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Leading Opinion

Hydrogel design for cartilage tissue engineering: A case study with hyaluronic acid☆

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ABSTRACT

Hyaline cartilage serves as a low-friction and wear-resistant articulating surface in load-bearing, diarthrodial joints. Unfortunately, as the avascular, alymphatic nature of cartilage significantly impedes the body's natural ability to regenerate, damage resulting from trauma and osteoarthritis necessitates repair attempts. Current clinical methods are generally limited in their ability to regenerate functional cartilage, and so research in recent years has focused on tissue engineering solutions in which the regeneration of cartilage is pursued through combinations of cells (e.g., chondrocytes or stem cells) paired with scaffolds (e.g., hydrogels, sponges, and meshes) in conjunction with stimulatory growth factors and bioreactors. A variety of synthetic and natural materials have been employed, most commonly in the form of hydrogels, and these systems have been tuned for optimal nutrient diffusion, connectivity of deposited matrix, degradation, soluble factor delivery, and mechanical loading for enhanced matrix production and organization. Even with these promising advances, the complex mechanical properties and biochemical composition of native cartilage have not been achieved, and engineering cartilage tissue still remains a significant challenge. Using hyaluronic acid hydrogels as an example, this review will follow the progress of material design specific to cartilage tissue engineering and propose possible future directions for the field.

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1. Introduction

Hyaline cartilage is the most prevalent form of cartilage throughout the body, serving as a low-friction and wear-resistant articulating surface in load-bearing, diarthrodial joints. Unfortunately, trauma and a variety of diseases can lead to damaged hyaline cartilage, and the avascular and alymphatic nature of cartilage significantly impedes the body's natural ability to repair and regenerate [1,2]. Current clinical methods to repair defective cartilage include autologous chondrocyte implantation (ACI), mosaicplasty, and microfracture, all of which are limited in their ability to regenerate functional cartilage both in terms of composition and mechanics [3]. Due to these shortcomings, research in recent years has focused on tissue engineering solutions in which the regeneration of cartilage is pursued through combinations of cells (e.g., chondrocytes or stem cells), scaffolds (e.g., hydrogels, sponges, and meshes), and stimulatory growth factors and bioreactors to guide tissue formation [4]. Even with promising advances in this field, functional properties comparable to native cartilage have not been realized, particularly when engineered constructs are evaluated in relevant large animal models.

The depth-dependent composition and structure of articular cartilage gives rise to its complex, non-homogeneous mechanical properties. Articular cartilage is generally composed of chondrocytes and a dense ECM, which mainly includes type II collagen and proteoglycans [5]. Structurally, articular cartilage is comprised of four different layers that can be distinguished from one another by collagen fiber alignment (Fig. 1) and proteoglycan composition. Moving from the articulating surface to the underlying bone, the superficial zone has aligned fibers parallel to the surface of the bone, the middle zone has unaligned fibers, the deep zone has aligned fibers perpendicular to the surface of the bone and the final calcified zone has little organization and is mineralized. Conversely,

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proteoglycan content is lowest in the superficial zones and increases with depth. Each layer also differs in thickness, ECM composition, and cellular morphology [6,7]. The depth-dependent alignment of collagen leads to important tensile and shear properties, whereas the depth-dependent proteoglycan content contributes more to the compressive properties of each zone, with the surface zone being 10–20 times less stiff than the deep zones [8,9]. Adding to the complexity in these functional properties, the defined collagen network restricts swelling of the tissue, while the negatively charged proteoglycans and low tissue permeability help the tissue swell and retain water [10]. Water within the tissue is critically important as it bears a significant portion of the applied stress under dynamic loading conditions [11]. This combination creates a pressurized environment that drastically increases the load bearing capacity while reducing the frictional coefficient of cartilage [12,13]. While many studies have addressed the overall bulk mechanical properties and composition of the native tissue, few have investigated the complexity of native tissue structure and function found in tissue-engineered cartilage.

Scaffolds intended for cartilage regeneration should fulfill many requirements, including adequate nutrient transport, adhesion to the defect site, minimally invasive implantation or injection, and degradability [14]. Furthermore, one of the most important requirements is the ability to provide the proper mechanical function (i.e., compressive, shear, and tensile properties), either *a priori* or through directed tissue formation. Both synthetic and natural materials have been explored as potential scaffolds in a variety of forms, including hydrogels, sponges, and fibrous meshes, for cartilage regeneration. Of these various material structures, the most commonly explored is hydrogels, which are water-swollen networks crosslinked by either covalent or physical methods. Hydrogels are particularly attractive because they can be non-invasively injected, fill defects of any size, and can homogenously suspend cells within a 3D environment [4]. The focus of this opinion paper will be on the evolution of hydrogels for cartilage tissue engineering applications, using a class of materials based on hyaluronic acid (HA) as an example to highlight many of the specific criteria used in material design for this application.

