Bone Reports 18 (2023) 101658

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

Post-traumatic osteoarthritis: A review of pathogenic mechanisms and novel targets for mitigation

Julian E. Dilley [a,b,c], Margaret Anne Bello [b,c], Natoli Roman [a,c,*], Todd McKinley [a,b,c,*], Uma Sankar [b,c,**]

[a] Department of Orthopaedic Surgery, Indiana University School of Medicine, Indianapolis, IN 46202, USA
[b] Department of Anatomy, Cell Biology and Physiology, Indiana University School of Medicine, Indianapolis, IN 46202, USA
[c] Indiana Center for Musculoskeletal Health, Indiana University School of Medicine, Indianapolis, IN 46202, USA

ARTICLE INFO

Keywords:
Post-traumatic arthritis
Intra-articular fracture
Inflammation
Cartilage
Subchondral bone
Synovium
Mitochondria
Apoptosis
Therapeutics

ABSTRACT

Post-traumatic osteoarthritis (PTOA) develops secondary to a joint injury and accounts for 12 % of all osteoarthritis. These injuries, often of the lower extremity joints, occur due to trauma or accidents related to athletic or military activities. They primarily affect younger individuals although PTOA can occur across the spectrum of age. Pain and functional disability caused by PTOA confer a heavy economic toll on patients, in addition to detrimentally affecting their quality of life. Both high energy injuries that cause articular surface fracture with or without subchondral bone disruption and low-energy injuries involving joint dislocations or ligamentous injury cause PTOA, albeit through different mechanisms. Regardless, chondrocyte death, mitochondrial dysfunction, reactive oxygen species production, subchondral bone remodeling, inflammation and cytokine release in the cartilage and synovium play integral roles in the pathogenesis of PTOA. Evolving surgical methods are focused on stabilizing articular surface and joint structure congruity. However, to date there are no disease modifying medical therapies against PTOA. Increased recent understanding of the pathogenesis of the subchondral bone and synovial inflammation as well as that of chondrocyte mitochondrial dysfunction and apoptosis have led to the investigation of new therapeutics targeting these mechanisms to prevent or delay PTOA. This review discusses new advances in our understanding of cellular mechanisms underlying PTOA, and therapeutic approaches that are potentially effective in reducing the self-propagating cycle of subchondral bone alterations, inflammation, and cartilage degradation. Within this context, we focus therapeutic options involving anti-inflammatory and anti-apoptotic candidates that could prevent PTOA.

1. Introduction

Post-traumatic osteoarthritis (PTOA) is a major contributor to disability worldwide across all age groups (Brown et al., 2006; Cross et al., 2014; Rivera et al., 2012; Whittaker et al., 2015). Currently, there are no disease-modifying therapies to prevent or mitigate the progression of the disease. PTOA typically occurs after a direct insult in the form of an intra-articular fracture (IAF), with incidence rates from 11 to 75 % depending on the joint involved (Doornberg et al., 2007; Giannoudis et al., 2005; Lutz et al., 2011; Marsh et al., 2003; Rademakers et al., 2004; Rademakers et al., 2007; Weigel and Marsh, 2002). The initial impact to the cartilage, combined with downstream pathobiological and pathomechanical changes, leads to disease development. PTOA can also result from chronic changes in the prevailing trans articular loading environment that can result from residual instability, incongruity, or malalignment. For example, PTOA (9–12 % at 5 years; 23 % at 10 years)

Abbreviations: PTOA, post-traumatic osteoarthritis; DMM, destabilization of the medial meniscus; ACL, anterior cruciate ligament; IAD, intra-articular destabilization; IAF, intra-articular fracture; ROS, reactive oxygen species; CAMKK2, calcium/calmodulin-dependent protein kinase kinase 2; CXCL10, C-X-C motif chemokine ligand 10; MMP, matrix metalloproteinase.

* Corresponding authors at: Indiana University School of Medicine, Department of Orthopaedic Surgery, IU Health Methodist Hospital, 1801 North Senate Blvd, MPC1 Suite 535, Indianapolis, IN 46202, USA.
** Correspondence to: U. Sankar, 635 Barnhill Drive, MS-5055, Indianapolis, IN 46202, USA.
E-mail addresses: jedilley@indiana.edu (J.E. Dilley), belloma@iu.edu (M.A. Bello), rnatoli@iuhealth.org (N. Roman), tmckinley@iuhealth.org (T. McKinley), usankar@iu.edu (U. Sankar).

https://doi.org/10.1016/j.bonr.2023.101658
Received 2 December 2022; Received in revised form 23 January 2023; Accepted 27 January 2023
Available online 30 January 2023

occurs after injuries that lead to instability of the joint, such as in an anterior cruciate ligament tear (ACL-t), joint dislocation or injury to other static and dynamic stabilizers of a given joint even after surgical repair (Bodkin et al., 2020; Rhon et al., 2019; Everhart et al., 2021). PTOA in acetabular fractures is clearly associated with residual malreduction leading to joint surface incongruity (Tannast et al., 2012; Ziran et al., 2019). Collectively, both acute mechanical damage from articular surface impact and chronic aberrant loading from residual changes in stability, congruity and alignment following an injury can lead to PTOA.

Current clinical practice for IAFs and major articular ligamentous injuries usually involves a surgical procedure to anatomically restore the articular surface, the ligament or tendon, respectively, and reestablish joint surface congruity, joint alignment, and joint stability to avoid chronically abnormal articular contact stresses and stress rates. The importance of articular surface congruity and joint stability is dependent on the injured joint (Canadian Orthopaedic Trauma, 2006; Carbonell-Escobar et al., 2017; Giannoudis et al., 2010; Tang et al., 2014; Thomson et al., 2008; Virkus et al., 2018). For instance, knee alignment and stability are more important than articular surface congruity, whereas in fractures of the superior weightbearing dome of the acetabulum in the hip joint, restoring articular congruity is very important in preventing PTOA (Giannoudis et al., 2005; Giannoudis et al., 2010). Residual incongruities can increase peak and mean stresses at the cartilage surface, which have been shown to lead to cartilage loss and PTOA progression in patients with fractures exceeding a specific stress threshold (3 MPa-seconds/gait cycle) (Anderson et al., 2011a; Segal et al., 2009; Li et al., 2008). Recently, weightbearing computed tomography (CT) technology has been introduced and it is likely that this method will allow much more precise analyses of changes in the residual mechanical environment in a joint (Willey et al., 2020; Day et al., 2020). However, even with these surgical treatments, it is not always possible to prevent the development of symptomatic PTOA as the initial impact damage may predominate the pathophysiology (Doornberg et al., 2007; Giannoudis et al., 2005; Lutz et al., 2011; Marsh et al., 2003; Rademakers et al., 2004; Rademakers et al., 2007; Weigel and Marsh, 2002).

In some cases, the magnitude of the original injury likely has the dominant effect on outcomes. Anderson et al. (Beardsley et al., 2005; Beardsley et al., 2002; Rao et al., 2019; Thomas et al., 2010; Anderson et al., 2016) developed a CT-guided assessment of articular fracture energy and generate a severity score capable of predicting PTOA risk in articular fracture patients. They observed a positive correlation between increased severity score associated with initial fracture dispersion with articular comminution and increased risk of moderate to severe PTOA. In this work, it has been shown that fracture energy thresholds exist that if exceeded, PTOA will likely result regardless of the residual mechanical environment.

Over the past two decades, a great increase in the understanding of the pathophysiology of PTOA has been achieved, with two overarching mechanisms emerging. The first of these mechanisms involves acute cartilage insult resulting in chondrocyte apoptosis and necrosis largely driven by dysregulated mitochondrial biogenesis and redox imbalance progressing to chronic inflammation and cartilage loss (Ayala et al., 2021; Coleman et al., 2018; D'Lima et al., 2001). The second mechanism is mediated by chronic changes in the residual mechanical environment that prevails in the joint following an injury such as ACL-t or posterior cruciate ligament tear (PCL-t), resulting from changes in congruity, alignment, and stability, and leading to subchondral bone remodeling, synovitis, cartilage degradation, and PTOA (Chen et al., 2017; Kapoor et al., 2011; Koike et al., 2015; Rai et al., 2017; Rieder et al., 2018; Wang et al., 2015; Wood et al., 2016).

This review will discuss the current understanding of the pathogenesis of PTOA after acute injury, current preclinical models, potential treatment targets, and therapeutics currently under clinical investigation. Further, we will discuss the mechanisms contributing to PTOA when chronic articular instability occurs due to traumatic joint injuries such as ACL-t or PCL-t. Joint malignment in gait and postural-alignment conditions such as knee varus or valgus deformation and flexion contractures result in degenerative OA – not PTOA (Tateuchi, 2019), will not discussed here.

2. Pathogenesis of PTOA – intra-articular fracture

2.1. Articular cartilage damage after acute trauma: mitochondrial dysregulation and chondrocyte apoptosis

It is estimated that articular fractures increase the risk of PTOA by 20-fold (Anderson et al., 2011b). A high energy impact to the articular surface, with or without subchondral bone fracture and displacement, results in localized tissue damage and significant chondrocyte death, both at the location of impact and its vicinity (Bajaj et al., 2010). Chondrocyte necrosis is predominant at higher loads and with complete osteochondral fracture (Ayala et al., 2021; Coleman et al., 2016; Milentijevic et al., 2005; Stolberg-Stolberg et al., 2013). Acute trauma to the cartilage damages chondrocyte cell integrity leading to an influx of Ca^{2+} and a leakage of intracellular material such as mitochondrial cytochrome C, triggering a wave of apoptotic responses in surrounding cells (D'Lima et al., 2001; Olson and Guilak, 2006). The current understanding of early cellular changes that occur after IAF describes an early window of increased mitochondrial electron transport chain (ETC) activity and elevated levels of reactive oxygen species (ROS) presumably generated at electron transport chain Complex I in chondrocytes, triggering the release of free oxygen radicals and metabolites within the impacted cartilage and activating intrinsic apoptotic pathways (caspases 3 and 9, and glycogen synthase kinase 3) in chondrocytes (Ayala et al., 2021; Coleman et al., 2018; D'Lima et al., 2001; Koike et al., 2015; Rieder et al., 2018; Wang et al., 2015; Wood et al., 2016; Wegner et al., 2019; Johnson et al., 2000) (Table 1).

Given these findings, investigators have evaluated different therapies to address mitochondrial dysfunction. Coleman et al. (Coleman et al., 2018; Coleman et al., 2017) conducted a series of studies demonstrating the integral role played by ROS and mitochondrial ETC imbalance in chondrocyte apoptosis and necrosis after supraphysiological loading. In vitro studies by this group demonstrated that chondrocyte mitochondrial dysfunction and increased superoxide release resulting from

Table 1
Mechanisms associated with PTOA pathogenesis following intra-articular fracture.

PTOA etiology	Pathogenesis mechanisms	References
IAF	Acute cartilage trauma:	
	- Chondrocyte apoptosis, mitochondrial dysfunction, and release of free oxygen radicals	(Ayala et al., 2021; Coleman et al., 2018; D'Lima et al., 2001; Koike et al., 2015; Rieder et al., 2018; Wang et al., 2015; Wood et al., 2016; Anderson et al., 2011b; Bajaj et al., 2010; Coleman et al., 2016; Milentijevic et al., 2005; Stolberg-Stolberg et al., 2013; Olson & Guilak, 2006; Wegner et al., 2019; Johnson et al., 2000; Coleman et al., 2017)
	- Synovial inflammation – CXCL10 expression, macrophage infiltration of synovium, Nox4, secretion of pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α by inflamed macrophages triggering cartilage catabolism	(Wegner et al., 2019; Furman et al., 2015; Dwivedi et al., 2022; Furman et al., 2014; Olson et al., 2015; Martini et al., 2005; Furman et al., 2018)
	- Synovial inflammation and subchondral bone alterations in trauma – MRL/Mpj super healer mice	(Ward et al., 2008; Clark et al., 1998)

repeated supraphysiological loading of cartilage explants could be suppressed by the administration of an antioxidant, *N*-acetylcysteine (NAC), and superoxide dismutase mimetics. Further, impacted osteochondral explants displayed increased chondrocyte viability when treated with cardiolipin, a mitochondrial-based apoptosis inhibitor. Finally, in a porcine pilon IAF model, treatment with the reversible mitochondrial complex I inhibitor amobarbital or oxidant scavenging with NAC significantly reduced PTOA at 6 and 12 months after injury (Coleman et al., 2018). Collectively, mitochondrial dysfunction plays a pathoetiologic role in chondrocyte death and dysfunction following a high energy impact (Table 1). In addition, translational level evidence has demonstrated that mitochondrial manipulation prevents IAF-induced PTOA.

