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Review

Stem Cell Applications in Orthopedics

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ABSTRACT

Various cells with the ability to differentiate sequentially and form tissues are formed for the formation of a new organism with the fertilization of the egg and sperm. At the same time, stem cells, with their differentiation, self-renewal, and renewal capacity, are a promising therapeutic field for the regeneration of tissue damage resulting from disease, providing immunological advantages. Stem cell applications are available in many orthopedic problems, ranging from osteoporosis to ligament injuries. However, while the most common mesenchymal stem cells and their varieties are applied in this field, studies have also been conducted with embryonic stem cells, pluripotent stem cells, and muscle-derived stem cells. When stem cell applications performed in various animal models and clinical studies are evaluated, bone formation and an increase in bone mineral density in bone-related problems, successful healing in union; cartilage regeneration and pain relief in cartilage; myelination of damaged neurons, functional improvement, improvement in various scores in spinal cord injuries; tendon healing in tendon injuries; successful results in rotator cuff lesions; regeneration and quality healing in ligament injuries; regenerative effect in meniscopathy; an increase in the extracellular matrix and disc structure-like formation in intervertebral disc degeneration; femoral head healing in femoral head osteonecrosis were observed. In this chapter, emphasizing the section on stem cell applications in orthopedics, it is highlighted that stem cells can be a therapeutic option for orthopedic problems due to their renewal and differentiation properties suitable for the characteristics of the region where they are transplanted.

Keywords: Bone defect, cartilage degeneration, regeneration, spinal cord injury, stem cell, tendon injury.

Stem cells are undifferentiated cells with the ability to differentiate into any cell type of an organism and self-renew.[1] Therefore, they contribute to the development and renewal of tissues and organs. The proliferation and differentiation of typical stem cells in early development and tissue regeneration are regulated through biochemical and biomechanical signals.[2,3]

Stem cells are found in adult and embryonic cells and are classified accordingly. Totipotent stem cells can divide or differentiate into any cell of the organism. Pluripotent stem cells create cells that have all germ layers, while multipotent stem cells have a narrower range than pluripotent stem cells and can specialize in separate cell lineages.[1,2]

There are oligopotent stem cells that can divide into several cell types such as white blood cells but cannot divide into red blood cells. In addition to all this information, there are unipotent stem cells with a special ability to repeatedly divide, promising a therapeutic application in regenerative medicine, and having the most limited differentiation ability. Only an example of the formation of dermatocytes from one cell type can be given for this last stem cell group.[1]

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The rapid regeneration or replacement of tissues or organs damaged by cancer, trauma, tissue injury, degenerative diseases, and age-related diseases is urgently needed. Since stem cells have self-renewal and differentiation properties, they are used to regenerate damaged tissues or organs. Thus, it has prepared the basis for regenerative medicine.[4,5]

Tissue engineering technology, on which stem cell regenerative medicine approaches are based, enables

the production of newly formed tissue in three-dimensional structure scaffolds that biologically gradient.[5-7] Ideal scaffold structures mimic the movement of the target tissue while supporting cell attachment and internal growth. It contributes to appropriate tissue perfusion by supporting angiogenesis and new blood vessel formation. Since it is not a substance that stimulates the host's immune system, it eliminates the need for systemic immune suppression.[5,8] In addition to these, growing tissues, organ fragments, or entire organs in the laboratory also covers long-term goals such as transplantation in cases where the body cannot heal itself. Thus, it could be a solution to the potential shortage of organs for donation and organ transplant rejection problems if it is formed from its own cells without organ-tissue compatibility problems.[4] Examples of commonly used stem cells include adult tissue-derived cells isolated via bone marrow, umbilical cord blood, mobilized peripheral blood, adipose tissue, and myocardial biopsy.[4,9,10]

