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The Use of Mesenchymal Stem Cell Secretome in Osteoarthritis: A Literature Review

Gede Agastya Pracheta Ewari[1], Dr. I Gusti Ngurah Wien Aryana, Sp. OT (K)[2]

[1]Resident of Orthopaedic & Traumatology, RSUP. Prof. I.G.N.G Ngoerah, Faculty of Medicine, University Udayana, Denpasar, Bali, Indonesia
[2]Consultant of Orthopaedic & Traumatology, RSUP. Prof. I.G.N.G Ngoerah, Faculty of Medicine, University Udayana, Denpasar, Bali, Indonesia

Corresponding Author: Gede Agastya Pracheta Ewari

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ABSTRACT

Osteoarthritis (OA) stands as the most prevalent musculoskeletal disorder among the elderly, affecting an estimated 303 million individuals globally in 2017, with projections indicating a 25% global population impact by 2040. Characterized by the progressive degradation of articular cartilage, formation of osteophytes, subchondral bone damage, and synovial membrane inflammation, OA's pathogenesis is multifactorial, involving inflammation, oxidative stress, and cellular aging, alongside contributors like obesity, gender, and genetics. Presently, therapeutic options remain limited to symptomatic relief, with interventions such as physiotherapy, pain management with anti-inflammatories, and viscosupplementation, culminating for many in total joint replacement surgeries, albeit with risks of thrombosis, infection, and increased healthcare costs.

In recent years, mesenchymal stem cells (MSCs) have emerged as a promising avenue for OA treatment due to their immunomodulatory, chondrogenic, and regenerative properties. Derived from various sources like bone marrow, adipose tissue, and umbilical cord tissue, MSCs offer potential in tissue repair and regeneration. Clinical studies have surged, with 227 registered trials on clinical.gov, reflecting growing interest in MSC therapy for OA. Particularly intriguing is the focus on MSC secretome, encompassing cytoprotective factors like growth factors, chemokines, cytokines, and hormones, which exert paracrine effects aiding differentiation, matrix synthesis, angiogenesis, tissue repair, and immunomodulation. Understanding the role of MSC secretome holds promise in reshaping OA management paradigms, offering avenues beyond symptomatic relief towards disease modification and joint preservation healing properties.

Keywords: Osteoarthritis, Joint Disease, Cartilage regeneration; Secretome; Stem cells.

1. INTRODUCTION

Osteoarthritis (OA) is the most common musculoskeletal disorder occurring in the elderly population. In 2017, it was estimated that around 303 million people worldwide experienced OA, with projections suggesting that it will affect 25% of the global population by 2040. OA is defined as a progressive degenerative disease characterized by the degradation and loss of articular cartilage components, osteophyte formation, subchondral bone damage, and inflammation of the synovial membrane. The pathogenesis of OA is multifactorial, involving mechanisms related to inflammation, oxidative stress, cellular

aging, and contributing factors such as obesity, gender, and genetic predisposition.
Currently, there are no approved therapies or procedures to prevent joint damage caused by OA. Current treatments, including physiotherapy, pain management with anti-inflammatory drugs, and viscosupplementation, are only symptomatic and aim to alleviate symptoms, especially pain. Eventually, many OA patients undergo total joint replacement. While surgery can improve mobility and reduce pain, it carries risks of thrombosis, infection, and increased costs. Therefore, the development of effective OA treatments has become a medical priority.
In recent years, mesenchymal stem cells (MSCs) have emerged as a promising regenerative cell-based therapy for conditions like OA. MSCs, adult stem cells isolated from various sources such as bone marrow, adipose tissue, and umbilical cord tissue, hold potential due to their immunomodulatory, chondrogenic, and regenerative properties. Clinical application of MSCs in OA patients has been increasing, with 227 clinical studies currently registered. It is proposed that the beneficial outcomes of MSC application should be associated with the secretome derived from MSCs, consisting of cytoprotective factors like growth factors, chemokines, cytokines, and hormones, which exert paracrine effects in processes such as differentiation, matrix synthesis, angiogenesis, tissue repair, and immunomodulation. The aim of this article is to review the role of the MSC secretome in osteoarthritis.

