Critical Reviews™ in Eukaryotic Gene Expression, 27(3):205–210 (2017)

Modeling Mesenchymal Stem Cells in TMJ Rheumatoid Arthritis and Osteoarthritis Therapy

N. Serakinci[1]* & G. Savtekin[2]

[1]Near East University, Faculty of Medicine, Department of Medical Genetics, Nicosia, Turkish Republic of North Cyprus; [2]Near East University, Faculty of Dentistry, Department of Oral and Maxillofacial Surgery, Nicosia, Turkish Republic of North Cyprus

*Address all correspondence to: Gokce Savtekin, Ph.D., Near East University, Faculty of Dentistry, Department of Oral and Maxillofacial Surgery, Nicosia, Turkish Republic of North Cyprus, E-mail: gokce.savtekin@neu.edu.tr or gokce_ces@hotmail.com

ABSTRACT: Stem cells have self-renewal capacity and an ability to differentiate into particular cell types generating mature cells. Mesenchymal stem cells (MSCs) have a significant role in tissue homeostasis, which leads into tissue regeneration. MSCs are rare pluripotent cells supporting hematopoietic and mesenchymal cell lineages. MSCs are also believed to have therapeutic power over temporomandibular joint (TMJ) disorders (TMDs). The most common type of TMD is articular disc displacement, which induces progressive degenerative changes. These changes lead to rheumatoid arthritis or osteoarthritis. In this review, use of human mesenchymal cells (hMSCs) for therapeutic treatment of inflammatory diseases of TMJ is discussed.

KEY WORDS: mesenchymal stem cells, rheumatoid arthritis, osteoarthritis

I. INTRODUCTION

Mesenchymal stem cells (MSCs) have definite characteristics. They have self-renewing ability, and they can give rise to variety of cell lineages within or across germ lines, including the mesodermal lineage (e.g., adipocytes, osteocytes, chondrocytes) and cells of other embryonic lineages.[1] MSCs secrete numbers of paracrine factors such as chemo-attractants for endothelial lineage cells, monocytes and macrophages, and inflammatory factors such as various chemokines and interleukins. MSCs communicate via chemokine signaling with extracellular matrix, which activates transcription of target genes in inflammation cells such as macrophages and lymphocytes.

Human mesenchymal stem cells (hMSCs) have a significant role in cartilage and osteochondral defect repair.[2,3] Chemokines and their receptors have been suggested to take a part in migration and homing ability of hMSCs.[4,5] Recent studies have demonstrated that bone-marrow–derived MSCs (BM-MSCs) reduce oxidative stress, apoptosis, and hippocampal damage in brain[6]; thus, hMSCs have antiapoptotic properties.[7] As shown with BM-MSCs, MSC-derived exosomes also contribute to tissue damage repair, inflammatory response suppression, and immune system modulation, but these findings should be discussed further.[8]

Temporomandibular joint disorders (TMDs) have distinctive findings including myalgia, headaches, and structural destruction. TMJ can be traumatized like other joints, and congenital anomalies can arise, when inflammatory diseases such as rheumatoid arthritis and osteoarthritis occur. The mandibular condyle needs to be changed surgically when TMJ defects become non-invasively repairable.[9]

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that is aggressively involved in multiple systems, and mostly affects arthrodial joints. Overgrowth of the synovial membrane and aggregation of activated T cells and macrophages lead to cartilage degradation and erosion of bone in the joints. The current etiology of RA remains unknown.[10] Currently available antirheumatic drugs (DMARDs) are the key therapeutic agents used to reduce systemic inflammation and synovitis. When arthritis cannot be controlled or when DMARDs cause toxic reactions, biological agents such as tumor necrosis factor (TNF) inhibitors and agents targeting interleukin (IL-) 1 and IL-6 pathways, T-cell costimulatory pathways, and B cells can be used.[11] DMARDs do not effectively

1045-4403/17/$35.00

prevent cartilage damage, and the effects of biological agents remain unclear. Therefore, new methods of RA treatment should be developed.[12]

Osteoarthritis (OA) is the most common degenerative joint disease in TMJ. It is characterized by severe degradation of cartilage and subchondral bone remodeling. In the pathogenesis of OA, abnormal subchondral bone remodeling plays an important role. No pharmaceutical or nonoperative therapy has shown significant efficacy in reversing or halting the progression of the disease, or in limiting the long-term treatment of pain-deterring factors and pain control.[13] In the absence of effective strategies for OA treatment, treatments that modify the disease should be investigated.

