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Role of adipose-derived stem cells in osteoarthritis

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Abstract. Osteoarthritis (OA), a widespread degenerative condition affecting the joints, is especially prevalent in the elderly population. While pharmacological interventions are available to alleviate pain associated with this condition, their therapeutic efficacy remains limited. Furthermore, the potential for adverse reactions may inhibit satisfactory clinical outcomes in OA treatment. Recent studies indicate adipose-derived stem cells (ADSCs), due to their ease of procurement and expandability, as a promising alternative. These cells serve as an essential source for bone tissue engineering, given their ability to differentiate into various cell types, and thus, their transplantation may offer a novel approach in OA treatment. The relative abundance of ADSCs in human and animal bodies, coupled with the ease of material collection, lends them unique advantages. This review explores the pathogenesis of osteoarthritis, the biological characteristics of ADSCs, mechanisms of chondrogenesis, and their therapeutic potential for OA. We also delve into various culture methods associated with these cells, with the objective of offering fresh insights for clinical OA management.

Keywords: osteoarthritis, adipose-derived stem cells, chondro-differentiation.

1. Introduction

OA is a common degenerative condition that impairs the health of the bones and joints, affecting approximately 7% of the global population with differing degrees of severity. Those aged 65 and older are disproportionately affected. The pathogenesis of osteoarthritis is multifactorial, involving a complex interaction between factors including aging, genetics, trauma, and obesity. The disease is distinguished by pathological alterations in all joint tissues, including cartilage, subchondral bone, ligaments, meniscus, joint capsule, and synovium [1]. Osteoarthritis imposes a significant burden on patients and their families, necessitating the development of effective treatment methods. Although surgical interventions and medications are available, the need for improved therapeutic efficacy remains.

In this context, mesenchymal stem cells (MSCs) arise as a promising technique for cartilage repair due to their capacity to differentiate into bone and cartilage cells and to secrete substances that promote tissue repair. MSCs are increasingly recognized for their role in osteoarthritis treatment due to their regenerative, anti-apoptotic, anti-inflammatory, anti-aging capabilities, and paracrine functions. MSCs considerably contribute to the improvement of osteoarthritis patients' quality of life by alleviating symptoms and enhancing joint function.

ADSCs, which are pluripotent cells that originate from adipose tissue and can differentiate into multiple cell types, are of particular interest. ADSCs exhibit minimal immunogenicity, maintain similar self-renewal capacities, and can be derived from numerous tissues, including bone marrow, adipose

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tissue, umbilical cord blood, and placenta. They perform essential roles in vital biological processes, such as angiogenesis, cell division, differentiation, and inflammation control. Recent research indicates that chondrocytes derived from ADSCs can extend the lifespan of osteoarthritic chondrocytes by delaying the onset of aging markers caused by inflammatory stress, thereby potentially contributing to the therapeutic effect. In addition, it is believed that ADSCs release signals that promote the growth of adipose tissue and blood vessels, suggesting a function in healing processes. Notably, following ADSC transplants, the body exhibits decreased rejection rates.

Consequently, this review aims to assess the progress of research and development in the field of ADSC therapy for osteoarthritis, to explore the dependable therapeutic directions and mechanisms of osteoarthritis, and to highlight the significance of research in bone tissue engineering and regeneration pathogenesis of OA.

Osteoarthritis was originally perceived as a disease of "wear and tear". The primary drivers behind this condition were thought to be chronic loading and compromised joint biomechanics, leading to the breakdown of articular cartilage and subsequent inflammation. This process would then result in stiffness, swelling, and loss of mobility. However, contemporary understanding posits that the pathogenesis of osteoarthritis involves both inflammatory and metabolic components [2]. One of the most detrimental effects of osteoarthritis is the substantial degeneration of articular cartilage that occurs over the disease's duration. This cartilage serves a crucial function by facilitating low-friction movement within joints and evenly distributing load-bearing stress. When osteoarthritis impacts a joint, it affects not only the cartilage but also the synovium, articular ligaments, and subchondral bone [3]. Various theories attempt to explain the underlying mechanism of osteoarthritis. One such theory suggests that the disintegration of cartilage triggers a foreign body response in synovial cells. This reaction instigates the production of proteases, spurs synovial angiogenesis, and leads to the secretion of inflammatory cytokines, which in turn contribute to further cartilage degradation. Other hypotheses emphasize the significant role played by activated synovial macrophages and the innate immune system in the progression of the disease [1].

