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Musculoskeletal changes following non-invasive knee injury using a novel mouse model of post-traumatic osteoarthritis

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SUMMARY

Objective: Post-traumatic osteoarthritis (PTOA) is a common consequence of traumatic joint injury, with 50% of anterior cruciate ligament (ACL) rupture patients developing PTOA within 10–20 years. Currently accepted mouse models of PTOA initiate symptoms using various methods, none of which faithfully mimic clinically-relevant injury conditions. In this study we characterize a novel non-invasive mouse model of PTOA that injures the ACL with a single load of tibial compression overload. We utilize this model to determine the time course of articular cartilage and subchondral bone changes following knee injury.

Design: Mice were euthanized 1, 3, 7, 14, 28, or 56 days after non-invasive knee injury. Knees were scanned using micro-computed tomography (μCT) in order to quantify subchondral trabecular bone, subchondral bone plate, and non-native bone formation (heterotopic ossification). Development of osteoarthritis (OA) was graded using the osteoarthritis research society international (OARSI) scale on histological sections of injured and uninjured knees.

Results: Following injury we observed a rapid loss of trabecular bone in injured knees compared to uninjured knees by 7 days post-injury, followed by a partial recovery of trabecular bone to a new steady state by 28 days post-injury. We also observed considerable non-native bone formation by 56 days post-injury. Grading of histological sections revealed deterioration of articular cartilage by 56 days post-injury, consistent with development of mild OA.

Conclusions: This study establishes a novel mouse model of PTOA, and describes the time course of musculoskeletal changes following knee injury, helping to establish the window of opportunity for preventative treatment.

Introduction

Osteoarthritis (OA) is characterized by degradation of articular cartilage and significant joint pain, often necessitating whole joint replacement[1]. OA is a major health concern, affecting over 27 million Americans and 151 million individuals worldwide. Post-traumatic osteoarthritis (PTOA) is commonly a long-term consequence of traumatic joint injury, with approximately 50% of individuals with anterior cruciate ligament (ACL) rupture or meniscectomy developing PTOA within 10–20 years[2]. While clinically diagnosable PTOA develops on a fairly long time scale, it is likely that structural changes occur much sooner, and cause irreversible changes to cartilage and bone within a short time after injury but before the appearance of painful symptomatic PTOA. If this is the case, the "window of opportunity" for providing treatments aimed at preventing PTOA may be confined to a short time following traumatic joint injury.

Animal models are critical tools for PTOA research, because they can dramatically shorten the time required to develop PTOA (approximately 8–12 weeks in mouse models)[3]. Currently accepted mouse models of PTOA initiate symptoms using various methods such as injecting collagenase into the joint[4,5], using a needle to induce cruciate transection in the closed knee[6], applying multiple bouts of mechanical loading[7], or using surgical techniques to transect or injure the ligaments of the knee or the medial meniscus[8–11]. These models do not faithfully mimic clinically-relevant injury conditions, due to invasive and non-physiologic injury methods. In addition, methods that utilize invasive surgical procedures may introduce confounding factors associated with the

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surgery itself, which may mask the native biological response to injury.

In this study we characterize a novel non-invasive model of knee injury in mice, which is simple to implement, highly reproducible, and closely replicates injury conditions relevant to humans. We utilize this model to determine the time course of articular cartilage and subchondral bone changes following knee injury in mice. We hypothesized that the early structural changes would appear soon after knee injury, and would progressively worsen until "diagnosable" OA is reached by 8 weeks post-injury, similar to other established mouse models of PTOA. Determining the time course of structural changes in musculoskeletal tissues of the knee joint will help establish the window of opportunity for treatments aimed at slowing or preventing PTOA following knee injury.

Materials and methods

Animals

Forty-eight adult male C57BL/6N mice (age 10 weeks at time of injury) were obtained from Harlan Sprague Dawley, Inc. (Indianapolis, IN, USA). Animals were kept in a housing facility for a 1-week acclimation period before injury. All animals were maintained and used in accordance with National Institutes of Health guidelines on the care and use of laboratory animals. This study was approved by our institutional Animal Studies Committee.

