Role of micro-fragmented adipose tissue in cartilage repair (Review)

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Abstract. Osteoarthritis (OA) is the most common degenerative joint disease, and one of the core factors in its development is articular cartilage damage. Due to the lack of vascular tissue in articular cartilage, if not treated in time, the damaged cartilage cannot regenerate spontaneously, thus leading to the occurrence of OA. Research has found that through a new type of fully enclosed device, lipogems®, micro-fragmented adipose tissue (MFAT) can be obtained by treating adipose tissue with mild mechanical force. MFAT does not require cell expansion, enzymatic treatment, or other major manipulations, and can maintain the complete stromal vascular niche. The present review discusses the latest research progress of the mechanism of MFAT in the repair of cartilage injury in OA, providing a new direction for the treatment of OA.

Contents

1. Introduction

Osteoarthritis (OA) is the most common degenerative joint disease, and one of the core factors in its development is articular cartilage damage (1-2). Due to the lack of vascular tissue in articular cartilage, if not treated in time, the damaged cartilage cannot regenerate spontaneously, thus leading to the occurrence of OA (3,4). At present, non-surgical methods beneficial to early lesions include intra-articular injection of sodium hyaluronate, platelet rich plasma and concentrated cytokines (5-8). Traditional surgical treatments include subchondral microfracture and autologous chondrocyte or cartilage transplantation (9-12). Due to the uncertainty and inconsistency of the results, none of these methods can achieve completely satisfactory results (13,14). Therefore, it is urgent to find an improved treatment to restore the structure and function of damaged cartilage.

Previous studies have found that through a new type of fully enclosed device, lipogems®, micro-fragmented adipose tissue (MFAT) can be obtained by treating adipose tissue with mild mechanical force (15,16). MFAT does not require cell expansion, enzyme treatment or other major operations, and can maintain an intact stromal vascular niche (17). In the present review, the latest research progress of the mechanism of MFAT in the repair of cartilage injury in OA was discussed, providing a new direction for the treatment of OA.

2. Overview of MFAT

MFAT can be obtained by treating adipose tissue with lipogems system (15,16); the adipose tissue is rich in content, widely sourced and easy to obtain in the body, and MFAT has strong anti-inflammatory and anti-apoptotic abilities (18-20). These adipose tissues can release cytokines, extracellular vesicles and numerous other regulatory information, improve the local microenvironment of injury, and obviously help to promote the repair of cartilage injury (21,22) (Fig. 1).

Advantages of MFAT include the following: i) MFAT is easy to obtain, rich in sources and does not need to be cultured *in vitro*; ii) MFAT is rich in components, including a large number of pericytes, mesenchymal stem cells (MSCs), growth factors, exosomes, and a complete three-dimensional biological scaffold with a highly reductive cell proliferation microenvironment; iii) the survival rate and homing inhibition rate of MFAT transplantation were significantly higher than those of MSCs, and the clinical effect was obvious; iv) the whole acquisition process of MFAT is completely closed, avoiding contact with air, reducing pollution, and does not require enzymatic treatment of fat or other additives, which will not damage the three-dimensional biological scaffold of MFAT

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Abbreviations: OA, osteoarthritis; MFAT, micro-fragmented adipose tissue; ECM, extracellular matrix

