

Clinical Application Prospect of Human Synovial Tissue Stem Cells

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Clinical Application Prospect of Human Synovial Tissue Stem Cells from Osteoarthritis Grade IV Patients in Cartilage Regeneration

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Abstract

Osteoarthritis (OA) is a joint problem that continues to increase in prevalence as life expectancy increases. OA can affect any joint, especially those that support body weight such as the knee and hip joint. Although both primary and secondary OA have the same clinical symptoms, it can be caused by different etiologies. OA is no longer considered a degenerative disease, although age is still a major factor. Various attempts have been made to regenerate joint cartilage damaged by OA. The use of stem cells in OA therapy is a very promising opportunity. Stem cells are undifferentiated biological cells and are multipotent to differentiate into specific cells. In principle, local stem cells are the best source of stem cells to regenerate the surrounding tissue. The synovial membrane is a tissue in the joint that can regenerate. After synovectomy surgery, repair, and growth of synovial tissue occur rapidly. Synovial tissue as a source of stem cells only provides a limited amount. One source of synovial tissue that can be used is tissue taken from the total knee replacement process in grade 4 OA patients. However, it is necessary to prove the potential of synovial tissue stem cells originating from old-age donors.

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Introduction

Osteoarthritis (OA) is a joint degenerative disease that affects many people throughout the world. OA is a very complex disease and can affect all joint components, especially joint cartilage and subchondral bone [1]. The main pathophysiology of OA occurs in cells and the extracellular matrix. The process of joint damage due to OA involves all joint components including joint cartilage, subchondral bone, ligament, meniscus, joint capsule, and synovial tissue. The complexity of the pathophysiology that occurs in OA makes no single therapy able to resolve the problem completely. So that the development of stem cells therapy is one solution to this problem [2]. Moreover, the use of stem cells originating from the synovial membrane (SM) is one of the best alternative sources [3].

The cause of OA is multifactorial so that until now the cause of OA is not known with certainty. In terms of etiology, OA is divided into two causes, primary and secondary OA. Primary OA occurs due to age, weight, and activity. Whereas secondary OA is caused by other diseases that affect the joints and can trigger the OA

process to occur faster such as: Joint infections, rheumatoid arthritis, gout, joint dysplasia, malalignment, and post-traumatic injuries that cause injury to parts of the joint such as anterior cruciate ligament rupture, torn meniscus, and intraarticular fractures. Abnormal development of joints, calcium crystal deposition, neuropathy, hemophilia, metabolic disorders (ricketsia, hemochromatosis, chondrocalcinosis, and ochronosis), and endocrine abnormalities (acromegaly, hyperparathyroidism, and hyperuricemia) can also cause secondary OA [4], [5], [6].

OA occurs because of interactions between systemic factors and local factors. Systemic factors include age, sex, genetics, hormones, and diet. Meanwhile, the local factors that play a role in the OA process are joint injury, obesity, and activity [7].

Pathogenesis

The main damage in OA occurs in joint cartilage, although in principle all joint components

also experience changes. Network changes in the OA process are the result of a combination of mechanical, cellular, and biochemical interactions [8]. Chondrocytes as the main constituent of joint cartilage have receptors to respond to biomechanical disorders around the cartilage, such as growth factors, cytokines, and other inflammatory mediators. In the OA process, there is an imbalance between pro-inflammatory cytokines that degrade the matrix, with anti-inflammatory cytokines and growth factors that prevent catabolic molecules.

Matrix metalloproteinase (MMP) is an enzyme that plays a role in the degradation of the matrix in OA. This enzyme is divided into five groups based on the specific substrate, namely collagenase, stromelysin, gelatinase, membrane-type MMPs (MT-MMP), and other types. MT-MMP has been identified in bone tissue. MT-MMP can initiate the activation of proMMP-2 and proMMP-13, where both enzymes can mediate damage to type II collagen in cartilage. Based on this information, it can be seen that MMP is responsible for cartilage destruction in OA [9], [10], [11]. Collagenases such as MMP-1, MMP-8, and MMP-13 can only degrade the helical domain of type II collagen, while MMP-3 degrades collagen types IX and XI [9]. MMP-13 plays a dominant role in the progression of cartilage degeneration with the main target being collagen [12].

