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SYSTEMATIC REVIEW

Post-traumatic Arthritis: An Update

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ABSTRACT

Post-traumatic arthritis (PTA) is a frequent cause of disability following trauma of weight-bearing joints and is associated with significant physical impairment and loss of function. The development of PTA often occurs after an articular fracture. Currently, the only treatment option available to orthopaedic surgeons in the management of an acute articular fracture is anatomic fracture reduction. The complex pathway involved in the development and progression of PTA after articular injury, however, remains unknown and largely unstudied. Pro-inflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) are upregulated in injured and degenerative joints and may play an important role in the pathogenesis of PTA. The central goal of ongoing research is to understand the sequence of biologic events—distinct from mechanical disruption of the joint surface—that cause progressive joint degeneration and ultimately the development of PTA. Promising new interventions on the molecular level have been shown to slow or halt the progression of these adverse events in animal models.

Keywords: Post-traumatic, Arthritis, Interleukin-1, Tumor necrosis factor-alpha.

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INTRODUCTION

Osteoarthritis (OA) is a painful disease of synovial joints characterized by progressive degenerative changes in articular cartilage, bone and other joint tissues. Post-traumatic arthritis (PTA) is a frequent cause of disability following trauma of weight-bearing joints, and it is estimated that nearly 12% of the nearly 21 million Americans with symptomatic OA have a post-traumatic etiology.[1,2] The physical impairment caused by arthritis of a single lower extremity joint is equivalent to that caused by end-stage renal disease or heart failure.[3] Unlike idiopathic OA, PTA tends to cause significant disability in young and middle-aged patients and costs the US economy over $7 billion annually in lost productivity and medical expenses.[2,4] Even with optimal treatment, displaced articular fractures in the lower extremity have a 10 to 20% incidence of PTA.[5] Currently, there are no approved therapies to prevent or address acute PTA, although patients with PTA represent a readily identified population at risk for developing arthritis and thus are ideal to test preventative and therapeutic measures.[6] This stems largely from the fact that the sequence of events leading to arthritis following an articular injury is not fully understood.

The development of PTA may follow a variety of joint injuries, but it most commonly and most rapidly occurs after fracture of the articular surface.[7] To date, the primary studies regarding articular fractures and subsequent arthritic change have focused on anatomic reduction of the articular surfaces to restore joint congruity,[7,8] as malreduction and instability have been associated with the development of PTA.[9,10] Despite a surgeon's best efforts, reduction of articular fractures invariably results in alterations in the magnitude and distribution of stress in the joint attributable to changes in congruity and contact areas.[7,11-13] This likely alters the biomechanical or biological properties of the cartilage and joint tissues.[7,14-16]

The complex pathway involved in the development and progression of PTA after articular injury, however, remains unknown and largely unstudied.[7] An articular fracture is a complex event with several injurious aspects, including mechanical insult to the joint tissues, rupture of ligaments and menisci, lesions to the synovium, compressive or shear damage to the articular cartilage, release of blood and marrow contents into the joint space, and potentially systemic polytrauma.[6,7] In the aftermath of these injurious events, two basic pathways in the pathogenesis of PTA have been proposed: (1) Apoptosis and/or necrosis of chondrocytes due to direct mechanical insult and joint incongruity which results in insufficient numbers of viable chondrocytes to support the complex cartilage matrix; and (2) the activation of an acute inflammatory cascade which may evolve into a chronic process leading to degenerative changes within the joint.[17-19] It is likely that both mechanisms contribute directly to the clinical manifestation of PTA, which depends on a number of factors at the cellular, molecular, joint and systemic levels (Fig. 1). An improved understanding of these pathologic events at the cellular and tissue levels may provide insight into new therapeutic approaches to prevent joint degeneration.[7]

The inflammatory response resulting from articular fracture is likely a significant factor in the progression of PTA, but its effect remains incompletely characterized.[20] Proinflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α), are upregulated in injured and degenerative joints and may play an important role in the pathogenesis of PTA similar to their role in primary OA of joints in patients without antecedent injury.[21,22] Cytokines in the IL-1 family appear to be the principal