2. Biological characteristics ADSCs

Given the right inducing conditions in a lab environment, these cells have the capacity to morph into various other cell types such as osteoblasts, chondrocytes, adipocytes, muscle cells, and nerve cells. Moreover, they have the ability to excrete an array of factors that promote angiogenesis and inhibit apoptosis, potentially contributing to cell survival, tissue recovery, and regrowth. The attributes of adipose tissue, such as ease of acquisition, ample cell count, broad availability, low risk of immune response, and stable cell characteristics, have propelled it to become a focal point in tissue engineering stem cell research in recent times [4].

3. Mechanism of ADSCs chondrogenesis

As per the findings presented by Antonio et al. [5] ADSCs can serve a protective function for various innate tissues. They exhibit immunoregulatory capabilities and can aid in tissue regeneration via soluble elements. The secretory proteome of ASCs, as identified, contains a wide range of growth factors. Some examples of these include HGF, GM-CSF, IL 6, 7, 8, and 11, TNF-α, VEGF, BDNF, NGF, and adipokines. Under hypoxic conditions, when HIF-1-alpha stabilizes, there is an observed increase in the secretion of VEGF by ADSCs.

According to a study referenced [6], VEGF is a crucial factor in bone regeneration, contributing to osteogenesis, and it is also instrumental in the creation of new blood vessels via the process of angiogenesis. Hans-Peter's experiment of inactivation of VEGF in mice showed that VEGF was a crucial signal regulating growth plate morphogenesis and inducing cartilage remodeling, which proved the importance of VEGF in chondrocyte breaking function and extracellular matrix remodeling [7]. VEGF also exists in fully mature hypertrophic chondrocytes [8]. The extracellular matrix of rat adipogenic stem cells was removed by collagenic enzyme digestion and gradually purified, and the fourth-generation ADSCs were bone induced, resulting in cell calcification, which proved again that ADSCs

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can perform bone differentiation and cartilage differentiation by inducing ASCs, and regenerate new cartilage tissue.

4. Mechanism of ADSCs in treating osteoarthritis

Recent research has demonstrated the paracrine function of ADSCs in preventing chondrocyte degeneration, while VEGF has also been proven to be a key regulator of ADSCs playings a paracrine role [9, 10]. With age, cartilage degrades and loses its matrix, and cartilage cells produce inflammatory mediators, leading to serious damage. In older adults, surgery should be avoided whenever possible, and some procedures only rebuild degraded cartilage, but do not slow or stop the process of joint inflammation that has built up. In the experiment of Hirotaka et al. [11], it was proved that the higher VEGF protein level in the ASCs transplantation group and the in vitro experimental results of ASCs conditioned medium supported the paracrine mechanism. In a study conducted by Li Mei et al. [12], an investigation into OA in rats was carried out. The findings indicated that, relative to the IL-1β +ADCS treatment group and the non-treated control group, TNF- and IL-6 mRNA expression levels both significantly decreased. However, no discernible rise in the expression of IL-10 was seen. From these observations, it can be tentatively inferred that ADSCs contribute to the deceleration of joint inflammation progression through paracrine mechanisms. Further investigation by Kuroda Isari et al. supports this view. The team injected ADSCs into the joints of albino rabbits. The ADSCs were found to home into the intra-articular soft tissues (including the subintima of the synovium and ligament) 8 weeks post anterior cruciate ligament injury (ACLI). The results suggested that the paracrine actions of ADSCs residing in the intra-articular soft tissues significantly aid in impeding the progression of cartilage degradation.

