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Basic Science of Intraarticular Fractures and Posttraumatic Osteoarthritis

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Introduction

Posttraumatic osteoarthritis (PTOA) represents end-stage organ level failure of an injured joint, typically occurring after an intraarticular fracture (IAF). The initial impact to the cartilage, combined with the ensuing pathomechanical and pathobiological response of the cartilage, lead to PTOA. However, the relative contribution of acute mechanical damage (AMD) versus exposure to chronic abnormal loading leading to joint degeneration is unknown. It is plausible that AMD and chronic abnormal loading processes potentiate each other, with initial impact energy acting as a determinant of how poorly the cartilage tolerates long-term mechanical changes. Alternatively, under certain circumstances either AMD or chronic abnormal loading may predominate in the process of cartilage degeneration. This may be apparent as some joint injuries progress rapidly to PTOA. [1,2], whereas others slowly degenerate. [3,4,5]

Current treatment for IAFs is primarily focused on restoring joint surface congruity to avoid chronically elevated articular surface contact stresses and/or instability. [4,6,7] Historically, the overwhelming emphasis placed on surgical restoration of articular surface congruity has led the majority of authorities to recommend invasive approaches to reduce and stabilize these injuries.[4,6,8] Unfortunately, such aggressive operations, especially in acutely injured limbs, can cause devastating complications. This has led other authorities to recommend minimally invasive operations for intra-articular fractures. [9–12]

Clinical decisions regarding interventions, including surgical approach, reduction strategies, internal fixation, and rehabilitation should be based on solid clinical evidence. Unfortunately, clinical evidence guiding treatment choices for IAFs is inconsistent. In fact,

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clinical evidence provides few rational answers and raises more questions in regard to treating IAFs. Questions such as to what degree does an articular surface need to be reduced, how can we accurately assess the amount of displacement after reduction and internal fixation, and how do you account for difficult-to-measure biologic differences between individuals with seemingly similar injuries remain unanswered.

Joints and regions within the same joint respond differently to IAFs. [13],[14],[15],[16] Clinical evidence shows that acetabular fracture outcomes are consistently correlated to accuracy of reduction. [4],[8] Compared to the acetabulum, incongruity is well-tolerated in tibial plateau fractures. [17],[18] There is little support for articular surface reduction to be within 2 mm. Authors have hypothesized that the relatively thick cartilage in this joint accounts for its tolerance of incongruity, but this is unproven.Because of clinical inconsistencies, optimal treatment of intraarticular fractures remains a hotly debated topic among orthopaedic trauma specialists. However, the arguments are based largely on anecdotal observation and intuition, rather than on rigorous scientific evidence. More importantly, the incidence of PTOA has changed very little over the past several decades, regardless of treatment specifics, suggesting the need for new treatment paradigms (Figure 1 and Figure 2).

A large body of scientific evidence has emerged demonstrating that the effects of AMD (chondrocyte necrosis, chondrocyte apoptosis, chondrocyte biosynthetic dysfunction) play an important, and possibly a dominant role in the etiology of PTOA. [19]-[24] Therefore, it is possible that the most effective treatment to prevent PTOA would be to mitigate or arrest the injurious effects of AMD. Such a strategy is certainly not novel. In stark contrast to treatment of IAFs, clinical outcomes of acute myocardial infarction and ischemic stroke have improved dramatically during the last several decades, with evolution of treatments directed at the acute damage to myocardial or neuronal tissue in the acute setting. [25],[26] Minimizing the acute injury at the tissue, cellular, and molecular level has been met with tremendous success in these patients.

Recent investigations have made significant progress in understanding PTOA by creating viable survival models of IAFs, understanding cellular level pathologic changes that occur after an impact injury, and by investigating promising interventions that prevent acute chondrocyte death after an impact. This manuscript summarizes recent basic scientific evidence presented at the 2009 Orthopaedic Trauma Association Basic Scientific Symposia on articular fractures.