2. Hydrogels used in cartilage repair

Hydrogels are useful in tissue engineering as they present cells a 3-D context for tissue formation and defect repair. These water-swollen networks provide a local microenvironment that can signal to cells through various chemical and mechanical signals and serve as a permeable matrix for the diffusion of soluble factors [15]. Hydrogels have been widely used for biomedical and tissue engineering applications, and there are a plethora of both synthetic and natural systems used for these purposes. This section will provide a broad overview of commonly used hydrogel materials for cartilage tissue engineering.

Synthetic hydrogels provide a well-defined, controllable scaffold to encapsulated cells and can be beneficial in elucidating the effects of isolated variables in material design. Poly(ethylene glycol) (PEG) hydrogels form the most prevalent class of synthetic materials for cartilage tissue engineering; PEG hydrogels are relatively inert and biocompatible and have been shown to support cartilage tissue formation by both chondrocytes and mesenchymal stem cells [16,17]. PEG has been modified to include lactic acid groups, RGD [18,19], and decorin moieties [20] to enhance degradation, viability, and chondrogenesis, respectively. Even with these modifications, PEG does not support chondrogenesis and cartilage-specific matrix production to the same degree as some natural materials, including alginate [21] and HA [22]. In response, PEG has been combined with a variety of natural materials and even modified with collagen-mimetic peptides to enhance chondrogenesis [23–25].

Natural materials are commonly used for cartilage tissue engineering due to their abundance, and because they possess many intrinsic pro-chondrogenic properties and are commonly involved in native cellular processes. Agarose and alginate, both polysaccharide-based and derived from seaweed, were two of the first materials used as hydrogels for cartilage tissue engineering [26]. Agarose has been shown to support chondrogenesis and resulted in the highest sGAG to DNA ratio when compared to type I collagen, alginate, fibrin, and polyglycolic acid [27]. Agarose gels have been employed extensively in cartilage tissue engineering and have helped to elucidate the effects of mechanical loading, TGFβ exposure, and differences between chondrocytes and MSCs [28–30]. Alginate is generally crosslinked with bivalent cations, commonly Ca^{2+}, and can support chondrogenesis [31,32] in a variety of 3D forms (beads and discs). RGD peptides have been incorporated into alginate gels to provide controllable cell adhesion sites; however, this system inhibits and/or reduces chondrogenesis of MSCs [31]. Moreover, other limitations to alginate include low mechanical stability and slow degradation.

Natural hydrogels based on proteins, such as collagen and fibrin, are also common for cartilage regeneration. Collagen is an

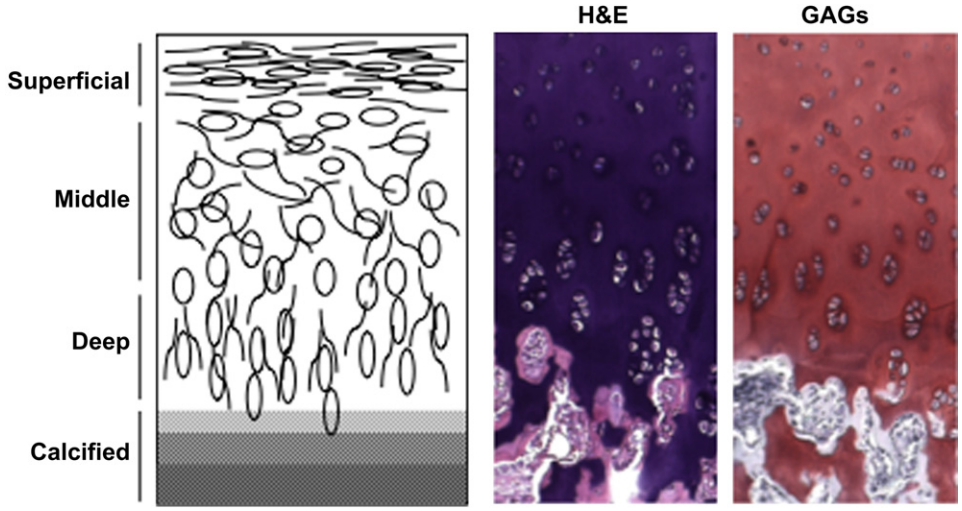

Fig. 1. Depth-dependent collagen alignment and cellular morphology in articular cartilage. H&E: hematoxylin and eosin; GAGs: alcian blue stain for glycosaminoglycans.

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