

Progress of Stem Cell Research in Knee Osteoarthritis

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Abstract. Knee osteoarthritis (KOA) is a degenerative condition that primarily affects people in their middle and advanced years. Meniscus wear, osteophyte production, and articular cartilage degeneration are its defining characteristics. Due to a lack of nutrients from the nerve and joint microvascular systems, articular cartilage finds it challenging to self-heal or repair after degenerative changes. In general, conservative therapy is ineffective, and joint replacement is only an option for patients with very advanced illness. Because of their differentiation capacity into many distinct types and their potent paracrine activity, stem cells are regarded as the best materials for tissue regeneration and repair. Fatty tissue, bone marrow, and umbilical cord all contain stem cells. In general, arthritic symptoms can be reduced by injecting stem cells into the knee joint cavity after isolation and in vitro multiplication. The efficacy of mesodermal stem cells (MSCs) in reducing signs and symptoms of KOA has been confirmed over time by a significant number of clinical trials on the topic. This article examines the outcomes of clinical research, therapeutic outcomes, current issues, and historical development prospects.

Keywords: Enter key words or phrases in alphabetical order, separated by commas.

1. Introduction

The survey found that knee osteoarthritis (KOA) affects many seniors over the age of 65, with a frequency of 33.6% in the United States and a larger prevalence of women (42.1%) than men (31.2%) [1]. The advanced knee joint will lose mobility as a result of KOA, which will substantially lower patient quality of life and place a financial strain on society. The pathophysiology of KOA is influenced by a number of variables, including metabolic syndrome, congenital hypo immunity, systemic mediators of inflammation, and synovitis. Immutable and modifiable risk factors are separated apart as KOA risk factors. genetic influences (genetic mutations that may predispose an individual to KOA) and congenital causes, which are unchangeable variables (inherited incorrect bone form around the knee). Weight, exercise routines, biomechanical elements, and dietary practices are examples of risk variables that can be changed. According to the disease's cause, the disease can be split into primary and secondary forms. The prevalence of the disease is rising annually as the population ages. Continuous research on knee osteoarthritis has helped to enhance understanding of the condition and produce effective treatment outcomes in recent years. To better the disease's response to treatment and aid patients in enhancing their quality of life, further research is still required. Traditional KOA therapies include both non-surgical and surgical procedures, weight loss, which greatly reduces discomfort, diet control, and exercise to lose weight [2,3]. Nonsteroidal anti-inflammatory oral medications are frequently used in clinical settings to treat KOA, but they have a limited ability to reduce pain and have clear negative effects [4]. As a result, topical NSAIDs, which are safer and have less side effects, are now more frequently advised [5]. Hyaluronic acid (HA) intra-articular injection is another often employed conservative treatment, but it is unsuccessful in patients with severe KOA. Increased focus has also been placed on the topical injection of platelet-rich plasma (PRP) in early-stage patients to lessen synovial hyperplasia and effusion [6]. However, the advantage to HA topical injection has not been proven. Traditional surgical techniques also include high tibia osteotomy (HTO), which can rectify the lower limb force line and perform orthopedics; crucial microscopic knee cleaning, which is employed in early KOA patients. It is well known that epicondylar joint replacement has the benefit of requiring less time and less blood loss [7]. TKA has established itself as the first line of treatment for advanced KOA with multiple ventricular

involvement. TKA has proven effective in treating knee valgus deformity and can also correct the lower limb force line on the basis of reducing the patient's pain.

Replacing damaged articular cartilage with chondrocytes or cartilage tissue is a viable treatment for KOA. Stem cell therapy has become more popular in recent years. The connective tissue called articular cartilage covers the epiphyseal surface, and the major characteristic of OA is progressive articular cartilage deterioration. Cell-based articular chondroplasties concentrate on either mature chondrocytes or mesenchymal stromal cells. Microfractures of the subchondral bone, which supports the cartilage and provides mechanical and nutritional support, can cause the release of undifferentiated mesenchymal stem cells from bone marrow, which aids in cartilage healing. However, spontaneous healing capacity of articular cartilage is extremely limited, and when this occurs, fibrous scar tissue typically takes the place of the lost cartilage. Since researches have proved that there is possibility to create human pluripotent stem cells that can differentiate into chondrocytes, stem cell therapy has emerged as a novel approach for the topical KOA treatment [8]. While MSC therapy with KOA had the advantage of significantly reducing pain without side effects, Kuah found that it significantly reduced pain at 3, 6, and 12 months compared with placebo [9]. However, the relevant research is still lacking and there are still many issues that need to be resolved. The research components of stem cell therapy for KOA are outlined in this article.

