Review Article

# The Role of Cytokines in Posttraumatic Arthritis

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## Abstract

The development of arthritis after joint injury is commonly known as posttraumatic arthritis (PTA). The inciting traumatic event may range from cartilage contusion and bone bruise combined with meniscus or ligament tear, to intra-articular fracture. End-stage PTA is often indistinguishable from primary osteoarthritis. However, knowing the time of the inciting traumatic event in a patient with PTA provides an opportunity to understand the events following joint injury that lead to the progression of arthritis. Joint injury often leads to mechanical alterations in loading of the injured joint, and restoration of joint mechanics through surgical repair remains an important aspect of treatment. However, the accuracy of joint reduction by itself does not account for the variability in outcome following joint injury, as evidenced by the fact that PTA remains a significant clinical problem. Emerging research in animal models and human subjects indicates that several inflammatory cytokines and related inflammatory mediators are elevated following joint injury. Data from animal studies and early clinical trials suggest that early inhibition of the intra-articular inflammatory response may improve clinical outcomes.

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Joint injuries with or without associated disruption of the articular surface can begin a process of degenerative changes that can result in the severely debilitating condition known as posttraumatic arthritis (PTA).[1] The symptoms of PTA are joint pain, stiffness, and decreased function. There is no recognized classification of or diagnostic criteria specific to PTA aside from standard osteoarthritis (OA) scoring methods.

PTA is a clinical diagnosis that is based on a combination of symptomatic complaints and radiographic changes suggestive of articular degeneration after fracture or other joint injury.[1,2] Arthritis that develops after joint injury has been referred to as posttraumatic OA (PTOA) and as PTA. PTA has a particular predilection for the age groups with the highest likelihood of sustaining serious joint injuries, namely, young and middle-aged adults.[3]

A recent attempt to estimate the burden of disease suggests that PTA may be responsible for up to 12% of the 21 million cases of OA in the United States, accounting for as much as $3 billion in healthcare costs annually.[3] Despite continued improvements in clinical and surgical management of joint injuries in recent years, including intra-articular fractures, the prevalence of PTA remains high.[4]

Treatment strategies are often similar for both end-stage symptomatic PTA and end-stage primary OA.

However, relative to primary OA, patients with PTA have equally poor or worse treatment outcomes. Multiple reasons for this have been cited. Patients with PTA tend to mirror the characteristics of a trauma population, with younger age of onset, greater desired activity levels, and a greater need for high functional performance.[1,5,6] Age at presentation and the demands for high activity levels pose a treatment challenge because the standard practice is to reserve joint arthroplasty for persons in the fifth decade or later and because other types of salvage surgery may not result in satisfactory outcomes for patients with high activity levels.[1] Several outcome studies report lower long-term functional scores and higher complication rates following total joint arthroplasty to manage end-stage PTA than to manage primary OA.[7,8] Aseptic loosening and septic failure are the most common complications in patients with PTA. These complications are in part attributable to residual malalignment, which can lead to suboptimal component positioning; changes in the soft-tissue envelope and ligamentous structures; and adhesions and alterations in the extensor mechanism.[8]

Although different joint injuries are known to cause PTA, the resulting cellular and molecular changes that lead to PTA have only recently begun to be discerned. Several researchers now believe that PTA is the result of a multifactorial process of the whole joint. The processes that lead to PTA likely are mediated by interactions between the tissues in the joint, including articular cartilage, synovium, systemic factors present in synovial fluid, and subchondral bone.[4,9] Mounting evidence suggests that the host response to injury, including the role of proinflammatory cytokines, may be an important mediator of these interactions between the different tissue types within the joint.

New knowledge is available concerning inflammation and how it may contribute to the pathogenesis of PTA after joint injury. We believe that recognizing the contribution of these factors will help pave the way for the development of interventions, including biologics, to augment the clinical care of joint injuries in the effort to restore function and prevent the development of PTA. The clinical and experimental studies reviewed use different criteria to objectively grade and evaluate PTA. These include clinical scores, radiographic changes, and histologic evidence of joint degeneration. Although the relationship between structural changes in the joint and the clinical symptoms of PTA are not fully understood, objective measures of joint degeneration are widely accepted as surrogate measures of PTA severity.