2.1 OSTEOARTHRITIS

2.1.1 DEFINITION

Osteoarthritis is a degenerative joint disorder that occurs in the cartilage, characterized by pain upon pressure on the affected joint (Zhang et al, 2016). Chronic atrophy in osteoarthritis affects all parts of the joint, including the cartilage, joint lining, ligaments, and the bone underneath. Cartilage loss, osteophyte formation, and subchondral bone sclerosis in osteoarthritis patients can lead to pain, disability, and decreased quality of life. Structural changes can be observed radiologically, including evidence of joint space narrowing, osteophyte formation, and bone remodeling around the joint. Osteoarthritis can occur in any synovial joint in the body but most commonly affects large joints (such as the knees and hips), hands, and the spine. (Valdes, 2018)

2.1.2 ETIOLOGY

The exact causes of osteoarthritis remain controversial due to its multifactorial nature. Based on its etiology, osteoarthritis consists of two types: primary OA and secondary OA. In primary OA, also known as idiopathic, individuals develop degenerative joint disease without any preceding abnormalities. In this type, the aging process occurs prematurely and is accelerated in individuals with genetic factors, without known contributing factors. Other factors such as excessive joint use can hasten this degenerative process. Primary OA is most common in adult women, emerging spontaneously in middle age and gradually progressing with aging. This type of osteoarthritis is typically found in middle-aged white women and is generally polyarticular, with acute pain in the distal interphalangeal joints followed by swelling known as nodules.
Secondary OA develops as a result of trauma or diseases causing damage to the joint cartilage. Secondary type occurs more frequently than the primary type and is generally more common in men. Secondary degenerative joint diseases more commonly affect weight-bearing joints such as the hips, knees, and intervertebral discs in the lumbar spine. Several conditions that can lead to degeneration in this secondary type include congenital joint abnormalities (such as developmental dysplasia of the hip or clubfoot), joint infections (septic arthritis), non-specific joint inflammation (rheumatoid arthritis), metabolic arthritis (gout), hemarthrosis, trauma, joint instability, extra-

articular deformities, osteonecrosis, and others (A. Jones & Doherty, 2005).

2.1.3 RISK FACTOR

One of the risk factors for osteoarthritis is obesity, where obesity is the strongest risk factor for knee osteoarthritis. The effect of obesity on the development and progression of osteoarthritis primarily occurs through increased stress on weight-bearing joints. Three to six times the body weight is exerted on the knee joints when the body is supported on one leg. Increased body weight further multiplies the load on the knee joints during walking. Research indicates that the higher the Body Mass Index (BMI), the greater the risk of developing knee osteoarthritis (Grazio, 2009).

Obesity exacerbates osteoarthritis symptoms, with obese individuals experiencing more severe osteoarthritis symptoms. Obesity not only initiates the onset of osteoarthritis but also results from the inactivity of osteoarthritis patients. Besides increasing mechanical pressure on bones leading to cartilage damage, obesity is indirectly associated with osteoarthritis occurrence through systemic factors. Apart from obesity as a risk factor, knee trauma history such as cruciate ligament damage and meniscal tears are also risk factors for osteoarthritis onset. Age and gender significantly influence osteoarthritis occurrence. Age is the primary risk factor for osteoarthritis onset, with prevalence and severity increasing with age. Women are twice as likely to be affected as men. Although the prevalence of osteoarthritis is roughly equal between men and women before the age of 45, above the age of 50, osteoarthritis is more prevalent in women, especially in the knee joints (Klippel, 1994).

2.1.4 PATHOGENESIS

Initially, osteoarthritis was believed to result from wear and tear of the joint surface, but now the mechanisms of osteoarthritis are much more complex. Osteoarthritis involves the degeneration of cartilage, abnormal bone remodeling, osteophyte formation, and joint inflammation. All four components of the synovial joint are involved in the pathological process of OA, including the meniscus, cartilage, subchondral bone, and synovial membrane (Mobasheri and Batt, 2016).

Osteoarthritis is not just a result of aging but also involves disturbances in the homeostasis of cartilage metabolism with structural damage to proteoglycan and collagen in cartilage. Mechanical and chemical disturbances such as age, obesity, and excessive joint use are important factors that stimulate the formation of abnormal molecules and cartilage degradation products in the joint synovial fluid, leading to joint inflammation and chondrocyte damage.

