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Cartilage Tissue Engineering Approaches: Current Therapies and Technological Advances

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COLUMN ARTICLE

The management of chondral lesions is still a clinical challenge for orthopaedic surgeons. Articular cartilage is a well-organized tissue with a very low self-regeneration capacity due to its avascular nature. Therefore, the repair of damaged articular cartilage is critical to prevent further deterioration and the progression of osteoarthritis (OA) [1]. Current surgical treatment options for cartilage repair lesions include autologous chondrocyte implantation (ACI), autologous osteochondral graft transplantation, arthroscopic debridement, microfracture surgery, and finally, prosthetic joint implantation for severe joint degeneration [2]. However, these surgical interventions are not long-term clinical solutions due to unsuitable donor tissue availability, the formation of non-functional fibrocartilage with inferior mechanical properties, donor site morbidity, or the limited durability of the implanted prosthesis [3]. To overcome these drawbacks, new tissue engineering approaches directed to reconstitute the natural structure and function of cartilage are needed. Promising strategies involving transplantation of engineered cartilage substitutes require the association of three critical ingredients: cells, bioactive factors and biomaterials (Figure 1) [4,5].

The main cell sources used in cartilage tissue engineering approaches include stem cells and primary cells, such as chondrocytes [6]. Nevertheless, the limited number of adult articular chondrocytes that can be harvested from native cartilage and the differentiation process that chondrocytes undergo during in vitro expansion limit their use [7]. On the other hand, stem cells can be easily isolated and grown ex vivo, which make them ideal for cell based therapies. Furthermore, stem cells have the ability to self-renew and the capacity to differentiate into multiple types of specialized cells including: chondrocytes, osteocytes, adipocytes and myocytes. In particular, adipose stem cells (ASCs) represent a promising cell source for treating chondral defects as a large number of cells can be obtained through a simple liposuction [8,9].

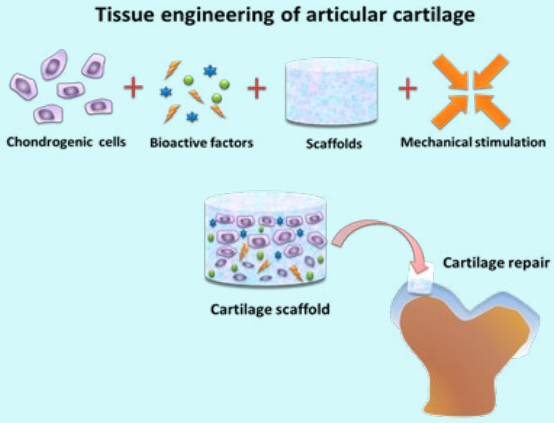

Figure 1: Tissue engineering strategies for the regeneration of chondral lesions.

Biological signals play a critical role in the differentiation of stem cells into the chondrogenic lineage. Several growth and transcription factors are involved in cartilage development at different specific stages and levels. Among the most commonly signaling molecules used to guide cells to a differentiated chondrogenic phenotype are: transforming

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growth factor-β (TGF-β) subfamily members, insulin-like growth factors (IGFs), fibroblast growth factors (FGFs), bone morphogenetic proteins (BMPs), and sex determining region Y (SRY)-box (SOXs). In fact, a strategy to improve bioactivity of scaffolds designed for cartilage tissue repair is the control of growth factors/drug delivery within the engineering scaffolds [10].

Environmental factors, such as oxygen, mechanical strain and pressure are also involved in the chondrocyte differentiation process, becoming the control of these factors vital for tissue engineering approaches [11]. In this sense, novel bioreactor systems, together with mathematical modeling of their characteristics, have been recently developed. Indeed, in order to recreate biological and biomechanical properties of native cartilage bioreactors have emerged as valuable devices for stimulate cell ingrowth in 3-D constructs with a variety of physical cues, including compression, hydrostatic pressure, or fluid shear stress [12].

Finally, an ideal scaffold for cartilage tissue engineering should be (i) biocompatible, to minimize any immunological responses and to favors cell growth and integration with the adjacent tissue; (ii) biodegradable, with a gradual and controlled resorption following new tissue formation; (iii) porous, to promote exchange of nutrients, gases, and wastes and (iv) structurally and mechanically compatible to support tissue growth and to withstand the weight-bearing forces in the articulation [13]. A variety of natural and synthetic biomaterials have been used to fabricate scaffolds for cartilage tissue engineering. Among the natural materials, collagen and hyaluronic acid, normal constituents of the articular cartilage extracellular matrix, have been extensively tested. Other natural materials include agarose, alginate, and chitosan [14]. Regarding synthetic polymers, the most widely used include poly(glycolic acid) (PGA), poly(lactic acids) (PLA), poly(lactic-co-glycolic acid) (PLGA), and poly(ε-caprolactones) (PCL). The combination of both natural and synthetic biomaterials improve the biocompatibility and enhance the mechanical properties of the scaffold [15].

To date, a range of techniques has been employed for manufacturing cartilage tissue constructs. Conventional production methods for three dimensional (3D) scaffolds include: electrospinning, fiber deposition, freeze-drying, gas foaming and salt leaching [16]. However, these techniques lack precise control of internal structural features and topology. Current research involves the use of technologies with higher precision that allow the reproducibility of the resulting implants. In this sense, 3D bioprinting, has emerged as an exciting and innovative manufacturing technology that enables the distribution of different cells and supporting biomaterials to create organized 3D tissue constructs with high spatial resolution [17]. 3D bioprinting has been successfully used to create a variety of cartilage scaffolds by using a variety of materials that have been used in FDA-approved devices/systems [18]. In addition, cartilage structures can be 3D printed using MRI and CT images as blueprints permitting the production of cartilage construct with a specific size and shape to fit the cartilage defected area [19,20].

In conclusion, tissue engineering strategies have rapidly evolved and have great potential for the translation of cartilage regeneration treatments into the clinic. However, more research is needed to determine what combinations of materials, cells and biofactors are necessary to induce and maintain a functional and stable tissue that better mimics native cartilage. Furthermore, more focus must be paid to the mechanical properties, shape, organization and degradation rate characteristics of scaffold-based approaches to improve cartilage tissue repair and regeneration.

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