CHONDROCYTE APOPTOSIS AFTER ARTICULAR FRACTURE IN HUMANS

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INTRODUCTION

Post-traumatic arthritis (PTA) is a rapidly developing form of secondary osteoarthritis that often follows injury to a joint. While the changes resulting from this disease process have been extensively documented, the specific initiating factors remain unknown. One theory suggests that elevated stresses from residual incongruities or malalignment are the likely culprits; however, PTA also occurs in fractures healing without incongruity or malalignment. Thus, it is likely that other mechanisms are involved. The hypothesis in this work is that the initial impact of trauma results in cell death, either from initial impact or by triggering chondrocyte apoptosis.

METHODS

Articular fracture fragments too small to be used in the surgical reconstruction were obtained from 28 patients, ages 18 to 80 (mean 49 years) undergoing ORIF of intra-articular fractures of the lower extremity between 1 and 41 days (mean 7 days) after injury. Two control specimens were obtained from patients undergoing mosaicplasty where the harvested plugs were unusable due to fracture just below the subchondral plate. The tissue was fixed, decalcified, embedded and sectioned perpendicular to the joint surface. Staining with safranin-O, and immunohistochemistry for type II collagen was performed. The TUNEL assay was used to identify cells with fragmented DNA. Histomorphometry was performed in the superficial cartilage (between 0 and 250 microns from the surface), the middle cartilage, and the deep cartilage (within 250 microns of the tidemark). In each zone, five 0.1mm² fields were evaluated for the total number of cells, as well as the number of cells demonstrating DNA fragmentation. Specimens were grouped based on the time between injury and retrieval, with early specimens retrieved within the first 24 hours of injury, intermediate specimens retrieved between 2 and 9 days after injury, and the late group retrieved between 10 and 41 days after injury. Repeated measures analysis of variance with a Bonferroni-Dunn post-hoc correction was used to determine the significant effects of location in the articular cartilage. The density of living cells in the articular cartilage was similar in all three zones; however, the percentage of apoptotic cells was significantly less in the superficial zone (27 +/- 6%) than in the superficial zone (43 +/- 7%; one-factor ANOVA p < 0.05, Bonferroni-Dunn p < 0.02 between groups). This difference was greatest in the group retrieved more than 10 days after injury, where the deep zone had only 1/6th as many apoptotic cells as the superficial cartilage (Figure 2).

RESULTS

Dead or dying cells were present in all specimens (Figure 1). In the control specimens, the center of the mosaicplasty cores demonstrated few positive cells in any of the zones (<2%). However, in the samples retrieved from patients with impaction fractures, the percentage of TUNEL positive cells ranged from 0 to 100% in each zone, with an average of 35% of cells staining positive in each specimen.

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Figure 2: Percentage of cells with DNA fragmentation in each of the three cartilage regions of the fracture fragments as a function of time from impaction injury.

CONCLUSIONS

Cell death, or apoptosis, has been implicated as a possible etiology for osteoarthritis. This study demonstrates that this process also occurs in articular cartilage after intra-articular fracture. While rates of apoptosis in osteoarthritis have been reported to average 15% (1), in the fracture patients studied here, the average rate was more than twice this value (35%). Apoptosis rates in normal cartilage are less than 1% (1), a rate similar to that seen in the mosaicplasty specimens used in this study as controls. Thus, in the first 48 hours after an impaction of sufficient magnitude to cause intra-articular fracture, articular chondrocytes die at an increased rate, in fact, a rate which is more than double than that seen in end-stage osteoarthritis. These findings suggest that in some patients, regardless of the type or quality of the surgical repair, the initial injury force devitalizes the majority of chondrocytes in the articular cartilage. It is believed that apoptosis leads to the release of degradative enzymes, which ultimately destroys the cartilage and leads to arthritis. The high rate of cell death noted here may explain the connection between impact injury and post-traumatic arthritis in humans.

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REFERENCE