A potential biological mechanism for meniscus involvement in osteoarthritis.

INTRODUCTION
Meniscus injury is a known predisposing factor for osteoarthritis (OA), but the mechanisms by which meniscus injury leads to OA are unknown. Matrix metalloproteinases (MMPs) are enzymes involved in joint tissue destruction in OA. This study sought to identify the expression pattern of MMPs produced by aged and degenerative menisci that could contribute to the development of OA.

METHODS:
Due to difficulty obtaining normal young adult human menisci, the effects of aging were studied using menisci from ten healthy young and old vervet monkeys. Monkey knees were graded for meniscus and cartilage degradation morphologically and bone changes were evaluated with computed tomography (CT) imaging. Cytokine and MMP production from monkey meniscal explants were measured by protein array and immunoblotting. Human menisci (n=15) and cartilage tissue were obtained from patients undergoing total knee arthroplasty (TKA) for end-stage OA, and cells were isolated for culture. Human menisci were also graded prior to culture. Primary human OA cell cultures were stimulated with inflammatory cytokines, either interleukin-(IL)-1, IL-6, or transforming growth factor (TGF) for two or 24 hours. MMP expression was measured by protein array, immunoblot, and gene expression analysis. Spearman-rank correlations methods were used to analyze vernet knee morphologic scores, and Kruskal-Wallis one-way analysis of variance on ranks with post-hoc Tukey test analyzed age and degeneration comparisons (α=0.05). Our Institutional Review Board approved the human tissue specimen for exemption status.

RESULTS SECTION:
Meniscus degradation scores were significantly greater in old versus young monkeys in lateral and medial compartments (p=0.002). Medial and lateral compartment cartilage degradation was also significantly greater in old monkeys (p<0.001). Cartilage degradation score correlated with the meniscus degradation score from the corresponding compartment within the same joint (medial compartment, p<0.001; lateral compartment, p<0.05). Degradation scores of the medial meniscus correlated with the lateral scores (p<0.001) and no significant difference existed between medial and lateral meniscus scores. Monkey CT scans demonstrated osteoarthritic changes in aged joints (example of one young-old pair shown in Figure 1). Young monkeys did not exhibit any signs of osteoarthritic changes, while 80% (4/5) of old monkeys had osteophyte formation and evidence of subchondral bone cyst formation.

Aged and degenerative meniscus secreted increased amounts of MMP-1, -8 (Figure 1C) and -3 and the cytokines IL-6 and IL-7 when compared to younger and non-degenerative menisci. In humans, OA patient age demonstrated a trend in predicting the grade of the menisci at time of TKA (p=0.089). Human OA meniscus cultures secreted MMP-1, -3 and -8, while OA chondrocytes secreted primarily MMP-3 (Figure 2) and -13. Meniscal cells were more responsive to IL-6 (Figure 3) which stimulated MMP-1, -3 and -8 production although both IL-1 and TGF-a influenced gene expression. Chondrocytes were more responsive to IL-1 which stimulated MMP-13 production.

DISCUSSION:
Aged and degenerative menisci produce increased amounts of matrix-degrading enzymes and inflammatory cytokines relative to young and non-degenerative menisci, which is consistent with a biologic role of the meniscus in OA. Monkey menisci in degenerative joints produced similar patterns of cytokine and MMP production identified in human OA meniscus primary cultures. These MMP patterns in monkeys correlated with osteoarthritic changes on CT scan. Human OA menisci and chondrocytes respond to cytokines with unique patterns of increased MMP production, likely due to the different matrix compositions of these tissues. Although both meniscus and chondrocyte cell responses were studied in culture, the primary cultures demonstrated increased MMP production in response to cytokines known to be integral to the response of chondrocytes in OA pathogenesis in vivo. The dynamic relationship between the meniscus and cartilage likely extends beyond biomechanical involvement to actual biologic interactions between the tissues in the development of OA. Further investigation into the factors released by aging and degenerative menisci should provide new targets to improve meniscus repairs and to prevent joint tissue destruction in OA.

SIGNIFICANCE:
Aged and degenerative menisci produce increased amounts of matrix-degrading enzymes and inflammatory cytokines, which is consistent with a biologic role of the meniscus in OA.

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