2. Stem cell therapy mechanism

MSCs are a type of stem cells which are used to treat KOA. MSCs from the mesoderm, with multi-directional differentiation ability, can also be isolated and cultured from bone marrow, umbilical cord, placenta, tendon, pulp, and fat and other tissues, and joint injury (such as cartilage ischemia or injury) can cause the release of chemicals. Additional research has demonstrated that MSCs' paracrine functions play a critical role in nourishing cartilage and mending damage by activating cell signaling pathways [10,11]. MSCs also play an immunomodulating role in inhibiting dendritic cell maturation, activation of T lymphocytes in vivo, and antibody secretion; inhibit B lymphocyte activation, proliferation, and antibody secretion; and alter macrophage polarization and pro-inflammatory cell differentiation [12]. MSCs aid in the development of cartilage, which is regulated by signals such as bone morphogenetic protein (BMP) signalling and transcription factor Sox9 and Runx2. Additionally, MSCs have considerable paracrine activity, in which growth factors and cytokines promote chondrocyte proliferation in feedback loops and nourish cartilage through angiogenesis [13,14]. Additionally, MSCs have inherent immunomodulatory abilities that can lower inflammatory reactions and support the proliferation and local stem and progenitor cell differentiation, increasing angiogenesis, cell survival, and differentiation, and preventing the role of local cell and tissue fibrosis [15].

3. Preclinical stem cell therapy studies

Even though the underlying mechanism of therapeutic action of MSCs is still largely unknown, there is a need to evaluate animal research and offer impartial support for additional clinical trials. In order to evaluate intervention efficacy, animal models are frequently applied before conducting clinical trials. Rats are most often used animal models for knee OA in preclinical studies, and anterior cruciate ligament transection is the most frequently utilized OA induction technique. Additional chemical agents that can cause OA models in animals include papain, quinolones, and collagenase [16]. According to the research conducted on animals, treating OA illness with local intra-articular injections of MSCs, MSC-derived exosomes, MSC-loaded stent implants, and MSC suspensions with carrier media is successful [17]. By inducing endogenous cells, mesenchymal stem cells function as regenerative cells transplanted on scaffolds in three dimensions to repair damaged cartilage. Various stents, including polylactic acid-co-glycolic acid, polyethylene glycol, polylactic acid, polyglycolic acid, collagen, gelatin, and fibrin, are now used to implant articular cartilage abnormalities in

experimental animals [18]. However, because of their safety profile, they are still not employed as a standard form of care in clinical settings. Using a heat-sensitive hydrogel composed of polyethylene glycol-polyN-isopropylacrylamide and biodegradable polycaprolactone to create a composite microfiber structure, Brunelle et al. find that hybrid scaffold system enhances the mechanical properties of the cell/scaffold structure while encouraging MSC differentiation into chondrocytes [19].

Exosomes released by MSCs are used to treat OA as well [20]. MSC exosomes contain large amounts of microRNA, which can accurately bind to the mRNA generated by their target genes and quiet expressed target genes or form multi-signal interaction networks [21]. MicroRNA-140 may be a protective factor in the development of OA in rat models. According to Tao et al., intra-articular injection of mesenchymal stem cells can help with cartilage regeneration and repair as well as OA-related cartilage degradation [22]. MSCs have the ability to significantly improve the local microenvironment, immunomodulatory, and anti-inflammatory biological activities by secreting bioactive molecules like exosomes, growth factors, cytokines, and anti-inflammatory factors; ultimately, this makes them the most straightforward and simple method of treating OA. In a rat model, Zhou et al., discovered that local intra-articular injection of mesenchymal stem cells generated from fat can lessen the pro-inflammatory cytokine secretion through autophagy induction, ultimately resolving the disease [23]. PRP/MSCs have been shown in preclinical tests to enhance knee function, and MRI analysis has shown that the restored tissue has satisfactory compatibility with the original articular surface cartilage tissue. In addition, HA and MSCs work well together to heal injured cartilage, possibly via boosting cartilage repair by reducing inflammation and chondrocyte death [24].