## Arthritis After Joint Injury Without Intra-articular Fracture

Joint injury without intra-articular fracture includes blunt injury to articular cartilage and the underlying bone, coupled with tearing or rupture of ligaments, menisci, and joint capsules. Although blunt injury frequently is studied as a component of joint injury, there is little clinical evidence that blunt injury in isolation leads to PTA. Soft-tissue ligamentous injury, however, has been shown to induce arthritic degeneration, as demonstrated in multiple in vivo animal models of anterior cruciate ligament (ACL) transection. Knee instability resulting from ACL transection results in changes in cartilage properties detected as early as 6 weeks after injury, with histologic changes occurring by 3 months, and progressive arthritic changes in the joint that parallel osteoarthritic degeneration occurring over the course of 18 to 54 months.[10,11]

Clinical studies add to the basic science evidence that increased age at the time of injury can add to the risk of joint degeneration. Sommerlath et al[12] reported that age at the time of knee injury involving both ACL and medial collateral ligament damage altered the risk of PTA. At 9 to 16 years after ACL rupture, 87% of patients aged ≥35 years at the time of injury had evidence of PTA, compared with only 58% of patients younger than 35 years at the time of injury. Meniscus injury is also associated with development of knee arthritis. Recent reports indicate that patients with complex tears and radial tears are at increased risk of developing arthritis.[13,14]

Current in vitro and in vivo studies have not been able to define the exact mechanisms that lead to degener-

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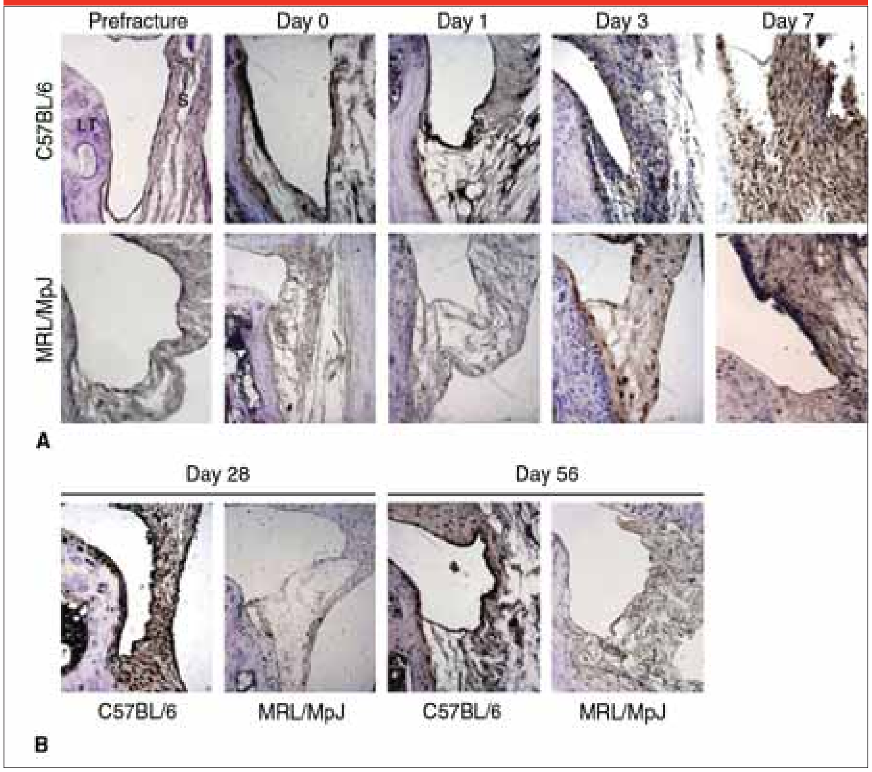
ative changes of the articular surface in unstable joints. It has been suggested that repetitive abnormal loading in the setting of clinical instability increases shear forces and supraphysiologic compressive forces on discrete regions of the joint surface, which leads to focal changes of cartilage wear.[15] Evidence suggests that mechanosensitive inflammatory and repair signals are both triggered by abnormal load.[15] The elucidation of these biological responses is critical for ultimately identifying the therapeutic targets that can prevent PTA.

