

Research progress on repair of osteochondral defects

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Abstract. In recent years, the incidence of arthritis is getting higher and higher, so the possibility of cartilage injury or even osteochondral defect is also increasing. Osteochondral tissue has also been found to be a complex structure, and a gradient change can be found in its physical properties and microstructure, etc. At present, there are many surgical methods for osteochondral injury, like microfracture, and each surgical procedure has both indications and defects. With the in-depth research of tissue engineering and the appliance of new materials, the research of osteochondral scaffolds is becoming more and more complex. This article not only gives a comprehensive introduction to osteochondral tissue, but also describes the commonly used surgical treatment of osteochondral injury, besides, summarizes the latest research progress of bionic scaffold materials. This review is to summarize the stage of osteochondral tissue repair currently and to provide reference value for the future study of osteochondral tissue repair.

Keywords: Osteochondral tissue, articular cartilage, osteochondral bionic scaffold.

1. Introduction

Articular cartilage plays a role of buffering and absorbing shock in daily joint movement. It cannot only make joint activities more flexible, but also reduce the discomfort caused by direct collision of bones and avoid mechanical damage to bones. Due to the absence of nerves and vascular structures in articular cartilage, even if there is a certain metabolic capacity, the self-repair of articular cartilage after injury is difficult to achieve. Based on the degree of injury, in addition to partial cartilage injury, articular cartilage injury also includes full-thickness cartilage injury as well as osteochondral defects. And some cartilage damage may evolve into serious osteochondral defects if not treated in time in the early stage [1]. Osteochondral damage can be caused by trauma, degeneration, cancer, connective tissue diseases and joint inflammation, such as osteoarthritis [2]. With the progression of osteoarthritis, articular cartilage is degraded or even partially absent, osteophytes are formed, and lesions extend to subchondral bone, causing osteochondral damage.

In view of the existence of gradient variations (including composition, mechanical properties, microstructure, physiological metabolism, etc.) from the surface to the deep parts (subchondral bone), these characteristics have to be fully considered when dealing with cartilage damage. At present, the surgical treatment methods for articular cartilage injury (knee joint) include arthroscopic surgery, microfracture, osteochondral transplantation and other methods. Nevertheless, due to the poor quality and biomechanical function of newly formed cartilage tissue, these defects cannot be ignored [3]. Recently, as tissue engineering and in-depth study of osteochondral interface structure improve by leaps and bounds, osteochondral biomimetic scaffolds fabricated by different materials such as natural biological materials, synthetic materials and composite materials have also been used to restore, maintain and improve damaged osteochondral tissue.

This article summarizes the characteristics of the osteochondral structure, as well as the present status and research progress of surgical repair and scaffold technology for osteochondral injury repair. The aim is to provide a reference for the further development of osteochondral repair.

2. Biological and mechanical properties of osteochondral tissue

Osteochondral tissue (OCT) is a composite tissue structure, mainly found in the joints of the body, formed by bone and cartilage tissues arranged in a certain pattern[4]. The most important structures are the articular cartilage (AC), the calcified cartilage zone (CCZ) and the subchondral bone (SSB) and In OCT, the AC accounts for 90%, while the SSB accounts for an almost equal proportion to the CCZ at 5% respectively [5]. When the composition of OCT is analyzed longitudinally using the articular surface as the reference plane, OCT can be subdivided into articular cartilage layers (including superficial, intermediate, and deep layers), tidal markers, CCZ, cement lines, and SSB. The biological and mechanical properties of OCT also show a clear gradient when analyzed longitudinally.

2.1. Articular cartilage (AC)

The uncalcified articular cartilage layer is consist of three layers: superficial, intermediate, and deep layers depending on the cell morphology and cell arrangement [3].

Superficial layer: The cartilage and the joint are not directly connected; the superficial layer, which is the outermost layer of cartilage, provides the connection [1,6]. The superficial layer consists of hyaline cartilage and is located directly beneath the cartilaginous articular surface. Joint motion is required under conditions of low friction, which is facilitated by the smooth and dense nature of the surface layer. The cells of the superficial layer are arranged in an oval shape and are tightly packed so that they are stronger and flatter and serve to protect the joint [5]. The structural components of the superficial layer can be subdivided into a white membrane and a cellular layer [6]. The white membrane provides a dense, solid barrier to the entire joint and serves to reduce joint damage. The superficial layer of cells has different physicochemical properties to structures such as the transition zone, and has the highest content of collagen and water, accounting for about 20 percent of all cartilage. Its role is to increase bone density, make cartilage elastic and resilient and maintain the metabolic balance of the AC. The superficial layer area is rich in collagen fibres and shows a high degree of organization, which cushions the friction formed between the articular surfaces [2,6].