Key words: OA, MFAT, cartilage, treatment

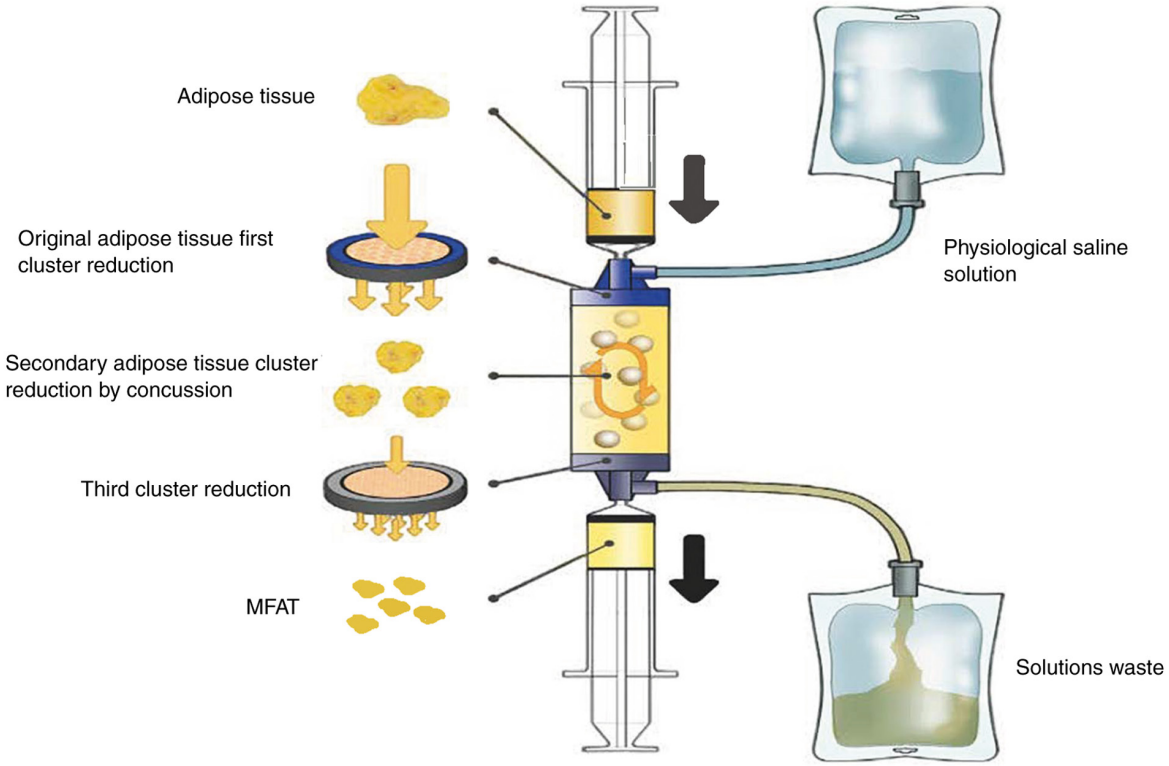

Figure 1. Schematic diagram of lipogems system operation principle. MFAT, micro-fragmented adipose tissue.

and the microenvironment of cell proliferation, is conducive to the release of various cytokines, and the obtained end products can be reinfused (23); v) the content of MFAT cytokines and exosomes is significantly higher than that of enzymatic treatment, which can significantly improve the ability of tissue repair and regeneration, including stem cell transformation, angiogenesis and 'homing' (16); and vi) MFAT is an autologous fat derivative, which is not from other xenogeneic sources and avoids the rejection reaction.

In a word, MFAT is rich in multifunctional cells, MSCs, exosomes and various cytokines, and MFAT has a strong promoting effect on the repair of tissue damage.

3. MFAT and repair of cartilage damage

OA is a chronic bone and joint disease characterized by articular cartilage damage and joint inflammation (24), and its main clinical manifestations are chronic pain and joint movement disorders, which seriously affect the quality of life of patients. Chondrocytes are the only cells in articular cartilage; degradation of cartilage extracellular matrix (ECM), apoptosis of chondrocytes and production of inflammatory factors are crucial to the pathological progression of OA (25,26). Therefore, inhibiting ECM degradation, alleviating chondrocyte apoptosis and inflammatory response can delay the pathological progression of OA. MFAT can transmit growth factors, extracellular vesicles and numerous other regulatory information to the microenvironment around the damaged cartilage, and promote the repair of cartilage damage (21,22).

