Applications of Tissue Engineering in Meniscus Repair

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Abstract. Knee meniscus injury has a high incidence, which can change the load-bearing structure of the knee joint, causing pain and further cartilage damage and osteoarthritis and other related diseases, and is difficult to prevent and treat effectively. Therefore, how to treat meniscus injury has become one of the hot issues concerned by patients and medical staff in recent years. Compared with simple meniscectomy, tissue engineering meniscectomy has fewer adverse effects and some techniques have achieved satisfactory results. At present, the meniscus tissue engineering treatment method is continuously developing and innovating. In this paper, the promising techniques of collagen scaffold implantation, silk fibroin scaffold implantation, hydrogel implantation and bone marrow stimulation were discussed, we hope to provide the basis for the further development of meniscus repair.

Keywords: Knee meniscus injury; collagen scaffold; silk fibroin scaffold; hydrogel; bone marrow stimulation.

1. Introduction

The function of meniscus is to distribute load, absorb shock and protect the cartilage tissue of the lower knee joint.Knee meniscus injury is receiving more and more attention from medical staff because of its inducing effect on knee osteoarthritis and rheumatoid arthritis and its widespread presence in the population [1]. Due to the different classification criteria and diagnosis methods of meniscus injury, there are certain differences in the statistical differences of the prevalence of meniscus injury. In a meta-analysis, 3761 knees of 2817 participants in 44 experiments were summarized. It was found that the total prevalence rate of meniscus tear was 10%, and the 95% confidence interval was 7% to 13%. The survey also found a significant relationship between the prevalence rate of meniscus tear and age together with gender. With age increasing, the prevalence rate of meniscus tear increased significantly, and the proportion of women in patients also increased with the increase of the prevalence rate [2]. Other data show that traumatic meniscus tear often occurs with ligament injury. 57% to 80% of patients with anterior cruciate ligament (ACL) tear will suffer from traumatic meniscus tear [3]. Due to the unique planing structure of meniscus and the lack of self-healing ability after injury in areas without blood supply, meniscus reconstruction has gradually become a research focus of researchers in the field of injury repair. This paper summarizes the repair technology and materials of knee meniscus injury in recent years, and provides several rounds of foundation for the treatment of knee meniscus sports injury.

2. Structure and Biochemical Properties of Meniscus

The knee meniscus is located in the knee joint capsule, between the femoral condyle and the surface of the tibia, and is a smooth crescent-shaped intervertebral disc [1]. The meniscus can be roughly divided into the medial meniscus and the lateral meniscus. The biochemical composition of meniscus is mainly dense extracellular matrix (ECM), in which 72% is water, 22% is collagen tissue, and 0.8% is glycosaminoglycans (GAGs). In collagen tissue, 80% is type I collagen, which is distributed throughout the meniscus, and 20% is type II collagen, which is basically distributed in the inner region [1,4]. The distribution and direction of type I collagen and type II collagen in different depths from the surface to the inside of the meniscus also have obvious differences, which endows the meniscus with complex mechanical properties, and the complex distribution of collagen is also the most challenging topic in the tissue reconstruction technology mentioned below [4].