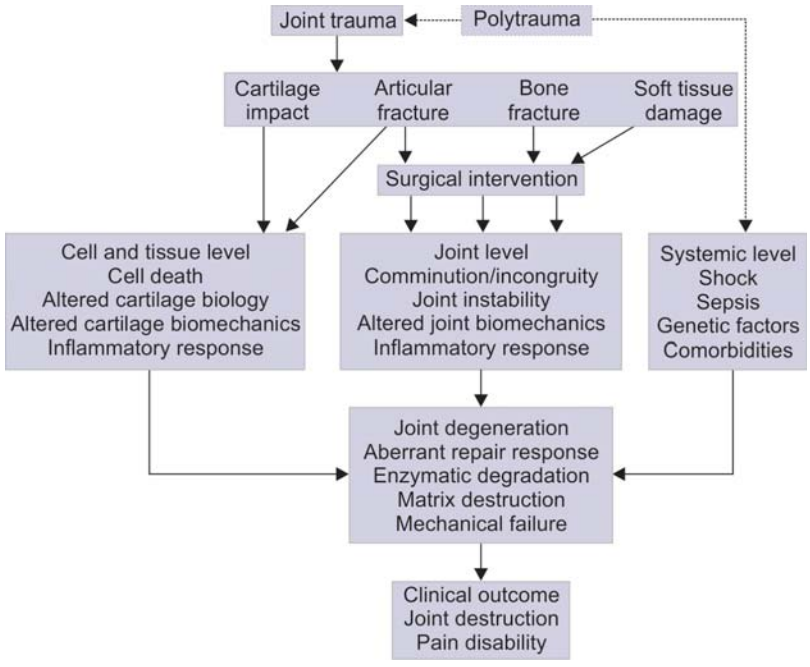

Fig. 1: Factors involved in the development of PTA after injury (adapted with permission from Furman et al)[7]

mediators of the acute post-traumatic response,[6] as increased IL-1 expression has been documented after mechanical joint injury and correlates with the severity of cartilage damage.[23] IL-1 induces mediators of joint pain and promotes cartilage matrix degradation by inducing expression of extracellular matrix-degrading enzymes, such as aggrecanases and matrix metalloproteinases (MMPs) that inhibit and reverse matrix synthesis.[6,24,25] Many catabolic and proinflammatory pathways are induced by upregulation of IL-1 and TNF-α.[25-27] Intra-articular delivery of IL-1 and TNF-α results in proteoglycan loss and inhibition of new proteoglycan synthesis;[28-34] and repeated injections or previous injury further potentiate joint degeneration.[35-37] Levels of other inflammatory mediators, including IL-6, have also been shown to be significantly increased in human synovial fluid after joint injury.[38,39]

The manner in which these cytokines and mediators influence sustained joint tissue inflammation and cartilage degeneration following articular trauma, however, remains unclear. Animal models represent the best opportunity to investigate these mechanisms. There are a variety of research approaches that may prove valuable in studying this condition.

One of the approaches is to study the natural history of an articular fracture as it develops PTA. To this end we have developed a murine model of closed articular fracture of the tibial plateau that results in progressive arthritic changes in the bone, articular cartilage, and other joint tissues consistent with PTA in the C57BL/6 mouse.[40] Because this is a closed system in which no arthrotomy or surgical reduction is performed, this model provides a unique opportunity to investigate the natural progression of events following an articular injury in a closed environment. The use of a murine model also allows the use of genetically modified or inbred strains to further isolate the genetic response to injury. In particular, in subsequent studies we have shown that the inbred MRL/MpJ strain, known as the 'superhealer', is protected from PTA and does not develop degenerative joint changes following articular fracture.[4]

To briefly summarize the studies in this area, MRL/MpJ mice exhibit a significantly diminished local and systemic inflammatory response following closed articular fracture compared to C57BL/6 mice, and this blunted reaction may explain their relative protection from the development of PTA in this fracture model. In mice that do develop PTA, articular fracture led to increased inflammatory gene expression in the synovium, increased inflammatory protein expression in the synovium, serum and synovial fluid, and increased activated macrophage infiltration of the synovium in association with progression to arthritis. Taken together, these findings suggest both a systemic response and a local intra-articular organ-level response of the joint to injury in C57BL/6 mice.[41] Importantly, they suggest that inhibition of the early inflammatory response, particularly of IL-1, may provide a novel pharmacologic approach to PTA after articular fracture.

PTA remains a difficult clinical problem to solve with considerable impact on patient quality-of-life and productivity. The central theme of ongoing research is that

acute joint injuries initiate a sequence of biologic events distinct from mechanical disruption of the joint surface that cause progressive joint degeneration and ultimately the development of PTA.[42] Considerable evidence from explant tissue and animal models suggest that an acute and sustained inflammatory response to joint injury may be central in the etiology of PTA, and promising new interventions on the molecular level have been shown to slow or halt the progression of these adverse events in animal models.[42] Multidisciplinary approaches are needed to develop clinically meaningful strategies to translate these and other basic science observations into clinically meaningful therapies.

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