A recent study found that 49 patients with knee OA (Kellgren-Lawrence III-IV) were treated with a single injection of autologous MFAT and knee arthroscopy; the results showed that arthroscopic injection of MFAT was a safe and effective method for the treatment of knee OA, which could significantly improve the IKDC and KOOS scores, and no major complications occurred in the 2-year follow-up after surgery (27). Another study also showed that the injection of MFAT can significantly improve the KOOS score and quality of life of patients, but it needs longer follow-up time to draw more definite conclusions and expand the indications (28). Ulivi *et al* (29) performed knee arthroscopy combined with MFAT in the treatment of knee OA; the follow-up results demonstrated that the serum biomarkers of cartilage deposition were significantly increased, indicating that the treatment of MFAT is effective. Yu *et al* (30) performed a single autologous MFAT injection in 20 patients, 40 knees in total, and the postoperative follow-up effect improved significantly without major complications. Malanga *et al* (31) directly injected MFAT into the knee joint with torn meniscus under ultrasound guidance and achieved favorable results, which also showed that MFAT was a safe and potentially effective treatment for patients with degenerative arthritis and knee pain with torn meniscus. A recent systematic review demonstrated that MFAT injection is effective in the treatment of symptomatic knee OA, which can significantly improve knee pain and function (32). Another systematic review also showed that MFAT can relieve pain and improve motor function in patients with knee OA in a short time, and this method is also effective and safe (33). Bisicchia *et al* (34) found that for symptomatic patients with focal cartilage injury of the knee joint, the operation of injecting MFAT plus micro fracture was more effective than the operation of micro fracture alone.

Desando *et al* (35) found that MFAT could induce CD-163 wound healing macrophages to migrate to injured cartilage

by injecting MFAT into rabbit OA model, indicating that MFAT can directly mediate cartilage tissue repair response and promote cartilage repair. Filardo *et al* (36) identified that MFAT can reduce synovial inflammatory response in rabbit OA model and play a protective role on cartilage. A 24-month follow-up study showed that a single intra-articular injection of autologous MFAT could significantly increase the content of glycosaminoglycan in articular cartilage, which indicated that MFAT could promote the synthesis of cartilage matrix and delay the progression of OA (37). Bosetti *et al* (38) showed that MFAT can induce chondrocyte proliferation and ECM production through paracrine, and provide cells that can regenerate or repair damaged or missing cartilage at the site of injury. Xu *et al* (39) through the study of rat cartilage injury model, found that MFAT significantly promoted the migration of chondrocytes; through histological evaluation, MFAT treatment produced tissues similar to normal cartilage, including regular tissue surface, a large amount of hyaline cartilage, complete subchondral bone reconstruction and the formation of corresponding type I, II and VI collagens. The aforementioned study demonstrated the promoting effect of MFAT on the repair of osteochondral defects. Ceserani *et al* (40) demonstrated that MFAT can induce vascular stabilization and inhibit inflammatory response through paracrine action, thus delaying the process of cartilage damage.

These studies have shown that MFAT can inhibit the inflammatory response and promote the repair of cartilage damage by transmitting growth factors, extracellular vesicles and numerous other regulatory information to the microenvironment surrounding the damaged cartilage, or through paracrine effects. Therefore, it is particularly important to further study the specific mechanism and related signaling pathways of MFAT in cartilage damage repair.

4. Conclusions and perspectives

OA is one of the most common degenerative joint diseases, and pain and activity limitation are its main symptoms; OA seriously affects the quality of life of patients and brings heavy economic burden to families and society (41). Although OA has been extensively studied, its pathogenesis remains to be fully elucidated, thus OA cannot be completely cured. MFAT plays an important role in the repair of cartilage injury in OA, but its specific mechanism of action and related signaling pathways are not yet fully understood, thus it requires further study. In general, the present review aims to delay the progression of OA and improve the quality of life of patients by elucidating the role of MFAT in the repair of cartilage damage and the reduction of inflammatory response in OA.

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Authors' contributions

JW and YS drafted the manuscript and revised the manuscript. HL, CW, YG and XJ contributed to manuscript conception. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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