Chondrocytes synthesize type II collagen to strengthen joints and proteoglycans to make the tissue elastic, maintaining the cartilage matrix to ensure proper joint cushioning. Cartilage lacks blood vessels, so the repair process in cartilage is very limited and differs from other tissues. The cartilage's response to stimulation involves chondrocytes producing new matrix to repair themselves. However, chondrocytes fail to synthesize quality matrix and maintain the balance between degradation and synthesis of the extracellular matrix, resulting in changes in collagen fiber diameter and orientation, altering cartilage biomechanics (Zlotnicki et al., 2016).

The articular cartilage that comprises knee joints is hyaline cartilage composed of proteoglycans and type II collagen. Subchondral bone provides support to the joint and is formed by type I collagen. The synovial membrane produces synovial fluid, composed of lubricin and hyaluronic acid, which nourishes cartilage and acts as a joint lubricant. The synovium consists of two types of synoviocytes: fibroblasts and macrophages. Synovial fibroblasts produce synovial fluid components, while synovial macrophages are typically dormant but become active in the inflammation process (Kuyinu et al., 2016).

Furthermore, an inflammatory mechanism occurs in response to joint injury. Joints release inflammatory cytokines such as

Interleukin-1 (IL-1), IL-6, IL-4, IL-13, and TNF-α, as well as enzymes that degrade cartilage such as aggrecanases and collagenases / Matrix Metalloproteinases (MMPs) (Gabay, 2006; Li et al., 2017). In OA, there is an increase in the release of inflammatory mediators, especially pro-inflammatory mediators such as IL-1β, TNF-α, IL-6, and Nitric Oxide (NO), into the joint cavity. These cytokines induce chondrocytes to produce proteases, chemokines, and eicosanoids such as prostaglandins and leukotrienes by binding to receptors on the chondrocyte surface and causing MMP gene transcription, leading to increased enzyme production. The release of MMP enzymes causes degradation of the cartilage matrix, leading to joint cartilage degradation. In this situation, chondrocytes experience hypertrophy and lose their ability to form new collagen matrix, inhibiting matrix synthesis and increasing cell apoptosis (Mobasheri and Batt, 2016).

Inflammation stimulates chondrocytes to release protease enzymes such as MMP and aggrecanase. These MMPs are then activated through a cascade involving serine proteinases (plasminogen activators), free radicals, and several types of membrane MMPs. This enzymatic cascade is controlled by various inhibitors, including TIMP and plasminogen activator inhibitor (PAI) (Amar et al., 2017). In the elderly, chondrocytes produce more inflammatory cytokines. Advanced glycation end products (AGEs) also play a role in this process. AGEs accumulate in cartilage in the elderly and bind to chondrocyte receptors, releasing pro-inflammatory cytokines and VEGF, which then cause cartilage degeneration (Siebuhr et al., 2014). Chondrocytes also release Vascular endothelial growth factor (VEGF), increasing synovial vascularization and vascular invasion into the joint. VEGF is released due to prolonged mechanical load on cartilage, leading to lesions in subchondral bone and accompanying pain (Mobasheri and Batt, 2016).

Abnormal remodeling occurs in subchondral bone, leading to calcification and the formation of subchondral cysts and osteophytes. Subchondral sclerosis, the end result of abnormal bone remodeling, occurs at the end of the osteoarthritis process (Bay-Jensen et al., 2016). The integrity of cartilage tissue depends on a complex network of type II collagen, proteoglycans, and various additional proteins such as fibronectin. These molecules are synthesized and integrated into the extracellular matrix (ECM) by chondrocytes. Loss of ECM in cartilage is associated with an increased rate of type II collagen breakdown by collagenase and simultaneous breakdown of aggrecan molecules. Aggrecan is the main proteoglycan in joint cart.