In another way of division, the meniscus is divided into circumferential region and radial region, and the latter one includes "red-red region", "red-white region" and "white-white region". The "red-red region" is the most densely distributed blood vessels, which are roughly in the outer third of the meniscus. The "white-white region" is located inside the meniscus, which is completely free of blood vessels, while the "red-white region" is located between the first two regions [1]. The blood supply of meniscus comes from the capillary network of synovial membrane. The blood vessels play an important role in transporting nutrients, growth factors and metabolic waste. In meniscus tear, the distribution of blood vessels is the decisive factor for whether the meniscus can regenerate cells. Due to the different distribution of blood vessels, the repair of lateral meniscus tear is generally considered to be easier than the repair of medial meniscus tear [5]. In a survey on the factors of reoperation after meniscus tear surgery in children, it was found that the reoperation rate of patients with "white-white region" meniscus tear was lower than that of patients with other parts of the tear (4% vs 13%), but this is because about 65% of patients with "white area" tear chose meniscus resection for treatment rather than meniscus repair, which is higher than that of patients with other parts of the tear. If this factor is excluded, there is no significant difference in reoperation risk between patients with "white white area" laceration and patients with other laceration [6]. This survey actually shows that the possibility of meniscus tear repair in the "white white area" is low and the treatment method is limited. In another experiment, JiKai Shen et al. used diffusion magnetic resonance imaging to analyze the 3D collagen network of porcine meniscus, and revealed the relationship between the distribution of meniscus collagen fibers and the distribution of blood vessels. The study found that the anisotropy fraction (FA value) of collagen network increased from 0.13 in "white white zone" to 0.26 in "red red zone", and the radial diffusion rate (RD value) was 1.0 in "white white zone" $\times 10^{-3}$ mm^2/s, 0.7 in "red-red zone" $\times 10^{-3}$ mm^2/s, and weak collagen network connection was found between "white white area" and "red-red area" [7].

3. Imaging Diagnosis of Meniscus Injury

There are many kinds of meniscus injuries, and the use of different classification basis and diagnostic criteria will lead to differences in the statistics of meniscus injuries. The choice of different diagnostic methods and their different accuracy will determine the choice of follow-up treatment options. Especially when judging whether meniscectomy is necessary, the shape of meniscus and the size of the damaged part should be fully confirmed. In general, meniscus injury can be divided into acute injury and degenerative disease. Acute injury is common in young people, including vertical shoes, flap shoes and mainly polar root shoes. Degenerative disease mainly occurs in people over 50 years old [3,8]. In a consensus, it is believed that the meniscus state should be evaluated through the combination of different diagnostic tests, including McMurray joint line tenderness test, Ege and Thesaly test [3]. Arthroscopy and magnetic resonance imaging (MRI) are widely recognized and used diagnostic methods. In recent years, imaging examination methods for meniscus injury are constantly innovating. In MRI diagnosis of meniscus injury, the commonly used method is Fat-suppressed fast spin-echo proton density-weighted image (FS FSE PDWI). Affected by the irregular tissue around the meniscus, the abnormal signal of meniscus tear itself is relatively small, and the accuracy of MRI diagnosis needs to be further improved. On the basis of the current AI (Artifical Intelligence) imaging diagnosis experience and based on deep learning, Jie Li et al. improved the defects of most imaging analysis in previous studies, such as sagittal plane, lack of coronal plane and cross section, and inconsistent inspection parameters such as slice thickness. Through convolution neural network, he obtained the characteristic image of meniscus MRI, and further used MASK R-CNN model for classification, regression and pixel-level mask diagnosis. MRI images of 924 patients were collected, studied and tested in combination with the diagnosis of arthroscopic surgery by experienced doctors. Based on the analysis of various data, it is believed that the accuracy of tear recognition of the MASK R-CNN model in different parts of the meniscus reaches 84% [9]. This study established a new MASK R-CNN analysis model. Compared with previous studies, the inspection items are more

comprehensive and the inspection parameters are unified. Compared with MRI, there are few studies on the diagnosis of meniscus injury using ultrasound technology. Shun-Jie Yang et al. took MRI diagnosis as the "gold standard", tried to prove the effect of ultrasound image in diagnosing meniscus injury, and found that it had significant diagnostic ability for some parameters during the development of discoid meniscus injury (DLM). The sensitivity, specificity and accuracy of AMA, MBA and PMA in diagnosing DLM reached 91.3%, 88.6% and 89.2%; 94.2%, 93.3% and 93.5%; 76.8%, 95.7% and 91.7% respectively [10]. Xibai Li et al. studied the direction of machine learning and automation in the diagnosis of discoid lateral meniscus by X-ray photographs, and used 160 radiographic images from normal people and patients diagnosed as discoid lateral meniscus for preprocessing, segmentation and important parameter measurement. Based on this, a model software was established. After testing, 97.5% of radiographic images were successfully segmented by software, and important parameters related to DLM were measured [11].The emergence of different diagnostic methods has continuously improved the loopholes of the previous technology, and the specificity and accuracy of diagnosis have been continuously improved. In particular, the diagnosis method based on machine deep learning has made up for the lack of experience of doctors to a certain extent. In addition, the patients diagnosed by MRI should not have metal in the body, and the patients must stay in a flat position during the photography process. The radiation diagnosed by X-ray radiography has certain harm to the human body. Both of these methods have certain limitations, while ultrasonic diagnostic equipment is portable and thus has unique advantages in use in remote areas.

