Archives of Oral Biology 83 (2017) 193–201

Contents lists available at ScienceDirect

Archives of Oral Biology

journal homepage: www.elsevier.com/locate/archoralbio

Review

A review of in-vitro fibrocartilage tissue engineered therapies with a focus on the temporomandibular joint

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ARTICLE INFO

Keywords:
Tissue engineering
Temporomandibular joint
Fibrocartilage
In vitro

ABSTRACT

The inability of fibrocartilage, specifically the temporomandibular joint (TMJ) disc, to regenerate and remodel following injury presents a unique problem for clinicians. Tissue engineering then offers a potential regenerative therapy. In vitro testing provides a valuable screening tool for potential tissue engineered solutions. The conclusions drawn for TMJ in vitro research were compared against state of the art fibrocartilage studies in the knee meniscus, and annulus fibrosus of the intervertebral disc (IVD). For TMJ disc regeneration, in vitro tissue engineered approaches, focused on cellular therapies with fibrochondrocytes, have displayed an inability to produce enough collagen, as well as an inability to recapitulate native mechanical properties. Biomaterial approaches have recapitulated the native properties of the TMJ disc, but their in vivo efficacy has yet to be determined. By comparison, the knee meniscus field is the most progressive in the use of stem cells as a cell source. The knee meniscus field has moved away from measuring mechanical properties, and are instead more focused on biochemistry and gene expression. IVD studies mainly use electrospun scaffolds, and have produced the best success in mechanical properties. The TMJ field, in comparison to knee meniscus and IVD, needs to employ stem cell therapies, new biomaterials and manufacturing techniques, and cutting edge molecular assays, in future in vitro approaches to screen for viable technologies to move to in vivo studies.

1. Introduction

Fibrocartilage is the type of cartilage found in temporomandibular joint (TMJ) discs, the annulus fibrosus of intervertebral discs (IVD), and the meniscus of the knee. The clinical necessity of investigating fibrocartilage is highlighted by the large numbers of individuals affected by degeneration of these joints. It is estimated that 10 million Americans are affected by temporomandibular joint disorders, as many as 5 million people are affected by lower back pain attributed to IVD degeneration (Sherman et al., 2010), and 600,000 knee surgeries are performed per year in the United States (Sweigart & Athanasiou, 2001).

Fibrocartilage differs from hyaline and articular cartilage in the ratio of type I collagen to type II collagen (Fig. 1). While articular cartilage is predominately collagen type II, fibrocartilage tissues as a group have higher collagen type I content, although the exact ratio can vary by tissue. The TMJ disc, for example, is almost 100% collagen type I (Anderson & Athanasiou, 2009), with trace amounts of collagen type II located in the intermediate zone. The knee meniscus has a heterogeneous distribution of collagen type I and type II, with the lateral head containing almost 100% collagen type I, while the medial head has a collagen I/II ratio of 0.6 (Cheung, 1987). The IVD also has heterogeneous distribution of collagen, with the inner and outer annulus fibrosus having collagen I/II ratios of 0.68 and 0.84, respectively (Eyre & Muir, 1976). These phenotypic differences between the TMJ and both the knee menisci and IVD can necessitate separate treatment modalities for the different tissues.

While current treatments exist for these distinct fibrocartilages, they generally rely on surgical methods that do not restore the original tissue. This is because the avascular nature of these fibrocartilage tissues does not promote healing on its own. As a result, researchers are turning to tissue engineered, cell based therapies as potential grafts for healing and remodeling.

The purpose of this review is to elucidate the progress of TMJ in vitro tissue engineering initiatives and compare to more advanced fibrocartilage fields, such as the IVD and knee meniscus. Recent studies will be reviewed here that focused on biochemical or biomechanical

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http://dx.doi.org/10.1016/j.archoralbio.2017.07.013
Received 21 February 2017; Received in revised form 19 July 2017; Accepted 20 July 2017

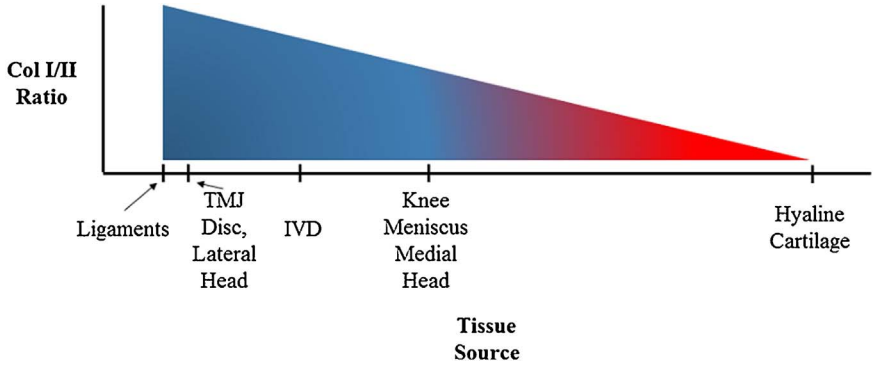

Fig. 1. Spectrum of cartilage based on collagen I/II ratio. Fibrocartilage skews towards the higher Col I/II ratio, with the TMJ disc having a Col I/II ratio of almost 1.0. The knee meniscus and IVD have a Col I/II ratio of 0.8. Hyaline and articular cartilage have a Col I/II ratio of near 0.0.

