Joint Injury and Post-Traumatic Arthritis

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Introduction

Nearly 21 million Americans are afflicted with symptomatic osteoarthritis, and an estimated 12% have a post-traumatic etiology, making post-traumatic arthritis (PTA) one of the leading causes of joint disability [4]. Furthermore, recent studies suggest that battlefield orthopaedic injuries represent the majority of long term disability in wounded soldiers in on-going military conflicts, and degenerative arthritis developing following injury is the most common reason for a wounded soldier to be considered unfit for return to duty [6]. Recent developments in injury severity assessment suggest that increasing fracture involvement of the articular surface may be predictive of developing PTA in humans [17]. The unique features of intra-articular fractures include impaction injury to the articular surface, disruption of the osteochondral composite layer, residual displacement of the articular surface, and exposure of the joint to blood and marrow contents. Previous clinical investigation identifies risk factors for the development of PTA as including: residual articular displacement, instability or subluxation of the joint following injury, and/or damage of the articular surface at the time of the injury [1, 5, 7, 12, 16]. At the present time, the state of the art treatment for displaced intra-articular fractures in major weight bearing joints involves anatomic restoration of the articular surface when possible and surgical stabilization of the fracture to allow early range of motion [7]. No pharmacologic intervention (systemically or locally) to the diarthrodial joint has been shown to decrease the incidence of PTA.

Etiology of Post-Traumatic Arthritis

Recent advances in injury severity assessment following fractures of the tibial plafond in human patients suggest that increasing levels of both energy of injury as well as increasing fracture area in the joint are predictive of developing PTA without considering reduction [17]. These same authors also found a critical threshold for residual articular displacement over which the development of PTA was more likely [10]. The mechanisms of development of PTA remain unclear. For example, the presence of residual articular malalignment is recognized to contribute to PTA [1, 2, 10]. However, the mechanisms involved in the transition of articular malalignment to development of whole joint PTA are not known. Several pathways have been proposed to play a role in development of PTA after fracture. These include apoptosis of articular chondrocytes with subsequent loss of viable chondrocytes to support the cartilage matrix, and activation of the inflammatory cascade within the joint leading to degenerative changes in the cartilage [3, 5, 8]. Recent studies using a murine closed joint fracture model suggest that an intra-articular response to joint injury with increased inflammation is associated with the development of PTA and that this response increases with severity of injury [9, 13]. However, very little is known concerning the acute intra-articular response following articular fracture in humans.

Experimental Models of Post-Traumatic Arthritis

To examine the mechanisms involved in the onset and progression of PTA in vivo, and to develop novel therapeutic approaches for treating PTA, we have developed a model of closed articular fracture in the mouse knee [9]. Initially, we developed methods to recreate closed intra-articular fractures of the mouse tibia and follow the post-traumatic healing process. Closed articular fractures were created in the left tibial plateau of adult male mice (28–35 g, C57BL/6). Fractures were more anterior in location and most commonly located in the lateral side of the tibial plateau. Nine mice were sacrificed at three time points: 2, 4,

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and 8 weeks post-trauma. Low energy and high energy fractures were created in this experiment. Histological sections of both the experimental and contralateral control limbs from the same knee joints were imaged using micro-computed tomography (microCT) and prepared for Safranin-O and fast green staining. At 8 weeks, degenerative changes were observed in the lateral loaded regions of the tibial condyle. Modified Mankin grades of degradative changes demonstrated significant changes in experimental limbs at 8 weeks.

In a follow-up study, we examined the influence of articular fracture severity on chondrocyte viability, morphological bone changes, circulating levels of inflammatory cytokines and cartilage and synovium derived biomarkers, and synovial changes after fracture [13]. Two groups of mice (C57BL/6) were subjected to articular fractures using the above method, and both simple and complex fractures of the tibial plateau were created. For low energy fractures at day 7, synovitis scores for fractured limbs were significantly higher than the non-fractured control limb at three sites: the lateral tibia, lateral femur, and medial tibia. For high energy fractures at day 7, synovitis scores for fractured limbs were significantly higher than the non-fractured control limb at all sites: the lateral tibia, lateral femur, medial tibia, and medial femur.

To examine the relationship between synovial fluid composition and PTA severity, we have developed a novel method to recover synovial fluid from the knee joints of mice [15]. This study provides the first direct evidence of accelerated joint tissue turnover in a mouse model responding

to acute joint injury. These data strongly suggest that mouse synovial fluid (SF) recovery is feasible and that biomarker analysis of collected SF samples can augment traditional histological analyses in mouse models of arthritis, similar to large animal models or clinical studies [14].

Following the development of the mouse model of intra-articular fracture induced PTA, we set out to identify mice with an altered healing response to intra-articular fracture. The MRL/MpJ strain of mice was of interest due to its unique tissue regeneration characteristics. In this study, we created simple fractures in MRL/MpJ mice and evaluated for signs of PTA [18]. Interestingly, we observed that the MRL/MpJ strain does not progress to PTA after fracture as compared to the C57BL/6 strain (Fig. 1). Furthermore, the MRL/MpJ strain shows greatly reduced presence of local and circulating pro-inflammatory cytokines such as interleukin 1 and tumor necrosis factor alpha.

Summary

Our studies in this murine model of PTA suggest that the response of the joint to injury is an organ level, or possibly even systemic response, and not simply a response of the cartilage in isolation [11]. This knowledge may be helpful in understanding how to translate findings from in vivo investigations into future therapies. There is a great need to understand the human response to injury. At

Fig. 1. Histologic evaluation of articular cartilage from contralateral control and experimental (fractured) joints in the coronal plane from a C57BL/6 mouse demonstrating cartilage disruption and degeneration, fibrocartilage, and loss of proteoglycan staining (red) and from the same compartment in a contralateral control and fractured joint from an MRL/MpJ mouse demonstrating articular cartilage disruption with no fibrocartilage and minimal loss of staining. Bars=100 μ m. F femur, T tibia, M meniscus. (Reprinted from Ward et al. [18] copyright 2008, with permission from John Wiley and Sons)

this time it is not clear whether the response to an articular fracture is similar in character to a response seen in other forms of osteoarthritis. The primary advantage of the intra-articular fracture model is a defined time point of disease onset. Focus on the articular fracture response may give clues to mechanisms that may be in play in other types of arthritis.

Disclosures Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent licensing agreements, etc) that might pose a conflict of interest with the submitted article.

Each author certifies that his or her institution approved the animal protocol for this investigation and that all investigations were conducted in the conformity of ethical principles of research.

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