4. Material and Type of Meniscus Support

4.1. Collagen scaffold

The preparation of collagen scaffolds by electrospinning is a mature method for fabrication of collagen scaffolds. This technique produces microdroplets mainly by stretching polymer solutions under controlled electric fields, and further drying results in stretched micrometer/nanometer-scale diameter fibers [12]. Zhi Yang et al combined electrospinning technology (ESP) with 3D printing technology (3DP) to construct composite biological scaffolds, in which 3DP produces large fibers (using PLC as material) , the composite scaffold with $70.46 \pm 2.48\%$ porosity and 392.17 ± 36.06 μm pore size was obtained from ESP. In the experiment, rat dermal fibroblasts were implanted into the composite scaffold, and the repair function of this artificial soft tissue was verified by using a defective rat abdominal wall model, the results showed that the composite scaffolds were non-toxic to the cell infiltration and growth process, and could effectively promote tissue repair and angiogenesis [13].

Erik W. Dorthé et al. explored a way to generate type I collagen scaffolds by pneumatic spinning, in which a collagen solution of 9% WT/vol was selected to produce scaffolds after crosslinking by glutaraldehyde. After reducing the elastic modulus of scaffolds by hydration, the porosity of collagen scaffolds was 48%, and the pore diameter ranged from 7.4 to 100.7 μm. In order to verify the repair effect of this kind of scaffold, IPFP-MSC were implanted into it. The survival rate of IPFP-MSC was $70.2 \pm 7.5\%$, it was found that the new tissue could combine with the original tissue of the host after it was implanted into the bovine meniscus [14]. It is worth mentioning that the experiments have confirmed that the collagen scaffold with the corresponding curvature can be generated by using the radial corrugated bending target as the collector, which is essential for the morphological structure design of the collagen scaffold, and provides the possibility of adapting the structure to the damaged part of the patient [14].

Type I collagen solution was used as raw material in the electrospinning and pneumatic spinning experiments mentioned above. However, in practice, there are many choices of raw materials for electrospinning and pneumatic spinning, for example, electrospinning technology can use metals, ceramics, etc. And the raw materials for vapor deposition include many synthetic polymers (such as polyurethane) and natural polymers (such as silk fibroin). In addition, Christopher Z Mosher et al. have explored a classic green spinning technique that is safer for the environment and human health

[15].The scaffolds produced by electrospinning have the disadvantages of low mechanical strength and difficult control of cell density, and the mechanical properties of scaffolds under different loads are not clear [12,16].

4.2. Silk fibroin scaffold

Silk fibroin is another possible raw material for meniscus graft scaffolds, and there has been relatively little research on silk fibroin compared to collagen, which has been extensively studied. The experimental results of silk fibroin scaffold show more shortcomings and imperfections. In the course of silk protein research, the first generation of silk fibers had satisfactory Biocompatibility and cartilage protection, but the instruments and tissues were not tightly fixed, at present, the study of silk fibroin scaffolds mainly focuses on the effect of the second generation silk fibroin fibers in meniscus repair [17].

