

REVIEWS

Research and progress of cartilage tissue-engineering scaffold materials

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Abstract

Due to the limited self healing capacity of human cartilage, the repair of defects gives rise to a challenging clinical problem. Cartilage tissue engineering provides a new method to solve cartilage repair. However, the search for a suitable biological vector material has long been the focus of research interest in this regard. In this paper, the present situation of cartilage tissue engineering vector materials is reviewed.

Key Words: Cartilage tissue, Scaffold material

Since the 1980s, tissue engineering has been proposed as an alternative and innovative way to address tissue regeneration problems, whose basic principle is to construct a new cartilage tissue for transplantation in vitro.

Kaihara et al.^[1] defined cartilage tissue engineering as “A new field, tissue engineering, applies the principles of biology and engineering toward the development of biological substitutes that restore, maintain, or improve tissue function”. There is no blood vessel in cartilage tissue, and the cell composition is single, so cartilage tissue engineering is progressing rapidly. Its development meets with a large demand of artificial cartilage for cartilage defect reconstruction.^[2,3]

Cartilage tissue engineering aims to synthesize cartilage cells and extracellular matrix into functional structures like normal cartilage. The three basic methods are listed as follows:^[4,5] (1) Isolation and culture of cells or cell substitutes in vitro. This method is available to provide defective tissues and organs with cells that functions. (2) Application of factors that provoke tissue growth. The success of the method highly relies on the purification and mass production of the factors involved, and the techniques for introduc-

ing these factors into target tissue. (3) Application of the cell-matrix functional structure. A closed structure in which cells are separated from the body by a membrane that allows nutrients and metabolites to diffuse, but the macromolecular proteins are not involved. This kind of structure is either implanted in vivo or connected in vitro. The other is an open structure. Cells attached to the matrix are implanted into the body to fuse into tissue. The open structure of cell-matrix is the core of tissue engineering technique to repair cartilage defect.

There are three main requirements for the study of articular cartilage tissue engineering:^[6] (1) A sufficient number of normal “seed” cells; (2) Proper extracellular matrix; (3) Regulate the proliferation of seed cells and maintain the cytokines phenotype.

At present, the research of vector materials for articular cartilage tissue engineering mainly involves the natural polymer carrier materials, synthetic materials, composite materials, three-dimensional porous scaffolds and their hydrogels can be classified according to morphology of the prefabricated.

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1 Natural polymer carrier material

Natural materials could be obtained from animals or human bodies. Its network structure, composition and biomechanical environment are suitable for the growth, development and metabolism of seed cells. The materials can be degraded, such as chitosan, alginate, fibrin gel, hyaluronic acid (HA), gelatin, collagen, collagen gelatin, collagen sponge, and so on. The most prominent advantages are low antigenicity, good biocompatibility, cell recognition signal, which are conducive to cell behavior, but the gelation process controllability and mechanical strength is relatively poor.

1.1 Collagen

Collagen is the most important water insoluble fibrin as well as abundant structural protein in human body, which accounts for about 25% of the total body protein and constitutes the skeleton of extracellular matrix. As a semi crystalline fiber in the extracellular matrix, collagen performs resistance to tension and elasticity and acts as a function of cell migration and development. It could be found in all kinds of animals. Wakitani and Wawvbach^[7] discovered the expression of type II-collagen in the matrix by co-culture of type-I collagen and chondrocytes, and the formation of cartilage was confirmed by histochemistry. It can be concluded that type-I and type-II collagen can be used as scaffold materials for cartilage tissue engineering. Type I and type II collagen can be used as a good material for inclusion of additives because of their special recognition signal, which is beneficial to the adhesion, proliferation and differentiation of chondrocytes. While their disadvantages are listed as follows: lack of flexibility, low tensile strength, unfavourable cartilage repair in the weight-bearing area, over-rapid degradation, insufficient initial strength and so on.^[8]

1.2 Fibrin

Fibrin derives from natural extracellular matrix and is characterized by good biocompatibility. Fibrin gel is a kind of solid network which can be formed, modified and adhered to and degraded by fibrin monomer under the action of thrombin. It not only provides three-dimensional space for cell survival but also leaves enough time for gel formation by slowing down the aggregation of thrombin and its conversion from liquid to gel.^[9] Hendrickson et al.^[10] injected the mixture of chondrocytes, fibrinogen and thrombin into the defects on the lateral trochlea of the distal femur of horses, and found the hyaline cartilage formed after 1 month containing large amounts of glycosaminoglycan and type-II collagen. The adhesion, proliferation and matrix of fibrin glue can promote cell secretion, but as a three-dimensional scaffold, it is not able to provide enough mechanical strength,

which is a common shortcoming shared by all natural biological materials. Moreover, it is difficult to obtain in large amounts due to its source of blood. However, it is still a good scaffold material for small range of cartilage repair in non bearing areas.

2 Synthetic material

Synthetic material is a kind of organic macromolecule polymer with good physical and mechanical properties. It can meet different needs by regulating molecular weight and its distribution. As a scaffold for cartilage tissue engineering, it can induce the adhesion, proliferation and differentiation of chondrocytes, such as polylactic acid (PLA) and polyglycolic acid (PGA), copolymer of polylactic acid and polyglycolic acid (PLGA) and polyvinyl alcohol (PVA). The biggest drawback is that the surface of the material is lack of site which can be identified by the cells. Moreover, it doesn't show any biological activity, and the degradation products of the material may contain some toxicity.