2.2. *Cartilage-synovium-subchondral bone crosstalk after acute cartilage trauma*

Mitochondrial dysfunction and release of free oxygen radicals, resulting in chondrocyte cell death following acute trauma, also lead to elevated levels of the pro-inflammatory cytokine interleukin (IL)-6 in chondrocytes, which activates downstream mediators such as mitogen activated protein kinases (MAPK). Together with impact-mediated release of fibronectin fragments into the joint, this stimulates further chondrocyte death and matrix degradation in addition to initiating a cascade of inflammatory events in the joint capsule (Ayala et al., 2021; Coleman et al., 2018; D'Lima et al., 2001; Koike et al., 2015; Rieder et al., 2018; Wang et al., 2015; Wood et al., 2016; Wegner et al., 2019).

Inflammation of the synovium plays a role in the continued dysregulation of cartilage homeostasis and altered subchondral bone remodeling (Table 1). Analysis of human synovial tissue and fluid collected from patients with acute IAFs revealed increased synovial inflammation, as evidenced by the presence of $CD68^{+}$ macrophages in the synovial tissue and increased inflammatory biomarkers levels in the synovial fluid (Furman et al., 2015). Human osteochondral explants co-cultured with synovium after cartilage injury expressed inflammatory markers (IL-1, IL-6, IL-8, and tumor necrosis factor α (TNF-α)), and released glycosaminoglycan (GAG) and aggrecan fragments, compared to injured osteochondral plugs in monoculture (Dwivedi et al., 2022; Furman et al., 2014; Olson et al., 2015). Murine models of IAF showed acute (within 24 h of injury) expression of the chemokine C-X-C motif chemokine ligand 10 (CXCL10) in the synovial tissue and increased synovial inflammation in areas adjacent to the fracture and other joint compartments. Enhanced CXCL10 was also observed in human OA cartilage, implying that its prolonged expression in chondrocytes promotes chemotaxis of inflammatory macrophages into the synovium (Martini et al., 2005; Furman et al., 2018).

Synovial inflammation in PTOA is correlated with altered subchondral bone density, and IL-1β plays a role in both processes. Intra-articular treatment with an IL-1β receptor antagonist in conjunction with NADPH oxidase 4 (Nox4) at the time of IAF inhibited synovial inflammation and osteochondral damage, whereas its systemic treatment did not protect against PTOA (Wegner et al., 2019; Furman et al., 2014; Olson et al., 2015). Further, closed articular fractures performed in the "super healer" MRL/Mpj mice, that naturally produce extremely

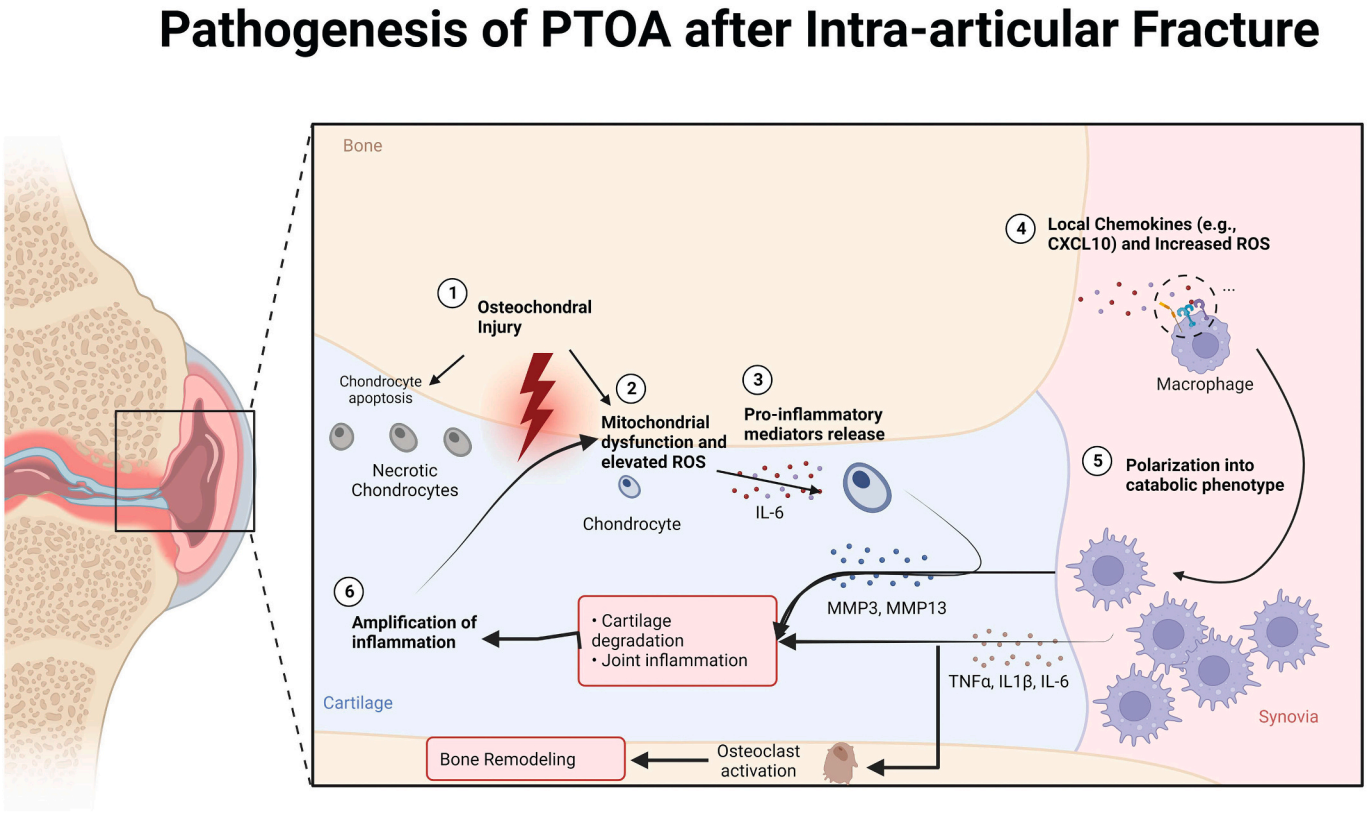

Fig. 1. Schematic review of cross talk between cartilage, bone, and synovial tissue in the pathogenesis of PTOA in the setting of acute chondral injury. Acute supraphysiological loading of cartilage resulting in osteochondral fracture results in chondrocyte necrosis at the direct area of impact, and mitochondrial dysregulation and chondrocyte apoptosis in adjacent chondrocytes. This results in the release of inflammatory mediators such as IL-6 which stimulates remaining chondrocytes to release MMPs. Direct injury also causes damage to the synovial tissue leading to polarization of resident macrophages that release TNFα, IL1β, and IL-6, and MMPs into the synovial fluid. This along with the MMPs released from chondrocytes leads to cartilage degradation. These inflammatory mediators also cross into the subchondral bone leading to osteoclastogenesis and activation resulting in bone remodeling, and release of MMPs into the synovial fluid leading to further cartilage catabolism. These activities promote recruitment of monocytes and polarization of macrophages in the synovium. These interplaying mechanisms lead to increased bone subchondral bone remodeling, synovial inflammation, and cartilage catabolism which are hallmarks of PTOA.

low levels of IL-1β and TNF-α, did not progress to PTOA even when the fractures were not reduced or internally fixed (Ward et al., 2008). Notably, MRL/Mpj mice did not display synovitis, their synovial fluid possessed lower levels of pro-inflammatory cytokines and higher levels of anti-inflammatory cytokines and their subchondral bone was unaltered. Thus, synovial inflammation plays a key role in subchondral bone pathology following IAF (Ward et al., 2008; Clark et al., 1998).

Taken together, these studies imply that the chondrocyte and synovial inflammatory responses that lead to subchondral bone alterations and PTOA following acute cartilage injury are at least impart incited by chondrocyte mitochondrial dysfunction, ROS release and apoptosis at the point of impact and vicinity (Fig. 1). Blocking these early cellular events in the chondrocytes is protective against PTOA as demonstrated in pre-clinical translational models of IAF. On the other hand, inhibiting synovial inflammation in the impacted joint could also restrict subchondral bone pathology and PTOA as a sequela of chondrocyte dysfunction, ROS release and death.

3. Pathogenesis of PTOA – chronic aberrant loading of cartilage

3.1. Chondrocyte dysregulation in chronic aberrant loading

Joint injuries including IAF, and major ligamentous injuries can result in chronic changes in the prevailing trans-articular stress environment in a joint. For example, an ACL-t can result in PTOA secondary to habitually elevated shear stresses which leads to chondrocyte apoptosis, cartilage degradation, synovial inflammation, and subchondral bone remodeling (Arunakul et al., 2013; Heard et al., 2011; Maerz et al., 2021; Mevel et al., 2022; White et al., 2022; Liu et al., 2016; Tochigi et al., 2011). Similarly, changes in knee stresses after meniscal damage leads to loss of chondrocytes as early as 3 days post-operatively, and a complete loss of chondrocytes and cartilage degradation at later time points in small animal models (David et al., 2017). Aberrant loading of the joint surface is associated with elevated levels of inflammatory markers such as IL-1β and IL-6 released by synoviocytes and chondrocytes into the joint microenvironment and their downstream mediators such as inducible nitric oxide synthase (iNOS) and NO (He et al., 2018; Abramson, 2008). This is coupled with decreased expression of markers of cartilage anabolism (type II collagen (COL2), aggrecan), and increased levels of markers of cartilage catabolism (ADAMTS-4, ADAMTS-5, MMP-13, MMP-3) in chondrocytes (Liu et al., 2016; Huang et al., 2020) (Table 2). Even after the restoration of joint biomechanics through surgical restoration of joint stability, such as ACL reconstruction, MMP-13 levels remain elevated for a prolonged period.

Meniscal damage, osteophyte formation and alterations in the subchondral bone also occur despite the restoration of joint mechanics (Narez et al., 2021). Patients who underwent ACL reconstruction developed subchondral thickening and sclerosis in the injured knee compared to their uninjured knees (Bhatla et al., 2018; Kroker et al., 2018). These changes in the subchondral bone were noted prior to any discernible changes in cartilage thickness (Bhatla et al., 2018). Other investigators have noted changes in loading and chondrocyte response to loads after ACL injury. Mice with bilateral ACL-t had increased loads across the tibiofemoral joint during gait, in contrast to mice with unilateral ACL-t had decreased loads across the injured limb during gait (Kotelsky et al., 2022). In both unilateral and bilateral ACL-t groups, chondrocytes in the early post-operative period were highly mechanosensitive demonstrating high levels of chondrocyte necrosis/apoptosis. However, at 8 weeks post-injury, only the chondrocytes isolated from the bilateral ACL-t groups had elevated apoptosis/necrosis to loading compared to controls (Kotelsky et al., 2022). In contrast to these reports, Li et al. (Li et al., 2022) investigated the role of regimented loading of the knee after ACL-t in a murine model and showed that mechanical loading was chondroprotective. Mechanical loading increased expression of the mechanoreceptor Piezo1 in ACL-t knees to control levels which aided in recruitment of stem cells to areas of damaged articular cartilage as well as promoted the expression of the chondrogenic differentiation marker SOX9 (Li et al., 2022). Aberrant mechanical loading following trauma also elicits changes in the synovium, as discussed below, by triggering inflammatory responses by synoviocytes and resulting in synovial tissue hyperplasia, immune cell infiltration and joint inflammation. Thus, changes in joint mechanical loading following injury or trauma detrimentally affects the subchondral bone, cartilage and synovium during PTOA pathogenesis.

Table 2
Pathogenic mechanisms associated with chronic aberrant loading-induced PTOA.

