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Review article

Cell-laden hydrogels for osteochondral and cartilage tissue engineering

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ABSTRACT

Despite tremendous advances in the field of regenerative medicine, it still remains challenging to repair the osteochondral interface and full-thickness articular cartilage defects. This inefficiency largely originates from the lack of appropriate tissue-engineered artificial matrices that can replace the damaged regions and promote tissue regeneration. Hydrogels are emerging as a promising class of biomaterials for both soft and hard tissue regeneration. Many critical properties of hydrogels, such as mechanical stiffness, elasticity, water content, bioactivity, and degradation, can be rationally designed and conveniently tuned by proper selection of the material and chemistry. Particularly, advances in the development of cell-laden hydrogels have opened up new possibilities for cell therapy. In this article, we describe the problems encountered in this field and review recent progress in designing cell-hydrogel hybrid constructs for promoting the reestablishment of osteochondral/cartilage tissues. Our focus centers on the effects of hydrogel type, cell type, and growth factor delivery on achieving efficient chondrogenesis and osteogenesis. We give our perspective on developing next-generation matrices with improved physical and biological properties for osteochondral/cartilage tissue engineering. We also highlight recent advances in biomanufacturing technologies (*e.g.* molding, bioprinting, and assembly) for fabrication of hydrogel-based osteochondral and cartilage constructs with complex compositions and microarchitectures to mimic their native counterparts.

Statement of significance

Despite tremendous advances in the field of regenerative medicine, it still remains challenging to repair the osteochondral interface and full-thickness articular cartilage defects. This inefficiency largely originates from the lack of appropriate tissue-engineered biomaterials that replace the damaged regions and promote tissue regeneration. Cell-laden hydrogel systems have emerged as a promising tissue-engineering platform to address this issue. In this article, we describe the fundamental problems encountered in this field and review recent progress in designing cell-hydrogel constructs for promoting the reestablishment of osteochondral/cartilage tissues. Our focus centers on the effects of hydrogel composition, cell type, and growth factor delivery on achieving efficient chondrogenesis and osteogenesis. We give our perspective on developing next-generation hydrogel/inorganic particle/stem cell hybrid composites with improved physical and biological properties for osteochondral/cartilage tissue engineering. We also highlight recent advances in biomanufacturing and bioengineering technologies (*e.g.* 3D bioprinting) for fabrication of hydrogel-based osteochondral and cartilage constructs.

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Contents

1. Introduction

Osteochondral interface defects commonly involve lesions of both articular (hyaline) cartilage and underlying subchondral bone that are caused by trauma, disease, or aging. Different from the vast majority of other tissues, cartilage is basically avascular and low in cellularity in nature [1]. Cartilage thus lacks the ability to self-heal due to the absence of abundant nutrients and proper progenitor cells. When a cartilage defect is left untreated, however, the joint irrevocably and progressively deteriorates, leading to osteoarthritis and eventually, disabilities [2]. Cartilage-related tissue defects and diseases are the most common cause of disability, representing around 6% of disabled people of 30 years and older [3–5]. Current treatment strategies for osteochondral interface and full-thickness cartilage defects include microfracture (marrow stimulation) [6–8], autologous chondrocyte implantation [9–12], and osteochondral autografts and allografts [13–16], among others. Despite their common uses in the clinic, notable limitations and drawbacks still exist. The microfracture treatment drills tiny holes that penetrate the cartilage and the subchondral bone to bring in blood flow and bone marrow from surrounding tissues. Induced cartilage and bone regeneration/remodeling are expected due to the introduction of stem cells and biomolecules at the defects. However, it may lead to the formation of fibrocartilage that has inferior biofunctions compared to articular cartilage [17–19]. The autologous chondrocyte implantation strategy has been used clinically to regenerate articular cartilage for two decades with satisfactory surgical outcome to certain extent. Nevertheless, there are still drawbacks including shortage of chondrocyte source, long chondrocyte harvesting time, difficulty of chondrocyte solution fixation, periosteal hypertrophy and ablation [20], as well as low effectiveness for aged patients [21]. It should also be noted that autologous chondrocyte implantation is incapable to repair osteochondral interface and full-thickness cartilage, which require