**Figure 1**




Increased synovial macrophage infiltration in tissue samples from C57BL/6 mice compared with MRL/MpJ mice following intra-articular fracture. Immunohistochemical (F4/80) staining was used to assess macrophage infiltration in the lateral synovium of fractured limbs in the first week after fracture (**A**) and at 28 and 56 days after fracture (**B**). (Original magnification ×400.) LT = lateral tibia, S = synovium. (Reproduced with permission from Lewis JS Jr, Furman BD, Zeitler E, et al: Genetic and cellular evidence of decreased inflammation associated with reduced incidence of posttraumatic arthritis in MRL/MpJ mice. *Arthritis Rheum* 2013;65[3]:660-670.)

## Arthritis After Fracture

### The Role of Reduction

Management of displaced intra-articular fractures involves careful surgical reduction of the articular surface and fracture fixation.[5,16] Multiple studies have shown that anatomic restoration of the articular surface reduces the progression of joint degeneration radiographically after fracture.[5,16,17] Even with anatomic articular reduction, however, the incidence of PTA is significant. The rate of PTA development varies by anatomic location, with the highest rates following intra-articular ankle fracture, followed by hip fracture and knee fracture.[5,18] The rates reflect the observed likelihood of developing PTA after injury, not the observed rates of arthritis in a population, as many of these patients may receive surgical reconstruction of the arthritic joint. Additionally, the mechanism of cartilage degeneration beyond the focal site of the joint injury is unclear. Recent studies suggest that this propagation of arthritis involves an organ-level response, with involvement of tissues in the joint beyond the articular cartilage.[4,9] These observations suggest that additional factors beyond articular reduction influence the development of PTA.

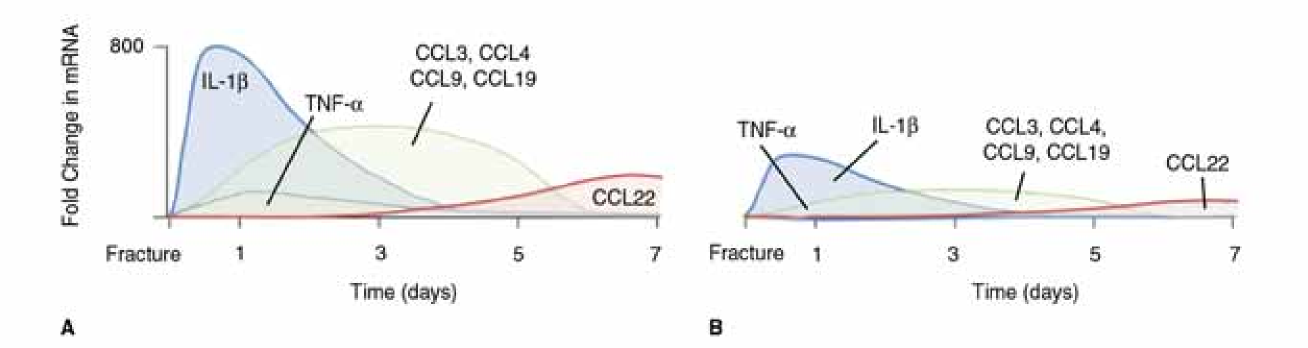
### Inflammatory Factors

To better understand the natural history of PTA after articular fracture, Furman et al[19] developed a technique of creating displaced intra-articular fracture in the tibial plateau of mice without opening the surrounding soft-tissue envelope. This model reliably develops arthritic changes in the joint by 8 weeks after fracture in adult C57BL/6 mice. The same investigators identified that the superhealer strain of mice (ie, MRL/MpJ) is less prone to developing degenerative changes following articular fracture.[20] The key findings associated with the development of PTA are significant synovial cellular hypertrophy within 7 days of fracture, intense postfracture synovitis that increases with increasing energy of injury, and a prolonged presence of activated macrophages in the synovium[21] (Figure 1).

Elevated levels of proinflammatory cytokine gene expression (eg, interleukin [IL]-1β) in synovium have been measured early in the postfracture course, along with a subsequent increase in chemokines, which are signaling molecules that increase inflammatory cell recruitment to the tissue[9,21] (Figure 2).

