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Tissue Engineering—Review

Recent Progress in Cartilage Tissue Engineering—Our Experience and Future Directions

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ABSTRACT

Given the limited spontaneous repair that follows cartilage injury, demand is growing for tissue engineering approaches for cartilage regeneration. There are two major applications for tissue-engineered cartilage. One is in orthopedic surgery, in which the engineered cartilage is usually used to repair cartilage defects or loss in an articular joint or meniscus in order to restore the joint function. The other is for head and neck reconstruction, in which the engineered cartilage is usually applied to repair cartilage defects or loss in an auricle, trachea, nose, larynx, or eyelid. The challenges faced by the engineered cartilage for one application are quite different from those faced by the engineered cartilage for the other application. As a result, the emphases of the engineering strategies to generate cartilage are usually quite different for each application. The statuses of preclinical animal investigations and of the clinical translation of engineered cartilage are also at different levels for each application. The aim of this review is to provide an opinion piece on the challenges, current developments, and future directions for cartilage engineering for both applications.

1. Introduction

Cartilage defects in orthopedic sites and in head and neck regions are frequently caused by trauma, cancer removal, aging, or congenital diseases. Since cartilage is avascular, aneural, and alymphatic, and contains only a sparse population of a single cell type (chondrocyte), its ability to regenerate after injury is hindered [1,2]. Major traditional procedures for cartilage repair include microfracture (marrow stimulation) [3], autografts [4], and autologous chondrocyte implantation (ACI) [5]. Although successful in some aspects, each of these methods has limitations such as unmatched property of the repaired region, lack of integration, and donor-site morbidity [6–8].

Tissue engineering provides a prospective alternative strategy by seeding chondrogenic cells into or onto biodegradable scaffolds in order to engineer cartilage for defect repair [9]. In orthopedic applications, the engineered cartilage is usually used to repair defects in an articular joint or in a meniscus in order to restore the joint's load-bearing function and relieve pain. In head and neck applications, cartilage is usually engineered for the repair or reconstruction of an auricle, trachea, nose, larynx, or eyelid for an aesthetic or functional purpose. The challenges faced by the engineered cartilage for each application are quite different. In orthopedic applications, the engineered cartilage needs to integrate with the adjacent native cartilage as well as, in many cases, with the subchondral bone. The mechanical properties of the engineered cartilage should always match those of the adjacent tissue in order to enable survival and function within the biomechanically arduous joint environment [8]. The engineered cartilage also needs to cope with inflammatory mediators in cases with degenerative wounds. In head and neck applications, however, the engineered cartilaginous grafts are often required to

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be chondrogenically stable with superb biocompatibility so that they can survive and function in subcutaneous or intramuscular implantation sites, which lack chondroinductive cues and are characterized by acute immune response. In many cases, the engineered cartilage also needs to possess a specific shape with large volume and/or specialized function. As a result, engineering strategies to generate cartilage are usually quite different for each application. The statuses of preclinical animal investigations and of the clinical translation of engineered cartilage are also at different levels for each application.

Our group has been devoted to cartilage tissue engineering research for both applications for more than 20 years. Our specialty and research emphasis involve the *in vitro* regeneration of cartilage using different seed cell sources for the repair of different types of cartilage, and their preclinical large-animal evaluations. In this review, we provide an opinion piece on the developments in seed cell strategy, scaffold design, and preclinical animal investigation, as well as on the status of clinical translation, for both applications. We also summarize encountered challenges and future requirements.

2. Tissue-engineered cartilage for orthopedic reconstruction

Owing to upward trends in both life expectancy and youth obesity, a steady increase in the prevalence of osteoarthritis (OA) is expected [10,11]. Meanwhile, the incidence of athletic injury is also increasing. As a result, a major application of engineered cartilage is that of orthopedic practice to repair cartilage defects caused by traumatic or pathological injuries. Since the most important function of orthopedic cartilage is to bear weight, engineered neocartilage should ideally be able to: ① integrate not only with the subchondral bone, but also with the adjacent cartilage for stable load distribution and mechanotransduction; ② match the mechanical properties of the adjacent native cartilage in order to avoid tissue degradation caused by strain disparity; ③ be resistant to load under large deformations and motions; and ④ recapitulate the distinct zonal architecture in order to recreate the structure-function relationship of the native cartilage. The challenges of engineering biomechanically suitable cartilage have been thoroughly described in a review paper [8]. Moreover, engineered cartilage should be able to deal with the inflammatory environment of a degenerative cartilage.

Study activities to address these criteria have been sustained during the past two decades. The optimal cell source and scaffold are being explored. Preclinical large-animal investigations have been conducted. Many engineered cartilages for orthopedic reconstruction have realized clinical translation or even gained market access. However, despite the continuous progress in this field, no research activity has generated cartilage that can entirely mimic the properties and structure of native cartilage.