PTOA etiology	Pathogenesis Mechanisms	References
Joint instability	Chronic aberrant loading – cartilage:	
	- Altered joint biomechanics, expression of inflammatory mediators by chondrocytes leading to enhanced cartilage catabolism and diminished cartilage anabolism	(Arunakul et al., 2013; Heard et al., 2011; Maerz et al., 2021; Mevel et al., 2022; White et al., 2022; Liu et al., 2016; Tochigi et al., 2011; David et al., 2017; He et al., 2018; Abramson, 2008; Huang et al., 2020; Han et al., 2018)
	- Anti-inflammatory mechanisms: PLC-γ, CaMKK2, Nox4	(Wegner et al., 2019; Mevel et al., 2022; Takeuchi et al., 2021)
	- Therapeutics used in the clinic targeting inflammation	(Sherman et al., 2015; Bajpayee et al., 2017; Heard et al., 2015; Stefani et al., 2020; Takeuchi et al., 2021)
	Chronic aberrant loading – subchondral bone:	
	- Uncoupled bone remodeling in early PTOA and uncoupled bone formation in late PTOA – osteophytes and cysts	(Jiang et al., 2021; Bertuglia et al., 2016; Couchourel et al., 2009)
	- Enhanced release of TGF-β1from bone matrix by osteoclasts, recruitment of osteoblasts, neovascularization	(Hayami et al., 2004; Hayami et al., 2006; Zhang et al., 2019; Janssens et al., 2005; Zhen et al., 2013; Cui et al., 2016; Fermor et al., 2005; Kean et al., 2016; Wu et al., 2020)
	- PDGF-BB and Netrin release by osteoclasts leading to angiogenesis and sensory nerve innervation of subchondral bone and cartilage	(Su et al., 2020; Zhu et al., 2019)
	- Osteoclast secreted molecules and exosomes	(Larrouture et al., 2021; Lofvall et al., 2018; Cherifi et al., 2021; Liu et al., 2021)
	- Osteoblast-chondrocyte crosstalk in aberrant loading-induced PTOA	(Lavigne et al., 2005; Jiang et al., 2022; Sun et al., 2022; Sanchez et al., 2005a; Sanchez et al., 2005b; Prasadam et al., 2012; Lin et al., 2018; Wu et al., 2021; Wu et al., 2016; Zhang & Wen, 2021)
	- Therapeutic targeting of osteoclast activity	(Disease-modifying effects of a novel cathepsin k inhibitor in osteoarthritis, 2020; Lampropoulou-Adamidou et al., 2014; She et al., 2017; Ziemian et al., 2021; Fernandez-Martin et al., 2021; Fernandez-Martin et al., 2020; Xing et al., 2016)
	Chronic aberrant loading – synovium:	
	- Mechanisms mediating synovial macrophage activation - NLRP3/ Inflammasome, TRPV-1 and TRPV-4, alarmins, TLR4, CaMKK2	(Mevel et al., 2022; Blom et al., 2007; Ebata et al., 2021; Arya et al., 2021; Escolano et al., 2021; Lv et al., 2021; Maruyama et al., 2019; O'Conor et al., 2016; Wojdasiewicz et al., 2014; van den Bosch et al., 2016; Cremers et al., 2017; Schelbergen et al., 2012)
	- Mechanisms in inflamed synovial fibroblasts – IL-6, Resistin, IL-17, VCAM1.	

The emerging theme from preclinical and clinical studies is that inflammation is a hallmark of chronic aberrant loading-induced PTOA and may augment chondrocyte sensitivity to aberrant loading. The amount of loading experienced by inflammation-primed chondrocytes appears to influence the preservation or degradation of cartilage. Increased inflammation also correlates with enhanced catabolic and inflammatory marker expression by chondrocytes (Fig. 2) (Heard et al., 2011; Huang et al., 2020; Han et al., 2018). Corticosteroids, such as dexamethasone, have been shown to mitigate the inflammatory response to TNF-α and IL-6, while decreasing GAG loss in cartilage and increasing proteoglycan synthesis (Lu et al., 2011). Currently, dexamethasone is used in clinical management of OA to alleviate pain. However, most of the traditional injections in clinic leave the joint compartment and enter the systemic circulation within hours to days, limiting their ability to reliably target chondrocytes (Habib, 2009). In addition, the high doses delivered from clinical injections lead to reductions in chondrocyte and synoviocyte viability and metabolism (Sherman et al., 2015). Recent advances have been made with low dose delivery vehicles of dexamethasone to damaged cartilage in preclinical models of ACL-t (Bajpayee et al., 2017) and acute injury (Heard et al., 2015; Stefani et al., 2020). When dexamethasone was delivered at a low dose via micro-particles, decreased cartilage catabolism was noted in a canine model of PTOA, but no changes were observed in inflammatory mediators at 1 month compared to controls (Stefani et al., 2020). In a rabbit model of PTOA via ACL-t or a drilled defect, intra-articular injection of dexamethasone immediately after surgery reduced inflammatory mediators and MMP-3, and partially protected against PTOA (Bajpayee et al., 2017; Heard et al., 2015). However, prolonged treatment (up to 3 weeks) leads to systemic toxicity (Bajpayee et al., 2017), which may limit its clinical utility as a chronically administered agent to prevent OA. Glucocorticoids directly affect bone cells and their chronic use to treat PTOA will detrimentally affect the subchondral bone.

Colchicine is another common anti-inflammatory agent that is utilized in clinical practice to treat PTOA (Table 2). In murine DMM models, colchicine treatment decreased chondrocyte apoptosis and catabolic marker expression, and increased chondrocyte anabolic markers (Takeuchi et al., 2021). Colchicine was also shown to decrease MMP13 expression on human chondrocytes in vitro in response to IL-1β treatment (Takeuchi et al., 2021). Aberrant mechanical stress upregulates IL-1β and TNF-α signaling in chondrocytes, resulting in the phosphorylation of phospholipase C gamma (PLC-γ), which then interacts with tubulin and promotes Ca^{2+} release from the endoplasmic reticulum. Increase in intracellular Ca^{2+} promotes chondrocyte apoptosis and cartilage catabolism via MMP-13 upregulation while decreasing cartilage anabolism (Takeuchi et al., 2021), and these processes are blocked by colchicine.

As elevated Ca^{2+} is associated with chondrocyte apoptosis and cartilage catabolism, targeting Ca^{2+}-stimulated signaling pathways may prevent PTOA. One such protein involved in intracellular Ca^{2+} signaling is Ca^{2+}/calmodulin (CaM)-dependent protein kinase kinase 2 (CaMKK2), a serine/threonine protein kinase (Lu and Means, 1993; Dadwal et al., 2018). Mevel et al. (Mevel et al., 2022) recently reported CaMKK2 to be elevated in the articular cartilage of mice that underwent DMM and associated with elevated levels of inflammatory and catabolic

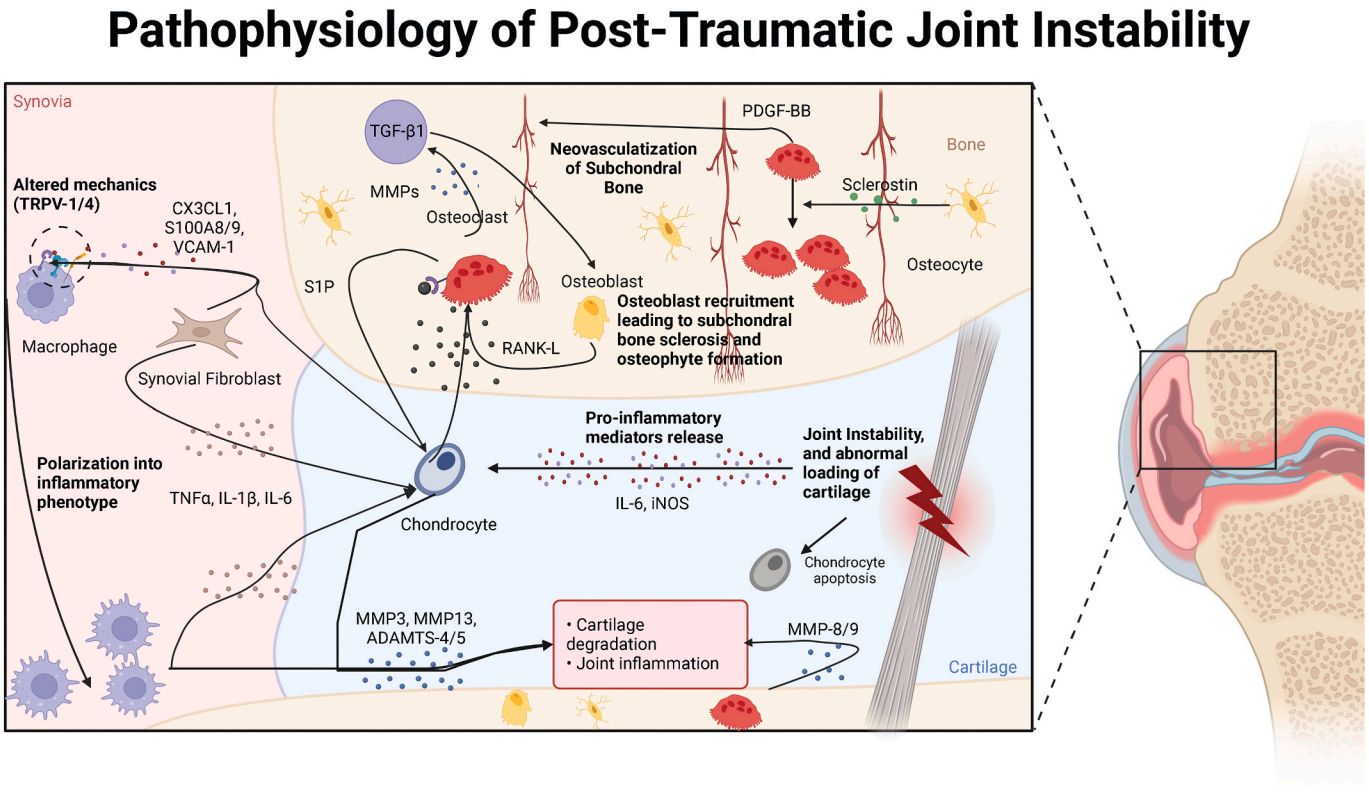

Fig. 2. Schematic review of cross talk between cartilage, bone, and synovial tissue in the pathogenesis of PTOA in the setting of chronic aberrant loading. Aberrant loading leads to increased shear stresses in the cartilage leads to the release of inflammatory mediators such as IL-6 and iNOS. Aberrant loading also leads to activation of mechanoreceptors in macrophages and fibroblasts in the synovial tissue leading to recruitment of monocytes to the synovium and polarization of macrophages in the synovium. Inflammatory mediators from macrophages, synovial fibroblasts and chondrocytes lead to production of MMPs from chondrocytes, macrophages and osteoclasts into the synovial fluid which results in cartilage catabolism. In addition, chondrocytes release RANKL which stimulates osteoclasts leading to an overall catabolic bone turnover. Osteoclasts also release PDGF-BB which recruits endothelial cells to the subchondral bone. This allows neovascularization of the subchondral plate. Further osteoclast activity leads to release of TGF-B1 from the osteoid matrix which stimulates osteoblastic bone formation. Osteoblasts enhance the activities of osteoclasts by secreting RANKL. These interplaying mechanisms lead to increased bone subchondral bone remodeling, synovial inflammation, and cartilage catabolism which are hallmarks of PTOA.

marker expression by chondrocytes. In contrast, the genetic ablation or pharmacological inhibition of CaMKK2 protected against pathologies associated with PTOA. Specifically, CaMKK2-deficient chondrocytes were protected against IL-1β induced activation of the IL-6-Stat3-MMP13 pathway that mediates inflammation and cartilage catabolism (Mevel et al., 2022; Liu-Bryan, 2015). These studies show that Ca^{2+} signaling downstream of IL-1β is an integral part of chondrocyte inflammatory and catabolic pathways in chronic aberrant loading-induced PTOA.

In addition to inflammation, there is evidence of mitochondrial dysfunction and ROS after alteration of normal joint forces. In a rabbit DMM model, mitochondrial respiration was decreased in the load bearing medial femoral condyle and tibial plateau, and there was evidence of increased proton leakage at 4 weeks after surgery that preceded histological changes indicative of PTOA in the affected joint compartment (Goetz et al., 2017). Nox4, a member of a family of enzymes that generate ROS, is associated with elevated H_2O_2 production and PTOA phenotype in a mouse model of tibial compression-induced acute ACL-t. Genetically ablating or pharmacologically inhibiting Nox4 was protective against early joint changes in this model (Wegner et al., 2019). These studies suggest that mitochondrial dysregulation and ROS may contribute to PTOA in the setting of chronic joint instability either through secondary signaling or acute cellular injury like IAF (Fig. 2). These mechanisms and inflammatory signaling in chondrocytes could be therapeutically targeted to mitigate PTOA.