This proinflammatory response of the joint after fracture occurs in the different tissue types involved in the

**Figure 2**




Graphic representation of the timeline of increased inflammatory response in C57BL/6 mice (**A**) and MRL/MpJ mice (**B**) in the 7 days following joint injury. The relative gene expression of cytokines interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) was elevated first, followed by an elevation in relative gene expression of chemokine (C-C motif) ligands CCL3, CCL4, CCL9, and CCL19; macrophage inflammatory proteins; and finally, macrophage-derived chemokine CCL22. (Reproduced with permission from Lewis JS Jr, Furman BD, Zeitler E, et al: Genetic and cellular evidence of decreased inflammation associated with reduced incidence of posttraumatic arthritis in MRL/MpJ mice. *Arthritis Rheum* 2013;65[3]:660-670.)

joint injury, including cartilage, bone, synovium, and ligaments. Cytokines likely access these tissues via synovial fluid, in a manner similar to the delivery of nutrients and metabolites to articular cartilage. Joint injuries are associated with significant changes in synovial fluid levels of analytes that could contribute to joint degeneration.[22] These include an increase in several notable proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), IL-1, mediators such as nitric oxide, and matrix metalloproteinases (MMPs).[18] MMPs and aggrecanases are enzymes known to degrade the proteoglycan matrix of articular cartilage.[1] Other metabolites, often referred to as damage-associated molecular patterns (DAMPs), have also been implicated.[23] DAMPs are generated through mechanical or proteolytic degeneration of joint tissues such as cartilage extracellular matrix, and they serve to stimulate an innate immune inflammatory response.[23]

Another notable response to mechanical injury is chondrocyte cell death, which has been associated with cartilage degeneration and ultimately, the development of PTA.[24] Chondrocyte cell death after initial mechanical trauma is thought to occur in two phases. Immediate chondrocyte necrosis occurs along the intra-articular fracture lines, presumably in response to the acute mechanical injury. Subsequently, a delayed wave of chondrocyte death occurs beyond the area of initial injury; this wave is thought to be mediated by apoptosis, or programmed cell death.[25,26] It has been hypothesized that the apoptosis that extends the chondrocyte zone of injury occurs in response to the release of reactive oxygen species, inflammatory mediators, or degradative enzymes; treatments to mitigate these factors within 48 hours of injury have been shown to reduce the fraction of nonviable chondrocytes.[27]

Studies report an increase in chondrocyte apoptosis after mechanical injury in both animal and human articular cartilage following joint trauma, as measured by increased caspase levels.[25] Caspases are enzymes that regulate apoptosis. Proinflammatory cytokines may also propagate chondrocyte apoptotic cell death in a dose-dependent manner.[6] Mechanical injury may also lead to a decrease in synthesis of collagen and glycosaminoglycan; it is thought that the overwhelming inflammatory response prevents new matrix synthesis and recovery from this suppression.[18,28] A recent study using freshly harvested human tibias created an injury similar to a distal tibial plafond fracture with impact loading.[26] The authors reported the gradual development of a wave of cell death across the tibial plafond. Only a single limb at a time was available to test acutely, however. There was no control group. Chondrocyte viability was determined by assessing the superficial layer of the articular surface. Other studies have shown preservation of viability in layers of the articular cartilage below the surface, especially away from the fracture surfaces.[29]

In contrast, no effect on chondrocyte viability was observed in a porcine model using whole joint knee transarticular impact loading without fracture.[29] The addition of impact with an articular fracture led to profound changes in cartilage, including decreased chondrocyte viability at the fracture edges, increased levels of MMPs and aggrecanases, and increased sulfated glycosaminoglycan release.[29]

## Damage-associated Molecular Pattern Molecules

The role of DAMPs is another topic of interest.[23] These endogenous molecules, such as endogenous DNA and other cartilage matrix breakdown products, are released by stressed or dying cells. It has been suggested that DAMPs may contribute to the inflammatory pathways that lead from mechanical injury to cartilage degradation.[23] Some researchers have proposed that the release of DAMPs from cartilage following fracture is a potential mechanism by which cartilage injury and chondrocyte death may promote a proinflammatory, immunostimulatory response in the joint. Experiments have shown that chondrocyte apoptosis and necrosis result in double-stranded DNA (dsDNA) release and that the amount of cell death may correlate with this dsDNA release.[30] The increased surface area of cartilage matrix exposed after fracture is thought to enhance the release of cell debris and inflammatory molecules from the cartilage into the surrounding area. This can lead to a peak in the inflammatory mediators after intra-articular fracture and may progress to an acute or chronic inflammatory process resulting in PTA.[21] Thus, the sequestration of DAMPs may be another potentially fruitful area for developing novel treatments for the prevention of PTA.