2.1 PGA

PGA is a highly crystalline and hydrophilic linear polyester, showing better solubility in water. Liu YC et al.^[11] replanted the cartilage cells of rabbit auricle which were firstly planted on the modified PGA scaffold, and found that the cartilage tissues were generated afterwards. However, the degradation half-life of PGA is about 2 weeks. Therefore, the degradation rate is too high to provide sufficient supporting strength prior to formation of engineered cartilage. Thus, its use as a candidate of scaffold material alone is hindered.

2.2 PLGA

PLGA is a copolymer of PLA and PGA in a certain proportion, inheriting features from both sides, which not only meets the need of sufficient strength support, but also is conducive to cell attachment growth. Uematsu et al.^[12] repaired cartilage defects with mesenchymal stem cell-PLGA scaffold complex in rabbits. 12 weeks after transplantation, the white tissue of the defect was seen to be covered with smooth and glossy surface and histologically hyaline cartilage. PLGA scaffolds are able to support progenitor cell differentiation and induce chondrogenesis in vivo. In recent years, it has been found that the biological effect can be enhanced by changing the preparation methods and scaffold modification.

3 Composite

The composite material combines two or more biocompatible biodegradable materials with complementary characteristics in a certain proportion and manner, and is made from appropriate preparation process in order to meet the requirement for tissue engineering structure and performance optimization of three-dimensional scaffold. Modification and other biomimetic process such as physical/chemical methods (embedding, crosslinking, hybridization, ion implantation etc.), and biological methods (drug activation, gene activation, signal molecule activation) were performed to retain the advantages and overcome the disadvantages of the materials. Composite carrier materials not only make up for the shortcomings of single material but also enhance the advantages of composite to meet the needs of tissue engineering.

3.1 Chitosan-collagen composite scaffold

Collagen is the main component of connective tissue in human body, characterized by low solubility, low immunogenicity, good histocompatibility and compatibility, and cell proliferation promotion,^[13] however its mechanical properties are poor. Chitosan is the only positively charged alkaline polysaccharide with non-toxic, no-stimulation nature, characterized by high biocompatibility, degradation and so on. It is widely used in artificial skin, bone repair materials, surgical suture, and anticoagulation.^[14] The number of cartilage specific matrix increased obviously when chitosan was selected as the substrate to culture rabbit bone marrow stromal cells. The tissue-engineered cartilage achieved good outcomes for repairing full-thickness cartilage defect in rabbit.^[15] Its molecular chain is fiber rigid structure, containing a large number of positively charged amino and hydroxyl groups. Macromolecular poly dielectric composite in combination with collagen improves the mechanical strength of collagen, and it has good biocompatibility, transparency and mechanical properties and controllable degradation absorption rate. Shi D et al.^[16] mixed chitosan and type II collagen to prepare the porous materials, and found that the mechanical strength of the materials was enhanced, and it was suitable for the application of tissue engineering by physical and chemical tests.

3.2 Collagen-PVA composite

PVA shows good Young's modulus and tensile strength, which is suitable for many soft tissues,^[17] whereas the abil-

ity of PVA to adsorb cells is limited.^[18] Therefore, combination with collagen makes it more suitable for the study of cartilage tissue engineering materials via promoting its cell adhesion. Ye CT et al.^[19] combined collagen and PVA composite to develop gel-like materials, and evaluated the cell compatibility and histocompatibility of the materials. The cells could grow in three dimensions of collagen-PVA without any toxic and side effects. After 4 weeks in vivo, the foreign body disappeared, and the materials and tissues fused with each other. These results show that the materials have good cell compatibility and histocompatibility, and can be used as implant material and tissue substitute material in soft tissue.

3.3 PLA/PGA calcium polyphosphate fiber-collagen composite scaffold

The three-dimensional macroporous scaffold manufactured from synthetic materials such as PLA and/or PGA has many advantages, such as good mechanical properties, controllable degradation time, easy to shape and so on. It is widely used in the fabrication of three-dimensional scaffolds for tissue engineering. But the disadvantages of the hydrophobicity of the materials, the lack of cell recognition signals and acidic degradation products restrain the applications as scaffold materials in tissue engineering.

Calcium polyphosphate fiber is a kind of high strength material with good biocompatibility and biodegradability. The degradation products are weakly alkaline and can partially neutralize the acidic products produced by the degradation of polyester materials. Microporous three-dimensional scaffolds derived from natural materials such as collagen, agarose and alginate are widely used in the preparation of three-dimensional scaffolds for tissue engineering due to their strong hydrophilicity and cell compatibility. The cartilage cells and collagen solution are inoculated into calcium polyphosphate fiber-poly-L-lactin acid (PLLA) macroporous scaffold after intensive mixing. It not only owns good mechanical strength and easy shaping and other advantages of three-dimensional macroporous scaffold, but also plays the role of collagen gel in cell encapsulation and adhesion. The cell scaffold composite constructed by the above methods can reach mature soon in vitro.^[20]

Conflicts of Interest Disclosure

The authors have no conflict of interest related to this article.

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