Tibial compression-induced knee injury

Knee injury was induced by a single overload cycle of tibial compression, using a system similar to those previously described for studies of bone adaptation[12–14]. Briefly, the tibial compression system consisted of two custom-built loading platens; the bottom platen that held the flexed knee, and the top platen that positioned the foot, with the ankle flexed at approximately 30° [Fig. 1(b)]. The platens were aligned vertically and positioned within an electromagnetic materials testing machine (Bose ElectroForce 3200, Eden Prairie, MN, USA). Mice were anesthetized using isoflurane inhalation, then the right leg of each mouse was subjected to a single dynamic axial compressive load (1 mm/s loading rate) to a target compressive load of 12 N. This loading method causes a transient anterior subluxation of the tibia relative to the distal femur [Fig. 1(a)]. Knee injury was noted by a release of compressive force during loading [Fig. 1(c)]. Sham injury was performed by

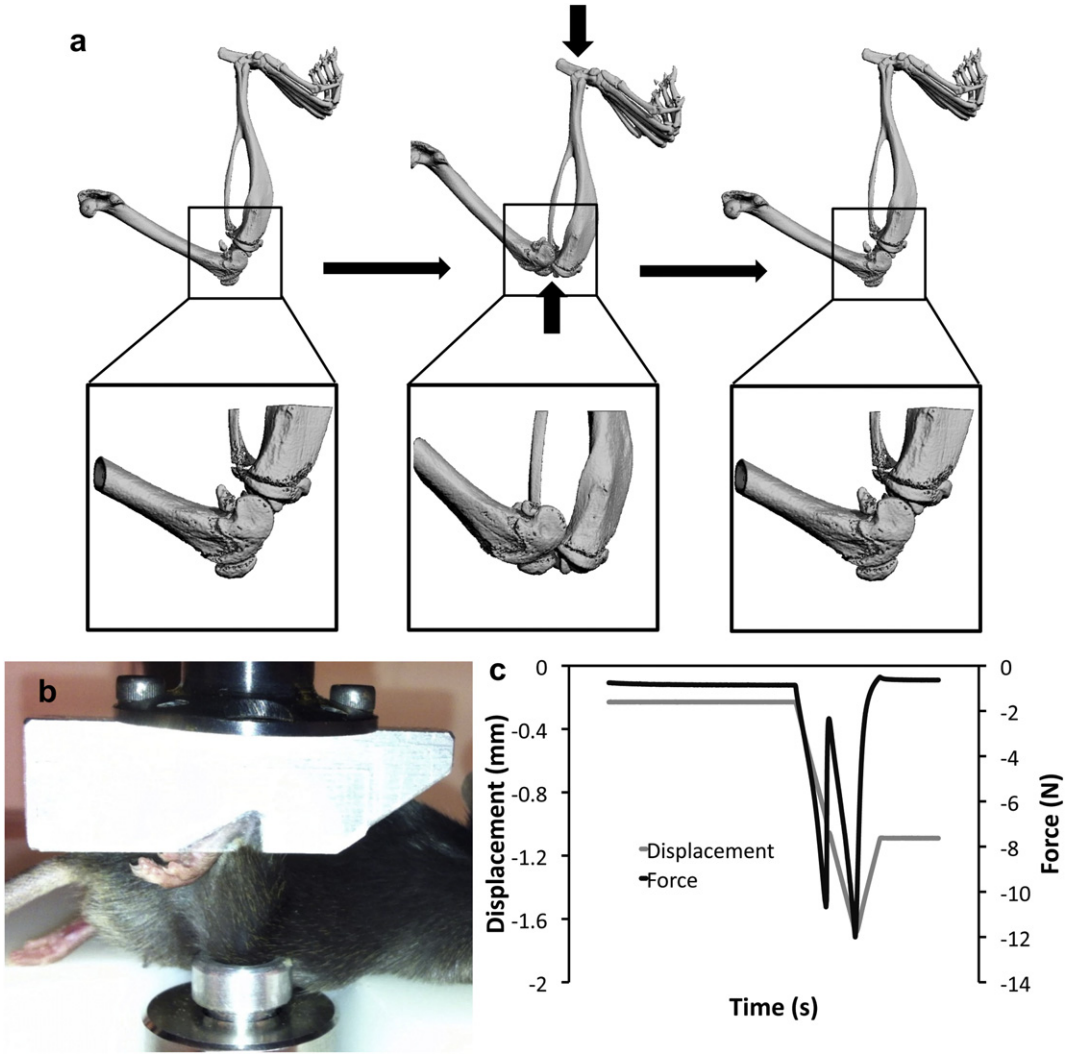

Fig. 1. Injury mechanism. (a) Tibial compression loading caused a transient anterior subluxation of the tibia relative to the distal femur. After release of compressive force, the joint returned to its original alignment, maintaining the joint function. (b) An anesthetized mouse with the right lower leg in the tibial compression loading system. (c) Knee injury during tibial compression loading was identified by a release of compressive force during the loading cycle, with a continued increase in actuator displacement.