## The Role of Cytokines

Cytokines are signaling molecules produced by nearly all cell types to exert autocrine-, paracrine-, or endocrine-level effects. Many families of cytokine have been characterized, within which individual cytokines demonstrate immunostimulatory or proinflammatory activity.[31] Others possess anti-inflammatory or immunoregulatory activity.

In the setting of intra-articular injury, the balance of these signals and the downstream activities they induce determine progressive joint destruction leading to PTA or resolution of injury and return to cartilage homeostasis. The interplay of proinflammatory versus anti-inflammatory, or chondroprotective, cytokines in response to joint injury is increasingly recognized as having an integral role in the pathway to PTA.[31]

### Proinflammatory Cytokines

Evidence for the role of inflammatory cytokines in the development of PTA has emerged from several clinical and basic science studies. The association between ACL injury and PTA has been established, with studies reporting that >50% of patients with ACL tear exhibit PTA at long-term follow-up.[32] Evidence for the role of cytokines has been documented in clinical studies of the ACL-deficient knee as well as after ACL reconstruction.[22,33] This is supported by findings of elevated levels of proinflammatory cytokines detected in synovial fluid by 4 weeks after injury.[33]

Several studies have identified the proinflammatory cytokine IL-1 as a principal mediator of the acute inflammatory response after joint trauma. Expression of IL-1 surges after joint injury and correlates with the severity of cartilage injury.[9,18] IL-1 expression is thought to be upregulated by several cell types, including chondrocytes, synoviocytes, and infiltrating inflammatory cells. IL-1 stimulation increases mediators of joint pain and factors that promote cartilage matrix degradation by inducing extracellular matrix–degrading enzymes such as MMPs and decreasing extracellular matrix synthesis.[34]

MMP molecules represent a family of endopeptidase enzymes that can cleave extracellular matrix proteins in the process of tissue remodeling. MMPs have been implicated as mediators of joint degeneration following intra-articular fracture. The presence of MMPs may result in breakdown of tissue components and may be one means by which DAMPs could be generated and heighten and extend the proinflammatory joint tissue response to injury.[34,35] Proinflammatory cytokines such as IL-1 and TNF-α in the joint have been found to significantly upregulate MMP gene expression.[36] Both IL-1 and TNF-α are reported to upregulate MMP-3 steady–state mRNA expression in the joint tissues.[34,37] Thus, some researchers believe that inhibition of IL-1– and TNF-α–mediated upregulation of MMP expression holds great promise as a potential therapy for PTA.[37]

One key area of development is characterizing the effects of IL-1 inhibitors in joint injury. IL-1 receptor antagonist (IL-1Ra) inhibits IL-1α and IL-1β by competing with IL-1α and IL-1β binding to IL-1 receptor type I.[33,37] In canine models of OA, in vivo intra-articular injection of the IL-Ra gene via a viral vector has been shown to inhibit the development of structural changes in PTA.[36] Diacerein, an agent that blocks the effects of IL-1, is reported to inhibit IL-1–mediated degradation of human cartilage harvested from patients with OA, as well as animal cartilage in vitro.[38] A recent study found elevated levels of IL-1β in synovial fluid following acute knee injury, thereby documenting its relevance to human joint injury.[39] The use of IL-1Ra has been associated with a decrease in knee arthrofibrosis in patients with limited early range of motion following arthroscopic procedures.[40]

The clinical effect of IL-1Ra in complete ACL injuries was examined in a recent randomized controlled pilot trial.[33] Eleven patients with acute ACL injury were randomized to receive a single intra-articular injection of IL-1Ra (ie, anakinra 150 mg) or an equal volume of saline placebo. The double-blinded treatment was administered at a mean of 2 weeks after injury. Administration of IL-1Ra within the first month following severe knee injury resulted in less knee pain and improved function over a 2-week interval. Moreover, significant reductions in synovial concentrations of IL-1α and serum concentrations of hyaluronan suggested a beneficial anti-inflammatory effect of IL-1Ra in the setting of acute joint injury. These findings suggest that intra-articular injury—in this case ligamentous—is associated with symptoms of pain and decreased function that are mediated, at least in part, by inflammatory cytokines. They also suggest that acute neutralization of these immune factors following injury provides symptomatic benefit.