The osteogenic, chondrogenic, and adipogenic *in vitro* potential of mesenchymal stem cells (MSCs) support MSC applications in orthopedic injuries.[5,11] Clinical applications of MSCs derived from bone marrow [bone marrow-derived stem cells (BMDSCs)] are used in the treatment of orthopedic conditions such as joint cartilage repair and osteoarthritis (OA), rheumatoid arthritis (RA), rotator cuff injuries, tendons, spinal cord, meniscus lesions, and bone defects. Additionally, they can be used to treat non-union, avascular necrosis of the femoral head, and to support growth in osteogenesis imperfecta (OI), also known as brittle bone disease.[12]

BIOLOGICAL PROCESS OF STEM CELLS

After fertilization of the sperm and egg, the blastocyst is formed, and short-lived embryonic stem cells (ECSs) cover its inner wall. It consists of two different types of cells: the inner cell mass (ICM) and trophectoderm (TE). These cells turn into epiblasts and stimulate fetal development. Meanwhile, the blastocyst regulates the ICM microenvironment, while the TE continues to develop extra-embryonic structures necessary for successful structures such as the placenta. The TE creates a special supportive structure, while ICM cells remain undifferentiated, pluripotent, and proliferative. Therefore, ECSs contribute to the formation of any cell type in the organism. The source of human embryonic stem cells (hESCs) is ICM cells.[1,13] During embryogenesis, cells form clusters called germ layers, which become the endoderm, mesoderm, and ectoderm.[1,14] The endoderm can differentiate into the intestine, lungs, and liver, while the mesoderm can differentiate into bone, muscle, and blood, and the ectoderm can differentiate into brain and skin cells.[1] Ultimately, each cluster contributes to the formation of differentiated cells and tissues of the fetus and later, the adult organism.[1,14] hESCs differentiate into one of the germ layers and then become multipotent cells whose ability is limited only to cells within the germ layer.[1]

Adult or somatic stem cells do not differentiate and are found among the undifferentiated cells after the development of the entire body. Their multiplication period is longer than that of ECSs. However, it is possible to convert adult stem cells into pluripotent stem cells. The functions of adult stem cells are to repair, regenerate, and contribute to the growth of cells lost every day. Therefore, they have limited differentiation ability. Mesenchymal stem cells found in many tissues, particularly in the bone marrow, can be transformed into bone, cartilage, and fat cells. Neural cells contribute to the formation of nerve cells, oligodendrocytes, and astrocytes. Hematopoietic stem cells (HSCs) are responsible for the formation of all types of blood cells, such as red, white, and platelets. Additionally, skin stem cells are responsible for the formation of keratinocytes, which make up the protective layer of the skin.[1]

APPLICATIONS ON CARTILAGE

Cartilage, which has an elastic and smooth connective tissue, has four functions. These are providing shape and support, cushioning for smooth joint formation between bones, and promoting the growth of long bones, making cartilage an important element for the musculoskeletal system. Cartilage injuries, especially in young populations and athletes, can lead to chronic problems, as well as cartilage degeneration and OA in the aging population.[15,16]

Current surgical approaches for cartilage injuries include arthroplasty, microfracture, and autologous chondrocyte implantation.[17,18] On the other hand, degenerative OA, a widespread health problem worldwide, negatively affects the physical and mental health of the patient and is a source of disability.[19,20]

The weak healing capacity of cartilage, particularly in adult cartilage, is due to its lack of vascularity and innervation. In addition, defects larger than two to four millimeters cannot be healed.[2,21,22] Mesenchymal stem cell therapy, particularly for cartilage lesions and OA, is a potential therapeutic research area.[23]

In many preclinical animal studies on knee OA models, it has been reported that MSCs can support cartilage and subchondral bone repair. Mesenchymal stem cells have been shown to be able to differentiate into various functional tissue cells and to promote the regeneration of damaged cartilage and the resolution of pain problems.[19,24,25] Its therapeutic effect can be explained by direct differentiation from MSCs to chondrocytes and optimization of the intra-articular environment.[19,26]

Chondrogenic differentiation capacity can be improved with various growth factors, chemical materials, and scaffold applications.[19,27,28] The paracrine effect is increased cartilage regeneration without direct contact.[19,29] Various meta-analyses that included randomized controlled trials have shown that MSC therapy is effective in reducing pain and improving clinical symptoms of OA.[19,30-32] In an experimental study, two patients with full-thickness articular cartilage defects in their patellae showed significant improvements in their walking abilities two years after receiving autologous MSCs.[17,33]

