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REVIEW ARTICLE **OPEN ACCESS**

"A Regenerative Approach of Stem Cell Therapy for Arthritis Pain Management"- A Review

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ABSTRACT
Stem cells have the capacity to regenerate and give rise to a variety of cell types. Painkillers and steroid injections have their limitations. When the effects of the drug wear off, pain typically returns. That is so because they do nothing to address the underlying issue that is contributing to arthritis pain. Up until recently, the only options were to numb the pain with medicine or to take symptomatic relief. Modern medical science offers better options. These novel therapy approaches treat your ailment with your own blood cells. TGF-1, VEGF, IL-6, and MCP-1 are only a few of the cytokines and factors that are abundant in cell therapy and are crucial for tissue remodeling and repair. In-depth preclinical and clinical research has been conducted to examine the therapeutic potential of cells in the treatment of arthritis. The proliferation, differentiation, and activity of T cells can be controlled by stem cells, and the amount of pro-inflammatory cytokines produced can be decreased. MSCs have been shown through experimental animal models and human clinical studies to have positive therapeutic benefits in reducing pannus development and reducing inflammation, bone erosion, and joint deterioration.
Keywords: *Cell therapy, Stem cells, Cytokines, Mesenchymal cells, Growth factors and Immunosuppression.*

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INTRODUCTION

Arthritis is indeed an umbrella term for diseases that trigger joint ache and inflammation, in addition it is described by painful inflammation along with joint stiffness [1]. Arthritis is a disease of the tendons (areas where our bones meet and move). Arthritis is usually characterized by joint inflammation or degenerative changes of bones (breakdown). Whenever we move the joint, these modifications may lead to pain. Arthritis is most mainly encountered in the feet, knees, hands, hips, and lower back.

Parts of a joint

Soft tissues such as articular cartilage cushion and support our joints, restricting our bones from rubbing around each other. This connective tissue also allows our joints to move flexibly and without pain. Some joints have a membrane called synovial, which is a padded chamber of fluid that greases the joints. Many joints, including our knees, are supported by ligaments along with tendons. Tendons link muscles to bones, whereas ligaments link bones to one another [2].

Types of Arthritis

The common types of arthritis include the following.

Ankylosing spondylitis is an arthritic disorder that causes inflammation of the joints and ligaments in the spinal column.

Gout is a type of arthritis that is distinguished by flares that typically occur in the big toe or a lower limb.

The most familiar example of chronic arthritis in children is juvenile idiopathic arthritis.

The most seen form of arthritis is Osteoarthritis (OA), which is more common among elderly people.

People with psoriasis may develop psoriatic arthritis. It damages the skin, ligaments, and tissues that adhere to the bone.

An infection in our bodies triggers reactive arthritis. Symptoms usually go away on their own after a few weeks or months.

Rheumatoid arthritis, abbreviated as RA, is an inflammatory disease in which the immune system attacks healthy joint tissue [3].

RHEUMATOID ARTHRITIS (RA)

RA is a long-term systemic condition which can cause impairment to joints, fibrous tissue, connective tissues, muscles, and tendons, thereby having a significant effect on society. The global prevalence of RA is approximately 5 per 1000 persons. With a mean age of 55, women are approximately two to three times more probable than males to be identified as having the condition. Pre-RA is characterized by a high number of circulating self-antibodies, higher levels of pathogenic both chemokines and cytokines, and aberrant cell metabolism. The proceeded stage of the illness is distinguished via intense and incapacitating severe pain which impairs the sufferer's standard of lifestyle. Insufficient managing disease triggers the progression of the disease, which eventually directs to bone destruction, devastation, and abnormalities. Initially, over 50 percent of patients with RA were handicapped, unable to work full-time, and faced a higher risk of death. However, advances in disease biology and exceptional success in RA treatment have resulted in the creation of more efficient treatment techniques that have improved disease action control, the level of discomfort, and bone destruction. Currently used drugs for RA treatment involve glucocorticoids (GCs) and Disease-modifying antirheumatic drugs. Along with these, NSAIDs also known as nonsteroidal anti-inflammatory drugs are the commonly used treatments for pain relievers. Because of their powerful anti-inflammatory properties, GCs are utilized in conjunction with NSAIDs or DMARDs. DMARDs, among the conventional treatments mentioned above, have shown a great promise to improve symptoms and prevent progression of disease in people suffered from RA; nevertheless, they are expensive and have substantial side effects. Furthermore, despite substantial pain relief documented in several randomized controlled studies, several patients continue to practice clinically significant stages of residual pain in spite of treatment and remain prejudiced or resistant to these medications [4].