ACL injury clearly increases the risk for the development of degenerative changes. Thus, it can be extrapolated that early treatment of inflammatory factors may not only improve symptoms but may also help restore joint kinematics and halt the degenerative process that leads to PTA. Similar clinical studies following intra-articular fracture are needed to evaluate this theory.

A recent study investigated intra-articular injection of purified mesenchymal stem cells from the C57BL/6 and MRL/MpJ super-healer strains of mice.[41] The control group of mice injected with saline after fracture demonstrated PTA after 8 weeks, but the delivery of C57BL/6 or MRL/MpJ mesenchymal stem cells to the joint showed histologic scores similar to those in the control and experimental limbs, indicating prevention of PTA changes in the experimental mice. The mesenchymal stem cell treatment influenced cytokine levels in both the synovial fluid and serum. Elevated levels of IL-10 were noted. IL-10 is thought to have anti-inflammatory effects, and it has been shown to provide a therapeutic effect in the treatment of early OA.[42] The anti-inflammatory cytokine IL-4 has also demonstrated chondroprotective potential.[42]

## Chondrocyte Death and Posttraumatic Arthritis

The mechanisms and consequences of chondrocyte death following joint injury is another area of research. Investigators have examined cell necrosis caused by injury, as well as the onset of programmed cell death (apoptosis), which may provide a therapeutic target for PTA. For example, caspases are involved not only in the initiation and regulation of chondrocyte apoptosis but also in mediating innate immune responses to DAMPs through conversion of the precursors of IL-1β and IL-1α to their active form.[43] It has been proposed that caspase inhibition may be able to mitigate the pathologic effects of IL-1 cytokines.[43]

Beneficial effects of caspase inhibitors in decreasing the development of PTA have been reported in animal models. For example, a rabbit model of surgically induced femoral condyle articular injury requiring arthrotomy showed a significant decrease in short-term chondrocyte death ($P < 0.01$) and a significant increase in cartilage thickness ($P = 0.01$) in knees treated with intra-articular injections of caspase inhibitor compared with control knees.[44]

In a different study, one dose of surfactant P188 was shown to promote chondrocyte survival, inhibit apoptosis, and protect cartilage integrity.[45] This investigation was performed on freshly harvested ankle cartilage obtained from human tissue donors. P188 was found to have a stabilizing effect on cellular membranes; it inhibited glycogen synthase kinase-3 activation related to apoptosis as well as inflammation related to IL-6 signaling. It was therefore postulated that P188, either alone or in combination with growth factors, might have the potential to prevent the development of PTA.

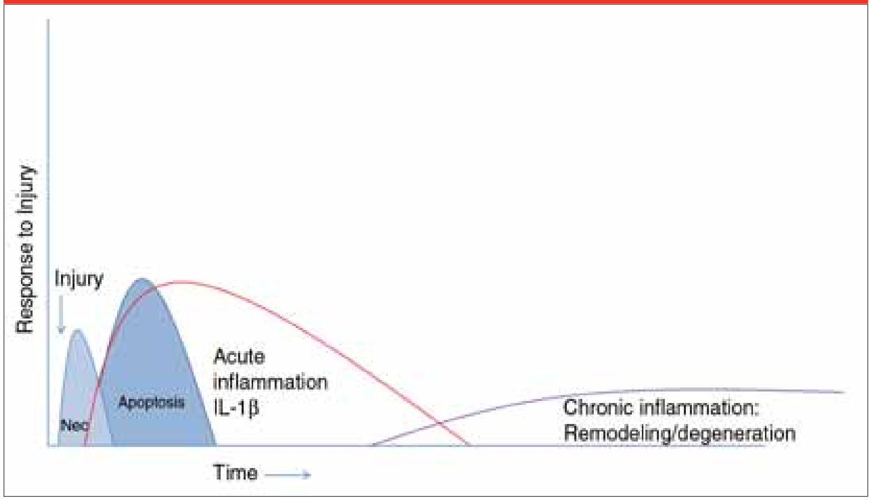
## Developing a Therapeutic Strategy for Posttraumatic Arthritis