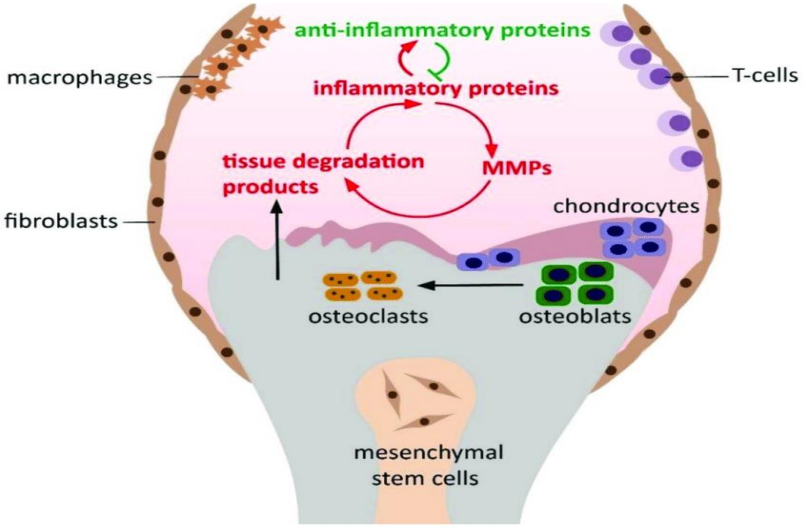

Figure 1: Pathogenesis of Osteoarthritis

2.1.5 Synovial Joint Anatomy

1. Cartilage

In osteoarthritis, the cartilage surrounding the joints undergoes damage. This can be caused by genetic disorders such as defects in type 2 collagen and other chondropathies, where mutations affect cartilage-related proteins, leading to accelerated osteoarthritis development. In non-traumatic osteoarthritis, cartilage softening occurs due to tissue damage to type 2 collagen, resulting in increased proteoglycan water absorption, which is considered an initial pathogenic factor.

2. Meniscus

In cases of osteoarthritis, the meniscus undergoes extrusion, which is the condition of losing articular cartilage. It is known that prolonged and neglected joint space narrowing is a major cause of osteoarthritis. Radiographs have shown that the loss of joint space is a consequence of medial meniscus extrusion from its normal position, indicating meniscus displacement. Additionally, MCL dysfunction can also be a major cause of meniscus extrusion, as the MCL acts as a medial meniscus restraint during jumps, knee extensions, and can play a role in preventing extrusion. Furthermore, tears in the posterior meniscus can lead to progressive osteoarthritis, as dynamic knee joint disorders cause abnormal pressure on the meniscus circle.

3. Bone

Like injuries to other joint tissues, bone trauma can cause malalignment or joint predisposition leading to abnormal pressure, thus accelerating osteoarthritis. Several types of bone dysplasia can also cause changes in joint biomechanics, subsequently resulting in osteoarthritis. The main factor often causing osteoarthritis is increased stiffness of the subchondral bone plate, which can initiate cartilage damage, especially fibrillation, as the integrity of both tissues is necessary for normal joint function.

4. Synovium

Synovitis may not be the primary initiator of osteoarthritis, but the significance of synovitis and joint inflammation in general as secondary factors involving pro-inflammatory cytokines drives progressive joint destruction. Osteoarthritis originating from synovial refers to a disease setting where osteoarthritis is primarily triggered by autoimmune primary synovial inflammation, septic arthritis, or crystals. (Mcgonagle et al, 2010)

2.1.6 Clinical Manifestations

The most common complaint in osteoarthritis is joint pain, especially when moving or bearing weight, which alleviates during rest. Pain often develops gradually over several years, typically in asymmetrical joints. Joint movement causing pain may result from capsule irritation, periostitis, and periarticular muscle spasms. Initially, pain is localized but can spread throughout affected joints as the disease progresses. This pain is often accompanied by swelling, reduced joint range of motion, and mechanical abnormalities. Limited motion is often associated with osteophyte formation and uneven joint surfaces due to cartilage loss or muscle spasms. Joint stiffness, which may occur after prolonged joint inactivity (gel phenomenon), usually resolves upon movement (Neumann, 2009).

2.1.7 Osteoarthritis Classification

Based on its etiology, Osteoarthritis can occur either primarily (idiopathic) or secondarily. Secondary Osteoarthritis is caused by other conditions or diseases (IRA, 2014). According to Kellgren and Lawrence, the classification of Osteoarthritis in radiological examinations can be divided as follows:

Table 2.1 Classification of Osteoarthritis – Kellgren-Lawrence (Kohn, Sassoon, & Fernando, 2016)

Grade	Deskripsi grade Kellgren-Lawrence
KL grade 0	No radiological findings of osteoarthritis
KL grade 1	Doubtful narrowing of joint space and possible osteophytic lipping
KL grade 2	Definite osteophytes and possible narrowing of joint space

KL grade 3	Moderate multiple osteophytes, definite narrowing of joint space, small pseudocystic areas with sclerotic walls and possible deformity of bone contour.
KL grade 4	Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour.