OSTEOARTHRITIS (OA)

Established on the Globally Burden Disease Study 2017, it is long-lasting and most common chronic types of arthritis, disabling, and widespread joint illness, accounting for 23% of all musculoskeletal diseases. In summary, OA is triggered by the demise of cartilage in the articular region throughout the synovial joints and is more common in the elderly. Patients with OA have many years surviving with a disability, which renders it to be among the most prevalent causes of impairment. Patients having progressed forms of OA experience chronic pain and diminished limb function, resulting in a low standard of life. OA also imposes a significant clinical and financial impact [5]. Age, gender, and genetic susceptibility are all significant underlying contributors to OA. By 2030, OA is assumed to be the leading grounds of impairment in the people, with approximately 35 percent of people possibly suffering from it [6]. Low-grade chronic inflammation adds to signs and disease development. In OA, networks of various inherent proinflammatory risk signals, such as chemokines, cytokines, and alarmins, are triggered. Aside from inflammatory agents, biomechanical damage and oxidative stress also impair chondrocyte survival, resulting in morphological distinction and pro-catabolic reactions with the additional extracellular matrix (ECM), disintegration. A complete knowledge of inflammatory pathogenesis should aid in the identification of distinct OA subtypes in the number of people and result in the creation of novel options for treatment. There are minimal therapy choices for OA patients, and the majority of them focus on pain alleviation with inflammation control to enhance its intended purpose. Over many years, NSAIDs and corticosteroid injections have been widely used, but current therapeutic options have proven to have no effect on the gradual deterioration of ligament tissues [7]. These treatments, however, are unable to revive articular cartilage formation or alter degenerative processes. Patients having severe OA whose, situation is uncontrolled by conventional therapy benefit most from surgical arthroplasty. Surgical arthroplasty enhances the quality of life and ends up with long-term functional improvement. Meanwhile, uncertainty and illness are the most frequent drawbacks, needing additional joint adjustment surgery, especially in patients who are overweight. In recent decades, research and regenerative therapies for OA have advanced quickly with stem cell therapy. Chondrocytes can be formed from both induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs). Though, the tumorigenicity, inefficiency, and genomic inclusion of transgenic sequences of iPSCs/ESCs have raised significant interests. In contrast, mesenchymal stem cells (MSCs) are likely obtained using multiple adult tissues, like bone marrow and adipose tissues, offering a plentiful supply for regenerative therapy. MSCs might regulate immune responses via immunosuppressive and anti-inflammatory qualities by means of their paracrine activities, which is in supplement to their competence to develop into chondrocytes. Even so, MSC therapy demands many cells and has a dose-dependent impact. Recent research has revealed that extracellular vesicles are the mechanism by which MSCs' paracrine actions are mediated. Exosomes are a form of EV that ranges in size from 30-100 nm which are secreted by cells in every living system. Exosomes are composed of lipids, microRNA (miRNA), proteins, and RNA that are found in body fluids like cerebrospinal fluid and blood. Exosomes have been discovered to communicate with one another under diverse physiological and pathological situations [8].

REGENERATIVE MEDICINE

In 2008, the term “regenerative medicine” was elaborated as “the method of substituting, engineering, or recreating human/animal tissues, organs, or cells in order to re-establish or maintain conventional function”. “According to the Mayo Clinic Center for Regenerative Medicine, regenerative medicine is “... aimed on developing and employing novel treatments to repair tissues and organs and rebuild purpose failed due to ageing, illness, impairment, or faults”. We distinguish recreating medicine as a broad branch of medication from RMs as a distinct spectrum of assembled pharmaceutical goods. These items comprise in-vivo gene treatments (GTs) along with cell-based products (CBPs). Any produced pharmaceutical product that is made up of markedly changed live living animal cells or human tissues, independently or in conjunction with further non-cellular compounds, ingredients, parts, or strategies, which include gene-modified (GM) is termed as CBPs [9]. Regenerative medicine, also known as tissue regeneration, is a strategy for restoring or replacing damaged tissues that help with the operation, reconstruction, and intrinsic recovery. The advancement of regenerative medicine is currently hampered. For example, introducing stem cells through the proficiency to transform and restore has been regarded as promising for treating injured tissues and organs. MSCs with multiple lineages of differentiation might be employed for knee cartilage repair, although invasive implantation requires a high number of cells due to low targeting efficacy. External stimulation is another regenerative medicine approach for controlling cell renewal and regrowth of tissue in vivo [10].