3.2. Subchondral bone-cartilage crosstalk in chronic aberrant loading

Subchondral bone is integral to the development of PTOA in joints subjected to aberrant joint loading. Cartilage catabolism and degradation alter stress transfer into the adjacent subchondral bone leading to changes in its structure. In PTOA, there is evidence of subchondral bone remodeling preceding changes in hyaline cartilage (Bhatla et al., 2018; Kroker et al., 2018; Fang et al., 2018; Hayami et al., 2004; Hayami et al., 2006; Intema et al., 2010; Lavigne et al., 2005; Sulaiman et al., 2021). In early PTOA, with abnormal loading, microfractures occur in the subchondral bone resulting in the uncoupling of bone remodeling leading to increased osteoclast-mediated bone resorption, which renders the subchondral bone plate porous and thinner (Jiang et al., 2021; Bertuglia et al., 2016). This increased porosity enables increased penetration of subchondral bone and calcified cartilage by blood vessels and sensory nerves. Later stages of OA are characterized by increased osteoblast-mediated uncoupled bone formation leading to thicker subchondral bone plate and bone sclerosis (Jiang et al., 2021). The matrix secreted by OA osteoblasts possess an abnormal α1 to α2 type I collagen (COL1) ratio that impairs mineral deposition, which contributes to bone cysts and osteophytes (Couchourel et al., 2009). Targeting the early abnormal subchondral bone remodeling is actively being pursued as a therapeutic option to ultimately protect against residual changes in loading ultimately leading to PTOA (Table 2 and Fig. 2).

Transforming growth factor β1 (TGF-β1), a cytokine with roles in bone and cartilage homeostasis, is secreted and deposited into the bone matrix in a latent form by osteoblasts (Zhang et al., 2019). It is activated and released by acids and MMPs secreted by osteoclasts during bone resorption, whereupon it promotes osteoprogenitor proliferation and differentiation (Zhang et al., 2019; Janssens et al., 2005). Increased subchondral bone remodeling by osteoclasts in early PTOA releases increased levels of TGF-β1, which in turn recruits osteoblasts that promote bone formation and sclerosis. Elevated TGF-β1 is found in the subchondral bone of human OA patients and in rodent models of PTOA (Zhen et al., 2013). Targeted deletion of TGF-β1 in Nestin-positive mesenchymal stem cells attenuated whereas its activation promoted ACL-t-induced PTOA in mice (Zhen et al., 2013). Intraarticular injection of halofuginone, a TGF-β1 inhibitor, attenuated subchondral bone disease and PTOA in mice and rats that underwent ACL-t (Cui et al., 2016). Whereas localized inhibition of TGF-β1 in the subchondral bone protects against PTOA, its systemically targeting is not beneficial as the cytokine plays a crucial role in normal cartilage homeostasis. Moreover, being a potent anti-inflammatory agent, its systemic inhibition triggers massive inflammation (van der Kraan, 2018).

TGF-β1 also promotes angiogenesis in the subchondral bone during early OA (Table 2). Osteoprogenitors recruited by TGF-β1 promote neovascularization by type H blood vessels that further impair bone remodeling and alter bone mineral deposition by osteoblasts, resulting in the formation of bone cysts and osteophytes. Additionally, this increased angiogenesis of the subchondral bone leads to the blood vessels breaching the tidemark, as often observed in animal PTOA models and human OA samples. Neovascularization of the normally avascular articular cartilage alters the oxygen tension of nearby chondrocytes, causing a decrease in cartilage proliferation, while promoting their hypertrophy and enhancing their expression of inflammatory markers. This leads to decreases in COL2 and proteoglycan production and increased cartilage catabolism (Hayami et al., 2004; Hayami et al., 2006; Fermor et al., 2005; Kean et al., 2016; Wu et al., 2020). Neovascularization by H-type vessel formation has been shown to be mediated by focal adhesion kinase (FAK). Treatment with a FAK inhibitor in the subchondral bone of rats undergoing ACL-t attenuated subchondral bone remodeling, MMP-13 expression, and cartilage degradation (Wu et al., 2020).

Other studies have explored the molecular mechanisms underlying enhanced subchondral bone vascularization in early PTOA and found osteoclasts to play a major role. Mononuclear osteoclasts secrete enhanced levels of platelet-derived growth factor -BB (PDGF-BB) that activate PDGF-receptor β in pericytes to promote subchondral bone angiogenesis during initial stages of DMM-induced PTOA, and this neovascularization is visible even before cartilage degradation is apparent (Su et al., 2020). Targeted deletion of PDGF-BB in pre-osteoclasts attenuated subchondral bone angiogenesis and joint degradation in this model of PTOA (Su et al., 2020).

Along with angiogenesis, perivascular calcitonin gene-related peptide (CGRP) expressing sensory and sympathetic nerve fibers increasingly innervate the OA subchondral bone, often reaching the cartilage and causing pain in OA (Table 2). Magnetic resonance imaging studies indicate correlation between the number of subchondral bone marrow lesions and OA pain severity (O'Neill and Felson, 2018). Osteoclasts play a prominent role in the sensory nerve innervation of the subchondral bone in ACL-t-induced PTOA by secreting Netrin-1, an axon guidance molecule that promotes subchondral bone innervation. The conditional deletion of Netrin-1 or its receptor DCC (deleted in colorectal cancer) in osteoclasts attenuated sensory innervation of the subchondral bone and PTOA pain (Zhu et al., 2019). Moreover, inhibition of osteoclasts using the bisphosphonate alendronate or by conditionally deleting receptor activator of nuclear factor κ-B (NFκ-B) ligand (RANKL) in osteocytes attenuated these pathologies (Zhu et al., 2019).

Prostaglandin E2 (PGE2), produced by the cyclooxygenase 2 (COX-2) gene and secreted by osteoblasts, inflamed chondrocytes, and macrophages, is highly elevated in the OA subchondral bone (Mevel et al., 2022). Recent work by Jiang et al. (Jiang et al., 2022) shows that osteoblast-derived PGE2 acts via E prostanoid 4 (EP4) receptors in osteoclasts to promote PDGF-BB and Netrin-1 secretion by osteoclasts, type H blood vessel sprouting, and CGRP-positive sensory innervation of the subchondral bone, leading to pain hyper-sensitization and PTOA development in mice that underwent ACL-t. Oral administration of EP4 antagonist HL-43 attenuated subchondral bone angiogenesis and sensory innervation leading to reduced pain in this model (Jiang et al., 2022). Sun et al. (Sun et al., 2022) recently reported that whereas PGE2 is elevated in the OA subchondral bone, the conditional deletion of sensory nerve-specific EP4 attenuated subchondral bone sclerosis, innervation and PTOA in mice. These findings are especially significant as COX-2 inhibitors such as NSAIDs are routinely used in the clinic to alleviate PTOA pain but cause severe side-effects with long-term use in patients.

Many osteoclast-secreted molecules influence cartilage homeostasis. Osteoclasts release MMP-8 and MMP-9 when they are in contact with articular cartilage causing cartilage degradation in PTOA (Larrouture et al., 2021; Lofvall et al., 2018). They also secrete sphingosine 1-phosphate (S1P), a ceramide metabolite that increased MMP3 and MMP13 expression in chondrocytes (Cherifi et al., 2021). Conditional deletion of S1P in myeloid cells or intraarticular injection of the S1P neutralizing antibody sphingomab suppressed MMP13 expression by chondrocytes and attenuated cartilage catabolism and PTOA progression (Cherifi et al., 2021). Liu et al. (Liu et al., 2021) reported increased circulation of osteoclast-derived exosomes containing miRNAs in initial stages of ACL-t-induced PTOA in mice. Exosomal transfer of these osteoclast-derived miRNAs to chondrocytes suppressed their expression of tissue inhibitor of metalloproteases (TIMP-2 and TIMP3), which inhibit cartilage degradation. Conversely, conditional deletion of the key miRNA processing enzyme Dicer in osteoclasts, blocking exosome secretion by silencing ras-related protein 27a (Rab27a), or systemic administration of an osteoclast-targeted exosome inhibitor termed OCExoInhib attenuated PTOA progression in mouse models of surgically induced OA, revealing a novel therapeutic approach of targeting osteoclast-mediated exosomal transfer of TIMP-suppressing miRNAs (Liu et al., 2021). More recently, Zhao et al. (Zhao et al., 2022) reported that osteoclast-derived leukemia inhibitory factor (LIF) contributes to abnormal bone remodeling in early ACL-t-induced PTOA in mice.

Osteoblasts also have been shown to alter chondrocyte protein expression in models of PTOA. Increased levels of IL-6, NO, and MMPs are found in PTOA subchondral bone tissue (Lavigne et al., 2005). Chondrocytes co-cultured with osteoblasts from subchondral bone in PTOA display decreased SOX9 and anabolic protein expression. Subchondral bone osteoblasts increase expression of cartilage catabolic proteins via ERK1/2 and PI3K/AKT signaling pathways (Sanchez et al., 2005a; Sanchez et al., 2005b; Prasadam et al., 2012; Lin et al., 2018) Crosstalk may also be occurring via exosomes carrying miRNA from subchondral bone osteoblasts eliciting a decrease in cartilage anabolism and an increase in cartilage catabolism (Wu et al., 2021). Additionally, enhanced levels of sclerostin secreted by osteocytes in early-stage OA supports osteoclastogenesis that promote excessive subchondral bone remodeling, angiogenesis and innervation leading to cartilage degradation and PTOA pain (Wu et al., 2016; Zhang and Wen, 2021).

As mentioned earlier, cartilage degradation in early PTOA alters stress transfer into the subchondral bone, triggering rapid osteoclast activity, neovascularization, and innervation of the bone hastening disease progression. Therapeutically targeting subchondral bone osteoclasts could be beneficial for halting PTOA and the amelioration of associated joint pain. A randomized, double-blind, placebo-controlled phase 2a human clinical trial using the cathepsin K inhibitor MIV-711 showed significantly reduced OA subchondral bone and cartilage pathologies in patients, although it was not effective against pain more than placebo (Disease-modifying effects of a novel cathepsin k inhibitor in osteoarthritis, 2020). Hayami et al. (Hayami et al., 2004) found that treatment with the bisphosphonate alendronate in an ACL-t model reduced subchondral bone remodeling, osteoclast recruitment, and neovascularization in a murine model. Similarly, zoledronic acid treatment also decreased proteoglycan, cartilage degradation, and subchondral bone remodeling in a rabbit model with short duration of treatment (Lampropoulou-Adamidou et al., 2014; She et al., 2017). Ziemian et al. (Ziemian et al., 2021) demonstrated that the timing of bisphosphonate therapy influenced the ability to mitigate the progression of PTOA in a murine model. They found that treatment immediately after surgery with bisphosphonate therapy mitigated subchondral bone remodeling, osteophyte formation, and cartilage degradation, whereas delaying treatment for 2 weeks led to minimal protection against PTOA (Ziemian et al., 2021).

In contrast to these findings, long term systemic treatment of rabbits with bisphosphonates did not protect against subchondral bone remodeling or PTOA severity (Fernandez-Martin et al., 2021; Fernandez-Martin et al., 2020). This indicated that bisphosphonate therapy may be better utilized as a pre-emptive or early therapy against developing PTOA rather than mitigating further progression of established PTOA. A meta-analysis of randomized controlled human clinical trials indicates that bisphosphonate therapy may be effective in relieving pain and stiffness associated with OA, thus accelerating functional recovery from the disease, but not in preventing OA progression (Xing et al., 2016). Emerging evidence from mechanistic investigations in preclinical models indicate that the timing and duration bisphosphonate treatment will be critical for the alleviation of OA-associated pain and attenuating disease progression. Still, more research is needed to fully understand how the crosstalk between bone cells and chondrocytes influences PTOA.

3.3. Synovium-cartilage crosstalk in chronic aberrant loading

In addition to osteochondral alterations, substantial changes occur in the synovium during PTOA associated with chronic instability (Fig. 2). Macrophages and fibroblasts are the two major cell types in the synovium. Macrophages lining the synovial membrane serve an integral role in joint homeostasis by phagocytosing and clearing ECM components and other joint debris produced during normal activity, through their expression of scavenger receptors such as CD163 and Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) (Ambarus et al., 2012; Kurowska-Stolarska and Alivernini, 2017). Synovial fibroblasts, the main stromal cells of the joint, play a major role in joint lubrication by synthesizing components of the synovial fluid such as the glycosaminoglycan hyaluronic acid and the mucous glycoprotein lubricin or proteoglycan-4. They also play important roles in maintaining synovial macrophage homeostasis and cartilage integrity during normal joint loading (Lefevre et al., 2015). However, PTOA is associated with increased inflammatory macrophage infiltration of the synovial tissue, tissue hyperplasia and inflammation (Mevel et al., 2022; Takeuchi et al., 2021; Chang et al., 2021; Lin et al., 2021; Rzeczycki et al., 2021; Thomas et al., 2017; Gilbert et al., 2018; Liao et al., 2020). Mechanisms underlying synovial pathology in PTOA are extensively reviewed elsewhere (Lieberthal et al., 2015; Evers et al., 2022; Khella et al., 2021), and will only be briefly discussed here.