A review study on the classification of stem cell therapy for knee OA examined stem cell therapy in seven categories: cell donor, cell source, cell preparation, cell delivery method, lesion creation, simultaneous procedures, and evaluation. Briefly, cell donors are allosteric MSCs that can be derived from bone marrow or adipose tissue and obtained from other patients participating in the study, which can cause immune rejection and require invasive collection compared to autologous MSCs. The cell delivery method includes transplantation and injection methods. Transplantation involves directly placing MSCs onto the lesion area of the cartilage and is performed by having supportive materials such as collagen layers or structural scaffolds. The injection is the most common way of delivering cells into the joint space, where it localizes and helps regenerate cartilage formation, thus demonstrating the paracrine effect of MSCs. Common methods for creating lesions include chondroplasty, microfracture, and subchondral drilling. Stable cartilage lesion areas are produced, and the subchondral bone that receives the MSC transplant is stimulated. Additionally, the subchondral bone has roles such as providing a source of nutrition to the deepest layers of the joint cartilage and removing waste products. Procedures that can accompany MSC therapy include high tibial osteotomy, as well as meniscectomy and anterior cruciate ligament reconstruction. Clinical studies that have examined the effectiveness and reliability of MSC therapy have reported at least 12 months as the minimum evaluation period. Methods for cell preparation include expansion or isolation techniques. Stem cell sources include BMDSCs, which have superior osteogenic power and are considered a reliable gold standard. Adipose-derived stem cells have many characteristics such as abundant amounts, high chondrogenic potential, rapid proliferation, and less susceptibility to aging. Peripheral blood stem cells contain a large number of MSCs and endothelial progenitor cells, making them an applicable mixture. Placenta or umbilical cord sources are the main sources of MSCs and are accessible. Synovial-derived MSCs have superior abilities in osteogenesis and chondrogenesis. In addition to all of these, there are other sources available for cartilage, such as chondroprogenitors, which are a progenitor cell population that is particularly prone to differentiation into chondrocytes. They can be isolated from various tissues such as cartilage, meniscus, synovium, and adipose tissue.[15,34,35]

Articular chondrocytes are resident cell types that secrete extracellular matrix (ECM), and they are used due to their ability to multiply in a single-layer culture.[15] Hyaline cartilage, such as nasal septal cartilage made from ECM, is more capable of repairing articular cartilage than joint chondrocytes. Additionally, muscle stem cells (MuSCs) have provided successful results for cartilage healing. When MuSCs were transplanted into artificially created cartilage joint defects in rabbits, it showed a result that was close to chondrocyte transplantation in terms of type 2 collagen production.[2]

NERVE INJURIES

Spinal cord injury (SCI) is an injury that is accompanied by permanent impairment and social and economic losses. Sports and other traumas, car accidents, falls, tumors, and infections are common causes.[36] Various methods in the literature have not been found to be effective in achieving functional recovery after injury.[36,37] However, in the 1980s, the potential for central nervous system axons to turn into peripheral nerve grafts was discovered. Thus, the strong proliferation and differentiation potential of transplanted stem cells can enable the replacement of injured neurons, regulation of the microenvironment, facilitation of axonal regeneration, and bridging of the spinal cord through transplantation techniques.[36,38]

The possible mechanisms of action of stem cell-based therapies for SCI are as follows: Transplanted stem cells can differentiate into neurons

and glia cells, thereby creating new connections with host neurons, and can also replace damaged neurons in the spinal cord by rebuilding the neural circuit.[36,39]

Stem cell transplantation after an injury has been shown to protect spinal cord neurons from secondary changes by downregulating gene expression with inflammation and apoptosis while upregulating neuroprotective genes. This describes the mechanism of protecting host neurons and preventing apoptosis.[36,40]

Transplanted stem cells interact with surrounding tissues and in addition to ECM, produce neurotrophic factors such as neural growth factor and vascular endothelial growth factor. Thus, the microenvironment in the injury area changes and neural axon growth accelerates.