CELL THERAPY

Cell therapy replaces or repairs damaged organs or tissues by using stem cell (SC) derivatives, progenitor, and stem. To induce self-repair, the cells might be administered intravenously, surgically implanted within the damaged location, or gathered from the patient's self-tissues. Because of their built-in self-renewal as well as differentiation capacity, SCs are the most promising cellular source for these types of therapies [11]. Tissue-specific resident SCs might move to injury locations, develop, and restore injured cells, as well as release trophic factors essential for tissue reconstruction. However, in serious disease processes that require extrinsic cell therapy intervention, this self-repair strategy is insufficient. Cell treatments may employ two key modes of action. One is established on engraftment into damaged tissue to replace harmed cells or tissue. Another example is the activation of endogenous tissue self-treatment mechanisms via trophic impacts that result from cytokine along with growth factor (GF) release. Cell rehabilitation processes are intervened by therapeutic cell relocation and systemic administration of genomic as well as molecular medicines via genetically engineered cells.

THERAPEUTIC CELL TYPES

Embryonic stem cells (ESCs), which originate inside the cell mass of a developing embryo, can divide continuously, and can form any type of cell found in the three germ layers [12]. ESCs are competent in both revival and the ability to distinguish into almost any type of cell [13]. To successfully employ ESCs in cell treatments, current challenges must be overcome, such as devising dependable and reproducible techniques for transforming these cells into their intended derivatives. To ensure safety, teratoma generation, and immunological rejection after transplantation must be avoided, along with ethical norms [14].

Mesenchymal stem cells (MSCs), are recovered from placenta, adipose tissue, peripheral blood (PB), bone marrow (BM), and umbilical cord (UC), having the aptitude of stem cells to segregate into specific types of cell accompanying with numerous cell lineages [15,16]. MSCs obscure a wide range of cytokines, growth factors, anti-inflammatory, angiogenic substances, and chemokines, and have immunomodulatory characteristics [17]. Additionally, MSCs can stimulate the development of endogenous stem cells, allowing them to participate for tissue healing [18]. MSCs are being extensively studied in preclinical along with clinical research, yielding promising results for the treatment of Crohn's syndrome (CD), neurological disorders such as spinal cord injury (SCI), graft versus host disease (GvHD), cardiovascular disorders, complications of diabetes, stroke, cartilage as well as bone injury. Though, an array of clinical studies in the last stages have not succeed in fulfilling initial outcomes, and the circumstances of MSCs after systemic insertion remains uncertain [19]. Hematopoietic stem cells (HSCs) cultured from umbilical cord, bone marrow, and peripheral blood [20]. After transplantation, HSCs travel to the bone marrow where they regenerate themselves and rebuild the system of hematopoietic cells [21]. HSCs have been long recognized as the first-ever SCs to be identified and remain the only type of SC-based therapy endorsed to treat certain blood disorders. In addition, they have demonstrated potential in healing autoimmune disorders and are often used in conjunction with organ transplantation [22].

Mononuclear cells (MNCs) are monocytes, macrophages, hematopoietic progenitors, and lymphatic cells (lymphocytes, plasmatic cells) isolated from BM or PB. MNCs are studied intensively in clinical studies representing the therapy of severe limb ischemia, cardiovascular illness, and neurological conditions [20].

Endothelial progenitor cells (EPCs), recovered through the UC, BM, and PB, and account for around 1% of the overall regional MNC people. They distinguish themselves their manifestation of each of the HSC markers (e.g., CD133 and CD34) as well as the endothelium-specific marker VEGFR2 [23]. At the moment, not only one cell interface marker has ever been found as being specific to all new SC markers, and EPCs are constantly explored [24]. EPCs have a significant function in neovascularization, which represents an intended therapeutic effect for ischemic disorders.

Neural stem cells (NSCs) or neural progenitor cells (NPCs) are types of multipotent cells produced by mature and embryonic nervous system tissues [25]. NSCs are found within the subventricular region (SVZ) of the lateral ventricle and the sub granular region of the hippocampus dentate gyrus in adults. NSCs can also be separated from the spinal cord and the olfactory epithelium. Because of their capability to distinguish specific functioning neurons and glia, NSCs constitute an appealing option for therapies for neurological illnesses [26]. Using primary cells that are specialized to certain tissues, such as keratinocytes, chondrocytes, and myocytes, for cell therapy is constrained due to several technical difficulties. This is because the proliferation capacity, quality and efficacy of these cells are often unstable and restricted [27].