Intermediate layer: Intermediate layer is also called transition zone. The transition zone accounts for approximately 50% of the cartilage depth, in which the collagen fibres are significantly thicker and are obliquely organized [5]. The middle layer of cartilage is thicker than the superficial layer and contains more elastic fibres and chondrocytes. The cells in the transition zone are closer to elliptical or circular in morphology and are irregularly arranged. The transition zone has a higher level of protease and contains only a small amount of collagen [3,6]. These biological characteristics of the transition zone determine its physical properties in a way that helps to distribute the load evenly over the cartilage surface and acts as a good resistance to compression forces [6].

Deep layer: The deep layer accounts for about a quarter of the whole depth of the cartilage. The chondrocytes are arranged in a columnar pattern and are lined up in the same direction as the collagen fibers. The cartilage is thinner and more elongated in shape. The deep layer consists of a large amount of fibrous and dense connective tissue, the foundation of the entire cartilage structure. Compared with other layers, The water content is the lowest, due to the high content of proteoglycans and the fact that the diameter of the collagen fibers in this layer is more significant than in any other area. Besides, the collagen fibers are arranged differently, perpendicular to the cartilage surface tissue, and this arrangement is mechanically conducive to maximum resistance when subjected to pressure [6]. Based on these biological and physical properties, the deep layer provides strength and stability to the AC as a whole and can play a positive role in protecting the AC as a whole from injury.

2.2. Tidal markers

The tidal marker can be seen as a demarcation between the CCZ and the deep layer. It is used to inhibit vascular infiltration between the CCZ and the deep layer [4,6].

2.3. Calcified cartilage zone (CCZ)

Calcified cartilage is mineralized, hyaline cartilage, approximately 20 to 250 microns, which in healthy joints is generally located between the subchondral bone and the deep layer [1,6]. Calcium salts are deposited in its matrix, making it harder than normal cartilage. The structure of calcified cartilage consists of chondrocytes, which are embedded in an extracellular fibrous matrix that includes collagen and proteoglycan [3]. This embedded structure allows the CCZ to adhere more firmly to the SSB and the CCZ cushions the pressure between the cartilage and the SSB. The mechanical properties of calcified cartilage depend on its microstructure and are closely related to the distribution, cross-linking, and mineralization pattern of the collagen fibers. Typically, calcified cartilage has a high compressive strength and a low tensile strength. Because the mineralized matrix increases the strength and rigidity of the tissue, it is also stiffer and less deformable than hyaline cartilage [3].

2.4. Cement line

The cement line is a transitional area between the hyaline cartilage and the underlying skeleton on the surface of the joint. It is a thin, layered structure that separates the hyaline cartilage from the bone and acts as a boundary between the two tissues [6].

2.5. Subchondral bone (SSB)

The SSB is a dense, compact layer of bone that lies beneath the AC in the joint, which acts as a support for the cartilage and helps to distribute forces evenly across the joint surface. The structure of the SSB is characterized by a dense, compact outer layer and a more porous inner layer. The outer layer provides mechanical strength, while the inner layer contains bone trabeculae which, due to their porous nature, enable them to act as a good force distributor [3,6]. SSB has a rich blood supply, which is instrumental in maintaining the health of the OCT [6]. In terms of mechanical properties, SSB has high compressive strength and good resistance to fracture. SSB also has good energy absorption and can deform elastically under load and then return to its original shape [3]. These properties enable it to act effectively as a load-bearing structure for joints, supporting AC and helping to distribute forces evenly.

