Early Stages of Surgically-induced Osteoarthritis in Mice and Opportunities for Pharmacotherapeutic Intervention
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Introduction - Osteoarthritis (OA) is the most common form of arthritis and accounts for 50% of all chronic conditions in the elderly. One in two adults reported a chronic musculoskeletal condition in 2005, twice the rate of reported chronic heart or respiratory conditions51. In addition, persons aged 45 to 64 account for an increasingly greater proportion of total musculoskeletal disease treatment costs and lost wages, a trend that will continue for the next several decades52. Surgical treatment culminating in total joint replacement (TJR) remains the most effective therapy for late stage OA. Current treatment of pre-surgical OA consists of pain relieving medications (i.e. NSAIDs), physical therapy, and mechanical supports (i.e. braces, canes, and walkers). Despite the wealth of clinical data on OA, there is currently no cure for the disease. Our previous work in developing potential disease-modifying osteoarthris drugs (DMOADs) had yielded promising results, showing a decrease in OA cartilage lesion areas and histological grades (Figure 1). Interestingly, we noted that animals treated for only the first 3 weeks demonstrated near 6-week levels of OA reduction. These differences in treatment responsiveness necessitate a better characterization of the specific cellular phases of OA throughout the natural disease progression. The current study was undertaken to clarify this progression of early OA events.

Methods - OA was induced in the right knees of 10-week-old male 129 S6/SvEv (Taconic) mice via DMM surgery. Mice receiving sham surgery with no destabilization were used as negative controls. Both groups were sacrificed at 4, 8, 12, 16, and 20-day intervals in order to evaluate OA progression. Knees were harvested, processed, and sectioned at 6um intervals. Sections were stained for cartilage composition (Safranin-O) and scored for progression and severity of OA by 3 blinded observers using a 0-5 scale (modified Mankin System)48. Both ‘mean maximal’ scores (highest scores per knee), and ‘mean summed scores (sum of scores per knee) were generated using this scale. All scores were averaged across observers. Cartilage lesion area, subchondral bone area (sclerosis), and apoptosis (TUNEL method) were measured using a histomorphometric analysis package (ImageJ)50.

Results -

![Image 1](Figure 1. Early histological (modified Mankin scale) OA grade and stage changes in the surgically destabilized mouse knee.)

![Image 2](Figure 2. Apoptosis is an acute event following surgical induction of OA in the superficial zone.)

Conclusions - Analysis of OA histologic grade (mean maximal score) of the articular cartilage shows that the disease initiates very early post-injury and progresses rapidly in a linear manner in the earliest phase. Similarly, surrogate measures of OA stage (mean summed score and average lesion area) also suggest a very early onset of the disease. In addition, the progression of OA stage occurs in a phased manner (Fig. 1a&b). Underlying subchondral bone density changes, which were well-known to late-stage OA, are here shown to begin in the earliest stages, perhaps as an adaptive response to overlying cartilage damage. Apoptosis analysis (TUNEL) also reveals an immediate cell death response to meniscal injury in the superficial and middle zones of the articular cartilage (Fig. 2a&b). Apoptosis in the deeper mineralized zones of the articular cartilage initiates after the peak of upper zone cell death, suggesting a phased cell death response between upper and lower zones (Fig 2c). Similarly, analysis of the total number of cells (DAPI) shows a significant decrease in the amount of viable chondrocytes in the superficial and middle zones of articular cartilage (Fig. 2d). Taken together, these results suggest an opportunity and a need for early intervention in OA before the resulting articular changes (i.e. chondrocyte apoptosis) become irreversible. Specifically, consideration of anti-apoptosis based therapies could prevent much of the subsequent structural changes in articular cartilage.

References ---
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