MSCS AS NOVEL THERAPEUTIC AGENTS IN ARTHRITIS TREATMENT

In the last 10 years, MSC have acquired a lot of consideration in the scientific community. ASCs can be obtained in modest volumes through bone marrow, fat, and other tissues. Because of their competence to regenerate and inhibit the system that regulates immunity, MSCs have become a popular research topic. In vitro studies have revealed that MSC effectively suppresses the immune system through both paracrine action as well as cell contact. MSC suppresses cells such as B cells, dendritic cells, Th1 cells, and NK cells while activating regulatory T cells. MSC are extremely desirable patron cells because they stand rarely acknowledged by the immune response. This is because of their absence of MHC class II expression and only modest MHC class I expression. It is a normal phenomenon that there are single MSC floating in human joint synovial fluid (SF). Mesenchymal progenitor cells in SF are less abundant in RA than in OA. The recruitment of MSC to the joint by synovial fluid in RA may be hindered. Moreover, the development of the MSC in patients with RA may be concealed by the severity of synovitis or depleted as claimed via the noticed telomere size decrease regardless of previous therapies. The clinical activity of the autoimmune sickness had no effect on MSC's anti-proliferative function on PBMCs in-vitro [28].

MSC THERAPIES FOR THE MANAGEMENT OF OA [29]

Bone marrow-derived mesenchymal stem/stromal cells

The bone marrow stroma contains BMSCs, a symmetrical cell with similar characteristics to fibroblasts. Before the appearance of MSCs obtained using other tissues like amniotic fluid, umbilical cord as well as adipose tissue, MSCs were sourced from iliac crest bone marrow extract. BMSCs have remained standard as well as the most studied type of cell since they are regarded to have better efficacy over chondrogenic growth. Yet, only a few studies were concluded and published their findings.

Adipose-derived stem cells (ASCs)

ASCs, derived through adipose tissue, are a type of stem cell first identified as MSCs in 2001. Since then, their promise for therapeutic use in regenerative medicine, as well as tissue engineering has been extensively studied. Variations in their differentiation capability and cell apparent markers are what separate ASCs from BMSCs. BMSCs exhibit CD106 (a marker that contributes to MSC-mediated suppression of immune systems and the attachment of erythrocyte progenitor cells), whereas ASCs do not, and ASCs exhibit CD49d (a 4 an integrin included in assisting leukocyte mobility), whereas BMSCs do not. In contrast to BMSCs, ASCs might be acquired in large quantities through adipose tissues, which are plentiful throughout the body. A bone-marrow aspirate is composed of 0.001-0.004% BMSCs, whereas a lipoaspirate contains 2% ASCs. ASC isolation can be accomplished using suction lipectomy aspirates or dermatological adipose tissue sections, making it less hostile than BMSC extraction [29].

BASIC BENEFITS ASSOCIATED WITH MSCS OVER VARIOUS FORMS OF STEM CELLS TO ACQUIRE THERAPEUTIC APPLICATIONS

MSCs are preferred over different kinds of stem cells for therapeutic goals due to their comparative abundance, simplicity in isolation, multilineage variations potential, lower probability of cancerous renovation, immunomodulatory characteristics, and absence of ethical concerns.

Abundance and simplicity in isolation: Earlier research has revealed that MSCs initiate in the perivascular position, allowing them to be isolated through various types of tissues through the body, including adipose tissue, the placenta, bone marrow, peripheral blood, and the umbilical cord [30,31]. As these two sources are relatively abundant in the human body, dermatological adipose tissues and bone marrow remain the preferred foundations of acquiring MSCs [32].

Multilineage variations potential: MSCs have the capability to become various cell lineages, such as chondrocytes, adipocytes, and osteocytes, as well as cardiomyocytes, insulin producing cells and

oligodendrocytes making them a promising treatment option for degenerative diseases such as bone diseases, cardiovascular diseases and diabetes mellitus [33,34,35].