2.1. Seed cell options for tissue-engineered cartilage for orthopedic reconstruction

The implantation site of the engineered cartilage for orthopedic application is usually within the intra-articular space, in which chondroinductive cues in terms of cytokines and mechanical stimulations exist to promote the spontaneous chondrogenesis of the implanted cells and maintain their chondrogenic phenotype and function. Therefore, several different seed cell options exist: Chondrocytes [12], mesenchymal stem cells (MSCs) from different sources [13,14], (induced) pluripotent stem cells [15], and even fibroblasts [16] were reported as seed cell candidates to engineer cartilage for orthopedic applications. However, no consensus has been reached on which is to be accepted as the optimal cell source for current orthopedic cartilage engineering. Our group mainly focuses on two of the most clinically applicable seed cell sources: chondrocytes and MSCs.

2.1.1. Chondrocytes

Chondrocytes, the resident cartilage cells that are essential for cartilage-specific extracellular matrix (ECM) production, represent a logical choice of seed cells for cartilage engineering. Isolating chondrocytes from the joint surface is difficult, and would cause secondary injury leading to OA. Therefore, researchers have considered using non-articular "heterotopic" chondrocytes such as nasoseptal chondrocytes or auricular chondrocytes as an alternative cell source, since they are easier to harvest, associated with lower donor-site morbidity, and possess a higher proliferation rate [17–20]. However, it remains unclear whether heterotopic chondrocytes would produce cartilage with a desired type (such as hyaline cartilage) and function during defect healing. Chondrocytes from OA cartilage have also been tested as a seed cell candidate [21–23]. To use chondrocytes as a seed cell source, researchers need to deal with the issue of dedifferentiation by means of, for example, 3D microcarrier suspension culture [24,25], chondrocyte sorting [26], cytokine stimulation [27], or reduced oxygen tension [28], although too-extensively expanded chondrocytes may lose their capacity to re-differentiate [29]. Moreover, as evidenced in our previous study, chondrocytes may fail to form bone tissue in the subchondral bone region of an osteochondral defect (Fig. 1) [12,30].

2.1.2. Mesenchymal stem cells

To overcome the limitations of chondrocytes, MSCs gradually became the focus of many researchers [31]. MSCs can be harvested from a number of sources that do not affect cartilage activity, maintain multipotency after numerous expansions, and can be differentiated to generate both cartilage and bone—making the tissue-specific repair of osteochondral defects possible (Fig. 1) [30,32]. The immunosuppressive properties of MSCs, which are still maintained after their chondrogenic commitment, make off-the-shelf allogenic application practical [33,34]. Nevertheless, using MSCs as an alternative cell source for articular cartilage repair also presents several

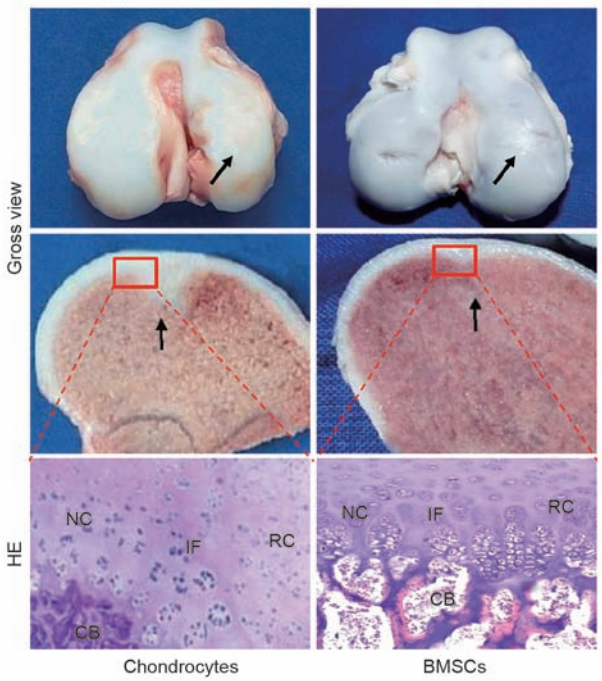

Fig. 1. Repair of autologous pig osteochondral defects by polyglycolic acid (PGA) scaffold loaded with chondrocytes or bone marrow stromal cells (BMSCs), respectively. Both cells realized cartilage repair with a smooth surface. Chondrocytes failed to realize tissue-specific repair in the subchondral region. HE: haemotoxylin and eosin; NC: native cartilage; IF: interface; RC: regenerated cartilage; CB: subchondral bone. Some of this data was published in Refs. [12,30].