Svenja Emmi Catherine Stein et al made the second generation silk fibroin implants by integrating the silk fibroin fiber web into the porous matrix in order to improve the poor integration of silk fibroin grafts with tissues and the possibility of dislocation. Twenty-seven Merino sheep were selected for the control experiment. After implantation of silk fibroin scaffold, some sheep still had the condition of scaffold degeneration. In addition, there were radial tears in the scaffolds and tissues. Compared with the non-transplanted group, the transplanted Merino sheep showed a similar degree of cartilage degeneration of the tibial plateau and osteophyte growth in some areas. In terms of mechanical properties, the experiment ensured that the balance modulus of the graft stent was similar to that of the natural meniscus before implantation, but after 6 months, the graft stent hardened significantly, and the transplanted group produced slightly more inflammatory cells than the control group. From the experimental results, silk fibroin transplantation did not show obvious repair, but still the stent and tissue can not bind tightly and produce inflammation defects. The study of silk fibroin scaffolds still needs to be improved and perfected, but it can not be denied that silk fibroin scaffolds transplantation is still a promising means of meniscus injury repair [18].

Daniela Warnecke et al further explored the biomechanical properties and structure of the second generation silk fibroin scaffoldds based on the widely accepted standards for meniscus replacement materials and previous experimental results for silk fibroin scaffolds. This study provides a basis for the potential use of silk fibroin scaffolds. In this experiment, the commercial silk fibroin fibers were first made between silk fibroin proteins. The mechanical properties of a dumbbell-shaped specimen were tested. The specimen has a limit tensile distance of 4.7 ± 0.9 mm and a limit tensile force of 51.0 ± 16.0 N, the average elastic modulus of the specimen is 5.4 ± 1.4 MPa, and the elastic modulus of this silk fibroin test sample was slightly lower than that of the medial side of native meniscus tissue, but this was thought to be improved by a higher density of fibrous scaffolds. In the indentation test, the stiffness of silk fibroin scaffolds increased by about 38% in 5 cycles, and the compression rate decreased from 8.0 ± 1.7% to 5.6 ± 1.0%, however, the mean compressive strain of silk fibroin stent was found to be closer to that of human meniscus than that of other types of stent. In the unconfined compression and creep tests, the synthetic equilibrium modulus of the scaffolds is 560 ± 310 kpa, and the viscoelastic creep response of the scaffolds is similar to that of human tissues. In structure, the porosity and pore size of silk fibroin scaffolds were 80.13 ± 4.32% and 215.6 ± 10.9 μm, respectively. In meniscus replacement, we should follow the principle that the structure and mechanical properties of the graft should be as close as possible to those of human meniscus. Tthe performance of silk fibroin scaffolds could be further improved by increasing the density of scaffolds and designing protein fibers to simulate the arrangement of collagen in the meniscus. This experiment proves the research value and application potential of silk fibroin scaffold [19].

Different manufacturing processes of silk fibroin scaffolds directly affect the performance of scaffolds, such as shape, porosity and so on. The preparation of silk fibroin scaffolds by electrospinning has been explored in many studies. Silk fibroin protein scaffolds have unique electrical properties. The materials obtained by crossing spider silk with silk and other materials have better electrical conductivity, the innovation of silk fibroin combining electrospinning technology is

that it can produce multiple threads at the same time like spider silk, and it is even possible to design and manufacture specific secondary structures using specific spinneret [20]. In addition, silk fibroin can also act as a component of meniscus scaffolds, for example, by adding silk fibroin to polylactic acid scaffolds, which, using electrospinning techniques, improves cell adhesion and degradability of the scaffolds [21].

4.3. Hydrogel

In recent years, hydrogel has been widely used in meniscus repair as a new tissue engineering biomaterial. Hydrogels are easy to manipulate and regulate, and have the function of transporting cells, proteins, and nutrient factors [22]. In tissue engineering applications, small molecules such as exogenous drugs and cells need to be filled into hydrogel scaffolds to form a system to function [22]. The hydrogel system is injected into the meniscus injury site via minimally invasive surgery, which is simple and easy to perform [23].