Lower probability of cancerous transformation: After displaying a restricted proliferative ability in culture, MSCs arrive at a condition of senescence, referred to as the 'Hayflick limit', thus prohibiting them from division [36]. Senescence is a reaction to stress, causing the arrest of cellular replication, thereby hindering the transmission of damaged cells, and lessening the chance of cancerous transformation [37].

Immunomodulatory characteristics: MSCs have the added benefit of having immunomodulatory qualities, allowing them to be employed as universal donor cells without the usage of immunosuppressive drugs. These characteristics include the release of anti-inflammatory cytokines that decrease adaptive and innate immune responses [38,39]. The reason for this is because MSCs have different surface markers that make them undetectable by the immune system. These markers include the absence of foremost histocompatibility composite class II expression, as well as the lack of the co-stimulatory cluster of differentiation (CD) fragments such as CD40, CD86, CD40 ligand, and CD80 [40]. Allogeneic MSCs are recommended to be potential treatment alternatives for patients who cannot satisfy the donor stem cell therapy criteria.

Absence of ethical concerns: In contrast to ESCs, MSCs can be obtained from a range of tissues within the body, meaning that the principled issues linked to ESCs are not applicable to MSCs. Even though ESCs have been the focus of much attention due to their pluripotency, their use for medical purposes has been debated due to potential safety risks of teratoma development, and ethical issues relating to their source [41,42].

HUMAN TISSUES ENCOMPASSING MSCS AND THE NUMEROUS POTENTIALS OF THESE CELLS

The ISCT MSC committee advises against referring to mesenchymal cells as "stem" cells until there is strong evidence, both here in the laboratory and in addition to the field, of their self-regenerating and differentiated abilities [43]. As earlier established that MSCs can be extracted from numerous parts of the human organs, and that the stem cell-like properties of those obtained from the adipose tissue, umbilical cord blood, bone marrow (BM), periosteum, dental pulp, and growth plate have been confirmed (Figure 1) [44,45,46]. In the treatment of arthritis, MSCs are often taken from four locations: adipose tissue, synovial membrane, bone marrow, and umbilical cord [47]. To identify an appropriate MSC source for treatment, one must consider both the positive and negative aspects of MSC procurement, such as the possible side effects, the quality and amount of cells, and the complexity and invasiveness of the isolation procedure [48]. Fridenshtein et al. initially sourced their material from bone marrow [49].

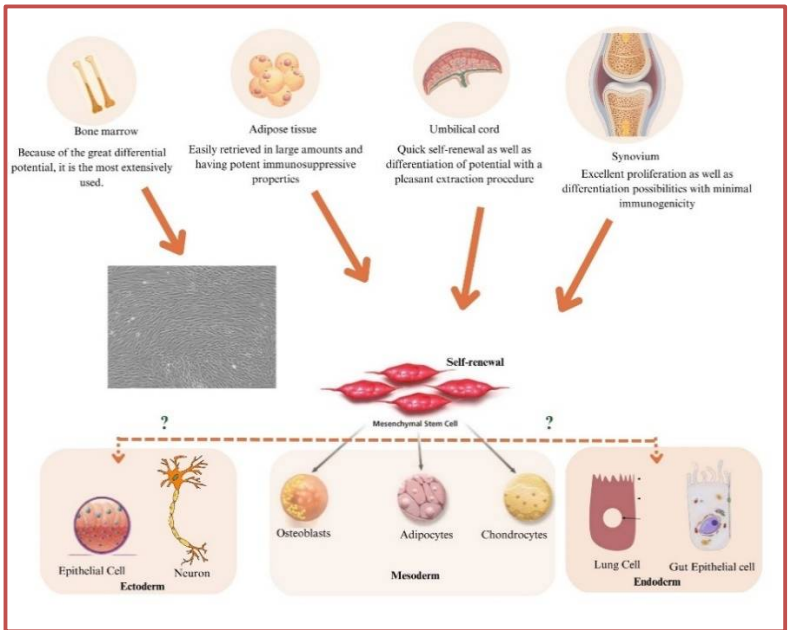

Figure 1: Isolations of MSCs from adipose tissue, umbilical cord, bone marrow, and synovium is possible, and the cells can be distinguished into osteoblasts adipocytes, myocytes, and chondrocytes [44,45,46]