Cartilage ECM components such as aggrecan released in increased numbers after chronic or acute trauma to the cartilaginous surface polarize synovial macrophages via NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3)/inflammasome mechanism (Blom et al., 2007; Ebata et al., 2021). Macrophages respond to aberrant mechanical loading stimuli through transient receptor potential vanilloid type receptors (TRPV) 1 and 4, which stimulate their polarization through the NLRP3/inflammasome mechanism (Arya et al., 2021; Escolano et al., 2021; Lv et al., 2021; Maruyama et al., 2019). Modulation of TRPV-1 and TRPV-4 receptor activity attenuated OA severity in a murine model (O'Conor et al., 2016). Activated macrophages produce IL-1β, which stimulates chondrocytes to express CX3CL1 to further attract peripheral monocytes with a pro-inflammatory phenotype to the synovium (Wojdasiewicz et al., 2014). In addition, alarmins S1008 and S100A9 released from the damaged cartilage enable the mobilization of pro-inflammatory monocytes to the synovium via CCL2 signaling (van den Bosch et al., 2016; Cremers et al., 2017). S100A8 and S100A9 exert an autocrine effect on chondrocytes to enable enhanced expression of catabolic markers and diminished expression of anabolic markers via toll-like receptor 4 (TLR4) signaling (Schelbergen et al., 2012). Activated macrophages also produce MMPs and Flightless-1 (Fli-1), which promote chondrocyte hypertrophy and cartilage degradation while decreasing cartilage anabolism via the Fli-1-TLR4-ERK1/2 pathway in chondrocytes (Blom et al., 2007; Ebata et al., 2021). CaMK family members including CaMKK2 play key roles in the regulation of macrophage responsiveness to TLR4 signaling (Racioppi et al., 2012). Indeed, CaMKK2 expression is elevated in inflamed synovial macrophages whereas its pharmacological inhibition or genetic ablation mitigated

synovial inflammation and hyperplasia in a murine DMM-PTOA model (Mevel et al., 2022).

Synovial fibroblasts become activated in OA and play a major role in joint inflammation and cartilage degradation through the release of proinflammatory factors such as IL-6 (Ramirez-Perez et al., 2022; Pearson et al., 2017; Yang et al., 2017). In addition, CX3CL-1 released from inflamed chondrocytes stimulates MMP production in synovial fibroblasts via NFκ-B and Wnt pathways (Hou et al., 2017; Lietman et al., 2018). Synovial fibroblasts express adhesion molecules such as vascular cell adhesion molecule type 1 (VCAM-1), which become elevated in PTOA via Resistin and IL-17 mediated pathways (Kalichman et al., 2011; Liu et al., 2013; Wu et al., 2022). Knockdown of Resistin attenuated PTOA in a murine ACL-t model through reductions in VCAM-1 positive fibroblasts and $CD68^{+}$ monocytes in the synovium (Chen et al., 2020). Additionally, activated fibroblast-like synoviocytes contribute to synovial fibrosis in OA, as reviewed elsewhere (Zhang et al., 2021; Maglaviceanu et al., 2021).

In summary, PTOA severity is mediated, in part, by the polarization of resident macrophages to a pro-inflammatory state, recruitment of pro-inflammatory monocytes to the synovial tissue, and production of inflammatory markers and MMPs from polarized macrophages and synovial fibroblasts leading to cartilage catabolism (Table 2 and Fig. 2).

4. Clinical therapeutic trials addressing PTOA

Several therapeutic targets for OA and PTOA identified in preclinical studies have made their way to clinical trials. An IL-1 receptor antagonist was trialed in the treatment of symptomatic OA of the knee but did not alleviate pain versus placebo (Cohen et al., 2011). There are several ongoing trials investigating novel therapeutics to prevent or mitigate PTOA. One double-blind randomized controlled trial that has begun recruiting is assessing the efficacy of intra-articular administration of amobarbital to prevent PTOA in patients that sustained a tibial pilon fracture based on success in a translational model (NCT04589611) (Coleman et al., 2018). Another trial investigating the efficacy of intra-articular dexamethasone to prevent PTOA after distal radius fracture has been completed as of 2020, but no results from the trial are available to date (NCT02318433). PTOA may develop even after restoration of joint mechanics and stability secondary to a pro-inflammatory state (Heard et al., 2011). As such, the therapeutic potential of the cysteinyl leukotrienes inhibitor, montelukast, to prevent PTOA after ACL reconstruction is being investigated in clinical trials (NCT04572256). Another study is current recruiting and evaluating the effects of the anti-fibrinolytic agent, tranexamic acid (TXA). TXA binds to plasminogen and prevents the formation of plasmin. There is a current human trial evaluating if treatment with TXA reduces intra-articular hemorrhage, inflammation, neovascularization and PTOA development after ACL injury (NCT03552705).

5. Conclusion and future directions

PTOA is a multifactorial disease that occurs after an acute impact injury to the cartilage or due to adverse changes in chronic loads resulting from incongruity, instability and malalignment. Treatment options have been remarkably stagnant over decades and have essentially entirely focused on surgical restoration of joint congruity and stability. Collectively, surgical options have clearly reached an efficacy limit as rates of PTOA remain high regardless of improvements in surgical methods. Accordingly, investigators are aggressively pursuing interventions directed at treating the acute mechanical damage to the cartilage. Evidence over the past 2 decades has shown that the pathophysiology of acute injury to the chondral surface is partially mediated by mitochondrial dysfunction in response to elevated oxygen tension and ROS generation, leading to chondrocyte apoptosis and cartilage catabolism and associated progression of inflammation (Fig. 1). Recent mitoprotective interventions have shown promise in preventing PTOA in the preclinical setting, and amobarbital is under clinical investigation as a therapeutic agent to prevent PTOA. Pathophysiologic events secondary to adverse chronic changes in joint loading leading to PTOA have become better defined opening other therapeutic opportunities to prevent PTOA after chronic aberrant loading. There is substantial crosstalk between the tissues involved in PTOA (Fig. 2). Osteoblasts and osteoclasts contribute to elevated cartilage catabolism and decreased anabolism via signaling to chondrocytes in PTOA. Bisphosphonate therapies have shown promise in alleviating bone disease and OA pain in preclinical models and in the clinic. Activated synovial macrophages release inflammatory factors such as IL-6 that further exacerbate cartilage catabolism and suppress anabolism. Several clinical studies are underway investigating anti-inflammatory agents in preventing PTOA.

Much future research remains be done investigating the role of different joint tissues in the pathogenesis of PTOA and determining which one or combination of tissues, resident cells and mechanisms would be the optimal targets to prevent PTOA. Although there are similarities in the pathogenesis of PTOA resulting from acute intra-articular injury and chronic aberrant loading, the contribution of mitochondrial and inflammatory mediators appears to differ between the two etiologies. Thus, IAF results in an acute initial effect of chondrocyte apoptosis and/or necrosis at the point of impact, which triggers mitochondrial dysfunction and ROS generation, leading to further chondrocyte apoptosis and cartilage catabolism. In addition, chondrocyte apoptosis may diminish anabolic function to support regional matrix production and turnover. This then stimulates inflammation in chondrocytes and synovium, eventually also affecting subchondral bone remodeling (Fig. 1). On the other hand, PTOA originating from chronic aberrant loading of the joint following an injury such as ACL-t or PCL-t occurs primarily via an inflammatory route that leads to global joint alteration affecting subchondral bone, synovium and cartilage (Fig. 2). These differences could help identify unique targets for treatment of both PTOA etiologies.

Funding

This work was supported by DoD Peer Reviewed Medical Research Program – Investigator-Initiated Research Award W81XWH-20-1-0304 from the U.S. ARMY MEDICAL RESEARCH ACQUISITION ACTIVITY, a Comprehensive Musculoskeletal T32 Training Program from the NIH (AR065971), the Indiana Clinical and Translational Sciences Institute which is funded in part by National Institutes of Health, National Center for Advancing Translational Sciences, Clinical and Translational Sciences Award (Award Number UL1TR002529), and the National Institutes of Health – NIAMS R01AR076477.

CRediT authorship contribution statement

Julian Emerson Dilley: Conceptualization, Methodology, Investigation, Writing- Original draft preparation, and Writing - Reviewing and Editing. **Margaret Anne Bello:** Writing - Original draft preparation, Writing - Reviewing and Editing, and Investigation. **Todd McKinley:** Writing- Reviewing and Editing. **Natoli Roman:** Writing- Reviewing and Editing. **Uma Sankar:** Conceptualization, Writing- Reviewing and Editing, Supervision, and Project administration.

Declaration of competing interest

Julian Emerson Dilley, Margaret Anne Bello and Uma Sankar have no financial disclosures or conflicts of interest in relation to this study. Roman Natoli receives consultation fees from Quince. Todd McKinley receives royalties from Innomed.

Data availability

The data that has been used is confidential.

References

Abramson, S.B., 2008. Nitric oxide in inflammation and pain associated with osteoarthritis. Arthritis Res. Ther. 10 (Suppl. 2), S2.

Ambarus, C.A., Noordenbos, T., de Hair, M.J., Tak, P.P., Baeten, D.L., 2012. Intimal lining layer macrophages but not synovial sublining macrophages display an IL-10 polarized-like phenotype in chronic synovitis. Arthritis Res. Ther. 14 (2), R74.

Anderson, D.D., Van Hofwegen, C., Marsh, J.L., Brown, T.D., 2011. Is elevated contact stress predictive of post-traumatic osteoarthritis for imprecisely reduced tibial plafond fractures? J. Orthop. Res. 29 (1), 33–39.

Anderson, D.D., Chubinskaya, S., Guilak, F., et al., 2011. Post-traumatic osteoarthritis: improved understanding and opportunities for early intervention. J. Orthop. Res. 29 (6), 802–809.

Anderson, D.D., Kilburg, A.T., Thomas, T.P., Marsh, J.L., 2016. Expedited CT-based methods for evaluating fracture severity to assess risk of post-traumatic osteoarthritis after articular fractures. Iowa Orthop J. 36, 46–52.

Arunakul, M., Tochigi, Y., Goetz, J.E., et al., 2013. Replication of chronic abnormal cartilage loading by medial meniscus destabilization for modeling osteoarthritis in the rabbit knee in vivo. J. Orthop. Res. 31 (10), 1555–1560.

Arya, R.K., Goswami, R., Rahaman, S.O., 2021. Mechanotransduction via a TRPV4-Rac1 signaling axis plays a role in multinucleated giant cell formation. J. Biol. Chem. 296, 100129.

Ayala, S., Delco, M.L., Fortier, L.A., Cohen, I., Bonassar, L.J., 2021. Cartilage articulation exacerbates chondrocyte damage and death after impact injury. J. Orthop. Res. 39 (10), 2130–2140.

Bajaj, S., Shoemaker, T., Hakimiyan, A.A., et al., 2010. Protective effect of P188 in the model of acute trauma to human ankle cartilage: the mechanism of action. J. Orthop. Trauma 24 (9), 571–576.

Bajpayee, A.G., De la Vega, R.E., Scheu, M., et al., 2017. Sustained intra-cartilage delivery of low dose dexamethasone using a cationic carrier for treatment of post traumatic osteoarthritis. Eur. Cell Mater. 34, 341–364.

Beardsley, C.L., Bertsch, C.R., Marsh, J.L., Brown, T.D., 2002. Interfragmentary surface area as an index of comminution energy: proof of concept in a bone fracture surrogate. J. Biomech. 35 (3), 331–338.

Beardsley, C.L., Anderson, D.D., Marsh, J.L., Brown, T.D., 2005. Interfragmentary surface area as an index of comminution severity in cortical bone impact. J. Orthop. Res. 23 (3), 686–690.

Bertuglia, A., Lacourt, M., Girard, C., Beauchamp, G., Richard, H., Laverty, S., 2016. Osteoclasts are recruited to the subchondral bone in naturally occurring post-traumatic equine carpal osteoarthritis and may contribute to cartilage degradation. Osteoarthr. Cartil. 24 (3), 555–566.

Bhatla, J.L., Kroker, A., Manske, S.L., Emery, C.A., Boyd, S.K., 2018. Differences in subchondral bone plate and cartilage thickness between women with anterior cruciate ligament reconstructions and uninjured controls. Osteoarthr. Cartil. 26 (7), 929–939.