IAF Models

An ideal model to study IAFs would be a survival IAF animal model created by a physiologic realistic impact delivered across the joint surfaces. Furthermore, the model would be conducive to surgical and pharmaceutical intervention. Historically, survival IAF models have not been created with a physiologic impact. [27],[28] Recently, Backus and colleagues and Tochigi and colleagues have investigated chondrocyte death in IAFs created with realistic impulses in explanted whole joints from cows, pigs, and humans. [29],[30] Both authors reported that the majority of chondrocyte death occurred in proximity to the fracture lines in all three species. Backus and colleagues devised methods to impact explanted bovine knees. [29] Specimens sustained an IAF if the load was offset from the midline of the knee through the lateral tibial plateau. In contrast, specimens with identical impact energy delivered into the center portion of the knee did not fracture. They showed that fractured specimens had significantly decreased chondrocyte viability compared to unfractured specimens impacted with the same amount of energy. The authors concluded that supraphysiologic cartilage strains associated with actual fracturing of the cartilage were responsible for the increased chondrocyte death. Tochigi and colleagues had essentially

identical results in human ankle joints with chondrocyte death concentrated along fracture lines. [30]

Furman and colleagues have created the first in vivo IAF model fractured using physiologic impact. [31] The authors have developed techniques to deliver a fracture-level impact through the knee creating tibial plateau fractures. The model serves as means of inducing PTOA in the pursuit of identifying the mechanisms by which arthritis progresses following articular fracture. By producing clinically relevant articular fractures without disrupting the capsule, the natural history of healing and progression of PTOA can be studied. Using their mouse IAF model, these investigators have investigated the role of fracture-associated inflammatory mediators in the development of cartilage degeneration after an IAF using mice with genetic variance. Following articular fracture, C57BL/6 mice showed significant signs of PTOA, including loss of bone density, increase in subchondral bone thickness, increased cartilage degeneration [31] and increased levels of biomarkers of cartilage turnover. [32] In contrast, the MRL/MpJ strain of mice demonstrated significantly decreased cartilage degeneration following fracture. [33] Interestingly, the MRL/MpJ strain has been shown to produce decreased levels of pro-inflammatory cytokines interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) following LPS challenge of peritoneal macrophages. [34],[35]

Chondrocyte Death after Cartilage Impact

AMD is one of the most significant factors leading to PTOA. Treatment modalities are limited and have not provided consistent long-term results. An early consequence of cartilage injury is chondrocyte death. [21],[23],[24],[36] In the longer term, cell death is associated with matrix degradation in osteoarthritis. [37] Mechanistic links are highly likely, with matrix degradation resulting in loss of survival mechanisms and cell death contributing to matrix degradation [38] and calcification. [37] Researchers have consistently shown that chondrocyte death after impact is concentrated along cartilage matrix cracks and in the superficial layer of cartilage. [29],[30],[36]

Impacted chondrocytes die by either necrosis or apoptosis. Understanding the mode of cell death is significant in developing treatments for AMD. Apoptosis, or programmed cell death, can be mitigated by several bioactive agents. A series of studies examined the potential of preventing apoptotic chondrocyte death as a means of mitigating PTOA after an impact injury. Several in vitro and in vivo models of acute cartilage injury established that chondrocytes undergo apoptosis in response to mechanical injury. [19],[20],[39],[40],[41] Apoptosis is mediated by a cascade of aspartate-specific cysteine proteases or caspases. [42] Caspase inhibition was effective in preventing apoptosis in vitro: in bovine and human cartilage explants and in chondrocytes. [41] These results were repeated in a live model of OA in which apoptosis was reduced in chondrocytes treated with caspase inhibition in anterior cruciate ligament transected knees. [39]

Recently, Martin and colleagues have shown that chondrocytes in impacted bovine explants died primarily by necrosis. [22] Sixty-five percent of chondrocytes in these specimens died in the first twelve hours after impact. Minimal subsequent cell death occurred over the subsequent two days. In impacted specimens treated with N acetylcysteine, a potent scavenger of reactive oxidant species (ROS), within four hours of impact 48 hour chondrocyte viability increased to 70-80%. Specimens receiving treatment twelve hours after impact had no improvements in viability. The authors concluded that chondrocyte death occurred secondary to overproduction of ROS. Furthermore, they hypothesized that the chondrocyte mitochondria were the most likely source of the damaging acute impact-related ROS.