In addition, the differentiation of stem cells into interneurons and axonal sprouting can lead to the formation of bridges from the proximal and distal regions of the spinal cord to the injured area, promoting axonal regeneration and synapse formation.[36,41,42] This is seen as a mechanism that promotes myelin formation around remaining and newly growing neural axons.[36,43-45]

Stem cells used in spinal cord injury repair include neural stem cells, bone marrow-derived HSCs, adipose-derived stem cells, umbilical cord-derived stem cells, ECSs, and induced pluripotent stem cells (iPSCs), all of which have been reported to be effective.[36] In one study, adult LacZ transgenic mice femoral BMDSCs were applied to a rat model with SCI at the T10 level, resulting in support for myelination of regrowing axons in the spinal cord.[36,46]

In another study, after differentiating mouse neural stem cells from hESCs and applying them to SCI rat models at the T9-T10 level, the animals showed improved motor, wire-walking, and platform-hanging scores and supported injured nerve myelination.[36,47] Functional improvement was reported in primate models of SCI after the transplantation of human iPSCs.[36,48]

Survival of human neural stem progenitor cells was observed after implantation in an SCI primate model, with improvement in grip strength and spontaneous motor activity reported.[49]

Methods of stem cell transplantation include intramedullary, intrathecal, intraventricular, and intravascular methods. The most effective and invasive method is intramedullary, while the least effective and invasive method is intravascular.[36,50]

While appropriate timing for transplantation is necessary for stem cells to survive and for regeneration of the injured nervous system, there is no consensus on the appropriate timing. New trends that can accompany stem cell therapy include gene therapy, combining tissue engineering scaffolds, and using combinations of different stem cells.[36]

APPLICATIONS ON BONE

Bone defects can result from high-energy trauma or gunshot wounds, causing bone fragments to come out and this is one of the most challenging issues in orthopedic surgery.[51] The first stem cell studies for femoral defects involved the use of MSC-containing membranes. As a result, vascular endothelial growth factor, bone morphogenetic protein-2 (BMP-2), and transforming growth factor-beta were declared, and it was observed that they were significantly increased in the membranes.[51-54] Therefore, the question of whether it will enter the field of use for bone defect repair is raised.[51]

In another systematic review, preclinical results of derived from bone marrow used in fracture healing were investigated. It has resulted that BMDSCs increasing bone formation and mineral density.[51,55] Nonunion, one of the destructive problems, leads to higher morbidity and mortality rates.[51,56] In addition, interest in stem cell studies on nonunion is gaining momentum and successful results are being seen.[51]

In a study, BMDSCs and calcium sulfate were applied to a patient with tibial nonunion. Despite the six unsuccessful surgeries and resistance to other treatments previously undergone, it was reported that the application of BMDSCs and calcium sulfate provided healing in a short period of time.[51,57] The use of BMDSCs in seven patients with long bone nonunion resulted in successful outcomes.[51,58]

The combined use of BMDSCs and BMP1-3 in rat long bone nonunion was reported to increase type-I collagen and osteocalcin.[51,59] In addition, MSCs can be stimulated for osteogenic differentiation and can improve bone defects in animals.[2,60] Furthermore, it has been reported in several studies that follicle pluripotent stem cells (fPSCs) can differentiate into smooth muscle cells, muscles, chondrocytes, and osteocyte lineages *in vitro*. However, it has been observed that human fPSCs significantly increase the expression levels of osteocalcin, osteopontin, and collagen type 1 when cultured in an osteogenic medium.[61,62]

APPLICATIONS ON TENDONS

Tendons, which are collagenous connective tissues, are necessary for producing movement and transmitting force by connecting bone to muscle. Healthy tendons have a high tension capacity due to their high content of type 1 collagen. Tendon tissues, which do not have sufficient vascularization and use anaerobic energy systems, face weak healing capacity after acute or excessive use injury. In preclinical studies, cellular constructive studies have contributed to increasing and restructuring tenocyte numbers but have not repaired tendon tissue.[63] Mesenchymal stem cells can be isolated from bone marrow, adipose tissue, as well as anterior cruciate ligament and tendon tissue.[63-66]