3. Treatment of osteochondral injury

3.1. Surgical treatment

In order to meet the needs of clinical diagnosis and treatment, articular cartilage injury can usually be classified as different types and levels. For example, apart from partial cartilage damage, according to the thickness of the injury, it includes full-thickness cartilage damage. And based on the International Cartilage Repair Association cartilage injury grading system, under open or arthroscopic, articular cartilage injury can be classified as follows. Superficial, blunt notch and superficial cracking can be seen in Grade 1; in Grade 2, the thickness of cartilage lesion is less than half of cartilage full-thickness; while Grade 3 include loss of cartilage that is more than half of the depth of cartilage while the subchondral bone is still normal; Grade 4 describes full-thickness cartilage tear combined with subchondral bone exposure [7]. Usually cartilage injury of less than 2 square centimeters can be used debridement and lavage, microfracture, osteochondral autograft. The larger lesion can be treated with osteochondral allograft transplantation (OAT) or matrix-induced autologous chondrocyte implantation (MACI).

Arthroscopic debridement and lavage is to remove broken cartilage, hyperplastic synovium, osteophytes and loose bodies under arthroscopy to relieve pain and other symptoms. This treatment has the advantages of low cost, faster recovery and less trauma. But in contrast, this repair of cartilage damage is poor and easy to relapse [8]. Microfracture (MF) surgery is to stimulate the migration of stem cells by drilling holes in the subchondral bone plate, and achieve self-repair after colonization

in the injured area. The technique is easy to operate, and young patients usually recover better. However, it is easy to form fibrous cartilage, and the defect area is incompletely filled, and it is lack of long-term repair ability [9].

Autologous osteochondral transplantation mainly collects osteochondral plugs from areas with little effect on joint function, such as femoral intercondylar medial and lateral trochlear ridge and intercondylar fossa, then fills them into the defect of weight-bearing area later. The results of repair are mainly hyaline cartilage, which heals faster, while it is subject to the source of donor materials, so it is suitable for cartilage defects with a defect area of less than 2 square centimeters. Autologous transplantation can treat cumulative subchondral bone lesions (osteochondral plugs include hyaline cartilage and subchondral bone) without immunogenicity. However, due to the possible complications of the donor site and the difficulty in matching the contour shape of the extracted donor cartilage with the lesion site to make a consistent surface, this limits the application of autologous transplantation [10].

By analyzing the data to compare the outcomes after operation of OAT and MF surgery, it was found that from the perspective of Lysholm score, Tegner scale and International Cartilage Repair Society (ICRS) score, patients receiving OAT treatment may recover faster and even come back to the level of activity before injury [11]. In spite of that, due to the absence of long-term reports and the lack of uniform standards for recovery exercise, these two surgical methods still need to be selected according to the actual situation of patients.

It has been proved that osteochondral allograft transplantation is effective for various cartilage injuries. In particular, these grafts are useful for large and deep osteochondral lesions (larger than 2 square centimeters). In addition, the donor material is relatively easy to obtain, and can be prefabricated into various shapes and sizes to match the osteochondral of the injured area. There are more options for the regional matching of the repaired tissue, and there are no donor site injury complications. Nevertheless, the disadvantages of allogeneic osteochondral transplantation are also very obvious, such as immune rejection, degeneration, subchondral bone healing disorders and other complications, and the cost of this operation is much higher than that of autologous osteochondral transplantation [12].

Through a systematic review, to figure out the effectiveness of the treatment of autologous osteochondral transplantation and allogeneic osteochondral transplantation in knee osteochondral injury, the postoperative survival rates of the two groups were more than 85%, and the average improvement rate of prognosis was more than 65%, and there was no significant difference [13]. However, the correct choice of the two procedures remains crucial for the success and potential long-run survival of the graft.

To discover a better way to repair articular cartilage, the clinical study of autologous chondrocytes transplantation to repair cartilage defects was first reported in the 1990s. So far, autologous chondrocyte transplantation has developed and innovated to the third generation technology: the first generation applies autologous periosteum taken from the proximal tibia to seal and fix artificially cultured chondrocytes to the defect site, but there is a probability of autologous periosteal hyperplasia and hypertrophy, which requires arthroscopic debridement again; the second generation of autologous chondrocytes transplantation used collagen membrane to replace autologous periosteum. The third generation technology cultured chondrocytes in a three-dimensional matrix, called MACI [14], which was approved by the FDA in 2017. MACI can generate cartilage-like tissue with good biomechanical properties, and help patients improve symptoms and restore motor function better. MACI requires two stages (the first stage is to culture chondrocytes on the collagen membrane, and the second stage is to treat the injured site) and is expensive, which is the biggest limitation of this method [15].