One potential advantage in studying PTA is the known time point of onset of the disease state marked by the time of incidence of trauma.[1,6] The implication is that this identifies the beginning of a potential therapeutic widow for intervention. A better understanding of mechanisms and the timing of significant biologic events in the development of PTA will allow investigators to determine optimal timing for biologic interventions in the future.

Acute joint trauma causes three phases of tissue damage resulting from the cartilage injury and the response of the body to that injury. This concept is similar to that proposed by Anderson et al,[4] although they focused on the first 2 weeks after injury. This three-phase concept can be modified to provide a framework to consider potential opportunities for translational therapies. The early phase leads to chondrocyte apoptosis and a significant surge in proinflammatory cytokines, nitric oxide, free radicals, MMPs, and release of molecules from chondroid matrix damage. Therapies that would target this phase may need to be given immediately after injury—the equivalent of on the battlefield—to alter this early response. An intra-articular injection of a therapy that inhibits proinflammatory cytokines is a potential example of this type of intervention. Therapies targeting the second phase would focus on the downstream effects of the immediate response to injury. The third phase will include most of the events in the care of the joint injury. These range from surgical joint repair to restore early motion to the return of physiologic joint function. Although it is appealing to think of these phases as distinct events, overlap likely exists between these phases of tissue injury in vivo (Figure 3). The expanded three-phase model recognizes that the time course for the development of PTA may vary between anatomic locations and among patients.

The goal of therapeutic interventions is to decrease the inflammatory responses resulting from injury, minimize chondrocyte apoptosis, limit matrix degradation of articular cartilage, and enhance new extracellular matrix production.[4,21] No all-encompassing solutions to these challenges currently exist; however, researchers are working on several fronts. Most of the emerging evidence is arising from animal studies.

**Figure 3**




Graphic representation of the three phases of tissue damage that are theorized to occur following intra-articular fracture. This contributes to direct chondrocyte death, with evolution of acute and inflammatory response, which is felt to contribute to joint-level degenerative changes. IL = interleukin, Nec = necrosis. (Adapted with permission from Anderson DD, Chubinskaya S, Guilak F, et al: Post-traumatic osteoarthritis: Improved understanding and opportunities for early intervention. *J Orthop Res* 2011;29[6]:802-809.)

## Summary

A growing body of evidence supports the notion that the development of PTA after intra-articular fracture and other joint trauma involves more than the mechanical problems caused by the joint injury itself. Several factors contribute to the development of PTA. Basic science and clinical evidence support the idea that there is a postinjury inflammatory phase that involves the entire joint, leading to a complex pathogenesis of PTA through interactions among the different joint tissues, including a significant contribution by the synovium because of its role in maintaining synovial fluid and its capacity for cytokine production and robust potential for inflammatory cell recruitment.[9,21,33]

Multiple investigators are beginning to recognize the pivotal role of proinflammatory cytokines in cartilage degradation following trauma.[4,9,28,33,34,36] These new and exciting findings of the pathogenesis of PTA are spearheading the development of potential biochemical and/or biologic therapeutic interventions. It is likely that a critical treatment window of opportunity exists for preventing PTA after the initial mechanical trauma. This knowledge provides us with a clear mandate to explore the hypothesis that early intervention may mitigate the harmful effects of inflammatory cytokines and prevent progression to PTA.

Biologic treatment strategies in isolation cannot be successful, nor can they replace the current principles of surgical management of intra-articular fractures. It is anticipated, however, that the optimal timing and combination of these interventions may halt, if not prevent, the progression from intra-articular injury to PTA.

## References

*Evidence-based Medicine:* Levels of evidence are described in the table of contents. In this article, reference 33 is a level I study. References 12 and 14 are level III studies. References 3, 7, 8, 13, 17, and 32 are level IV studies. References 1 and 4-6 are level V expert opinion.

References printed in **bold type** are those published within the past 5 years.

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