Other enzymes that play a role to degrade the cartilage matrix are **disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)**. Aggrecanase has the most central role with MMP to degrade the matrix as ADAMTS-4 and ADAMTS-5. ADAMTS-4 is active during cartilage degeneration and its expression is increased in degenerative cartilage. ADAMTS-5 is present in normal cartilage and OA conditions [12].

Other mediators in an anabolic activity besides anti-inflammatory cytokines and growth factors are the tissue inhibitors of metalloproteinase (TIMP), which include the main inhibitors of tissue. TIMP is produced by fibroblasts and chondrocytes. Genomically, there are four types of TIMP, namely TIMP-1, TIMP-2, TIMP-3, and TIMP-4. TIMP-1 is a protective mediator and appears to be exceptionally high in OA in synovial fluid. TIMP-1 and TIMP-2 are both present in the SM of OA [13], [14], [15]. The expression of mRNA from TIMP by chondrocytes in OA cartilage is higher than TIMP by normal cartilage chondrocytes. MMP activity can be inhibited by TIMP in tissue destruction, although not significantly. A balance between MMP and TIMP activity is needed to maintain cartilage homeostasis. Research found increased MMP expression in early OA, both in humans and experimental animals. These results strongly indicate that OA therapy design is needed to specifically inhibit MMP [9].

The pathophysiological process in OA joints is also the result of mediating pro-inflammatory cytokines

and enzymes that degrade the matrix in catabolic activity [16]. Complex molecular mechanisms that overlap with each other produce tissue damage to the joints [13]. The molecular mechanism of OA is explained through the involvement of cytokines, chemokines, and inflammatory mediators in chondrocyte metabolism, which includes anabolism and catabolism activity [17], [18]. Unbalanced chondrocyte metabolism is caused by the overproduction of pro-inflammatory cytokines and enzymes that play a role in degrading the matrix. This is related to the decreased anabolic signaling, resulting in the destruction of the extracellular matrix and continued to cartilage degradation. The disruption of cartilage homeostasis is also caused by the presence of oxidative stress that results from reactive oxygen species (ROS). Furthermore, the process of catabolism will occur through cell apoptosis induction, destruction of matrix components, increased production of enzymes that will degrade the matrix and inhibit matrix synthesis, and oxidation of intracellular and extracellular molecules. An increase in catabolism activity and decreased anabolism activity cause a disturbed balance of extracellular matrix and consequently cartilage degradation. An imbalance between anabolic and catabolic activity at the molecular level results in OA, where the primary injury response occurs in joint cartilage [19], [20]. The overall condition of the joint depends on the expression of adequate growth factors, such as increased synthesis of transforming growth factor β (TGF- β) and insulin-like growth factor (IGF) in the extracellular matrix [12], [13].

In the process of OA, interleukin-1 (IL-1) and tumor necrosis factor- α (TNF- α) lead to chemotaxis and leukocyte degranulation. These cytokines also increase the expression of inflammatory mediators and the activity of several proteolytic enzymes such as MMPs and aggrecanase that play a role in degrading joint cartilage [10], [13], [20], [21], [22]. Molecules included in pro-inflammatory cytokines include IL-1 β (IL-1 β), TNF- α , IL-6, IL-15, IL-17, and IL-18 [7], [13], [14], [16], [23] (Figure 1).

IL-1 β is one of the most influential cytokines in the pathogenesis of OA and is widely produced by synovial and chondrocyte macrophages in the OA joint [14]. These cytokines can induce inflammatory reactions and catabolic effects independently [16]. The role of IL-1 β in pathogenesis is to suppress the production of type II collagen and proteoglycans and stimulate synovial cells to release MMPs [14]. IL-1 β cytokines also release proteoglycans from the extracellular matrix into the synovial fluid. Besides, IL-1 β can inhibit the synthesis of collagen types II, IX, and XI, as well as stimulate the production of abnormal proteoglycans, and decrease TIMP expression [13]. As for its role in stimulating, the production of ROS, such as peroxide and hydroxylate radicals that can damage joint cartilage directly [16].

