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The inhibition by interleukin 1 of MSC chondrogenesis and the development of biomechanical properties in biomimetic 3D woven PCL scaffolds

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ABSTRACT

Tissue-engineered constructs designed to treat large cartilage defects or osteoarthritic lesions may be exposed to significant mechanical loading as well as an inflammatory environment upon implantation in an injured or diseased joint. We hypothesized that a three-dimensionally (3D) woven poly(ε-caprolactone) (PCL) scaffold seeded with bone marrow-derived mesenchymal stem cells (MSCs) would provide biomimetic mechanical properties in early stages of *in vitro* culture as the MSCs assembled a functional, cartilaginous extracellular matrix (ECM). We also hypothesized that these properties would be maintained even in the presence of the pro-inflammatory cytokine interleukin-1 (IL-1), which is found at high levels in injured or diseased joints. MSC-seeded 3D woven scaffolds cultured in chondrogenic conditions synthesized a functional ECM rich in collagen and proteoglycan content, reaching an aggregate modulus of ~0.75 MPa within 14 days of culture. However, the presence of pathophysiologically relevant levels of IL-1 limited matrix accumulation and inhibited any increase in mechanical properties over baseline values. On the other hand, the mechanical properties of constructs cultured in chondrogenic conditions for 4 weeks prior to IL-1 exposure were protected from deleterious effects of the cytokine. These findings demonstrate that IL-1 significantly inhibits the chondrogenic development and maturation of MSC-seeded constructs; however, the overall mechanical functionality of the engineered tissue can be preserved through the use of a 3D woven scaffold designed to recreate the mechanical properties of native articular cartilage.

1. Introduction

Articular cartilage shows little capacity for repair in response to traumatic injury or degenerative conditions such as osteoarthritis. In this regard, there has been increasing interest in the development of tissue engineering strategies for cartilage repair or regeneration using autologous chondrocytes or stem/progenitor cells such as adult bone marrow-derived mesenchymal stem cells (MSCs) or adipose derived stem cells (ASCs). However, there is little evidence of the long-term clinical success of such procedures as compared to less complex surgical methods such as microfracture [1]. While the reasons for these failures are not fully understood, cell-seeded scaffolds generally do not possess appropriate biomechanical functionality at the time of implantation, and they may require significant maturation time *in vitro* before achieving mechanical properties that can withstand joint loading *in vivo* (e.g., [2,3]). In many cases, the repair site shows incomplete cell differentiation and a lack of formation of hyaline cartilage *in vivo* [4].

One potential cause of graft failure that is not often considered is that injured and osteoarthritic joints exhibit significantly higher levels of pro-inflammatory cytokines. For example, interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α), as well as pro-catabolic enzymes and mediators such as metalloproteinases (MMPs), aggrecanases, prostaglandins, and nitric oxide are over-expressed in these joints and can cause tissue degradation, pain, and inflammation [5–7]. While the effects of IL-1 on chondrocytes have been characterized extensively (e.g., [8]), recent studies have also demonstrated the deleterious effects of IL-1 on the chondrogenesis of ASCs [9] and MSCs [10–15], as well as tissue engineered cartilage comprising chondrocytes seeded in scaffolds of agarose [16,17] or collagen [18,19]. Furthermore, IL-1 and TNF-α inhibit the integrative repair of cartilaginous tissues such as the meniscus [20], via upregulation of MMPs [21] and the inhibition of cell proliferation [22]. Thus, the inflammatory environment of the injured joint may have

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