2.1.8 History Taking

Knee osteoarthritis can be diagnosed based on clinical symptoms and radiological imaging with X-rays. Symptoms experienced by patients vary individually, ranging from joint pain, fatigue, mood changes, to difficulty sleeping. Several epidemiological studies on knee osteoarthritis confirm knee joint injury as a major risk factor for the development of osteoarthritis (Soloman et al., 2005; Salter, 2008).

2.1.9 Evaluation

1. Synovial Fluid Analysis

Synovial fluid in OA patients typically shows normal results, with the fluid being clear or colorless, occasionally slightly yellowish. The leukocyte count is < 2000 cells/mm3. The fluid is obtained by intra-articular injection into the asymptomatic joint (Cesare, 2017).

2. X-ray Examination

Common radiological findings for knee osteoarthritis include joint space narrowing accompanied by cartilage loss. Osteophytes form due to cartilage loss, along with subchondral sclerosis. Osteophytes are the most specific feature for assessing knee OA. Radiological classification systems for OA typically rely on joint space narrowing (JSN), osteophytes, or both (Carrilon, 2008). Various radiological grading systems are available, such as the Kellgren-Lawrence, Ahlback, Menkes, or OARSI (Osteoarthritis Research Society International) systems. The most commonly used grading system is the Kellgren-Lawrence (KL) system, which assesses radiological features of knee OA on a scale of 0-4 based on osteophyte and joint space narrowing (Cesare, 2017).

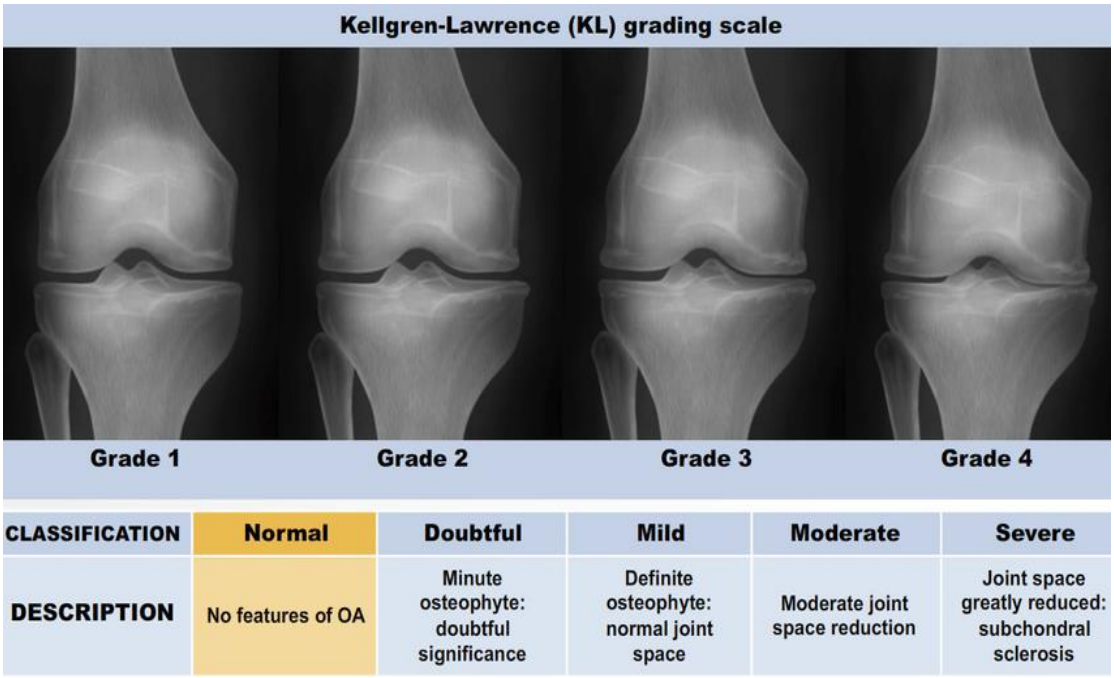

Figure 2.2 Knee X-Ray of Osteoarthritic Patients

3. MRI Examination

Several semi-quantitative assessment systems are available for MRI examinations. The Whole Organ Magnetic Resonance Imaging Score (WORMS) is the oldest and most commonly used semi-quantitative assessment system for grading OA. WORMS evaluates cartilage, bone marrow lesions,

subchondral cysts, bone attrition, effusion, synovitis, osteophytes, meniscal tears, and cruciate ligament tears (Cesare, 2017).