4. Clinical stem cell studies

Based on the findings of completed studies, mesenchymal stem cell therapy (bone marrow, fat, and umbilical cord) has shown excellent efficacy in the study of osteoarthritis illness. Worldwide clinical trials using MSC treatment for OA have been put into practice. In China, there are currently 6 studies registered in clinicaltrials.gov. The majority of clinical trials have used doses of MSC in the range of 1.18~150 / kg, which is the current range for the ideal dose of MSC treatment for OA [25]. According to Matas et al's assessment of the efficacy of single and repeated MSC treatments for patients, the pain experienced by many MSC treatments for patients is much lower than that experienced by a single MSC therapy [26]. Injecting human umbilical cord MSCs into the joint cavity to treat degenerative knee arthritis has been shown in clinical trials to significantly enhance patient quality of life and joint function [27]. A severe case of knee OA was described by Centeno et al. After six months of injection of bone marrow, MSCs grown in phosphate buffer suspension, the ROM score rose and the VAS pain score fell [28]. At a 6-month follow-up, the European Union reported a phase I trial on a preliminary series of 18 patients and found that MSCs produced from fat decreased the pain and function component scale of WOMAC [29]. Recent clinical research found that grade 3 OA patients responded better to MSC implantation than grade 4 OA patients [30]. As a result, MSC-based therapy ought to be more effective at stopping or slowing the development of OA disease in its early stages. Although it is critical to show the initial effectiveness of intra-articular MSC injection in patients with severe KOA, prospective and placebo-controlled trials are needed to verify the efficacy of this therapy.

5. Discussion

Stem cell treatment KOA is a novel method; in the conventional approach, patients would suffer significant harm from analgesics and anti-inflammatory drugs, and related surgical procedures could result in unanticipated complications. However, as mesenchymal stem cell research has advanced, it has demonstrated benefits in the management of KOA. Huang carried out a meta-analysis on the clinical efficacy and safety of stem cell therapy for KOA [31]. The findings revealed that stem cell therapy has the benefit of significantly reducing pain without side effects when compared to

conventional methods, but pertinent research is still insufficient and there are still many issues to be resolved. The source, dose, route, and evaluation criteria of MSCs for the treatment of KAOA remain the two main practical challenges facing the clinical application of MSCs. It has been suggested to use in vivo tracking methods to monitor MSCs' therapeutic effects. For instance, Ferumoxytol, a nano-iron oxide particle, was utilized in 2018 for the in vivo tracking of MSCs in mice [32]. Understanding where MSCs move and how they behave after injection may be made possible by tracing technologies, and the resolution of these issues will provide more opportunities for clinical therapy and MSC mechanism research. MSC has emerged as a promising therapeutic treatment for OA, despite the fact that there is still a lack of concrete evidence to support its durability. The best source of cells, however, is still in the verification stage of the current clinical experimental research and does not have a unified standard for the cell tissue source, dose, injection frequency, cell culture method, transplantation method, follow-up time, or method used to evaluate the improvement of MSC. Therefore, further research on the MSCs' mode of action, optimum source, perfect cell dose, ideal target patient population, and ideal administration technique is still required. Overall, MSC treatment of OA will have a greater chance of being implemented in the future.

6. Conclusion

Although these preliminary studies have demonstrated the therapeutic effect of stem cells, their long-term therapeutic effect requires additional research. This article primarily discusses the research prospects of stem cells in the treatment of KOA and compares the advantages and disadvantages of conventional treatments. Additional reliable studies with larger sample sizes and randomized controls are necessary to obtain a higher level of proof and fully standardize and optimize the treatment of MSCs for KOA disease. After medication treatment and surgical treatment, regenerative medicine has emerged in recent years as a new disease treatment strategy. With the advancement of clinical research, stem cells from both domestic and foreign sources have been used to treat KOA. It is believed that the majority of KOA patients can improve symptoms such as pain and delay the progression of KOA.

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