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Growth factor supplementation improves native and engineered meniscus repair in vitro

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ABSTRACT

Few therapeutic options exist for meniscus repair after injury. Local delivery of growth factors may stimulate repair and create a favorable environment for engineered replacement materials. In this study we assessed the effect of basic fibroblast growth factor (bFGF) (a pro-mitotic agent) and transforming growth factor β3 (TGF-β3) (a pro-matrix formation agent) on meniscus repair and the integration/maturation of electrospun poly(ε-caprolactone) (PCL) scaffolds for meniscus tissue engineering. Circular meniscus repair constructs were formed and refilled with either native tissue or scaffolds. Repair constructs were cultured in serum-containing medium for 4 and 8 weeks with various growth factor formulations, and assessed for mechanical strength, biochemical content, and histological appearance. Results showed that either short-term delivery of bFGF or sustained delivery of TGF-β3 increased integration strength for both juvenile and adult bovine tissue, with similar findings for engineered materials. While TGF-β3 increased proteoglycan content in the explants, bFGF did not increase DNA content after 8 weeks of culture. This work suggests that in vivo delivery of bFGF or TGF-β3 may stimulate meniscus repair, but that the time course of delivery will strongly influence success. Further, this study demonstrates that electrospun scaffolds are a promising material for meniscus tissue engineering, achieving comparable or superior integration compared with native tissue.

1. Introduction

The meniscus is a C-shaped fibrocartilage in the knee that transmits load from the femur to the tibia [1,2]. The unique architecture and composition of the meniscus, consisting of aligned collagen bundles and centrally located proteoglycan, allows it to withstand both tensile and compressive forces in order to transfer loads and maintain joint stability during movement [3]. Due to the high stresses imparted on the tissue [4] both acute and degenerative tears are common, and the natural repair capacity is limited, especially in the inner avascular regions [5]. Of the 850,000 meniscus surgeries performed annually in the USA [6] resection is the most common technique to alleviate symptoms associated with meniscal tears. However, this procedure can result in joint incongruency and significant stresses on the adjacent cartilage, which can lead to premature degeneration (i.e. osteoarthritis) [7,8]. Few procedures exist to repair the meniscus, and those that are performed do not restore native tissue structure and function. Thus there is a need for novel strategies to improve meniscus repair.

Delivery of biological factors may stimulate tissue repair either alone or in combination with mechanical stabilization. Early work in this area delivered vascular endothelial growth factor (VEGF) from sutures to stimulate blood vessel formation in the damaged region [9]. However, delivery of VEGF from sutures failed to improve healing in vivo in a number of studies, perhaps due to suboptimal time courses of delivery [10,11]. Rather than modulating the vascular supply, another approach is to alter biosynthesis and matrix assembly at the repair site. During repair, new matrix must be formed by nearby cells to bridge the wound gap, creating a mechanically stable interface. Increasing the amount of matrix deposited by each cell or increasing the overall number of cells (or a combination of the two) may improve repair. One of the most potent stimulators of matrix deposition in meniscal cells is transforming growth factor β3 (TGF-β3) [12–16], although other growth factors such as bFGF, PDGF-AB, IGF-1 and EGF can all increase matrix production [17]. Basic fibroblast growth factor (bFGF) strongly stimulates the proliferation of meniscus cells in monolayer culture as well as in tissue engineered constructs [17–20]. For this reason both TGF-β3 and bFGF were identified as potential meniscus repair factors by Kasemkijwattana et al. [21], and Imler et al. showed that TGF-β3 stimulated protein and proteoglycan deposition to a greater extent than bFGF in meniscus explants [16]. Due to the ability of these growth factors to stimulate matrix deposition and increase cell number, they are promising candidates for promoting repair of avascular meniscus tears as well as the maturation and integration of engineered materials in vivo.

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