4. CT Examination
CT (Computed Tomography) is the preferred method for assessing cortical bone and soft tissue calcifications. It is the primary technique for evaluating facet joints. CT arthrography is the most accurate method for assessing articular cartilage surface damage due to the high contrast between cartilage, contrast agents, and bone. The use of this method is limited due to cost, invasiveness, and radiation effects (Cesare, 2017).

2.1.10 Management of Knee Osteoarthritis
1. Non-Operative Management
The initial therapy for symptomatic knee osteoarthritis includes patient education and physical therapy. Exercise programs have shown satisfactory results, but benefits decline after 6 months if exercise is discontinued. The American Academy of Orthopedic Surgeons (AAOS) recommends this therapy. Weight loss is crucial for knee osteoarthritis and is indicated for patients with symptomatic arthritis and a BMI above 25. The best way to lose weight is through diet and exercise. Drug therapy is also a first-line treatment for symptomatic knee osteoarthritis. There are many types of NSAIDs available, and the choice of medication depends on the physician. The duration of NSAID administration should be considered based on effectiveness, side effects, and past medical history (Hsu, 2019).

2. Operative Management
For patients with severe OA, surgery is an effective option. Surgical procedures include arthroscopic debridement, joint debridement, bone decompression, osteotomy, and arthroplasty. Although surgical intervention can relieve joint pain in OA, joint function may not always be adequately restored, so pre- and post-operative physical therapy should be well-prepared. Types of arthroplasty include Unicompartmental Knee Arthroplasty (UKA), Partial Knee Replacement (PKR), and Total Knee Arthroplasty (TKA)/Total Knee Replacement (TKR). UKA is indicated for uni-compartmental knee osteoarthritis, especially in older patients aged over 60 years. TKA is the preferred operative therapy for patients who fail conservative therapy and those with arthritis involving more than one compartment. TKA is a good intervention for patients with severe knee osteoarthritis pain. The advantages of Partial Knee Replacement over Total Knee Replacement include faster rehabilitation and recovery, lower morbidity rates, and minimal pain (Hsu, 2019).

2.2 Secretome Mesenchymal Stem Cell
The MSC secretome is a collection of biologically active molecules and extracellular vesicles (EVs) released by MSCs. It consists of EVs, exosomes, microvesicles, membrane particles, peptides, and proteins (cytokines). Data indicates the presence of over 60 cytokines/chemokines identified in the MSC secretome. The secretome has been shown to play a role in most of the benefits of MSCs through paracrine and anti-inflammatory effects (Galderisi & Giordano, 2014). For this reason, recent research has focused on the MSC secretome. The secretome is currently considered a potential substitute for MSCs in cell therapy due to its comparable ability to enhance tissue regeneration and modulate immune responses (Eleuteri & Fierabracci, 2019).
The secretome was first discovered by Timmers et al., who fractionated MSCs and found that components measuring 50 to 200 nm exhibited the most activity (Timmers et al., 2007). Subsequent characterization studies identified this fraction as EVs, which are endogenous lipid nanoparticles that mediate the transfer of their contents across cellular boundaries (Guescini et al., 2010; Andaloussi et al., 2013; Romancino et al., 2013; Forterre et al., 2014).
EV is a generic term accepted by the International Society for Extracellular Vesicles (ISEV) to describe vesicles

produced by MSCs. These vesicles lack a nucleus and the ability to replicate, and they are released by cells into the extracellular space (Théry et al., 2018). EVs are found in various biological fluids such as blood, urine, saliva, amniotic fluid, and milk (Iraci et al., 2016), and they can interact with recipient cells through direct binding or ligand-receptor binding (Kahroba et al., 2019).

EVs released by cells can be classified into different subtypes based on their physical features such as size or density. Small EVs (sEVs) typically have a size below 200 nm, while medium/large vesicles are characterized by a size larger than 200 nm. EV classification is also based on their biochemical composition, including the presence of transmembrane proteins or glycosylphosphatidylinositol (GPI), cytosolic or periplasmic proteins, and proteins associated with non-EV structures.