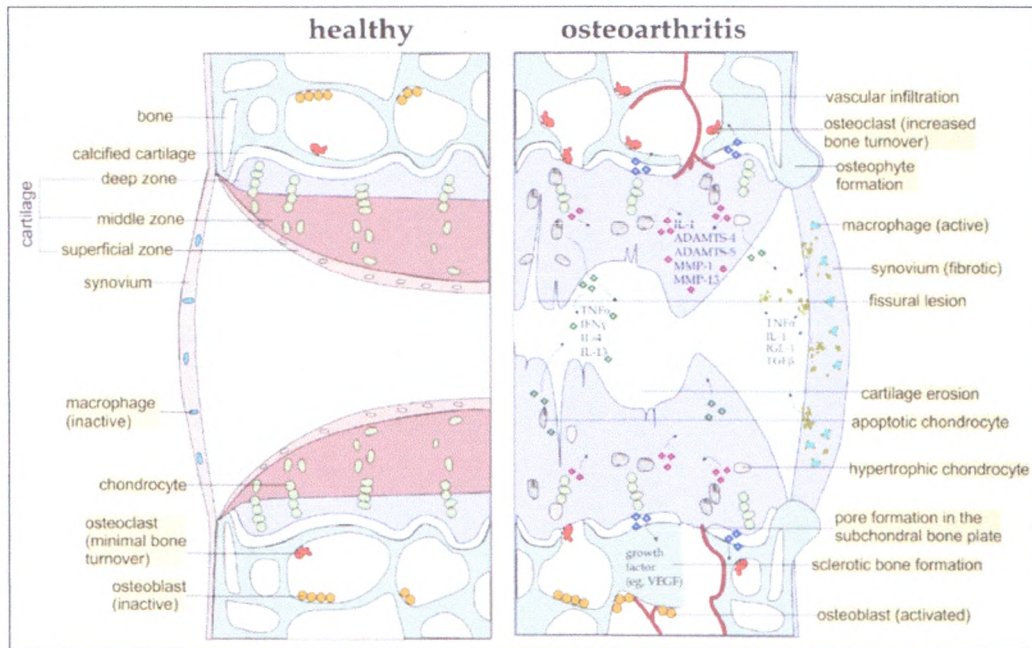


Figure 1: Signaling pathway and structural changes in osteoarthritis joint cartilage

Besides IL-1 β , TNF- α is an important inflammatory cytokine associated with the pathophysiological process when OA occurs. There is a synergy between the two cytokines of the many phenomena of OA. In the OA disease process, TNF- α affects the blockade of chondrocyte synthesis from proteoglycan components, proteoglycan protein binding, and type II collagen [16].

Stem Cells Therapy for OA

OA is caused by a complex pathophysiological mechanism involving cytokines and inflammatory mediators, and as of to date no single drug has been able to overcome the inflammatory mediators involved. Various attempts of therapy are used to regenerate the tissue around the knee joint, especially cartilage joints, to reduce the complaints caused by OA and help the knee joint to function optimally. Current developing treatments are derived from a cellular product such as platelet-rich plasma, bone marrow aspirate, and mesenchymal stem cells (MSC) [24].

Stem cells possess a therapeutic effect through differentiation ability, immunity regulation, anti-inflammatory, improving microenvironmental conditions, and enhancing the regeneration process [25]. MSC

have multipotent progenitor capabilities derived from adult stem cell (ASC) populations that can be found in some tissues such as bone marrow, peripheral blood, adipose tissue, synovium tissue and fluid, placenta, and umbilical cord. A cell qualifies as an MSC if it meets the requirements set by the International Society for Cellular Therapy. The terms of conditions are having the ability to stick on the surface of the cup when cultured in a plastic adherent cup and having a cluster of differentiation proteins surface molecules, namely CD73, CD90, and CD105. Unlike hematopoietic stem cells, MSC do not express CD34, CD14, CD45, and human leukocyte antigen-DR. Furthermore, they can differentiate through three main pathways of mesenchymal, that is: Osteogenic (becoming bone cells/osteocytes), chondrogenic (becoming cartilage cells), and adipogenic (becoming fat cells/adipocytes) [26]. With its chondrogenic potentials, MSC and their immunosuppressive characteristics become the major modalities in the treatment of OA.