The evidence for the ability of these cells to produce connective tissues without relying on transplantation or differentiation is increasing.[63,67]

Mesenchymal stem cells have soluble autocrine and paracrine growth hormones that support the survival of cells, increase the proliferation of endogenous connective tissue cells, stimulate mitosis in tissue progenitors, induce angiogenesis, and reduce apoptosis.[63,67-69] After allogenic MSCs were transplanted into the rabbit tendon, which was torn and sutured, the early histological and biological parameters of tendon healing improved or accelerated when the MSCs were transplanted into the tendon.[70] On the other hand, BMDSC transplantations were applied to various injured tendon regions, and improved tissue repair was observed, especially in patellar tendon injuries.[12]

Embryonic cells can provide an unlimited number of MSCs and connective tissue progenitors as they have more plasticity and proliferative potential than MSCs. Dermal fibroblasts (DFbs) have also entered the field of tissue engineering due to their abundant supply, ease of harvest, and re-programmability. They have the potential to differentiate into brain, glial, muscle, and fat lineages. *In vitro,* studies show promise for tendon engineering as well.[63] However, it is concerning that DFbs can be expanded, contracted, and induced to leave collagen similar to tenocytes, but they can also produce scar tissue.[63,71]

FEMORAL HEAD OSTEONECROSIS

Femoral head osteonecrosis (FHON) is defined as the occurrence of microfracture due to permanent loss of bone necrosis and reshaping following a disrupted subchondral microcirculation.[72,73]

Stem cell applications for femoral head osteonecrosis include HSCs, adipose MSC, allogeneic human umbilical cord-MSC, and peripheral blood MSC. Among these, HSC is the most commonly used. However, HSCs are generally used as bone marrow concentrates and are rarely cultured or used as bone marrow aspirates.[72,74]

Stem cell delivery is often combined with core compression. Other techniques include impaction allogeneic bone grafting, autoiliac cancellous bone grafting, and porous tantalum rod implantation procedures.[72] In addition to applying MSCs to the necrotic area of the femoral head, arterial injection has also been used in some studies.[72,75]

Medial circumflex femoral artery, lateral circumflex femoral artery, or obturator artery MSC transplantation has been performed through angiography. Its therapeutic effect has been observed without any significant side effects. On the other hand, it has been observed that MSCs applied into the artery migrate to the necrotic area of the femoral head and improve it, along with differentiating into osteoblasts.[72,76] However, more research is needed to determine which is more effective between topical application and arterial injection.[72] In fact, stem cell therapy is concerning in terms of the process and osteogenic activity of MSCs in the ischemic and hypoxic microenvironment that the osteonecrotic area.[72,77]

It has been reported that the survival rate of transplanted stem cells in ischemic tissue is low.[72,78] However, it has been observed in animal models that cells transplanted into osteonecrotic areas can survive, proliferate, and differentiate into osteoblasts. Moreover, there are similar conclusions that MSCs do not suffer damage in a low-oxygen microenvironment and support an osteogenic phenotype in cellular experiments. However, this needs to be verified for humans. Another issue is appropriate patient selection for better results. Patients in the first and second stages (early) of the disease may be a more suitable choice, while cases in the third and fourth stages may be prone to poor outcomes.[72] In addition, it has been reported that patients with osteonecrotic hips resulting from trauma have better outcomes than those with FBON developing without trauma.[72,79]

In conclusion, stage, size, morphology, and etiology may be important factors affecting the outcome of FHON treatment.[72]

INTERVERTEBRAL DISC DEGENERATION

Progressive changes that damage the composition, structure, and function of the disc are called intervertebral disc (IVD) degeneration, and it is a chronic process. It is faster and/or more severe than disc degeneration due to normal aging. Characteristics of IVD include the progressive loss of proteoglycans and water content in the nucleus pulposus (NP), the filling of the NP space with fibrocartilage, irregularity of the annulus fibrosus (AF), and the formation of osteophytes in the adjacent vertebral bone.[80]