EVs are characterized by specific cargoes consisting of mRNA, microRNA (miRNA), proteins, or DNA. These genetic materials are protected from the oxidative extracellular environment and can be transferred to distant cells to modulate tissue repair processes (Cantaluppi et al., 2012; Borges et al., 2013). The use of the secretome, particularly EVs derived from MSCs, in cell therapy is rapidly evolving as a promising option. The MSC secretome can overcome safety issues associated with the use of live cells, ethical concerns related to cell source, and immune compatibility issues.

The MSC secretome is considered a potential bioactive pharmaceutical component, where its vesicular component, containing transmitted genetic information between various cell types, holds promise as a drug delivery system, especially due to its homing ability, opening opportunities for specific compound and target (drugs, proteins, etc.) delivery to damaged lesions (Bari et al., 2018). A secretome-based approach should also minimize biological variability, allow for precise dosing, and thus lead to the development of safe and effective therapy strategies with predictable outcomes.

The isolated secretome of EVs from MSCs is the best alternative for cell-free therapy due to its low immunogenicity, high biocompatibility, and low cytotoxicity to tissues. They can also be used for nano-regenerative treatment as they can be engineered to target specific cells or tissues and serve as drug carriers.

2.2.1 Use of Secretome Mesenchymal Stem Cell in Osteoarthritis

The secretome in conditioned media produced by mesenchymal stem cells (MSCs) can stimulate the repair of cartilage defects. There is abundant evidence from various in vitro and in vivo studies demonstrating the potential outcomes of MSC secretome on osteoarthritis (OA). The improvements can be observed morphologically as thickening of the cartilage, increased number of chondrocytes, regular joint surface, and histologically, there is evidence of repair in the joint cartilage matrix (Soetjahjo et al., 2018; Chen et al., 2019).

Histological studies using immunohisto-chemistry also show increased expression of TGF-β, SOX-9, aggrecan, and type II collagen, which are pathways involved in the formation of hyaline cartilage repair after administration of MSC secretome. Not only repair, but other studies also indicate that the secretome can provide protective effects on joint cartilage by increasing the expression of the COL2A1 gene, which functions in forming collagen matrix components and reducing apoptosis in chondrocytes. MSC secretome has been found to be distinct from other secretomes. Its distinctions include the presence of angiogenic factors, lower levels of matrix metalloproteinases (MMPs), high production of TGF-β, and the presence of anti-inflammatory chemokines and cytokines that enable MSCs to control inflammation (Zhou et al., 2020).

Collagen II and aggrecan are produced to maintain extracellular matrix homeostasis. Many cytokines are considered as paracrine signaling sources acting as immunomodulators, anti-inflammatory,

angiogenic, and cartilage repair agents. However, only a few cytokines have been identified. Specifically, thrombospondin-2, cell-to-cell interactions, and cell-to-matrix interactions mediate glycoprotein responsible for activating signaling pathways in chondrogenesis and cartilage regeneration through ERK and p38/MAPK signaling pathways (Kim et al., 2015).

Thrombospondin-1 is also found in the MSC secretome, which can regulate TGF-β/Smad pathway activation in chondrocytes for cartilage regeneration. As an anti-inflammatory effect, prostaglandin E2 acts as an alternative macrophage activation, inhibits dendritic cell maturation, and reduces NK cell cytotoxicity. IL-10 also acts as an anti-inflammatory cytokine to decrease TNF-α, IL-1β, IL-6 (Arrigoni et al., 2020).

In addition to cytokines, the secretome also contains extracellular vesicles (EVs) with RNA KLF3-AS1, which can inhibit miR-206 that may cause OA development and aging (overexpressed in OA). EVs also contain miR-21 as an anti-inflammatory effect to reduce TNF-α-induced apoptosis regulation. Moreover, to halt OA progression, EVs containing miR-92a-3p can act as Wnt inhibitors and suppress the expression of ADAMTS4 and ADAMTS5 to delay OA progression. As a regenerative process, there are EVs containing miR-140-5p to promote chondrocyte proliferation and migration and inhibit chondrocyte hypertrophy through the Wnt5a/NFκB and Wnt5b/JNK pathways (Bousnaki et al., 2020)