5. In vitro culture method of ADSCs

In the human body, there are usually three different types of fat cells: white, brown, and beige. The white fat, which is found in the arms, thighs, hips, and belly, is made up of white cells that are kept under the skin or close to the organs. Brown fat is a type of fat that helps the body store energy and keep it warm. It is usually found in babies, but also in adults to a lesser extent, mainly in the neck and shoulders. Beige fat functions halfway between brown fat cells and white fat cells. Beige cells can help burn fat instead of storing it. ADSCs are usually derived from white fat and are separated from the fat tissue located in the abdomen by procedures such as subcutaneous liposuction or direct excision techniques. After the adipose tissue is obtained, it is first washed with a phosphate buffered saline solution. The required stromal vascular fraction (SVF) was then separated by collagenase treatment, centrifugation, washing and filtration, refer to Figure 1 for detailed steps. From the research conducted by Lee et al. [13], they deduced that the optimal condition for the separation of the stromal vascular fraction (SVF) was a treatment duration of 40 minutes with 0.1% type I collagenase. Refer to the image below for further clarification. The SVF is comprised of various cell types, including ADCS, fibroblasts, monocytes, macrophages, lymphocytes, and preadipocytes. These SVFs were subsequently seeded in petri dishes and cultured under conditions of 37℃ and 5% CO2. The culture medium was replaced every three days. Upon reaching a cell growth of 80%-90%, passaging was performed, and the cells were subsequently treated with Gibco BRL for passaging culture [13, 14].

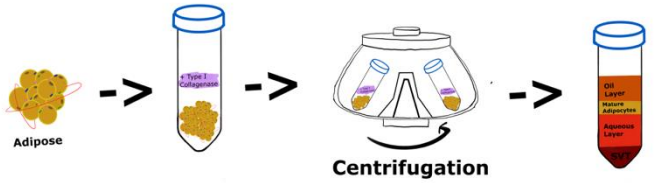

Figure1. Methods and procedures of ADSCs extraction.

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6. Osteogenic induction and morphological changes of ADSCs

Cells from the fourth generation were procured and introduced into an osteogenic induction medium. This medium was composed of fetal bovine serum, dexamethasone, ascorbic acid, and β-sodium glycerophosphate. These components were utilized for the purpose of fostering osteogenic induction culture. 14,28 days after osteogenic induction, alkaline phosphatase and cicarin red were stained, respectively, and glycerin gelatin sealed. After 2 weeks of osteogenic induction, the cell morphology changed, showing irregular shape or polygonal shape, and the cell volume increased slightly. Four weeks after osteogenic induction, red mineralized nodules were observed by alizarin red staining, and the intracellular alkaline phosphatase activity was measured by calcium and cobalt staining, and graying black granular or massive precipitates were observed in the cytoplasm [15].

7. Conclusion

In patients with OA, the only treatment currently available cannot completely prevent the progression of joint degeneration. The treatment of cartilage defect and joint degeneration by ADSCs is a hot research point in the field of orthopedics. The benefits of ADSCs include facile sampling, little patient damage, good cell differentiation capacity, difficult apoptosis, and promotion of cartilage proliferation and differentiation. ADSCs can secrete a variety of cytokines during proliferation and differentiation, which can promote cartilage differentiation, chondroblast related gene expression, chondrocyte proliferation, and play a role in promoting cartilage regeneration and repair. At the same time, ADSCs also have paracrine effects on chondrocytes, which can not only regulate the proliferation of related cells and improve clinical symptoms, but also promote angiogenesis and tissue survival. Despite the fact that the mechanism through which ADSCs cure OA is not yet fully understood, its role in promoting cartilage differentiation and regeneration has been confirmed. Further progress in terminating OA or even reversing the development of OA has been made possible. However, there are still many problems to be solved, such as the optimal sampling site of ADSCs, the application mode of OA treatment, dosage and course of treatment, specific molecular markers of ADSCs, the molecular mechanism of ADSCs proliferation and differentiation, the safety assessment of ADSCs in vitro culture, and the selection of the optimal transplantation route and time window of ADCS. There is reason to believe that further research on the clinical transformation of ADSCs will promote the development of medical technology and open up a new way for the treatment of OA in the future.

Authors contribution

All the authors contributed equally and their names were listed in alphabetical order.

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