parameters. However, the fields are moving to novel biochemical and molecular biological techniques to analyze smaller quantities of the regenerated tissues. The first part of this review will focus on tissue engineered strategies for TMJ disc remodeling (Table 1). The second part will compare the TMJ disc to advances in knee meniscus (Table 2) and the annulus fibrosus of the IVD tissue engineering (Table 3). It is important to note that selection of the most recent studies precludes the reader from seminal works and the progression of the fields. This relevant data and knowledge can be found elsewhere (Aryaei, Vapniarsky, Hu, & Athanasiou, 2016; Athanasiou, Responte, Brown, & Hu, 2015; Chen, Duan, Zhu, Xiong, & Wang, 2014; Goldberg, Mitchell, Soans, Kim, & Zaidi, 2017; Gugjoo, Amarpal, Sharma, Aithal, & Kinjavdekar, 2016; Kazemnejad, Khanmohammadi, Baheiraei, & Arasteh, 2017; Scotti, Hirschmann, Antinolfi, Martin, & Peretti, 2013; Yu, Adesida, & Jomha, 2015;). However, none have directly compared in vitro regenerative medicine approaches for the TMJ disc to other fibrocartilages.

The three major biomechanical components analyzed in this review are collagen, GAGs, and DNA. Collagen is the primary biochemical constituent that imparts tensile strength to the tissue in vivo. Therefore, the recapitulation of the native composition and alignment of collagen can be necessary for a regenerative therapy to reproduce similar tensile properties to native tissues. GAGs are highly negatively charged branched molecules attached to proteogylcans. The negative charge attracts water, which allows GAGs to resist fluid flow and increases the compressive integrity of a tissue. DNA is reported where applicable to demonstrate the general cellularity of proposed therapies, since fibrocartilage is generally considered an acellular tissue.

2. Temporomandibular joint disc

The TMJ disc is a fibrocartilage disc (Fig. 2) that is positioned between the mandibular condyle and glenoid fossa of the temporal bone. During normal physiological function, the mandibular condyle slides anteriorly along the inferior surface of the TMJ disc, with the disc shielding the articular eminence from bone on bone contact. The native TMJ disc is composed of 24%/WW (wet weight) collagen and 0.6%/WW glycosaminoglycan (GAG) content (Kalpakci, Willard, Wong, & Athanasiou, 2011). The collagen is aligned in a ring around the periphery of the disc, and is aligned anteriorly-posteriorly throughout the intermediate zone of the disc. The TMJ disc produces tensile forces that are an order of magnitude higher (MPa) than compressive forces (kPa). It is important for any tissue engineered material to exhibit compressive and tensile strengths similar to those observed in the in vivo environment. Otherwise, the regenerative materials may rupture once implanted and require further intervention. We have chosen to review 12 recent publications on TMJ tissue engineering studies performed in vitro in the last 5 years (Table 1). The studies are presented chronologically, and the values reported are compared against native properties of the human TMJ disc (Kalpakci, Willard et al., 2011).

Anderson and Athanasiou in 2008 analyzed the effect of costal chondrocyte passage number on fibrocartilage tissue engineering (Anderson & Athanasiou, 2008). In this study, 2 million goat TMJ disc or costal cartilage cells were allowed to self-assemble in a scaffoldless approach. TMJ disc cell constructs produced 5 times less collagen (5%/WW) than native, which was more than costal chondrocytes at all passages. Also, TMJ disc cell constructs produced 10 times lower compressive (190 kPa compressive modulus) than native, 11 times lower ultimate tensile strength (UTS) (0.5 MPa) than native, and 16 times lower tensile modulus (2.28 MPa) than native (Table 1). All of these values were significantly higher than the other groups. However, these constructs were prohibitively smaller in size than costal chondrocyte constructs. This study is important because it attempted to establish a standard passage number for in vitro experiments, to ensure continuity among experiments and determine effects. This study suggested the efficacy of the costal chondrocytes, while demonstrating that TMJ disc cells would not be an appropriate cell source, even though these constructs produced greater biochemical components and withstood more mechanical forces.

In an effort to determine how growth factors could impact tissue engineered constructs, Johns and Athanasiou in 2008 investigated the effects of growth factors on cells for fibrocartilage tissue engineering (Johns & Athanasiou, 2008). In this study, 2 million goat costal cartilage cells were allowed to self-assemble in a scaffoldless approach. These constructs were cultured in DMEM with 1% ITS. The effect of transforming growth factor (TGF), insulin growth factor (IGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF) were investigated individually on the cultured cells, along with a non-growth factor control. After 6 weeks of culture, biochemically, the study found IGF produced the best results, with GAG production being 50 times that of native (81%/WW) and collagen production 2 times less than native (14%/WW). The best mechanical properties are achieved by the non-growth factor control, with tensile strength 20 times less than native (0.22 MPa) and modulus 60 times less than native (0.54 MPa) (Table 1). The paper supports that IGF has the best results based on total amount of biochemical constituents. However, if the percentage of GAGs and collagen per wet weight is used, TGF performs the best of the growth factors. Also, the study uses growth factors at varying concentrations (10 mM to 100 mM) depending on the growth factor, making it difficult to compare the groups.

Wang et al. in 2009 also investigated cell type for TMJ tissue engineering applications (Wang, Lazebnik, & Detamore, 2009). In this study, porcine hyaline cartilage and mandibular condylar cartilage cells were seeded at 50 million cells/ml scaffold onto non-woven PGA mesh. The scaffolds were cultured in DMEM with 10% FBS. Each cell type was also exposed to D-glucosamine 6-sulfate and IGF, both individually and in combination. After 6 weeks of culture, the hyaline cartilage cells outperformed the mandibular condylar cartilage cells in total GAG and collagen content. The IGF groups had the highest content of GAG (160 μg) and hydroxyproline (2.6 μg). The authors of this paper did not provide the biochemical values as percentages of the wet weight