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Update article

Cartilage tissue engineering: From biomaterials and stem cells to osteoarthritis treatments

C. Vinatier [a,b], J. Guicheux [a,b,c,*]

[a] Inserm UMRS 791, laboratoire d'ingénierie osteo-articulaire et dentaire (LIOAD), group STEP « skeletal tissue engineering and physiopathology », 44042 Nantes, France
[b] Université de Nantes, UFR d'odontologie, 44042 Nantes, France
[c] CHU de Nantes, PHU 4 OTONN, 44000 Nantes, France

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ABSTRACT

Articular cartilage is a non-vascularized and poorly cellularized connective tissue that is frequently damaged as a result of trauma and degenerative joint diseases such as osteoarthrtis. Because of the absence of vascularization, articular cartilage has low capacity for spontaneous repair. Today, and despite a large number of preclinical data, no therapy capable of restoring the healthy structure and function of damaged articular cartilage is clinically available. Tissue-engineering strategies involving the combination of cells, scaffolding biomaterials and bioactive agents have been of interest notably for the repair of damaged articular cartilage. During the last 30 years, cartilage tissue engineering has evolved from the treatment of focal lesions of articular cartilage to the development of strategies targeting the osteoarthritis process. In this review, we focus on the different aspects of tissue engineering applied to cartilage engineering. We first discuss cells, biomaterials and biological or environmental factors instrumental to the development of cartilage tissue engineering, then review the potential development of cartilage engineering strategies targeting new emerging pathogenic mechanisms of osteoarthritis.

1. Introduction

Articular cartilage may undergo many alterations due to inflammatory causes, trauma, or aging. These complications lead to decreased cellularity and further degradation of the cartilage extracellular matrix (ECM). Cartilage damage has been known for more than 200 years. In 1743, the Scottish doctor William Hunter wrote in an article of the Royal Society, "Since Hippocrates and until now, it is universally accepted that the ulcerated cartilage is embarrassing and that, once destroyed, can not be repaired". The absence of vascularization and proliferation of chondrocytes provides articular cartilage with poor self-healing capacity. The cartilage damage and associated catabolic processes are irreversible and lead to long-term development of osteoarthritis (OA).

OA is the most common joint disorder affecting a growing part of the aging population. The incidence of this degenerative disease increases with age and is a major health concern. Worldwide, more than 10% of men and 18% of women older than 60 years is estimated to be affected by OA. OA is accompanied by degradation of the articular cartilage, thickening of the subchondral bone, formation of osteophytes [1] and variable degrees of synovium inflammation [2]. In this context, the scientific community has been interested for many years in different strategies to regenerate a functional cartilaginous tissue. However, surgical techniques developed in an attempt to repair cartilage damage, such as the abrasive chondroplasty, microfracture and spongialisation [3], lead to the formation of transient fibrocartilaginous tissue. In parallel, transplantation of tissue with chondrogenic properties, such as periosteum and perichondrium transplants and osteochondral grafts (mosaicplasty), have been proposed.

Still today and despite advances in orthopedic surgery, treatment of the cartilage damage remains challenging. The existence of numerous limitations associated with the above-mentioned techniques such as graft instability, calcification, and restricted applications to focal lesions have led to the development of new therapeutic strategies based on cell therapy and tissue engineering. Tissue engineering, a field of research that emerged during the 1990s [4], was defined by Langer and Vacanti in 1993 as "an interdisciplinary field that applies the principles of engineering and the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function" [5].

* Corresponding author. Inserm UMRS 791, laboratoire d'ingénierie osteo-articulaire et dentaire (LIOAD), group STEP « skeletal tissue engineering and physiopathology », 1, place Alexis-Ricordeau, 44042 Nantes cedex 1, France.
E-mail address: jerome.guicheux@inserm.fr (J. Guicheux).

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In this review, we focus on the different components of tissue engineering applied for cartilage engineering. We discuss the promising development of cartilage engineering strategies targeting recently identified pathogenic mechanisms of OA.

2. Articular cartilage tissue engineering

Tissue engineering is an emerging discipline that combines the principles of engineering and biological sciences to develop biological substitutes that can notably restore the functions of altered tissues [5]. This discipline is based on an association of biomaterials, cells and biological or environmental factors, also known as the "tissue engineering triad" (Fig. 1). Cartilage tissue engineering has greatly benefited from recent advances in material engineering and in our understanding of the role of growth factors and stem cells in tissue regeneration.

