fluorescence in situ hybridization and exhibit comparative genomic hybridization (Kim *et al.* 2015a, b). Sub-atomic hereditary testing can proceed as an investigation of quality articulation identified with telomere length, osteogenic, adipogenic, and chondrogenic separation. Fig. 1 shows a few attributes and tests that can be viewed as quality control of cell treatment utilizing MSC. The pragmatic use of these prescribed tests can be normalized to accomplish affectability and explicitness between labs. In 1995, the main clinical preliminary utilizing refined and extended MSCs was done and bone marrow tests were obtained from the unblemished pluripotent undeveloped cells of 23 patients with hematological malignancies- from the test seat to the clinical 502 reductions. In this examination, since no unfavorable impacts of MSC infusion were noticed, Lazarus and associates presumed that MSCs obtained from malignancy patients can be gathered, extended *in vitro* and intravenously imbued without harmfulness (Lazarus *et al.* 1995). Many finished clinical preliminaries have shown the adequacy of MSC mixture for illnesses including intense myocardial ischemia, liver cirrhosis, amyotrophic horizontal sclerosis and unite versus-have infection (Otto and Wright 2011).

Conclusion

Mesenchymal stem cells use as universal "off the self" and promising therapeutic tools for regenerative cell therapy and immunomodulation. Consequently, MSCs should be extended widely *in vitro* without influencing the genomic characteristics and separation attributes of the cells. However, the culture's expansion may sometimes produce cytogenetic and molecular changes. These changes during several sections may cause malignant cell transformation. Accordingly, it is imperative to utilize various techniques for quality control to test the security and adequacy of MSC for cell therapy. Many investigations have shown that MSCs are progressively broadly utilized in treating cardiovascular disorders, neurodegenerative illnesses, bone imperfections and breaks, fiery joint inflammation and hematopoietic undifferentiated cell transplantation. Bone marrow-MSC has possible clinical applications in hematopoietic stem cell transplantation. As an assistant cell treatment, it can advance the quick recreation of hematopoietic function after hematopoietic stem cell transplantation, prevent treatment transplant failure, and graft anti-tumor effect. Although these investigations have shown positive outcomes, it is important to proceed with logical exploration to explain some significant focuses: the characteristics of proper cell passage during MSCs culture to ensure genomic stability. It is important to decide the ideal cell portion and the quantity of MSC imbuements during the treatment time; long-term follow-up to portray the positive clinical impacts and contrary clinical impacts that the utilization of MSC might deliver. Nevertheless, further investigation is required to clarify fundamental questions about the mechanism of handling immune response by mesenchymal stem cells.

Author Contributions

All authors contributed equally.

Conflict of Interest

No conflict of interest.

Data Availability

All of the data is available within this review article.

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