Blom, A.B., van Lent, P.L., Libregts, S., et al., 2007. Crucial role of macrophages in matrix metalloproteinase-mediated cartilage destruction during experimental osteoarthritis: involvement of matrix metalloproteinase 3. Arthritis Rheum. 56 (1), 147–157.

Bodkin, S.G., Werner, B.C., Slater, L.V., Hart, J.M., 2020. Post-traumatic osteoarthritis diagnosed within 5 years following ACL reconstruction. Knee Surg. Sports Traumatol. Arthrosc. 28 (3), 790–796.

Brown, T.D., Johnston, R.C., Saltzman, C.L., Marsh, J.L., Buckwalter, J.A., 2006. Posttraumatic osteoarthritis: a first estimate of incidence, prevalence, and burden of disease. J. Orthop. Trauma 20 (10), 739–744.

Canadian Orthopaedic Trauma, S., 2006. Open reduction and internal fixation compared with circular fixator application for bicondylar tibial plateau fractures. Results of a multicenter, prospective, randomized clinical trial. J. Bone Joint Surg. Am. 88 (12), 2613–2623.

Carbonell-Escobar, R., Rubio-Suarez, J.C., Ibarzabal-Gil, A., Rodriguez-Merchan, E.C., 2017. Analysis of the variables affecting outcome in fractures of the tibial pilon treated by open reduction and internal fixation. J. Clin. Orthop. Trauma 8 (4), 332–338.

Chang, L., Liu, A., Xu, J., et al., 2021. TDP-43 maintains chondrocyte homeostasis and alleviates cartilage degradation in osteoarthritis. Osteoarthr. Cartil. 29 (7), 1036–1047.

Chen, D., Shen, J., Zhao, W., et al., 2017. Osteoarthritis: toward a comprehensive understanding of pathological mechanism. Bone Res. 5, 16044.

Chen, W.C., Lin, C.Y., Kuo, S.J., et al., 2020. Resistin enhances VCAM-1 expression and monocyte adhesion in human osteoarthritis synovial fibroblasts by inhibiting MiR-381 expression through the PKC, p38, and JNK signaling pathways. Cells 9 (6).

Cherifi, C., Latourte, A., Vettorazzi, S., et al., 2021. Inhibition of sphingosine 1-phosphate protects mice against chondrocyte catabolism and osteoarthritis. Osteoarthr. Cartil. 29 (9), 1335–1345.

Clark, L.D., Clark, R.K., Heber-Katz, E., 1998. A new murine model for mammalian wound repair and regeneration. Clin. Immunol. Immunopathol. 88 (1), 35–45.

Cohen, S.B., Proudman, S., Kivitz, A.J., et al., 2011. A randomized, double-blind study of AMG 108 (a fully human monoclonal antibody to IL-1R1) in patients with osteoarthritis of the knee. Arthritis Res. Ther. 13 (4), R125.

Coleman, M.C., Ramakrishnan, P.S., Brouillette, M.J., Martin, J.A., 2016. Injurious loading of articular cartilage compromises chondrocyte respiratory function. Arthritis Rheumatol. 68 (3), 662–671.

Coleman, M.C., Brouillette, M.J., Andresen, N.S., Oberley-Deegan, R.E., Martin, J.M., 2017. Differential effects of superoxide dismutase mimetics after mechanical overload of articular cartilage. Antioxidants (Basel) 6 (4).

Coleman, M.C., Goetz, J.E., Brouillette, M.J., et al., 2018. Targeting mitochondrial responses to intra-articular fracture to prevent posttraumatic osteoarthritis. Sci. Transl. Med. 10 (427).

Couchourel, D., Aubry, I., Delalandre, A., et al., 2009. Altered mineralization of human osteoarthritic osteoblasts is attributable to abnormal type I collagen production. Arthritis Rheum. 60 (5), 1438–1450.

Cremers, N.A.J., van den Bosch, M.H.J., van Dalen, S., et al., 2017. S100A8/A9 increases the mobilization of pro-inflammatory Ly6C(high) monocytes to the synovium during experimental osteoarthritis. Arthritis Res. Ther. 19 (1), 217.

Cross, M., Smith, E., Hoy, D., et al., 2014. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann. Rheum. Dis. 73 (7), 1323–1330.

Cui, Z., Crane, J., Xie, H., et al., 2016. Halofuginone attenuates osteoarthritis by inhibition of TGF-β activity and H-type vessel formation in subchondral bone. Ann. Rheum. Dis. 75 (9), 1714–1721.

Dadwal, U.C., Chang, E.S., Sankar, U., 2018. Androgen receptor-CaMKK2 Axis in prostate cancer and bone microenvironment. Front. Endocrinol. (Lausanne) 9, 335.

David, M.A., Smith, M.K., Pilachowski, R.N., White, A.T., Locke, R.C., Price, C., 2017. Early, focal changes in cartilage cellularity and structure following surgically induced meniscal destabilization in the mouse. J. Orthop. Res. 35 (3), 537–547.

Day, M.A., Ho, M., Dibbern, K., et al., 2020. Correlation of 3D joint space width from weightbearing CT with outcomes after intra-articular calcaneal fracture. Foot Ankle Int. 41 (9), 1106–1116.

Disease-modifying effects of a novel cathepsin K inhibitor in osteoarthritis. Annals of Internal Medicine 172 (2), 2020, 86–95.

D'Lima, D.D., Hashimoto, S., Chen, P.C., Colwell Jr., C.W., Lotz, M.K., 2001. Human chondrocyte apoptosis in response to mechanical injury. Osteoarthr. Cartil. 9 (8), 712–719.

Doornberg, J.N., van Duijn, P.J., Linzel, D., et al., 2007. Surgical treatment of intra-articular fractures of the distal part of the humerus. Functional outcome after twelve to thirty years. J. Bone Joint Surg. Am. 89 (7), 1524–1532.

Dwivedi, G., Flaman, L., Alaybeyoglu, B., et al., 2022. Inflammatory cytokines and mechanical injury induce post-traumatic osteoarthritis-like changes in a human cartilage-bone-synovium microphysiological system. Arthritis Res. Ther. 24 (1), 198.

Ebata, T., Terkawi, M.A., Hamasaki, M., et al., 2021. Flightless I is a catabolic factor of chondrocytes that promotes hypertrophy and cartilage degeneration in osteoarthritis. iScience 24 (6), 102643.

Escolano, J.C., Taubenberger, A.V., Abuhattum, S., et al., 2021. Compliant substrates enhance macrophage cytokine release and NLRP3 inflammasome formation during their pro-inflammatory response. Front. Cell Dev. Biol. 9, 639815.

Everhart, J.S., Jones, M.H., Yalcin, S., et al., 2021. The clinical radiographic incidence of posttraumatic osteoarthritis 10 years after anterior cruciate ligament reconstruction: data from the MOON nested cohort. Am. J. Sports Med. 49 (5), 1251–1261.

Evers, B.J., Van Den Bosch, M.H.J., Blom, A.B., van der Kraan, P.M., Koëter, S., Thurlings, R.M., 2022. Post-traumatic knee osteoarthritis; the role of inflammation and hemarthrosis on disease progression. Front. Med. (Lausanne) 9, 973870.

Fang, H., Huang, L., Welch, I., et al., 2018. Early changes of articular cartilage and subchondral bone in the DMM mouse model of osteoarthritis. Sci. Rep. 8 (1), 2855.

Fermor, B., Weinberg, J.B., Pisetsky, D.S., Guilak, F., 2005. The influence of oxygen tension on the induction of nitric oxide and prostaglandin E2 by mechanical stress in articular cartilage. Osteoarthr. Cartil. 13 (10), 935–941.

Fernandez-Martin, S., Permuy, M., Lopez-Pena, M., Munoz, F., Gonzalez-Cantalapiedra, A., 2020. No effect of long-term risedronate use on cartilage and subchondral bone in an experimental rabbit model of osteoarthritis. Front. Vet. Sci. 7, 576212.

Fernandez-Martin, S., Gonzalez-Cantalapiedra, A., Permuy, M., Garcia-Gonzalez, M., Lopez-Pena, M., Munoz, F., 2021. Histomorphometric quantitative evaluation of long-term risedronate use in a knee osteoarthritis rabbit model. Front. Vet. Sci. 8, 669815.

Furman, B.D., Mangiapani, D.S., Zeitler, E., et al., 2014. Targeting pro-inflammatory cytokines following joint injury: acute intra-articular inhibition of interleukin-1 following knee injury prevents post-traumatic arthritis. Arthritis Res. Ther. 16 (3), R134.

Furman, B.D., Kimmerling, K.A., Zura, R.D., et al., 2015. Articular ankle fracture results in increased synovitis, synovial macrophage infiltration, and synovial fluid concentrations of inflammatory cytokines and chemokines. Arthritis Rheumatol. 67 (5), 1234–1239.

Furman, B.D., Kent, C.L., Huebner, J.L., et al., 2018. CXCL10 is upregulated in synovium and cartilage following articular fracture. J. Orthop. Res. 36 (4), 1220–1227.

Giannoudis, P.V., Grotz, M.R., Papakostidis, C., Dinopoulos, H., 2005. Operative treatment of displaced fractures of the acetabulum. A meta-analysis. J Bone Joint Surg Br. 87 (1), 2–9.

Giannoudis, P.V., Tzioupis, C., Papathanassopoulos, A., Obakponovwe, O., Roberts, C., 2010. Articular step-off and risk of post-traumatic osteoarthritis. Evid. Today. Injury 41 (10), 986–995.

Gilbert, S.J., Bonnet, C.S., Stadnik, P., Duance, V.C., Mason, D.J., Blain, E.J., 2018. Inflammatory and degenerative phases resulting from anterior cruciate rupture in a non-invasive murine model of post-traumatic osteoarthritis. J. Orthop. Res. 36 (8), 2118–2127.

Goetz, J.E., Coleman, M.C., Fredericks, D.C., et al., 2017. Time-dependent loss of mitochondrial function precedes progressive histologic cartilage degeneration in a rabbit meniscal destabilization model. J. Orthop. Res. 35 (3), 590–599.

Habib, G.S., 2009. Systemic effects of intra-articular corticosteroids. Clin. Rheumatol. 28 (7), 749–756.