In 1990s, the process of separating and expanding individual bone marrow sourced MSCs (BMMSCs) in laboratory background was initially established, following numerous animal studies [50]. With repeated clinical trials attesting to its safety and effectiveness, BM-MSCs have developed the extremely depleted source of MSCs due to their incredible differentiation capacity [51]. Major drawbacks of BM-MSCs is the

varying yields, differentiation, and repair capability of the cellular material, which depend on the characteristics of the donor, like their health specification and stage [48]. Harvesting BM-MSC is a confronting and ineffective endeavor, with only 0.001–0.01% of bone marrow cells being MSCs. The possibility of infection during the process of isolating cells from the bone marrow must be considered. Therefore, a more productive and less intrusive approach is necessary, and researchers have strived to pinpoint new sources of extraction [51]. The concepts related to umbilicus blood (UCB) were approved as a supplementary source of MSCs in 2000. UCB-MSCs, harvested via a non-invasive method, possess a high rate of regeneration, and can be transformed into other cell types. Such characteristics accomplish these cells an ideal choice for tissue regeneration and immune system regulation. UCBMSCs have a significantly increased rate of proliferation, three to four times higher than AT-MSCs. It is believed that UCB-MSCs to generate numerous growth factors, e.g., collagen type 1, EGF, HGF, and GDF-11, which could help with skin rejuvenation. It has been reported that UCB-MSCs can reduce wrinkles and boost dermal density. Scientists have claimed that UCB-MSCs have greater clinical potential than BM-MSCs due to the benefits they provide. In contrast, UCBMSCs have been found to have undesirable features such as accelerated morphological alterations and hastened loss of proliferation potential, in addition to lower adhesion competence. In 2001, Human AT-MSCs emerged as a powerful reservoir of MSCs due to their vast availability and their capability to suppress the immune system. Compared to BM-MSCs, AT-MSCs have the potential to be procured in a enormous amount (further 500 times) with straightforward techniques and minor anesthesia. One plus side of AT-MSCs, they can be taken from many areas of the human body; nevertheless, AT-MSCs derived from distinct places have demonstrated diverse properties. Nepali along with his colleagues ascertained that detour AT-MSCs demonstrate extreme expressions of CD90, CD146, CD73, and CD105, but poorer expressions of CD45, CD31, and HLA-DR, in comparison to AT-MSCs sourced from abdominal. Kim and his teams observed an increase in HLA-ABC along with HLA-DR expression in AT-MSCs after IFNγ, thereby creating uncertainty of the feasibility of allogeneic AT-MSCs. To better comprehend the defining phenotypes of AT-MSCs and maximize their clinical efficiency, further research is necessary to examine patron-matched AT-MSCs from distinct isolation sites. Mesenchymal Stem Cells can also be acquired from the synovial membrane, aside from the more traditional tissue sources. In 2001, De Bari et al. pioneered the isolation of Synovial membrane-derived MSCs (SM-MSCs). Comparable to AT-MSCs, SM-MSCs that feature site-specific traits can be acquired from a variety of areas, such as the paralabral synovium and cotyloid fossa. Compared to other types of MSCs, SM-MSCs display remarkable proliferative capability, the capability to differentiate into varieties of lineages, and reduced immunogenicity. The prominent expression of collagenase type II, aggrecan, and SRY-box transcription factor 9 in SM-MSCs has resulted in greater chondrogenic potential, making them preferable to repair cartilage and joint homeostasis therapies. Sakaguchi et al., revealed that SM-MSCs and BM-MSCs demonstrated more adipogenic and osteogenic capabilities than other MSCs, although SM-MSCs were observed to have lesser cell expansion in vitro linked to BM-MSCs [52].

