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The Effects of Pro-inflammatory Cytokines on Functional Repair of the Meniscus

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1 Introduction

The menisci are C-shaped fibrocartilaginous tissues that are essential for normal biomechanical function of the knee. Damage or loss of meniscal tissue is associated with degenerative changes in the joint that ultimately lead to osteoarthritis. The influence of various biological and biomechanical factors on meniscal repair are not fully understood. We examined the hypotheses that increasing concentrations of the pro-inflammatory cytokines interleukin-1 (IL-1) or tumor necrosis factor-alpha (TNF) inhibit integrative repair of the knee meniscus in an *in vitro* model system, and that inhibitors of these cytokines will enhance repair.

2 Materials and Methods

Explants (8 mm diameter) were harvested from either the inner or outer zone of porcine medial menisci. To simulate a full-thickness defect, a 4 mm diameter core was removed and reinserted. Explants were cultured for 14, 28, or 42 days in the presence of 0–10 ng/mL of IL-1 or TNF. Explants were also cultured in the presence of IL-1 or TNF with IL-1 receptor antagonist (IL-1ra) or TNF monoclonal antibody (TNF mAb). At the end of the culture period, biomechanical testing, cell viability, and histological analyses were performed to quantify the extent of repair.

3 Results

Meniscal lesions in untreated samples showed a significant capacity for intrinsic repair *in vitro*, with increasing cell accumulation, tissue formation, and repair strength over time in culture. The presence of pathophysiologic concentrations of IL-1 or TNF significantly decreased the strength of meniscal repair in a dose-dependent manner (**Fig. 1**), accompanied by a decrease in cell and tissue accumulation in the repair site. The addition of IL-1ra or TNF mAb to explants prevented the effects of IL-1 or TNF, respectively.

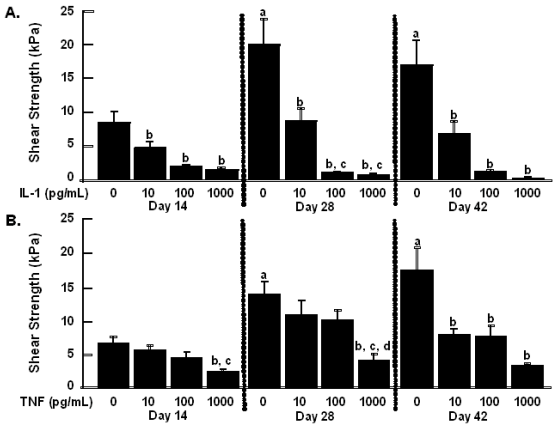

Figure 1 : IL-1 and TNF-α decrease the Interfacial Shear Strength of Repair. A. The strength of repair was measured after treatment of meniscal repair model explants with 0 pg/mL, 10 pg/mL, 100 pg/mL, and 1000 pg/mL IL-1 for 14, 28, and 42 days. a: $p < 0.05$ compared to day 14 control. b: $p < 0.05$ compared to controls at the corresponding time. c: $p < 0.05$ compared to 10 pg/mL treatment at the corresponding time. B. The strength of repair was measured after treatment of meniscal repair model explants with 0 pg/mL, 10 pg/mL, 100 pg/mL, and 1000 pg/mL TNF-α for 14, 28, and 42 days. d: $p < 0.05$ compared to 100 pg/mL treatment at the corresponding time. Mean+s.e.

4 Discussion

These studies document that physiologically relevant concentrations of IL-1 and TNF inhibit meniscal repair *in vitro* and therefore may also

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inhibit meniscal repair during arthritis or following joint injury. The finding that IL-1ra and TNF mAb promote integrative meniscal repair in an inflammatory microenvironment suggest that intra-articular delivery of IL-1ra and/or TNF mAb may be useful clinically to promote meniscal healing following injury.

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