In the process of differentiation chondrogenic culture, MSC are strengthened by the role of several growth factors such as IGF-1, fibroblast growth factor 2 (FGF-2), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF). Moreover, the potential of chondrogenic culture can also be increased by the addition of non-protein components such as dexamethasone and ascorbic acid. The oxygen tension factor is one of the factors that influence the occurrence of chondrogenic differentiation. Low oxygen levels can

trigger chondrogenic differentiation while Col2A1 and SOX9 gene expression also increase proteoglycan synthesis and type II collagen [27]. Physical stimulation can also affect calcium channels and the chondrogenic process. With an increase in concentration, intracellular calcium can initiate a signaling pathway which can increase the expression of a cartilage-specific gene and produce protein-specific cartilage during the differentiation process of MSC [28].

MSC are a multipotent type of ASC. Adult MSC can be isolated from several tissues such as bone marrow, adipose tissue, placenta, umbilical cord blood, periosteum, and other tissues that are the source of stem cells closest to damage. Compared to other sources, MSC derived from bone marrow and synovium have greater chondrogenic potential [29].

MSC have the immunosuppressive ability by lowering T cell proliferation through the secretion of pro-inflammatory cytokines. These cells also produce inflammatory mediators such as prostaglandins E2 and IL-6. Together with TGF- β , MSC improve the chondrogenesis process. Previous studies found that several growth factors, such as TGF- β , IGF-1, bone morphogenic protein (BMP), FGF, and EGF were used in *in vitro* cartilage tissue engineering to direct chondrogenic phenotypes, stimulate extracellular matrix production, and direct chondrogenesis [30], [31], [32].

In studies related to differentiation, adult MSC experienced changes that occur in the cellular microenvironment. Genes that do not show expression in specialized proresolving mediator (SPM) will appear when SPM differentiates into chondrocytes. These genes include glypican-3, cadherin-11, MMP-7 or type II collagen. On the contrary, other genes such as CX3CR1, MMP-1, and MMP-9 decreased the expression [33].

Possibility of Synovial Tissue Stem Cells from OA Patient Grade IV

SM can regenerate very well. This can be seen from the rapid growth of synovial tissue after synovectomy. This regeneration speed shows that the SM has the potential to repair damaged tissue and has potential as a source of stem cells. In different circumstances, the ability of synovial chondromatosis is a rare proliferative condition and the etiology is unknown. This raises the possible role of SM-MS in producing several intrasynovial cartilaginous nodules. MSC isolated from the SM called SM-MS or synovial mesenchymal progenitor cells, are known to have the same phenotype and function as MSC. The presence of MSC in the synovial layer raises questions about its origin. One of the possible origins of the presence of

MSC in the synovial layer is from blood that penetrates the synovial tissue or comes from bone marrow that is connected to the intraarticular space.

Local MSC in the joint can be found in almost all of the diarthrodial joint tissues, as shown in Figure 2. SM-MS has the same characteristics as other MSC sources, which can regenerate through chondrogenic, osteogenic, and adipogenic processes, and in certain circumstances have the ability of myogenesis. These stem cells are also found to have heterogeneous clonal abilities when applied to other types of populations. The studies that transplanted SMSC in mice found regeneration ability in anterior tibial muscle injury. When compared with other stem cell sources, those originating from tissues around the joints obtained SMSC with the highest chondrogenic ability [34].

The role of MSC in the synovial layer is related to the healing potential of tissue originating from the mesoderm. Furthermore, cells in the synovial layer are involved in the early osteoarthral disease. Bone marrow-MS (BM-MS) and SM-MS express different genes, including activin A, which are regulated in BM-MS. Unlike BM-MS, SM-MS derived from the SM maintains a proliferation rate and the potential for the formation of SM-MS which has a high self-renewal ability and multipotentiality inherent in a single cell. Single cells originating from SM-MS become heterogeneous during the expression process. Non-clonal plastic adherent synovial MSCs consist of a uniform set of cells. Koga *et al.* showed that synovium-derived MSCs transplanted in rabbits were converted into microenvironments [3].