Cells in the degenerating disc cannot produce enough ECM due to reduced numbers, changes in phenotype, or other factors. This results in a loss of general disc function and changes in disc structure during IVD degeneration. Stem cells that have the ability to migrate to various tissues and differentiate have been considered for use in IVD treatment. However, many literature studies have shown that MSCs differentiate toward a phenotype similar to that of a nucleus pulposus cell (NPC) in response to exogenous biochemical signals *in vitro*.[80,81] In a study, a stem cell therapy approach was developed to promote IVD cell renewal and more functional ECM synthesis in a degenerated disc. Adult human cells were studied *in vitro* to investigate interactions between MSCs and NPCs in a culture medium. The results of this two-week study showed that co-culturing human MSCs with human NPCs provided the greatest increase in ECM production. In addition, an *in vivo* study was conducted to examine stem cell survival and engraftment in live disc tissue by injecting rabbit MSCs into rabbit discs. The results of this study showed that MSCs survived for at least 24 weeks and that the graft was successfully applied to IVD tissue, with MSCs in the AF exhibiting a spindle shape similar to that of inner AF cells.[80]

OSTEOPOROSIS

Osteoporosis is defined by low bone mass and disrupted microarchitecture of bone tissue, leading to increased bone fragility and risk of fracture. While the goal of osteoporosis treatment is to maintain normal bone mass, current therapies include drug-based agents that either inhibit bone resorption or improve bone anabolism. The most commonly used agents among these are bisphosphonates, which target osteoclasts to prevent bone resorption.[82,84-86] Additionally, in the development process of osteoporosis, the capacity of HSCs to differentiate into osteoblasts decreases while their capacity to differentiate into adipocytes increases. This results in decreased bone formation and increased accumulation of bone marrow fat. In elderly mice, an increase in adipocytes and a decrease in osteoblasts have been observed alongside a decrease in HSCs.[82,87,88] Despite this, the local or systemic transplantation of autologous or allogeneic HSCs has been shown to be applicable in the treatment of osteoporosis in animal models.[82,87]

Local HSC transplantation was performed in an osteoporotic rabbit model created by ovariectomy, resulting in increased trabecular thickness, improved trabecular structure and bone hardness, and the development of new osteoids.[82] In another osteoporotic rat model created by ovariectomy, isolated HSCs from healthy rats were locally injected into the bone marrow, resulting in improved femur bone mass.[82,89] Additionally, it was observed that systemic injection of allogeneic adipose HSCs prevented bone loss in ovariectomy-induced bone loss.[82,91] Furthermore, local injection of autologous adipose HSCs resulted in improved trabecular bone quality, promotion of osteogenesis, inhibition of adipogenesis, increased HSCs, and new bone formation in osteoporotic mouse and rabbit models induced by age and ovariectomy, respectively. Further clinical studies are needed.[82,92,93] Additionally, concerns remain regarding the efficacy of HSCs in targeting bone marrow and the fate and survival of HSCs after transplantation.

OSTEOGENESIS IMPERFECTA

Osteogenesis imperfecta is characterized by general osteopenia, bone deformities, and fractures, and is defined as a genetic disorder of MSCs. Current treatments cannot achieve complete recovery.[51] Bone marrow-derived stem cell therapy in patients with OI has been reported to increase bone mineral density and reduces fractures in the long term.[51,94] In a mouse model of affected BMDSCs, a healthy mouse was applied to treat OI. This treatment has thus encouraged the differentiation of migrating cells into osteocytes. Additionally, it has partially contributed to the return of the disease phenotype through the synthesis of standard amounts of type-I collagen.[12,95]

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic autoimmune disease that affects joints and connective tissues and is associated with vascular, metabolic, psychological, and bone comorbidities. The characteristic features

of RA include chronic inflammation, immune responses against autoantigens, dysregulated cytokine networks, and activation of osteoclasts and chondrocytes.[96-98] Inflammation of the synovial membrane and cartilage leads to hyperplastic synovium and cartilage breakdown, resulting in bone erosion.[99,100]