STRATEGIES FOR ENHANCING MSC THERAPEUTIC EFFECTS

Due to the existing evidence of medicinal consequences of MSCs, researchers and clinicians exhibit striving to create new approaches to improve the capability of MSCs in arthritis therapy [53]. To increase efficiency of MSCs in treating RA, different approaches have been suggested to improve their immunomodulatory and anti-inflammatory action [54]. Coculture techniques, growth promoters and cytokines, receptor agonists, low oxygen levels, and autophagy can all be used to modify culture methods like “3D culturing”. The genomic alteration of MSCs is a completely different method [55]. Genes involved in cell existence, immunomodulation, and redevelopment is influenced by hereditarily modified structures that include viral vectors as well as plasmids [56]. Lim and colleagues' proposed technique of combining MSCs with IL-10-fabricating Tregs proved more efficient in regulating seditious processes in bones and inhibiting the formation of critical arthritis in mice than in uncombined cell treatment [57]. An alternative intriguing technique for improving MSC therapeutic efficacy is to culture the cells into three-dimensional spheroids. Since MSC preliminary acclimatizing in the sort of 3D culturing is yet to be investigated in a RA model, results from multiple studies aid the use of this strategy. Compared to adherent monolayer culture, 3D spheroid culture better replicates a natural physiological environment due to its strong cell-cell & cell-matrix interlinkage. Several investigations have found that cultured MSCs in a 3D microenvironment drastically enhanced their both immunomodulatory as well as anti-inflammatory action, owing to upregulated TSG-6 and COX-2 expression by MSC spheroids [58,59]. It has been demonstrated that MSC spheroids as well as MSCs derived from spheroids can inhibit TNF-α fabrication by LPS-activated peritoneal macrophages in-vitro, as well as inflammatory responses in an in-vivo mouse model of “zymosan-induced peritonitis”. Furthermore, the cultured 3D spheroid of MSCs produces elevated levels of IL-6, PGE2, TGF-1, and IDO than conventional two-dimensional monolayer culture, verifying the stimulation of MSC

immunomodulatory abilities in a 3D environment [60]. Autophagy and hypoxia are two other promising ways for increasing MSC immunomodulatory effects in RA therapy. Recent findings support the use of autophagy and hypoxia conditions for future MSC-based RA treatment. According to certain research, autophagy plays a significant function in shielding MSCs from ROS generated by oxidative stress or irradiation [61]. Starvation and the mTOR inhibitor rapamycin can trigger autophagy in MSCs. Hypoxia improves MSC immunomodulatory actions by boosting the production of immunoregulatory substances such PGE2 and IDO [62,63]. Human MSCs, when primed through hypoxia or IFN- γ, exhibited an immunosuppressive effect on CD4+ & CD8+ T cell proliferation. IFN- γ and hypoxia had a synergistic effect on T cell proliferation, resulting in a substantial decrease and enhanced production of IDO and HLA-G. It was revealed that the immune-modulating effect of MSCs might be amplified with the combination of cytokines that induce inflammation and lack of oxygen, as opposed to utilizing a single priming variable, which had a lesser impact [64]. Priming MSCs with pro-inflammatory cytokines is an attractive approach as it can improve their immunomodulatory and immunosuppressive capabilities [65]. MSCs are activated upon exposure to high levels of cytokines that trigger inflammation and exhibit strong properties that suppress immunity by producing an elevated amount of anti-inflammatory chemicals for example., NO, IDO, HGF, PGE2, TGF-β, and heme oxygenase. Considering that fact, MSC immunosuppressive characteristics are enhanced by preconditioning cells with high doses of proinflammatory cytokines. For example, MSCs preconditioned with IFN-γ and/or IL-1β have been proven to be more effective than untreated MSCs in suppressing CD8+ T cell degranulation, NK cell T cell proliferation, and macrophage activation, and the production of cytokines that trigger inflammation (TNF-α, IL-2, and IFN-γ) by activated T cells [66,67]. In contrast, IFN-γ treatment of MSCs increased the quantity of Tregs and the release of immunoregulatory and anti-inflammatory cytokines [68]. Sivanathan et al. demonstrated that preconditioning human MSCs with IL-17A was as valuable as IFN- therapy in reducing T cell activation and proliferation, as well as Th1 cytokine production (IL-2, TNF-α, and IFN-γ). Treating MSCs with IL-17A notably strengthened their capacity to generate provoked Tregs [69]. TNF-, IL-1/IL-1 preconditioning of MSCs has been shown in studies to increase their immunomodulatory capabilities. Combining preconditioning with IFN- and proinflammatory cytokines can potentially boost immunosuppression [55].

CONCLUSION

Treatment for inflammatory and degenerative disorders using cells is beneficial. Mesenchymal stem cells encourage tissue regeneration and repair. Instead of just covering up the pain, it aids in addressing the underlying issue. It can be used alone or in conjunction with other conventional therapy approaches to control the disease effectively. With their capacity to differentiate into bone and cartilage cells and their involvement in immune regulation, Mesenchymal stem cells offer new hope for the treatment of arthritis by reducing inflammation, possessing anti-fibrotic properties, and promoting vascular repair.

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AUTHORS CONTRIBUTIONS

All the authors contributed to the preparation of the final manuscript.

CONFLICT OF INTEREST STATEMENT

We declare that we have no conflict of interest.

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