Cells that originate from the human SM are known to have the best chondrogenesis potential among other mesenchymal cells and one of the sources that may be representative to repair damaged cartilage. One study revealed that SM-MS which was cultured with human autologous serum could differentiate into chondrocytes *in vitro*. However, the potential for estrogen is lower compared to cells implanted in fetal serum bovine. Synovial cells originating from older patients with OA can be reprogrammed into pluripotent cells in alginate culture by stimulating BMP-2 or BMP-7 in dexamethasone and non-serum conditions. The results show that the SM has the therapeutic potential for the treatment of joint cartilage damage using *in vitro* experiments because the human autologous serum is known to increase the proliferative potential of SM-MS through activating the PDGF signaling. Cells that resemble SM-MS can be found in healthy cartilage or cartilage that has OA [3].

Bone marrow cells that are embedded or present in growth factors such as TGF- β , BMP, and IGFs, have an important role in repairing cartilage damage. BMP especially BMP-7 and IGF-1 have shown the ability *in vitro* to stimulate chondrogenesis. The problem will remain in the complexity of the signaling pathways involved in chondrogenesis, which are

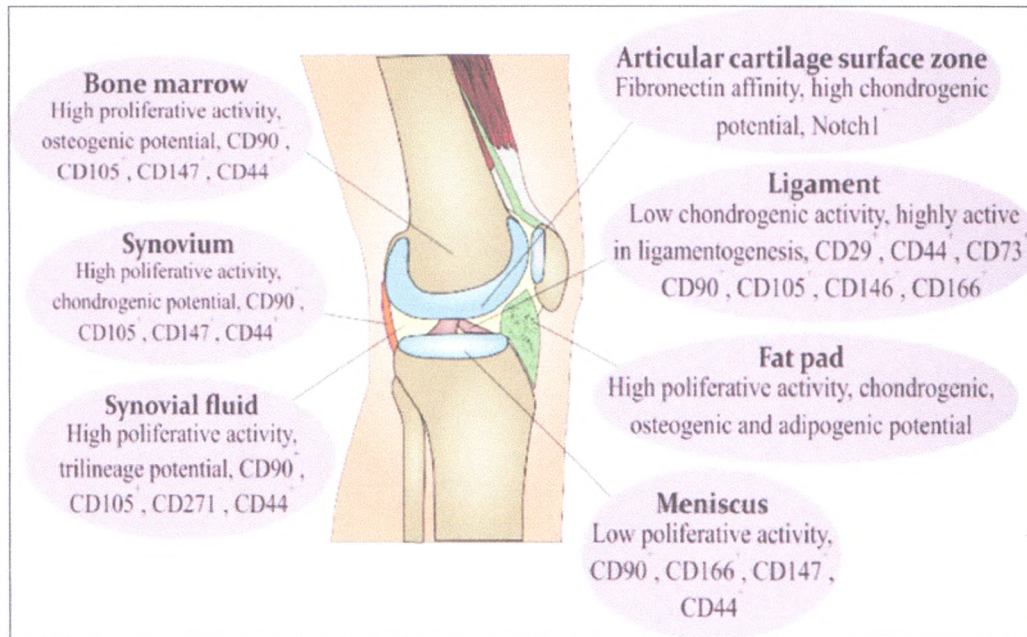


Figure 2: Characterization of stem cell surface markers of various tissues in the diarthrodial joint

stimulated by cell-to-cell contact. The profile of healthy and arthritis synovium fluid chemokines can contribute to the recruitment of human mesenchymal progenitors from bone subchondral tissue. Synovial fluid in healthy humans, patients with OA, and rheumatoid arthritis contain different levels of chemokines such as CCL22, CCL27, CXCL5, and CXCL12 which can inhibit the migration of human subchondral mesenchymal progenitors. Other chemokines that can be found in synovium fluid such as CCL2, CCL24, and CXCL7 do not affect mesenchymal progenitor cells. The number of SPM recruited by synovial fluid from patients with rheumatoid arthritis is lower than that of OA or normal humans. This shows that chemotactic factors contribute to the attractiveness of the progenitor. There are different aspects of cell morphology that come from healthy human synovium fluid and those suffering from OA. This comparison shows that the SPM-MS level in the normal knee joint increases 7 times during the initial phase of OA. SPM-MS may play a role in homeostasis, remodeling, and tissue repair through cell turnover [3].

Conclusions

MSC derived from the SM of the knee joint in patients with grade VI OA have the potential to regenerate joint cartilage.

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