Subsequently, the investigators impacted bovine specimens treated with rotenone, an irreversible inhibitor of electron transport in the mitochondria. [43] The premise of the experiment was that impact-related mitochondrial ROS production could be mitigated by blocking electron transport. Specimens receiving rotenone had a 3X reduction in injury-induced ROS production compared to untreated specimens. Furthermore, chondrocyte viability in treated specimens was 80% compared to 35% in untreated specimens 48 hours after impact. These data clearly implicate chondrocyte mitochondria in impact-related chondrocyte necrosis after an impact injury.

Discussion

PTOA is a devastating complication of IAFs which is estimated to cost 12 billion dollars annually. [44] Seventy-six percent of IAFs occur in patients less than 45 years old, [45] and patients who developed PTOA were 9 to 14 years younger than patients who developed primary OA in the lower extremity. [44] Unfortunately, reconstructive options, including arthroplasty and arthrodesis, fare poorly in younger patients. Therefore, the specific patient population that is most affected by IAFs is the population that is most devastated by PTOA. The incidence of PTOA is substantial. In patients sustaining acetabular fractures, approximately 20-25% develop PTOA. [4,8] Studies have shown that between 23% and 44% of patients develop PTOA after IAFs of the knee. [3,5] Likewise, more than 50% of patients with fractures of the distal tibial articular surface develop PTOA. [1,2] Interestingly, while surgical techniques have improved, the basic surgical premise has remained unchanged, focusing on restoring joint surface congruity, with no attention directed toward treatment of the AMD sustained by the cartilage. Furthermore, the outcomes of IAFs have changed little over decades (Figures 1 and 2).

PTOA is an organ-level disease incited by impact-associated tissue, cellular, and molecular level damage. Therefore, to account for all levels of injury, it is necessary to understand the pathoetiology of PTOA at the organ level. This emphasizes the need to create a realistic survival intraarticular fracture model. The IAF mouse model described by Furman represents an important technical breakthrough in studying PTOA at the organ level. [31] This model accounts for injury effects for all intraarticular tissue. However, the major drawback to the mouse model is the size of the animal. It is difficult to apply standard surgical fixation to such an animal, making it difficult to study the effects of reduction and fixation on PTOA.

The findings of both D'Lima and colleagues and Martin and colleagues demonstrate that AMD causes chondrocyte death. [19,20,22,39,40,41] Two different modes of chondrocyte death were demonstrated with cells dying by both necrosis and apoptosis. Interestingly, mitochondrial dysfunction plays a central role in both apoptotic and necrotic cell death. Apoptotic cell death is enacted by a series of reactions culminating in activation of cytosolic caspases. However, the cytosolic caspase cascades leading to apoptosis are initiated by several mitochondrial-derived molecules including cytochrome c and apoptosis initiating factor. Injury leads to mitochondrial depolarization which allows cytochrome c and apoptosis initiating factor to leak into the cytoplasm and initiate apoptosis. These observations are supported by the work of Huser and Davies which demonstrated that impacting equine cartilage led to mitochondrial depolarization over a three to six hour period. [46] Subsequently, at 48 hours, impacted chondrocytes had increased apoptosis. Furthermore, they showed that blocking mitochondrial depolarization or by blocking caspase enzymes significantly improved chondrocyte viability. In the studies by Martin and colleagues, the data clearly implicate mitochondrial-originated ROS as the damaging molecules leading to necrotic chondrocyte death. [22] Stopping electron transport significantly reduced ROS production and increased chondrocyte survival. [43] These findings illustrate an exciting cellular level opportunity to prevent impact-related AMD from leading to PTOA. In

summary, impact-related mitochondrial dysfunction appears to play a central role in both apoptotic and necrotic chondrocyte death.