2.1. Biomaterials

In tissue engineering, cells are generally seeded onto a scaffold, whose primary objective is to replicate the characteristics of the target-tissue ECM. By mimicking the ECM, biomaterials provide cells with an environmental structure able to support cell viability, proliferation and secretory activities. Many ECM-like scaffolds are available and have been considered for cartilage tissue engineering (Table 1). These biomaterials can be classified as synthetic or natural matrices, in which we can distinguish those based on proteins or polysaccharides [6]. The ideal biomaterial should be biocompatible to prevent inflammatory and immunological reactions. It must provide a favorable environment for the 3D maintenance of chondrocyte phenotype and be adhesive to enable attachment of the cells within the lesion. It must be permeable to allow the diffusion of molecules, nutrients and growth factors. Finally, it should be biodegradable enough to be integrated in the physiological processes of tissue remodeling and ideally, should be injectable, thereby allowing for implantation by minimally invasive surgery.

Table 1
Principal matrices used in cartilage engineering.

Matrices		
Type	Component	Commercial product name
Protein	Collagen	MACI®, Maix®, Atelocollagen®, MaioRegen®
	Fibrin	Tissucol kit®
	Silk	
Polysaccharides	Hyaluronic acid	HYAFF-11®
	Chitosan	BST-CarGel®
	Cellulose	
	Alginate	
Synthetic	Poly(lactic-co-glycolic acid)	Bio-Seed®-C
	Polylactic acid	
	Polyethylene glycol	

Among the protein-based matrices, membranes of type I and III collagen [7] are clinically used in the autologous chondrocyte transplantation kits Matrix associated chondrocyte implantation (MACI®; Verigen, Leverkusen, Germany) [8], Maix® (Matricel, Hezoenrath, Germany) and Chondro-Gide® (Geistlich Biomaterials, Wolhusen, Switzerland). A type I collagen gel (Atelocollagen®, Koken Co., Tokyo) has been used for the 3D culture and *in vivo* implantation of human autologous chondrocytes [9] and bone

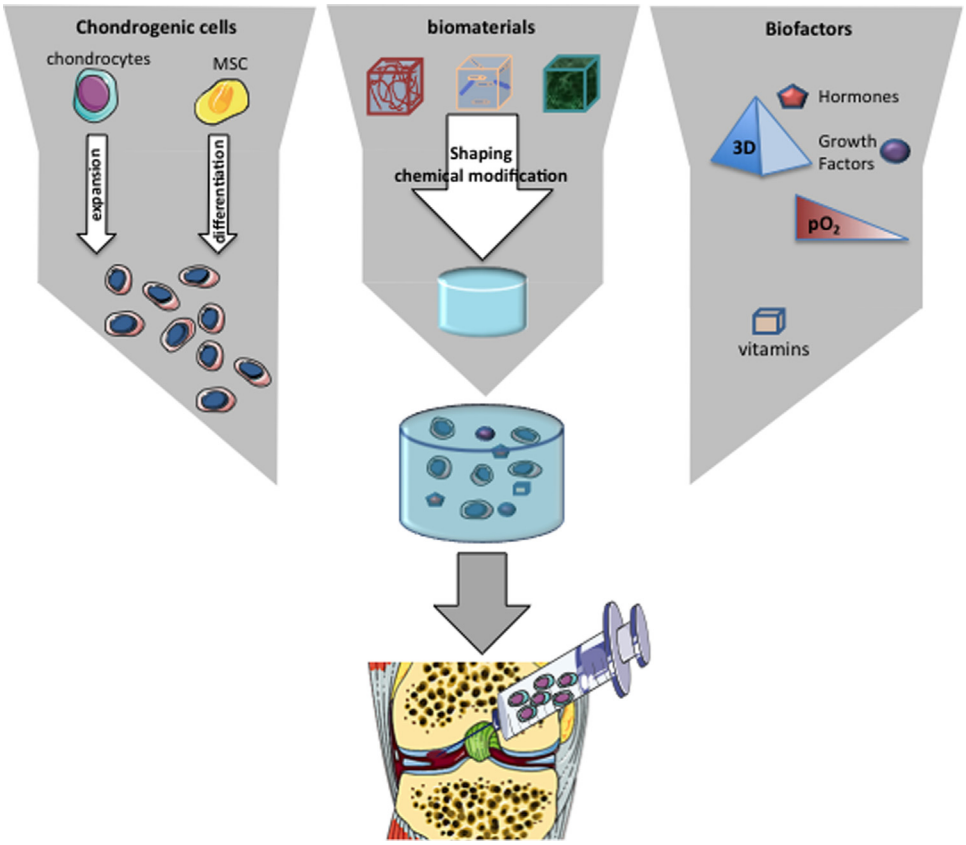

Fig. 1. The tissue engineering triad used for articular cartilage repair. The combination of chondrogenic cells (expanded chondrocytes or differentiated MSCs) with biomaterials and biofactors is crucial for the development of cartilage tissue-engineering strategies.