Gang Zhong et al investigated the efficacy of bone marrow mesenchymal stem cell (BMSCs)-filled ECM (extracellular matrix) hydrogels for full-thickness meniscus repair. The rat model was selected for the experiment, and the aim of this study was to compare the effects of meniscus extracellular matrix (mECM) hydrogel and collagen I encapsulated bone marrow stromal cells on meniscus repair by arthroscopic meniscus surgery. The decellularization of mECM will result in a loose and porous structure of the graft, which provides the necessary conditions for the migration of recipient cells into the graft. It was found that the content of dsDNA in MECM decreased significantly after decellularization, while the content of other components of meniscus, such as collagen, remained unchanged, and there were 10 μm to 40 μm pores in mECM [24]. mECM hydrogel group and bovine skin collagen I group effectively up-regulated the expression of fibrochondrocyte-related genes in the receptor, and the difference was that the expression of type I collagen protein in mECM group was 77.79% higher than that in bovine skin collagen group ($P < 0.05$) . A further study found that the cartilage platform on the tibia surface was smoother and less fibrotic after repair in the mECM hydrogel group compared with the bovine skin collagen group, and the ratio of bone volume to tissue volume (BV/TV) associated with trabecular and tibial bone increased by 33.82% and 46.42%, respectively [24]. The above results and data suggest that mECM hydrogel is a better graft scaffold than bovine skin collagen I, and its effect of reducing native meniscus tissue is satisfactory. Therefore, it has an inhibitory effect on osteoarthritis (OA) and related diseases, and has a good clinical application prospect.

Alessandra Marrella et al tried to use PVA as a biopolymer to design a 3D porous gelatinpva hydrogel as a meniscus graft. To design the porous structure of the gel, the experiment used a aerodynamics injection technique to mix alginate particles into the gel and remove the pores left by the particles in the gel. A gel with a porosity of 74.5 ± 15.9% and an average pore size of 104.5 ± 15.9 μm was obtained [25]. The porous structure provides the gel with greater swelling capacity, the storage modulus (e') of the meniscus was decreased to 0.24 ± 0.03 MPA, which was close to the mechanical properties of the human meniscus. The addition of gelatin plays an important role in the physiological activity of the hydrogel, ensuring the continuity of the hydrogel with the meniscus on the protein component and enabling the gel to match the natural meniscus profile morphology [25]. Although it is now widely accepted that meniscus allografts have better long-term outcomes than PVA-based grafts in the treatment of meniscus injury, especially without biological inertia, PVA-based hydrogels have unique advantages and remain a potential therapeutic option.

Although meniscus repair with hydrogel scaffolds has been extensively studied in animal models, this treatment is still not mature enough for clinical use. On the one hand, the side effects of some materials on the human body are difficult to predict in the absence of a well-defined matrix of regulatory factor changes following meniscus injury, and the majority of biomaterials bound to hydrogels have not been clinically approved [23]. On the other hand, it is difficult for existing hydrogel materials to completely restore the composition and properties of natural meniscus. The experiment indicated that the drug intervention is not good to the meniscus after the hydrogel

transplantation [22]. Mireille M. J. Karen. E Sthijns et al. proposed a conventional means of stimulating the production of ECM by cells in the receptor as an alternative to the implantation of ECM using exogenous substances, the general approach is to use synthetic materials to modulate the signaling pathways that regulate ECM production in the receptor [26]. This protocol may effectively solve the problem of poor efficacy of drug intervention for hydrogel grafts.

5. Bone marrow stimulation(BMS)

Bone marrow stimulation, or microfracture, is a proven tissue engineering technique for treating cartilage injuries, including meniscus tears. Minimally invasive surgery allows the bone marrow to enter the cartilage defect and promotes spontaneous repair of the injury site through regulatory factors and nutrients contained in the bone marrow and surrounding tissues. Experiments have shown that bone marrow-derived osteoclasts can efficiently absorb bone, whereas bone marrow and its surrounding tissues carry more cytokines associated with cartilage repair [27]. In another experiment, it was found that bone marrow adipogenic lineage precursors (MALPS) efficiently express Colony-stimulating factor 1(CSF1) , a growth factor required for osteoclast progenitors, plays an important role in bone resorption [28]. These experiments further confirm that bone marrow has multiple complex regulatory mechanisms for repairing cartilage damage.