The categories of RA treatment include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, non-biological disease-modifying anti-rheumatic drugs (DMARDs), and biological DMARDs.[96,98,101] NSAIDs are commonly used to relieve pain, while DMARDs and biological DMARDs are used to address unresolved treatment issues in RA patients. [96]

Cell therapy with MSCs has emerged as a promising new approach to unresolved treatment issues in RA patients. MSCs have initially attracted attention in the field of tissue and organ regeneration due to their self-renewal and regenerative capacity. However, their therapeutic potential has been extended to chronic inflammatory processes due to their immunomodulatory properties.[96,102]

Mesenchymal stem cells can reduce the metabolic reprogramming of different types of immune cells, slow down the proliferation rate of actively dividing cells, and prevent the secretion of inflammatory cytokines.[96] They contribute to the suppression of T helper 1 (Th1) cells and promote the expansion of regulatory T (Treg) cells, which has been reported in many inflammatory conditions.[96,103]

The most commonly used applications in RA experimental models are intravenous and intraperitoneal, in addition to intra-articular, peri-articular, intranodal, intramuscular, and subcutaneous methods, which are recommended alternative application routes with good outcomes. Many studies have reported that MSC infusions performed in the early stages of the disease are more effective. In five patients with ankylosing spondylitis (AS), an umbilical cord-MSC intravenous transfusion was performed, and it was observed that all patients' AS symptoms improved in the evaluation.[104]

In a model of antigen-induced arthritis created in mice, rodent MSCs were applied intra-articularly.[105] As a result, it was seen that it improved the severity of the disease and also reduced inflammation, joint swelling, and cartilage destruction. Autologous MSC intravenous injection was performed on 13 women with RA, and it was inferred that MSCs have an immunoregulatory effect on Treg cells in these patients.[99,106] In another study, a randomized controlled trial was conducted with 172 patients with RA prescribed with DMARD, and the umbilical cord-MSCs were administered intravenously to the group treated with stem cells. Two weeks after the injection, lower joint pain/swelling and higher quality of life were observed in the group treated with MSC compared to the control group. Furthermore, no serious side effects were reported in the study except for mild fever and chills.[99,107]

SARCOPENIA

Sarcopenia is defined as a continuous and progressive loss of skeletal muscle mass that is associated with aging.[108,109] It is a common occurrence in middle-aged and older populations and can result in limited mobility, as well as an increased risk of fractures, falls, and death.[108,110]

Throughout life, satellite cells (SCs), which are mononuclear myogenic cells located between the basal lamina of differentiated myofibers and the sarcoplasm, provide some of the components necessary for the repair and reconstruction of damaged parts. They are a type of quiescent mononuclear myogenic cell that plays a role in tissue repair by initiating and participating in the process, as well as maintaining homeostasis.[108,111] On the other hand, it is thought that pericytes (PCs), which are also known as MSCs, have multifaceted differentiation capabilities and regenerative capacity. Both of these cells share the common characteristic of contributing to skeletal muscle repair and regeneration, but they exhibit heterogeneous properties.[108] Additionally, it has been reported that PCs may be the precursors of SCs.[108,112] As a result, PCs may be functional in muscle regeneration in tissue engineering applications.[108,113]

ROTATOR CUFF LESIONS

Rotator cuff lesions, which are common in older adults and adults, are a condition that patients often encounter after shoulder trauma.[51,114,115] However, weaknesses and muscle pathologies such as compression are associated with tears in the rotator cuff.[51] Although tears can be successfully treated with open or arthroscopic techniques, the rate of re-tearing is high.[51,116,117]

In rats with infraspinatus lesions, they were treated with combined polylactic acid with BMDSCs or isolated polylactic acid. When compared with the isolated group, more successful results were observed in the combined group.[51,118]