Han, P.F., Wei, L., Duan, Z.Q., et al., 2018. Contribution of IL-1beta, 6 and TNF-alpha to the form of post-traumatic osteoarthritis induced by "idealized" anterior cruciate ligament reconstruction in a porcine model. Int. Immunopharmacol. 65, 212–220.
Hayami, T., Pickarski, M., Wesolowski, G.A., et al., 2004. The role of subchondral bone remodeling in osteoarthritis: reduction of cartilage degeneration and prevention of osteophyte formation by alendronate in the rat anterior cruciate ligament transection model. Arthritis Rheum. 50 (4), 1193–1206.
Hayami, T., Pickarski, M., Zhuo, Y., Wesolowski, G.A., Rodan, G.A., Duong, L.T., 2006. Characterization of articular cartilage and subchondral bone changes in the rat anterior cruciate ligament transection and meniscectomized models of osteoarthritis. Bone 38 (2), 234–243.
He, X.F., Li, W., Zhu, L.M., Zhang, J.W., 2018. Investigation for effects of iNOS on biological function of chondrocytes in rats with post-traumatic osteoarthritis. Eur. Rev. Med. Pharmacol. Sci. 22 (21), 7140–7147.
Heard, B.J., Achari, Y., Chung, M., Shrive, N.G., Frank, C.B., 2011. Early joint tissue changes are highly correlated with a set of inflammatory and degradative synovial biomarkers after ACL autograft and its sham surgery in an ovine model. J. Orthop. Res. 29 (8), 1185–1192.
Heard, B.J., Barton, K.I., Chung, M., et al., 2015. Single intra-articular dexamethasone injection immediately post-surgery in a rabbit model mitigates early inflammatory responses and post-traumatic osteoarthritis-like alterations. J. Orthop. Res. 33 (12), 1826–1834.
Hou, S.M., Hou, C.H., Liu, J.F., 2017. CX3CL1 promotes MMP-3 production via the CX3CR1, c-raf, MEK, ERK, and NF-kappaB signaling pathway in osteoarthritis synovial fibroblasts. Arthritis Res. Ther. 19 (1), 282.
Huang, K., Cai, H.L., Zhang, P.L., Wu, L.D., 2020. Comparison between two rabbit models of posttraumatic osteoarthritis: a longitudinal tear in the medial meniscus and anterior cruciate ligament transection. J. Orthop. Res. 38 (12), 2721–2730.
Intema, F., Sniekers, Y.H., Weinans, H., et al., 2010. Similarities and discrepancies in subchondral bone structure in two differently induced canine models of osteoarthritis. J. Bone Miner. Res. 25 (7), 1650–1657.
Janssens, K., ten Dijke, P., Janssens, S., Van Hul, W., 2005. Transforming growth factor-beta1 to the bone. Endocr. Rev. 26 (6), 743–774.
Jiang, A., Xu, P., Sun, S., et al., 2021. Cellular alterations and crosstalk in the osteochondral joint in osteoarthritis and promising therapeutic strategies. Connect. Tissue Res. 62 (6), 709–719.
Jiang, W., Jin, Y., Zhang, S., et al., 2022. PGE2 activates EP4 in subchondral bone osteoclasts to regulate osteoarthritis. Bone Res. 10 (1), 27.
Johnson, K., Jung, A., Murphy, A., Andreyev, A., Dykens, J., Terkeltaub, R., 2000. Mitochondrial oxidative phosphorylation is a downstream regulator of nitric oxide effects on chondrocyte matrix synthesis and mineralization. Arthritis Rheum. 43 (7), 1560–1570.
Kalichman, L., Pantsulaia, I., Kobyliansky, E., 2011. Association between vascular cell adhesion molecule 1 and radiographic hand osteoarthritis. Clin. Exp. Rheumatol. 29 (3), 544–546.
Kapoor, M., Martel-Pelletier, J., Lajeunesse, D., Pelletier, J.P., Fahmi, H., 2011. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. Nat. Rev. Rheumatol. 7 (1), 33–42.
Kean, T.J., Mera, H., Whitney, G.A., et al., 2016. Disparate response of articular- and auricular-derived chondrocytes to oxygen tension. Connect. Tissue Res. 57 (4), 319–333.
Khella, C.M., Asgarian, R., Horvath, J.M., Rolauffs, B., Hart, M.L., 2021. An evidence-based systematic review of human knee post-traumatic osteoarthritis (PTOA): timeline of clinical presentation and disease markers, comparison of knee joint PTOA models and early disease implications. Int. J. Mol. Sci. 22 (4).
Koike, M., Nojiri, H., Ozawa, Y., et al., 2015. Mechanical overloading causes mitochondrial superoxide and SOD2 imbalance in chondrocytes resulting in cartilage degeneration. Sci. Rep. 5, 11722.
Kotelsky, A., Elahi, A., Nejat Yigit, C., et al., 2022. Effect of knee joint loading on chondrocyte mechano-vulnerability and severity of post-traumatic osteoarthritis induced by ACL-injury in mice. Osteoarthr. Cartil. Open. 4 (1), 100227.
Kroker, A., Bhatla, J.L., Emery, C.A., Manske, S.L., Boyd, S.K., 2018. Subchondral bone microarchitecture in ACL reconstructed knees of young women: a comparison with contralateral and uninjured control knees. Bone 111, 1–8.
Kurowska-Stolarska, M., Alivernini, S., 2017. Synovial tissue macrophages: friend or foe? RMD Open. 3 (2), e000527.
Lampropoulou-Adamidou, K., Dontas, I., Stathopoulos, I.P., et al., 2014. Chondroprotective effect of high-dose zoledronic acid: an experimental study in a rabbit model of osteoarthritis. J. Orthop. Res. 32 (12), 1646–1651.
Larrouture, Q.C., Cribbs, A.P., Rao, S.R., Philpott, M., Snelling, S.J., Knowles, H.J., 2021. Loss of mutual protection between human osteoclasts and chondrocytes in damaged joints initiates osteoclast-mediated cartilage degradation by MMPs. Sci. Rep. 11 (1), 22708.
Lavigne, P., Benderdour, M., Lajeunesse, D., et al., 2005. Subchondral and trabecular bone metabolism regulation in canine experimental knee osteoarthritis. Osteoarthr. Cartil. 13 (4), 310–317.
Lefevre, S., Meier, F.M., Neumann, E., Muller-Ladner, U., 2015. Role of synovial fibroblasts in rheumatoid arthritis. Curr. Pharm. Des. 21 (2), 130–141.
Li, W., Anderson, D.D., Goldsworthy, J.K., Marsh, J.L., Brown, T.D., 2008. Patient-specific finite element analysis of chronic contact stress exposure after intraarticular fracture of the tibial plafond. J. Orthop. Res. 26 (8), 1039–1045.
Li, J., Wang, X., Li, X., et al., 2022. Mechanical loading promotes the migration of endogenous stem cells and chondrogenic differentiation in a mouse model of osteoarthritis. Calcif. Tissue Int. https://doi.org/10.1007/s00223-022-01052-1 [Online ahead of print].
Liao, L., Zhang, S., Zhao, L., et al., 2020. Acute synovitis after trauma precedes and is associated with osteoarthritis onset and progression. Int. J. Biol. Sci. 16 (6), 970–980.
Lieberthal, J., Sambamurthy, N., Scanzello, C.R., 2015. Inflammation in joint injury and post-traumatic osteoarthritis. Osteoarthr. Cartil. 23 (11), 1825–1834.
Lietman, C., Wu, B., Lechner, S., et al., 2018. Inhibition of Wnt/beta-catenin signaling ameliorates osteoarthritis in a murine model of experimental osteoarthritis. JCIInsight 3 (3).
Lin, C., Shao, Y., Zeng, C., et al., 2018. Blocking PI3K/AKT signaling inhibits bone sclerosis in subchondral bone and attenuates post-traumatic osteoarthritis. J. Cell. Physiol. 233 (8), 6135–6147.
Lin, X., Wang, W., McDavid, A., Xu, H., Boyce, B.F., Xing, L., 2021. The E3 ubiquitin ligase itch limits the progression of post-traumatic osteoarthritis in mice by inhibiting macrophage polarization. Osteoarthr. Cartil. 29 (8), 1225–1236.
Liu, J.F., Hou, S.M., Tsai, C.H., Huang, C.Y., Hsu, C.J., Tang, C.H., 2013. CCN4 induces vascular cell adhesion molecule-1 expression in human synovial fibroblasts and promotes monocyte adhesion. Biochim. Biophys. Acta 1833 (5), 966–975.
Liu, Z., Hu, X., Man, Z., Zhang, J., Jiang, Y., Ao, Y., 2016. A novel rabbit model of early osteoarthritis exhibits gradual cartilage degeneration after medial collateral ligament transection outside the joint capsule. Sci. Rep. 6, 34423.
Liu, J., Wu, X., Lu, J., et al., 2021. Exosomal transfer of osteoclast-derived miRNAs to chondrocytes contributes to osteoarthritis progression. Nat. Aging 1 (4), 368–384.
Liu-Bryan, R., 2015. Inflammation and intracellular metabolism: new targets in OA. Osteoarthr. Cartil. 23 (11), 1835–1842.
Lofvall, H., Newbould, H., Karsdal, M.A., et al., 2018. Osteoclasts degrade bone and cartilage knee joint compartments through different resorption processes. Arthritis Res. Ther. 20 (1), 67.
Lu, K.P., Means, A.R., 1993. Regulation of the cell cycle by calcium and calmodulin. Endocr. Rev. 14 (1), 40–58.
Lu, Y.C., Evans, C.H., Grodzinsky, A.J., 2011. Effects of short-term glucocorticoid treatment on changes in cartilage matrix degradation and chondrocyte gene expression induced by mechanical injury and inflammatory cytokines. Arthritis Res. Ther. 13 (5), R142.
Lutz, M., Arora, R., Krappinger, D., Wambacher, M., Rieger, M., Pechlaner, S., 2011. Arthritis predicting factors in distal intraarticular radius fractures. Arch. Orthop. Trauma Surg. 131 (8), 1121–1126.
Lv, Z., Xu, X., Sun, Z., et al., 2021. TRPV1 alleviates osteoarthritis by inhibiting M1 macrophage polarization via Ca(2+)/CaMKII/Nrf2 signaling pathway. Cell Death Dis. 12 (6), 504.
Maerz, T., Newton, M.D., Fleischer, M., et al., 2021. Traumatic joint injury induces acute catabolic bone turnover concurrent with articular cartilage damage in a rat model of posttraumatic osteoarthritis. J. Orthop. Res. 39 (9), 1965–1976.
Maglaviceanu, A., Wu, B., Kapoor, M., 2021. Fibroblast-like synoviocytes: role in synovial fibrosis associated with osteoarthritis. Wound Repair Regen. 29 (4), 642–649.
Marsh, J.L., Weigel, D.P., Dirschl, D.R., 2003. Tibial plafond fractures. How do these ankles function over time? J. Bone Joint Surg. Am. 85 (2), 287–295.
Martini, G., Zulian, F., Calabrese, F., et al., 2005. CXCR3/CXCL10 expression in the synovium of children with juvenile idiopathic arthritis. Arthritis Res. Ther. 7 (2), R241–R249.
Maruyama, K., Nemoto, E., Yamada, S., 2019. Mechanical regulation of macrophage function - cyclic tensile force inhibits NLRP3 inflammasome-dependent IL-1beta secretion in murine macrophages. Inflamm. Regen. 39, 3.
Mevel, E., Shutter, J.A., Ding, X., et al., 2022. Systemic inhibition or global deletion of CaMKK2 protects against post-traumatic osteoarthritis. Osteoarthr. Cartil. 30 (1), 124–136.
Milentijevic, D., Rubel, I.F., Liew, A.S., Helfet, D.L., Torzilli, P.A., 2005. An in vivo rabbit model for cartilage trauma: a preliminary study of the influence of impact stress magnitude on chondrocyte death and matrix damage. J. Orthop. Trauma 19 (7), 466–473.
Narez, G.E., Wei, F., Dejardin, L., Haut, R.C., Haut Donahue, T.L., 2021. A single dose of P188 prevents cell death in meniscal explants following impact injury. J. Mech. Behav. Biomed. Mater. 117, 104406.
O'Conor, C.J., Ramalingam, S., Zelenski, N.A., et al., 2016. Cartilage-specific knockout of the mechanosensory Ion Channel TRPV4 decreases age-related osteoarthritis. Sci. Rep. 6, 29053.
Olson, S.A., Guilak, F., 2006. From articular fracture to posttraumatic arthritis: a black box that needs to be opened. J. Orthop. Trauma 20 (10), 661–662.
Olson, S.A., Furman, B.D., Kraus, V.B., Huebner, J.L., Guilak, F., 2015. Therapeutic opportunities to prevent post-traumatic arthritis: lessons from the natural history of arthritis after articular fracture. J. Orthop. Res. 33 (9), 1266–1277.
O'Neill, T.W., Felson, D.T., 2018. Mechanisms of osteoarthritis (OA) pain. Curr. Osteoporos. Rep. 16 (5), 611–616.
Pearson, M.J., Herndler-Brandstetter, D., Tariq, M.A., et al., 2017. IL-6 secretion in osteoarthritis patients is mediated by chondrocyte-synovial fibroblast cross-talk and is enhanced by obesity. Sci. Rep.UK 7.
Prasadam, I., Crawford, R., Xiao, Y., 2012. Aggravation of ADAMTS and matrix metalloproteinase production and role of ERK1/2 pathway in the interaction of osteoarthritic subchondral bone osteoblasts and articular cartilage chondrocytes – possible pathogenic role in osteoarthritis. J. Rheumatol. 39 (3), 621–634.
Racioppi, L., Noeldner, P.K., Lin, F., Arvai, S., Means, A.R., 2012. Calcium/calmodulin-dependent protein kinase kinase 2 regulates macrophage-mediated inflammatory responses. J. Biol. Chem. 287 (14), 11579–11591.
Rademakers, M.V., Kerkhoffs, G.M., Sierevelt, I.N., Raaymakers, E.L., Marti, R.K., 2004. Intra-articular fractures of the distal femur: a long-term follow-up study of surgically treated patients. J. Orthop. Trauma 18 (4), 213–219.