Mesenchymal stromal cells (MSCs) are nonhemodiopathic, multipotent stem cells that have been isolated from many human tissues such as bone marrow, synovium, fat, and muscle. Because MSCs have an immunosuppressive property and are prone to very potent differentiation, they have been widely used to treat tissue repair and immune disorders. Synovium-derived mesenchymal stem cells (SMSCs) possess immunosuppressive and multipotent differentiation characteristics as well as a greater ability to produce condyles. Thus, SMSCs can be useful for repairing cartilage damage caused by RA.[12] Essentially the treatments with the MSC are based on the migration of the cells to target tissue and the ability of the cells to transform into suitable cells. Therefore, direct and local implantation of the MSC has become an option for OA treatments.[14]

II. THERAPEUTIC USE OF HMSCS IN TMJ INFLAMMATORY DISEASES

Inflammation caused by TMJ arthritis is a serious health problem affecting people in every part of society. Although many applications have been tried and many studies have been conducted, the treatment of inflammation due to temporomandibular insertion remains lacking. The occurrence of TMJ disorders characterized by pain, limitation of jaw movements, clicks, creeping, and tenderness is related to many factors. Currently, occlusal splint, physical therapy, non-steroidal anti-inflammatory drugs (NSAIDs), DMARDs, arthrocentesis, arthroscopy, or open surgical techniques are being applied in TMJ arthritis treatment. Most of these treatments are insufficient to prevent arthritis.

Many mediators such as neutrophils, monocytes and/or macrophages, thrombocytes, complex and coagulation systems, cytokines, proteolytic enzymes, the arachidonic acid pathway, and the mitogenic protein kinase (MAPK) cascade are thought to play a role in the development of damage from TMJ.[15] The MAPK signal pathway associated with cytokine production and RA pathogenesis also regulates MSC differentiation, immunoregulation, and apoptosis, indicating that the MAPK signaling pathway is associated with RA sinovial MSCs.[16–18] These mediators are mostly caused by structural destruction of the entire tissue, including the synovial space. IL-6 is an important proinflammatory cytokine of RA associated with some systemic symptoms such as leukocyte activation, antibody production, and acute-phase mediator response. Moreover, IL-6 has been successfully targeted for RA treatments. Increased IL-6 expression in RA SMSCs is useful for showing the role of RA SMSCs in RA pathogenesis.[12,19] In another study, the effects of IL-10 and TGFβ1 on immune responses in RA were generally negative, whereas IL-1β, IL-6 and TNF-α are known to promote immune responses in RA. The effects of MSCs on these cytokines have been determined in a mouse model in which arthritis was experimentally induced. The findings support a reduced immune response by MSC transplantation.[20]

In another study, MSCs were triggered to secrete immunomodulatory factors by culturing them in the presence of inflammatory cytokines, TNF-α and IFN-γ.[21] The presence of TNF-α and IFN-γ in the culturing medium leads to a considerable increase in IL-6 secretion of MSCs, showing that MSCs generate an immunomodulatory response when they are stimulated by inflammatory cytokines. In that study, human synovium and cartilage explants were also cultured both separately and together to generate an environment similar to an *in vivo* OA inflammatory microenvironment. When synovium and cartilage explants were exposed to the factors secreted by MSCs in the presence of TNF-α and IFN-γ, inflammation-related genes such as IL-1 β, matrix-degrading genes, and proteins such as MMP-1 and MMP-1 were downregulated while suppressor

of cytokine signalling (SOCS)-1 was upregulated. Overall, the study showed that the factors generated by MSCs have anti-inflammatory and antidegradation activities on cartilage and synovium explants under the inflammatory condition of OA.[22]