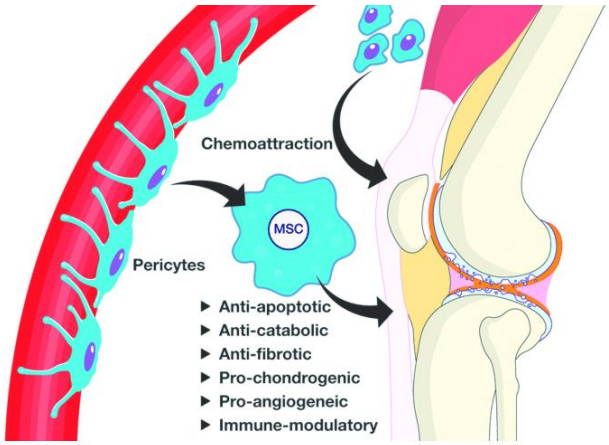

Figure 2.3 Mechanism of Secretome in Osteoarthritis

In the current landscape, a majority of researchers prefer to investigate MSC secretome for OA therapy. Secretomes with high expression of miRNA or lncRNA from MSCs have been reported to have significant effects on OA both in in vivo and in vitro studies. MSC secretome has been found to regenerate cartilage in several clinical trials using MSC treatment in OA patients (Bousnaki et al., 2020).

Kim et al. (2015) utilized MSCs embedded in fibrin glue and implanted via arthroscopic procedure in 49 patients. In this study, patients showed overall satisfaction with an increase in average IKDC and Tegner activity scores. Saphiro et al. (2016) used MSCs combined with platelet-poor plasma and injected into the knees of 25 patients. Significant improvements were found in ICOAP scores, VAS pain scores, and activity levels. Matas et al. (2018) administered MSCs as intra-articular injections into the knees of 26 patients. The results showed improvements in pain and function with lower WOMAC pain scores and VAS. No serious adverse effects were reported. Other clinical trials using MSCs by Pers et al. (2016), Freitag et al. (2019), and Lee et al. (2019) also showed improvements in pain and functional levels.

In vitro studies of MSC secretome for osteoarthritis therapy have also been

conducted. Saulnier et al. (2015) used horse MSC secretome to treat OA in IL-1β-stimulated rabbit synoviocytes as target cells, showing a decrease in MMP-1, MMP-3, MMP-13, IL1β, and TIMP, which could halt the progression of OA. Widowati et al. (2018) targeting human chondrocyte cell lines + IL-1β showed increased IGF-1 for chondrogenesis and decreased ADAMTS1, MMP-1, and MMP-3 to halt OA's pathological process. Wang et al. (2018) and Chang et al. (2019) also targeted human chondrocytes and showed increased MSC proliferation, cell viability, aggrecan, SOX-9, type II collagen, and decreased inflammatory factors and apoptosis. In vivo studies also demonstrated improved cartilage repair in 28 studies after applying secretome injections in OA animal models. The process of using secretome injections in OA models showed increased TGF-β, SOX-9, aggrecan, and type II collagen, which are the main pathways for cartilage repair and regeneration. However, clinical studies on MSC secretome for treating OA patients are still needed and ongoing (Bousnaki et al., 2020).

3. CONCLUSION

MSC-derived secretome can stimulate the repair of cartilage damage in osteoarthritis (OA). There is abundant evidence from both in vitro and in vivo studies indicating the potential outcomes of MSC secretome on OA. Improvements can be observed morphologically as thickening of the cartilage, increased number of chondrocytes, regular joint surface, and histologically, there is evidence of repair in the joint cartilage matrix. Similarly, histological studies using immunohistochemistry also show increased expression of TGF-β, SOX-9, aggrecan, and type II collagen, which are pathways involved in the formation of hyaline cartilage repair. Not only repair, but other research also indicates that the secretome can provide protective effects on joint cartilage by increasing the expression of the COL2A1 gene, which functions in forming collagen matrix components and reducing apoptosis in cells. Overall, MSC-secreted secretome stimulates cartilage repair, acts as anti-inflammatory, immunomodulatory, angiogenic, and anti-apoptotic agents through its cytokines and extracellular vesicles containing miRNA. MSC-secreted secretome is more stable and its production method is simpler compared to MSCs themselves

Declaration by Authors

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