Rademakers, M.V., Kerkhoffs, G.M., Sierevelt, I.N., Raaymakers, E.L., Marti, R.K., 2007. Operative treatment of 109 tibial plateau fractures: five- to 27-year follow-up results. J. Orthop. Trauma 21 (1), 5–10.
Rai, M.F., Duan, X., Quirk, J.D., et al., 2017. Post-traumatic osteoarthritis in mice following mechanical injury to the synovial joint. Sci. Rep. 7, 45223.
Ramirez-Perez, S., Reyes-Perez, I.V., Martinez-Fernandez, D.E., Hernandez-Palma, L.A., Bhattaram, P., 2022. Targeting inflammasome-dependent mechanisms as an emerging pharmacological approach for osteoarthritis therapy. iScience 25 (12), 105548.
Rao, K., Dibbern, K., Day, M., Glass, N., Marsh, J.L., Anderson, D.D., 2019. Correlation of fracture energy with Sanders classification and post-traumatic osteoarthritis after displaced intra-articular calcaneus fractures. J. Orthop. Trauma 33 (5), 261–266.
Rhon, D.I., Perez, K.G., Eskridge, S.L., 2019. Risk of post-traumatic knee osteoarthritis after knee injury in military service members. Musculoskelet. Care 17 (1), 113–119.
Rieder, B., Weihs, A.M., Weidinger, A., et al., 2018. Hydrostatic pressure-generated reactive oxygen species induce osteoarthritic conditions in cartilage pellet cultures. Sci. Rep. 8 (1), 17010.
Rivera, J.C., Wenke, J.C., Buckwalter, J.A., Ficke, J.R., Johnson, A.E., 2012. Posttraumatic osteoarthritis caused by battlefield injuries: the primary source of disability in warriors. J. Am. Acad. Orthop. Surg. 20 (Suppl. 1), S64–S69.
Rzeczycki, P., Rasner, C., Lammlin, L., et al., 2021. Cannabinoid receptor type 2 is upregulated in synovium following joint injury and mediates anti-inflammatory effects in synovial fibroblasts and macrophages. Osteoarthr. Cartil. 29 (12), 1720–1731.
Sanchez, C., Deberg, M.A., Piccardi, N., Msika, P., Reginster, J.Y., Henrotin, Y.E., 2005. Subchondral bone osteoblasts induce phenotypic changes in human osteoarthritic chondrocytes. Osteoarthr. Cartil. 13 (11), 988–997.
Sanchez, C., Deberg, M.A., Piccardi, N., Msika, P., Reginster, J.Y., Henrotin, Y.E., 2005. Osteoblasts from the sclerotic subchondral bone downregulate aggrecan but upregulate metalloproteinases expression by chondrocytes. This effect is mimicked by interleukin-6, -1beta and oncostatin M pre-treated non-sclerotic osteoblasts. Osteoarthr. Cartil. 13 (11), 979–987.
Schelbergen, R.F., Blom, A.B., van den Bosch, M.H., et al., 2012. Alarmins S100A8 and S100A9 elicit a catabolic effect in human osteoarthritic chondrocytes that is dependent on toll-like receptor 4. Arthritis Rheum. 64 (5), 1477–1487.
Segal, N.A., Anderson, D.D., Iyer, K.S., et al., 2009. Baseline articular contact stress levels predict incident symptomatic knee osteoarthritis development in the MOST cohort. J. Orthop. Res. 27 (12), 1562–1568.
She, G., Zhou, Z., Zha, Z., Wang, F., Pan, X., 2017. Protective effect of zoledronic acid on articular cartilage and subchondral bone of rabbits with experimental knee osteoarthritis. Exp. Ther. Med. 14 (5), 4901–4909.
Sherman, S.L., James, C., Stoker, A.M., et al., 2015. In vivo toxicity of local anesthetics and corticosteroids on chondrocyte and synoviocyte viability and metabolism. Cartilage. 6 (2), 106–112.
Stefani, R.M., Lee, A.J., Tan, A.R., et al., 2020. Sustained low-dose dexamethasone delivery via a PLGA microsphere-embedded agarose implant for enhanced osteochondral repair. Acta Biomater. 102, 326–340.
Stolberg-Stolberg, J.A., Furman, B.D., Garrigues, N.W., et al., 2013. Effects of cartilage impact with and without fracture on chondrocyte viability and the release of inflammatory markers. J. Orthop. Res. 31 (8), 1283–1292.
Su, W., Liu, G., Liu, X., et al., 2020. Angiogenesis stimulated by elevated PDGF-BB in subchondral bone contributes to osteoarthritis development. JCIInsight 5 (8).
Sulaiman, S.Z.S., Tan, W.M., Radzi, R., et al., 2021. Comparison of bone and articular cartilage changes in osteoarthritis: a micro-computed tomography and histological study of surgically and chemically induced osteoarthritic rabbit models. J. Orthop. Surg. Res. 16 (1), 663.
Sun, Q., Zhang, Y., Ding, Y., et al., 2022. Inhibition of PGE2 in subchondral bone attenuates osteoarthritis. Cells 11 (17).
Takeuchi, K., Ogawa, H., Kuramitsu, N., et al., 2021. Colchicine protects against cartilage degeneration by inhibiting MMP13 expression via PLC-gamma1 phosphorylation. Osteoarthr. Cartil. 29 (11), 1564–1574.
Tang, X., Liu, L., Tu, C.Q., Li, J., Li, Q., Pei, F.X., 2014. Comparison of early and delayed open reduction and internal fixation for treating closed tibial pilon fractures. Foot Ankle Int. 35 (7), 657–664.
Tannast, M., Najibi, S., Matta, J.M., 2012. Two to twenty-year survivorship of the hip in 810 patients with operatively treated acetabular fractures. J. Bone Joint Surg. Am. 94 (17), 1559–1567.
Tateuchi, H., 2019. Gait- and postural-alignment-related prognostic factors for hip and knee osteoarthritis: toward the prevention of osteoarthritis progression. Phys. Ther. Res. 22 (1), 31–37.
Thomas, T.P., Anderson, D.D., Mosqueda, T.V., et al., 2010. Objective CT-based metrics of articular fracture severity to assess risk for posttraumatic osteoarthritis. J. Orthop. Trauma 24 (12), 764–769.
Thomas, N.P., Wu, W.J., Fleming, B.C., Wei, F., Chen, Q., Wei, L., 2017. Synovial inflammation plays a greater role in post-traumatic osteoarthritis compared to idiopathic osteoarthritis in the Hartley Guinea pig knee. BMC Musculoskelet. Disord. 18 (1), 556.
Thomson, A.B., Driver, R., Kregor, P.J., Obremskey, W.T., 2008. Long-term functional outcomes after intra-articular distal femur fractures: ORIF versus retrograde intramedullary nailing. Orthopedics 31 (8), 748–750.
Tochigi, Y., Vaseenon, T., Heiner, A.D., et al., 2011. Instability dependency of osteoarthritis development in a rabbit model of graded anterior cruciate ligament transection. J. Bone Joint Surg. Am. 93 (7), 640–647.
van den Bosch, M.H., Blom, A.B., Schelbergen, R.F., et al., 2016. Alarmin S100A9 induces proinflammatory and catabolic effects predominantly in the M1 macrophages of human osteoarthritic synovium. J. Rheumatol. 43 (10), 1874–1884.
van der Kraan, P.M., 2018. Differential role of transforming growth factor-beta in an osteoarthritic or a healthy joint. J. Bone Metab. 25 (2), 65–72.
Virkus, W.W., Caballero, J., Kempton, L.B., Cavallero, M., Rosales, R., Gaski, G.E., 2018. Costs and complications of single-stage fixation versus 2-stage treatment of select bicondylar tibial plateau fractures. J. Orthop. Trauma 32 (7), 327–332.
Wang, Y., Zhao, X., Lotz, M., Terkeltaub, R., Liu-Bryan, R., 2015. Mitochondrial biogenesis is impaired in osteoarthritis chondrocytes but reversible via peroxisome proliferator-activated receptor gamma coactivator 1alpha. Arthritis Rheumatol. 67 (8), 2141–2153.
Ward, B.D., Furman, B.D., Huebner, J.L., Kraus, V.B., Guilak, F., Olson, S.A., 2008. Absence of posttraumatic arthritis following intraarticular fracture in the MRL/MpJ mouse. Arthritis Rheum. 58 (3), 744–753.
Wegner, A.M., Campos, N.R., Robbins, M.A., et al., 2019. Acute changes in NADPH oxidase 4 in early post-traumatic osteoarthritis. J. Orthop. Res. 37 (11), 2429–2436.
Weigel, D.P., Marsh, J.L., 2002. High-energy fractures of the tibial plateau. Knee function after longer follow-up. J. Bone Joint Surg. Am. 84 (9), 1541–1551.
White, M.S., Brancati, R.J., Lepley, L.K., 2022. Relationship between altered knee kinematics and subchondral bone remodeling in a clinically translational model of ACL injury. J. Orthop. Res. 40 (1), 74–86.
Whittaker, J.L., Woodhouse, L.J., Nettel-Aguirre, A., Emery, C.A., 2015. Outcomes associated with early post-traumatic osteoarthritis and other negative health consequences 3–10 years following knee joint injury in youth sport. Osteoarthr. Cartil. 23 (7), 1122–1129.
Willey, M.C., Compton, J.T., Marsh, J.L., et al., 2020. Weight-bearing CT scan after tibial pilon fracture demonstrates significant early joint-space narrowing. J. Bone Joint Surg. Am. 102 (9), 796–803.
Wojdasiewicz, P., Poniatowski, L.A., Kotela, A., Deszczynski, J., Kotela, I., Szukiewicz, D., 2014. The chemokine CX3CL1 (fractalkine) and its receptor CX3CR1: occurrence and potential role in osteoarthritis. Arch. Immunol. Ther. Exp. (Warsz.) 62 (5), 395–403.
Wood, S.T., Long, D.L., Reisz, J.A., et al., 2016. Cysteine-mediated redox regulation of cell signaling in chondrocytes stimulated with fibronectin fragments. Arthritis Rheumatol. 68 (1), 117–126.
Wu, L., Guo, H., Sun, K., Zhao, X., Ma, T., Jin, Q., 2016. Sclerostin expression in the subchondral bone of patients with knee osteoarthritis. Int. J. Mol. Med. 38 (5), 1395–1402.
Wu, H., Xu, T., Chen, Z., et al., 2020. Specific inhibition of FAK signaling attenuates subchondral bone deterioration and articular cartilage degeneration during osteoarthritis pathogenesis. J. Cell. Physiol. 235 (11), 8653–8666.
Wu, X., Crawford, R., Xiao, Y., Mao, X., Prasadam, I., 2021. Osteoarthritic subchondral bone release exosomes that promote cartilage degeneration. Cells 10 (2).
Wu, T.J., Chang, S.L., Lin, C.Y., et al., 2022. IL-17 facilitates VCAM-1 production and monocyte adhesion in osteoarthritis synovial fibroblasts by suppressing miR-5701 synthesis. Int. J. Mol. Sci. 23 (12).
Xing, R.L., Zhao, L.R., Wang, P.M., 2016. Bisphosphonates therapy for osteoarthritis: a meta-analysis of randomized controlled trials. Springerplus 5 (1), 1704.
Yang, F., Zhou, S., Wang, C., et al., 2017. Epigenetic modifications of interleukin-6 in synovial fibroblasts from osteoarthritis patients. Sci. Rep. 7, 43592.
Zhang, L., Wen, C., 2021. Osteocyte dysfunction in joint homeostasis and osteoarthritis. Int. J. Mol. Sci. 22 (12).
Zhang, Z., Zhang, X., Zhao, D., et al., 2019. TGF-β1 promotes the osteoinduction of human osteoblasts via the PI3K/AKT/mTOR/S6K1 signalling pathway. Mol. Med. Rep. 19 (5), 3505–3518.
Zhang, L., Xing, R., Huang, Z., et al., 2021. Synovial fibrosis involvement in osteoarthritis. Front. Med. (Lausanne) 8, 684389.
Zhao, X., Ma, L., Guo, H., et al., 2022. Osteoclasts secrete leukemia inhibitory factor to promote abnormal bone remodeling of subchondral bone in osteoarthritis. BMC Musculoskelet. Disord. 23 (1), 87.
Zhen, G., Wen, C., Jia, X., et al., 2013. Inhibition of TGF-β signaling in mesenchymal stem cells of subchondral bone attenuates osteoarthritis. Nat. Med. 19 (6), 704–712.
Zhu, S., Zhu, J., Zhen, G., et al., 2019. Subchondral bone osteoclasts induce sensory innervation and osteoarthritis pain. J. Clin. Invest. 129 (3), 1076–1093.
Ziemian, S.N., Witkowski, A.M., Wright, T.M., Otero, M., van der Meulen, M.C.H., 2021. Early inhibition of subchondral bone remodeling slows load-induced posttraumatic osteoarthritis development in mice. J. Bone Miner. Res. 36 (10), 2027–2038.
Ziran, N., Soles, G.L.S., Matta, J.M., 2019. Outcomes after surgical treatment of acetabular fractures: a review. Patient Saf. Surg. 13, 16.