The MSCs that are derived from TMJ may be used in the repair and regeneration of TMJ cartilage and subchondral bone.[23] Many studies have shown that MSCs derived from the synovial fluid and synovium obtained from patients with TMJ disorders express common MSC markers such as CD90, CD44, CD105, and CD73, and but do not express CD34 and CD45.[23,24] Moreover, fibroblast-like, spindle-shaped morphology was observed for these cells, and when they were cultured in conditions stimulating their differentiation *in vitro*, these cells were able to differentiate into osteogenic, chondrogenic, adipogenic, and neurogenic lineages.[23,25] The determination of the tissue-specific MSC source is important because it can suggest a mobilization of MSCs to the site of TMJ repair (Figure 1). However, this finding needs to be further investigated. Another

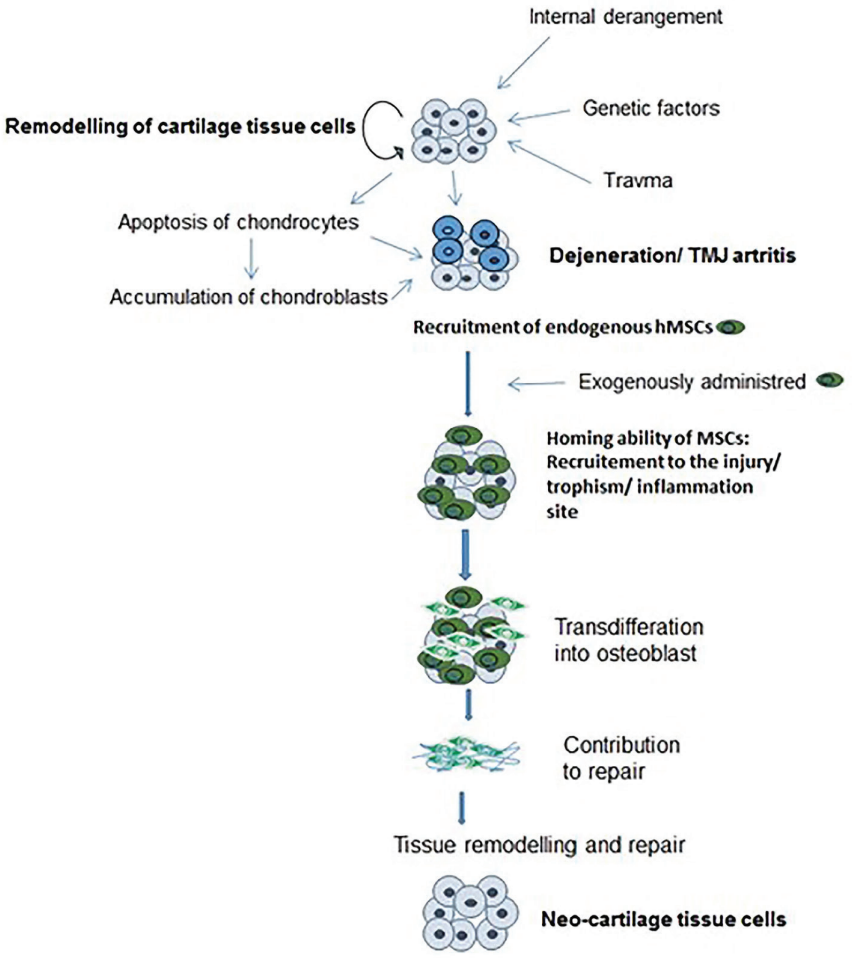

FIG. 1: hMSCs mediated gene therapy targeting TMJ arthritis. MSCs show the characteristics of self-renewing themselves as well as differentiating into different cells. hMSCs play an important role in TMJ therapy once TMD/inflammation develops hMSC recruits to inflammation site. When locally administered, they may undergo transdifferentiation with the microenvironmental stimuli. As hMSCs show homing property to inflammation/injury site, they can contribute to tissue stroma repair. These properties indicate the great potential for hMSCs to be used in TMJ arthritis therapy as a stem-cell–mediated targeted therapy strategy.

study also showed that cartilage tissue regeneration can be improved by the MSC-secreted factors while they lead into prevention of OA progression.[26]

