EARLY INTERVENTION STRATEGIES FOR ACUTE CARTILAGE INJURY: AN EX-VIVO PORCINE KNEE MODEL

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INTRODUCTION

- Traumatic injury to cartilage has been shown to lead to Post-Traumatic Osteoarthritis (PTOA) [1].
- The acute phase of PTOA is characterized with increased expression of aggrecanases and inflammatory cytokines in the injured cartilage [2].
- Early intervention therapies aim to be administered during the acute phase for the prevention of PTOA development.
- Our objective was to determine the effect of Interleukin Receptor Antagonist Protein (IRAP), Hyaluroran (HA), Dexamethasone (DEX), and Mesenchymal Stem Cell (MSC) treatment as early intervention strategies by examining the changes in microRNA (miRNA) and mRNA expression in cartilage at 8 hours after impact injury.

MATERIALS & METHODS

- Custom impact device was used to create replicable injury ex-vivo to intact porcine knee joint [3]. Injury was caused by dropping a 10kg weight one time from 1m directly above the knee in extension.
- One hour after impact 20μg/mL IRAP (n=5), 15mg/mL HA (MW 1.9 MDa) (n=4), 4mg/mL DEX (n=5) or 5x10^6 P4 MSCs (n=3) in 1mL saline was intra-articularly injected. Control legs (no injury) (n=22) and injury legs (injury, no treatment) (n=5) received saline injection.
- At 8 hours post-injury, cartilage samples were harvested for genetic expression analysis. Genetic expression of miR-140 (regulates ADAMTS-5) miR-125b (regulates ADAMTS-4), miR-27b (regulates MMP-13), ADAMTS-5, MMP-3, IL-1β, and TNF-α were analyzed by RT-PCR.
- Groups were compared by one-way analysis of variance followed by Tukey’s post-hoc test. A p-value <0.05 was considered significant.

RESULTS

- Expressions of IL-1β and TNF-α in cartilage were significantly decreased in IRAP and DEX-treated joints as compared to injury (both ANOVA p<0.001) (Figure 1A & B).
- Expression of ADAMTS-4 was significantly lower in DEX-treated joints as compared to injury and HA-treated joints (ANOVA p<0.001) (Figure 1C). Expressions of ADAMTS-5 and MMP-3 were significantly lower in DEX- and IRAP-treated cartilage as compared to injury, MSC, and HA groups (ANOVA both p<0.001) (Figure 1D & E).
- Expression of miR-140 in cartilage was significantly up-regulated after IRAP treatment as compared to control, injury, MSC, and DEX groups (ANOVA p<0.001) (Figure 2A). After HA treatment, miR-140 expression was also significantly up-regulated as compared to control and injury.
- Expressions of miR-125b and miR-27b were significantly up-regulated after IRAP and HA treatment as compared to control, injury, MSC, and DEX groups (both ANOVA p<0.001) (Figure 2B & C).

DISCUSSION

- The results of this study support the hypothesis by demonstrating that therapeutic early intervention during the acute phase of injury can significantly alter the genetic injury response in injured cartilage.
- HA and MSC treatment did not have any effect on the inflammatory and catabolic response of injured cartilage within the first 8 hours of injury. However, the beneficial effects of HA may take place beyond the acute time frame as suggested by increased miR-125b and miR-140 expressions after treatment.
- IRAP treatment increased expressions of miR-140, -125b, and -27b in cartilage, indicating increased inhibition of ADAMTS-5, ADAMTS-4, and MMP-13, respectively [4,5,6] as shown by reduced aggrecanase and inflammatory genetic expressions.
- As a corticosteroid, DEX passes freely through the chondrocyte cell and nuclear membrane and binds to an intracellular glucocorticoid receptor [7] and directly inhibits the up-regulation of aggrecanases and inflammatory cytokines at the transcriptional level, thereby not modulating expressions of the miRNAs examined.
- Clinically, these findings support the potential of early intervention strategies for the prevention of cartilage degeneration after impact injury.

REFERENCES