For level 1 randomized clinical trials, it was found that cartilage repair technology has higher quality tissue repair ability, lower failure rate and better recovery activity by searching different databases, besides, in comparison with MF, the results of OAT and ACI and MACI were significantly better, and OAT showed worse outcomes than MACI during 1-year follow-up [16]. In order to better

compare the long-term effects of these types of surgery on patients, longer-term follow-up of representative populations is needed to investigate the effectiveness of these surgical interventions.

Up to now, there are increasingly means for the treatment of osteochondral injury in clinical practice. No matter what treatment method is used, such diseases can be accurately treated according to the specific conditions of patients after mastering the advantages and defects of these methods

3.2. Tissue engineer repair-scaffold

In recent years, the feasibility of organizing repair projects to treat cartilage damage has been increasingly recognized. Among them, the use of scaffold materials is very important. The ideal bio-scaffold materials need to simulate the physiological environment of extracellular mechanism, which promotes and helps the cells maintain phenotype and functions. Therefore, the scaffold materials have the following characteristics. (1) having good mechanical properties and better plasticity, which can provide a good growth environment for neonatal cartilage cells; (2) possessing good biocompatibility, which is conducive to cell adhesion and non-toxic, besides, it cannot cause inflammation in the body, or immune rejection; (3) containing a suitable aperture, a higher porosity and a connected micro-porous structure similar to natural bone, which may provide good conditions for cell growth and adhesion. (4) holding excellent surface activity, which can guide the behavior of internal planting cells and maintain the vitality and phenotype of cells; (5) owing good biodegradability, degradation products are harmless to the body; (6) being easy to obtain and mass production, as well as cost-effective [17]. Common bone cartilage bio-scaffold materials are classified into following.

3.2.1 Natural biological materials

These materials support mainly includes collagen, gelatin, fibrin, hyaluronic acid, alginate, agarose, chitosan, silk protein, etc. The main advantage is that these stems from natural materials, which have biochemical properties similar to cartilage. The biological materials can provide a suitable microenvironment in vitro to maintain the phenotype of chondrocytes and continuously support cartilage regeneration while degrading slowly [18]. However, the mechanical properties may be poor in most of the scaffolds made of natural biomaterials, which limits their application as load-bearing scaffolds.

3.2.2 Compound synthetic materials

These kind of materials mainly include polyethylene glycol, polycaprolactone, polylactic acid, polyglycolic acid, polylactic acid-glycolic acid, etc. Synthetic polymers have good controllability in structure, mechanical properties and composition compared with natural polymers. They can be customized for specific applications and their chemical properties are easier to modify. In addition, synthetic polymers can be mass-produced and provide more renewable results than natural polymers [19]. Usually, natural scaffold materials have the risk of being a vector of infectious diseases, while synthetic materials do not need to worry about this problem.

3.2.3 Composite scaffold materials

A single type of cartilage scaffold materials, due to its single composition, cannot meet the needs of repairing cartilage tissue defects. Based on a variety of natural materials (chitosan, carrageenan, hydrogel and gelatin, etc.) and synthetic materials, a variety of materials are synthesized. The synthesized composite materials can complement each other and make up for the shortcomings of the performance of a single material, becoming a scaffold material more suitable for tissue engineering cell culture.

4. Conclusion

Osteochondral damage is a clinically widespread and serious joint disease. This article systematically expounds the biochemical composition and basic functions of osteochondral tissue

structure from superficial layer to subchondral bone, also describes the current surgical treatment methods for osteochondral injury and briefly summarizes the materials for osteochondral scaffold repair from the perspective of tissue engineering.

With the deepening understanding of osteochondral structure and the continuous development of tissue engineering, there are more and more clinical treatment methods for osteochondral injury, and the materials used for osteochondral scaffolds are constantly updated. No matter what kind of treatment method is used, mastering its advantages and disadvantages, and adopting personalized treatment plan according to the specific situation of injury is the key and difficult point to consider when dealing with such problems. Although osteochondral scaffolds have been able to simulate the structure of natural osteochondral tissue units and have good effects in vitro and in vivo experiments, long-term clinical studies have not provided satisfactory results. With the continuous development of molecular biology and materials science, the problem of osteochondral injury can be addressed through multidisciplinary cooperation.

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