In this study, a hemimeniscectomy rat model was used, and the rat or human BM-derived MSCs were injected to the knee joints of these rats.[26] The amount of BM-derived MSCs declined very quickly, however, as the expressions of genes such as Indian hedgehog (Ihh), parathyroid hormone-like hormone (PTHLH), and BMP-2 were high. This helped the upregulation of rat type II collagen gene and, thus, cartilage repair. Other studies have also shown the trophic effects of MSCs on chondrocytes *in vitro*.[27,28] Zhang et al. studied the trophic effects of MSCs on growth and matrix formation of fibrochondrocytes.[29] Fibrochondrocytes were cultured with periodontal ligament (PD)-derived MSCs or cultured in conditioned medium of PD-derived MSCs. Proliferation and matrix deposition of TMJ-derived fibrochondrocytes were highly elevated when fibrochondrocytes were cultured in a conditioned medium of PD-derived MSCs.[29]

In addition, the expression of chondrogenic genes including aggrecan and type I and II collagens increased. Moreover, the distribution of proliferative fibrochondrocytes in pellets cultured in conditioned medium of PD-derived MSCs and in pellets cultured in periodontal ligament (PD)-derived MSCs were similar. Therefore, soluble factors generated by PD-derived MSCs are the main sources of the advantageous impacts of MSCs on the proliferation and matrix formation of fibrochondrocytes (Figure 1).[17]

III. LIMITING FACTORS AND DIFFICULTIES OF MSC USE IN TMJ INFLAMMATORY DISEASES

Recruitment of endogenous hMSC to the TMJ inflammatory site has been shown to be low; therefore, exogenous MSC injections, which lead to infections (0.002%), together with the high risk for infection development MSCs have low grafting efficiency as well as potency.[30] The limited division potential of hMSCs also restraining their therapeutic application. especially considering the high number of cells required for therapy in humans.[31]

It has been previously shown that forcing the hMSCs to produce a large scale of cells may have an impact on neoplastic transformation.

In addition, malignant transformations have also been reported in rodent models of hMSC populations.[31,32,33,34,35,36] This finding has raised concerns regarding whether hMSCs can lead to spontaneous malignant transformation when cells forced to extensive expansion.

Exogenously administered hMSCs may be systemically infused within developing tumors in animal models for glioma, colon carcinoma, gastric cancer, ovarian carcinoma, Kaposi's sarcoma, and melanoma.[37,38] Although these studies support the possibility of neoplastic transformation of hMSCs during *in vitro* expansion, which is still controversial, the molecular pathogenesis behind such mechanism has not yet been fully established. Therefore, the use of hMSCs still requires close monitoring before and after their therapeutic use.

IV. CONCLUSIONS AND FUTURE DIRECTIONS

hMSCs have been proposed to have great therapeutic potential due to their homing abilities to the inflammation and injury site. In addition to their homing ability, these cells easily transdifferentiate into osteoblasts via stimuli in the microenvironment. Very long-term MSC studies have shown that the presence of side effects is very low; to date, there has been no evidence of secondary infection or tumor.[39]

Currently, preliminary advances are made in the preclinical and clinical trials. However, a larger volume of high-quality evidence and large-scale randomized control trials with long-term follow-up are required.

When cartilaginous tissue is considered, MSCs can be easily collected, expanded, and differentiated into cartilaginous tissue. The application of MSCs in cartilaginous tissue generation studied significantly both *in vivo* and *in vitro* provided promising results for their application. When patient safety and hyaline cartilage generation were considered, promising results were obtained in human clinical trials.[40]

MSCs also have some drawbacks, such as their potential for hypertrophy and tumorigenicity. However, Wakitani et al. studied the safety of

autologous MSC transplantation for cartilage repair in patello-femoral and by following up patients for about a decade. They showed that exogenous and autologous MSC transplantation did not lead into any tumorigenic and infectious activity.[40] These findings suggest that, if closely monitored, autologous MSC transplantation can be used in clinical applications. *In vivo* and *in vitro* studies investigating the role of MSCs in TMJ disc and cartilage tissue repair are ongoing; however, further studies are required to investigate the use of MSC in clinical applications for TMD treatment.[41,42]

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