Acta Biomaterialia 8 (2012) 3754–3764

Contents lists available at SciVerse ScienceDirect

Acta Biomaterialia

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

Variations in chondrogenesis of human bone marrow-derived mesenchymal stem cells in fibrin/alginate blended hydrogels

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ARTICLE INFO

Article history:
Received 18 January 2012
Received in revised form 24 May 2012
Accepted 20 June 2012
Available online 28 June 2012

Keywords:
Chondrogenesis
Mesenchymal stem cells
Fibrin
Alginate
Hydrogel

ABSTRACT

Fibrin and alginate hydrogels have been widely used to support chondrogenesis of bone marrow-derived mesenchymal stem cells (BM-MSCs) for articular cartilage and fibrocartilage tissue engineering, with each material offering distinct advantages and disadvantages. Attempting to produce a gel scaffold exhibiting beneficial characteristics of both materials, we fabricated fibrin/alginate blended hydrogels at various blend ratios and evaluated the gel morphology, mechanical properties and their support for BM-MSC chondrogenesis. Results show that when the fibrin/alginate ratio decreased, the fibrin architecture transitioned from uniform to interconnected fibrous and finally to disconnected islands against an alginate background, with opposing trends in the alginate architecture. Fibrin maintained gel extensibility and promoted cell proliferation, while alginate improved the gel biostability and better supported glycosaminoglycan and collagen II production and chondrogenic gene expression. Blended gels had physical and biological characteristics intermediate between fibrin and alginate. Of the blends examined, FA 40:8 (40 mg ml^{-1} fibrinogen blended with 8 mg ml^{-1} alginate) was found to be the most appropriate group for future studies on tension-driven BM-MSC fibrochondrogenesis. As BM-MSC differentiation appeared to vary between fibrin and alginate regions of blended scaffolds, this study also highlighted the potential to develop spatially heterogeneous tissues through manipulating the heterogeneity of scaffold composition.

1. Introduction

Tissue engineering offers the potential to treat damaged or diseased tissues with functional replacements composed of biocompatible scaffolds seeded with appropriate cells [1]. However, there are significant challenges for developing fibrocartilaginous tissues with appropriate compositions and structures. Fibrocartilaginous organs such as the knee menisci are highly organized, heterogeneous tissues with macroscopic and microscopic heterogeneities in extracellular matrix (ECM) composition and cell phenotype. The radially inner region of the meniscus has an ECM most similar to articular cartilage, with relatively high levels of collagen II and the large proteoglycan aggrecan, while its surface and outer regions have more fibrous ECM with lower levels of these components [2–5]. In the radially middle and outer regions, collagen II, aggrecan and other quantitatively minor ECM components are concentrated in the tie sheaths and the matrix compartment surrounding the primary circumferential collagen bundles [3,6], producing a highly heterogeneous matrix architecture at the meso-scale. The cells are also spatially heterogeneous, with gradual radial variations in cell morphology [7] and gene expression profiles [8] from rounded, chondrocyte-like cells in the inner region to spread, fibroblast-like cells in the outer region. Disruption of this structure due to traumatic injury or age-related degradation may lead to altered joint biomechanics and the onset of osteoarthritis [9] but, like articular cartilage, meniscal fibrocartilage has a poor intrinsic repair capacity due to its limited vascularity [10].

Human bone marrow-derived mesenchymal stem cells (BM-MSCs) have been widely used for tissue repair or regeneration purposes due to their potential for multi-lineage differentiation and self-renewal [11,12]. However, appropriate types or combinations of signals will be required to produce fibrochondrogenic differentiation with desired cell phenotype and ECM structures [13]. Preliminary studies indicate that combinations of fibrogenic and chondrogenic soluble factors may encourage development of a fibrochondrocytic phenotype by BM-MSCs in vitro [14]. Physical cues may also interact with soluble factors to influence MSC differentiation. The use of chondrogenic media in conjunction with natural cell-adhesive scaffolds (e.g. fibrin or gelatin) may induce fibrocartilaginous tissue formation [15]. Aligned nanofibrous topography induced fibrogenic differentiation of BM-MSCs that were cultured in chondrogenic medium [16], producing higher collagen I expression and lower aggrecan expression than developed

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http://dx.doi.org/10.1016/j.actbio.2012.06.028