LIGAMENT INJURIES

Knee injuries are quite common and have been reported to require surgical repair in 17-61% of cases.[51] Especially in anterior cruciate ligament (ACL) injuries, ACL fibroblasts and MSCs have been reported to have a regenerative effect.[51,119] When the effectiveness of MSCs applied for the treatment of medial collateral ligament injuries in rats was evaluated, it was found that there was less inflammation and high-quality healing in a short period of time.[51,120]

MENISCOPATHY

Meniscopathy, which is common in every age group, leads to biomechanical changes in the knee joint if it progresses. If left untreated, osteoarthritic changes occur in the knee joint.[51] In a massive meniscal defect pig model, BMDSCs were evaluated by magnetic resonance imaging and it was observed that MSCs could support meniscal regeneration.[51,121]

In conclusion, stem cells contribute to the development and regeneration of tissues and organs due to their self-renewal, differentiation, and transformation abilities. During embryogenesis, cell layer clusters are observed with the blastocyst formed by the fertilization of the egg and sperm. Thus, cells and tissues that can differentiate into each one are formed first in the fetus and then in the adult organism. Stem cells found in both embryonic and adult cells are classified. The differentiation potential of cells in each class varies. Especially in trauma, cancer, tissue injury, and many other diseases, tissue regeneration has become an urgent focus, and therefore stem cell therapy has been introduced. Ultimately, the concept of regenerative medicine emerged, along with tissue engineering technology, which provides three-dimensional structural scaffolds. This contributes to new tissue production, mimicry of target tissue movement, and appropriate tissue perfusion. In addition, due to their osteogenic, chondrogenic, and adipogenic potential, the use of MSCs is encountered in many orthopedic problems. Mesenchymal stem cell application for cartilage injuries and OA is a therapeutic research area that results in functional cell differentiation, cartilage regeneration, resolution of pain, and optimization of the intra-articular environment. Adipose-derived MSCs provide an advantage in terms of high availability among MSC sources, while synovial-derived MSCs have superior osteogenic and chondrogenic ability. Other cell sources for cartilage repair include chondroprogenitors, articular chondrocytes, nasal septum cartilage, and even MuSCs can be included. Stem cell applications in SCI, which encompasses important goals such as healing damaged neurons and providing axonal regeneration, use various MSCs, iPCSs, hESCs, and neural stem cells as cell sources. Stem cell treatments applied in SCI animal models have shown increased myelination of grown axons, functional recovery, myelination of injured nerves, and improvements in motor and various scores. In light of all this information, there is a need for an increase in stem cell research in this field in the future. It has been reported that the use of MSCs in bone defects, fractures, and non-union areas increases various growth factors, increases bone formation and mineral density, and provides successful results in terms of union. MSCs applied in osteoporosis models are reported to support trabecular thickness increase, osteogenesis, new bone formation, bone mineral density increase, and bone mass increase. Mesenchymal stem cells applied in OI lead to an increase in bone mineral density without complete healing and reduce bone fragility. For unresolved problems in RA, MSCs contribute to their regenerative capacity and immunomodulatory effects. Indeed, various studies have reported that MSCs reduce joint swelling or degeneration, inflammation, and pain, and improve clinical symptoms. Mesenchymal stem cells, hESCs, and DFbs may be used in tendon injuries. Especially with their growth hormone secretion properties, MSCs can increase endogenous connective tissue cell proliferation and support tendon healing. Mesenchymal stem cells applied in ligament injuries resulted in regenerative effects and high-quality healing. It is reported that MSC application shows successful results in rotator cuff lesions, while MSC application has been reported to provide regenerative effects for the meniscus in meniscopathy. *In vitro* and *in vivo* MSC applications have been reported to increase ECM production and exhibit AF cell-like needle shape in MSCs in IVD degeneration, respectively. The most commonly used MSC in femoral head osteonecrosis has been observed to promote femoral head healing and osteoblast differentiation. However, factors such as stage and etiology affect the treatment. Finally, muscle-derived stem cells and SCs may be useful for muscle repair and regeneration. Further studies are needed on these cells. Stem cells applied for therapeutic purposes can provide various improvements depending on the characteristics of the transplanted areas. Animal and clinical studies on stem cell applications in orthopedic conditions will still be needed in the future.

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