In conclusion, mechanisms linking IAFs to PTOA are beginning to be understood at the cellular and molecular level. Organ-level survival models provide optimal opportunity to investigate pathoetiologic processes and therapeutic interventions for IAFs. Developing cellular and molecular level therapeutic interventions will be necessary to improve the current stagnant outcomes of IAFs.

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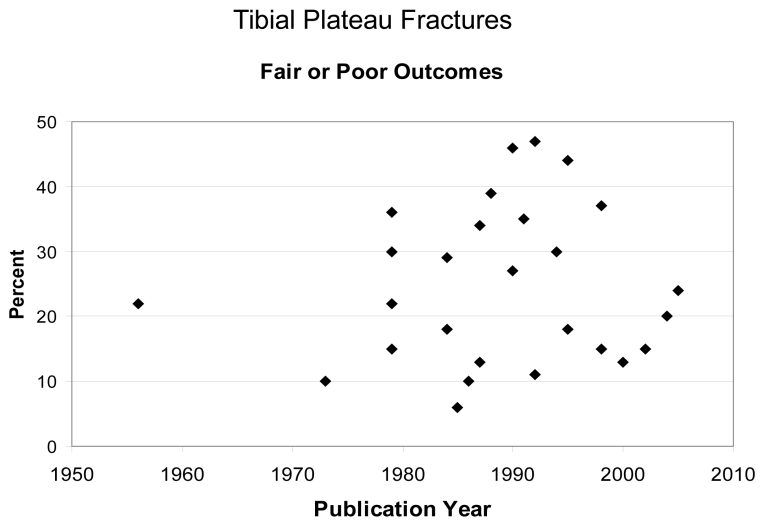

Figure 1.
Percent fair and poor outcomes from tibial plateau fractures over approximately 50 years. Outcomes have changed little over a five decade span.

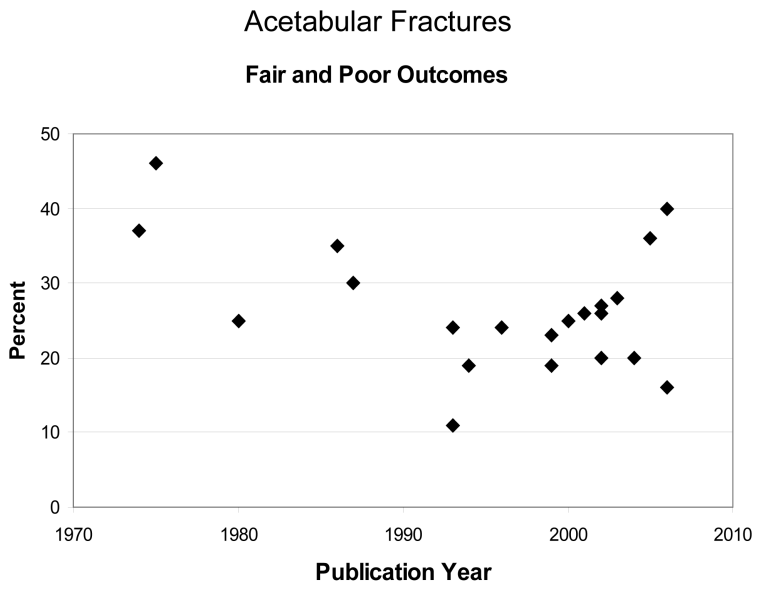

Figure 2.
Percent fair and poor outcomes from acetabular fractures over approximately 30 years. Outcomes have stagnated, especially over the past 20 years.