Although bone marrow stimulation is a mature therapy in both theory and practice, there are few reports about it in recent years. Ariyanto Arief et al administered bone marrow stimulation to three patients diagnosed with grade III osteoarthritis and recorded the results. The basic procedure involves making an incision on the anterolateral and anteromedial sides of the knee as an arthroscopic door, removing all the unstable cartilage and its adherent cartilage to provide conditions for the formation of a bone marrow clot, the subchondral bone was perforated or microfractured at approximately 3 to 4 mm intervals using an arthroscopic cone, and HA 2.5 ml (10 mg ML) and triamcinolone acetonide 5 ml (10 mg ML) were injected into the joint after the arthroscopic door closure. Preoperative and postoperative WOMAC scores, serum levels of interleukin 15(IL-15) , and MRI Amadeus scores were compared. WOMAC scores and IL-15 levels significantly decreased, while MRI AMADEUS scores slightly increased, showing a good therapeutic effect [29]. Bone marrow stimulation therapy has a satisfactory therapeutic effect, but patients with osteoarthritis or meniscus injury often prefer to be treated with tissue replacement, therefore, more studies comparing the efficacy and experience of different therapies may be needed to show the benefits of bone marrow stimulation.

Michele Venosa et al investigated the use of platelet-rich plasma (PRP) and its association with adipose-derived Mesenchymal stem cell (AD-MSC) in the repair of cartilage injury based on microfracture techniques for cartilage injury. Thirty-eight patients with a single-compartment cartilage defect of the knee were investigated and divided into PRP and PRP-ADMSC combined injection groups. The results showed that the IDKC scores of the two groups were significantly increased after treatment, and the average score of the combined injection group was 78.2±2.2, which was slightly higher than that of the PRP group. The KOOS scores of the two groups were similar, however, the KOOS score of the combined injection group was higher than that of the preoperative group, and the combined injection of PRP and AS-MSC had a slight therapeutic advantage in Vas and AF-12 scores. After a second arthroscopic procedure a year later in some of the patients in need, a smooth fibrocartilage surface was found in both groups, but abnormal cartilage mineralization was observed in the group injected with PRP only [30]. Overall, the combination of PRP and AD-MSC in the microfracture technique further enhanced the repair effect, and there was some synergy between the two, the results showed a good improvement on microfracture surgery.

A study by Marina V. Volkova et al showed that after hypoxic preconditioning or oxygen acclimatization of bone marrow Mesenchymal stem cell, bone marrow Mesenchymal stem cell increased the expression of a variety of cytokines and growth factors and enhanced their proliferative potential, in addition, hypoxic preconditioning can enhance the tissue immune response and angiogenesis [31]. Other studies of bone marrow stimulation techniques have focused on cuff tears.

Yi Zhou et al repaired cuff tears with techniques of combined remnant preservation and bone marrow stimulation (RP-BMS) , showing greater shoulder abduction and more intact tendon tissue in the RP-BMS group compared with conventional repair method. The rate of tendon net was 3.70% , which was significantly decreased [32]. In a meta-analysis, the results obtained a recurrence rate of 18.15% after treatment of rotator cuff injury with bone marrow stimulation techniques, which was lower than that in the control group (31.07%) . But in other measurements such as Constant Score, UCLA Score, and VAS Score, the results did not show significant differences in bone marrow stimulation techniques compared with the control group [33]. These experiments provide a similar reference and scientific basis for the improvement of meniscus injury by bone marrow stimulation.

6. Conclusion

From the tissue engineering meniscus repair methods discussed in this article, each has some advantages and disadvantages, and none is perfect, the problem of meniscus repair still needs a lot of research effort. It should be noted that different treatment techniques may have a good therapeutic effect on certain types or specific populations of meniscus injuries, individualized treatment according to each patient's specific condition and individual needs may be one of the important directions to improve the treatment level of meniscus injury repair in the future. In general, collagen scaffolds and hydrogels are widely used in meniscus transplantation, and bone marrow stimulation is one of the most mature and effective repair techniques. The repair process of meniscus tissue itself and the related mechanism are still not completely understood, which is a huge obstacle to the further development of meniscus repair methods, we need more experimental data on natural meniscus to support the development of tissue engineering therapy.

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