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A Current Review of Molecular Mechanisms Regarding Osteoarthritis and Pain

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Abstract

Osteoarthritis afflicts millions of individuals across the world resulting in impaired quality of life and increased health costs. To understand this disease, physicians have been studying risk factors, such as genetic predisposition, aging, obesity, and joint malalignment; however have been unable to conclusively determine the direct etiology. Current treatment options are short-term or ineffective and fail to address pathophysiological and biochemical mechanisms involved with cartilage degeneration and the induction of pain in arthritic joints. OA pain involves a complex integration of sensory, affective, and cognitive processes that integrate a variety of abnormal cellular mechanisms at both peripheral and central (spinal and supraspinal) levels of the nervous system. Through studies examined by investigators, the role of growth factors and cytokines has increasingly become more relevant in examining their effects on articular cartilage homeostasis and the development of osteoarthritis and osteoarthritis-associated pain. Catabolic factors involved in both cartilage degradation *in vitro* and nociceptive stimulation include IL-1, IL-6, TNF- α , PGE2, FGF-2 and PKC δ , and pharmacologic inhibitors to these mediators, as well as compounds such as RSV and LfcinB, may potentially be used as biological treatments in the future. This review explores several biochemical mediators involved in OA and pain, and provides a framework for the understanding of potential biologic therapies in the treatment of degenerative joint disease in the future.

Keywords

Osteoarthritis; cartilage; biochemical mediators; osteoarthritic pain

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Introduction

Osteoarthritis (OA), a debilitating degenerative joint disease predominantly found in elderly individuals, is the principal source of physical disability resulting in increased health care costs and impaired quality of life in the United States [1]. The disease imparts a profound economic impact on today's society, with healthcare costs exceeding \$60 billion per year and OA aggregate costs increasing to \$185.5 billion per year based on 2007 data [2, 3]. By the year 2030, an estimated 25% of the adult population in the United States will be afflicted with OA resulting in some form of disability [4, 5]. While several risk factors have been associated with OA, including genetic predisposition [6], aging [4], obesity [7], and joint malalignment [8], the pathogenesis of OA remains largely unknown [4–6, 9–11].

Current non-arthroplasty treatment options for OA are short-term or ineffective, and fail to adequately address the underlying pathophysiological and biochemical mechanisms involved with cartilage degeneration and the induction of pain in arthritic joints. Investigations have been undertaken to focus on understanding many of these processes, with the goal of developing novel biological therapies that may slow and/or reverse cartilage degradation and provide pain relief. Here, we will review several biochemical mediators involved in OA, with an emphasis on factors mediating cartilage breakdown and the induction of pain in degenerative conditions.

Pathophysiology of Osteoarthritis

Under normal conditions, articular chondrocytes maintain a dynamic equilibrium between synthesis and degradation of extracellular matrix (ECM) components, including collagen type II and aggrecan, the most abundant proteoglycan (PG) in articular cartilage [11, 12]. In osteoarthritic states, however, a disruption of matrix equilibrium leads to progressive loss of cartilage tissue, clonal expansion of chondrocytes in the depleted regions, induction of oxidative states in a stressful cellular environment, and eventually, apoptosis of cells [9, 13]. With progression, there is usually an increase in both degradation and synthesis of ECM molecules within the joint, with an overall shift toward catabolism over anabolism. Chondrocyte metabolism is unbalanced due to excessive production of inflammatory cytokines and matrix-degrading enzymes, in conjunction with a downregulation of anabolic signaling, eventually leading to the destruction of ECM and subsequent cartilage degradation. Oxidative stress elicited by reactive oxygen species (ROS) further disturbs cartilage homeostasis and promotes catabolism via induction of cell death, breakdown of matrix components [14], upregulation of latent matrix-degrading enzyme production [15], inhibition of matrix synthesis, and oxidation of intracellular and extracellular molecules [11, 16]. Clinically, degradation of the ECM results in the gradual impairment of articular cartilage, often accompanied by pain and physical disability. Such cartilaginous changes also elicit profound pathological remodeling in the subchondral bone, typically in the form of sclerosis and osteophyte formation (Figure 1).

A series of catabolic and anabolic mediators have been found to play key roles in articular cartilage homeostasis and the development of OA (Figure 2). Many of the specific signaling cascades underlying the effects induced by catabolic and anabolic growth factors and cytokines remain inadequately characterized, but recent efforts have begun to further our understanding. Upregulation of catabolic processes and/or downregulation of anabolic processes leads to disruption of matrix equilibrium and subsequent cartilage degradation [14, 16–18]. The goal of biologic therapies is to impede joint destruction via inhibition of catabolic activity and/or upregulation of anabolic activity, thereby slowing or preventing the progression of OA. Previously, Ellman and colleagues presented a concise review of the literature on important factors involved in cartilage homeostasis [19]. Here, we focus on

specific mediators that not only stimulate the induction of cartilage degradation, but also participate in nociceptive sensitization.

Osteoarthritis and Pain

Clinically, pain is the most prominent and disabling symptom of OA. Arthritic pain is associated with inferior functional outcomes and reduced quality of life compared with a range of other chronic conditions [20]. OA pain involves a complex integration of sensory, affective, and cognitive processes that integrate a variety of abnormal cellular mechanisms at both peripheral (joints) and central (spinal and supraspinal) levels of the nervous system [10, 21–22] (Figure 3). Acute, adaptive pain, such as that following injury or surgery, serves a protective function and generally disappears after the injury heals [21]. In contrast, maladaptive chronic pain that persists beyond normal healing time or for more than 3–6 months may be considered pathologic as a symptom of ongoing disease. As OA-associated pain continues, severity and functional disability worsen due to a lack of effective preventative measures [5]. Research efforts have recently focused on the pain pathways involved in OA, as a better understanding of these molecular mechanisms may allow for the development of new therapeutic strategies to improve function and rein in the associated increase in healthcare costs [23–24].

Nociceptors are located throughout the joint in tissues peripheral to cartilage, including the joint capsule, ligaments, periosteum and subchondral bone [1, 25]. Joint cartilage and synovial injury influences peripheral afferent and dorsal root ganglion (DRG) neurons and sensitizes symptomatic pain perception through the dynamic interactions between neuropathic pathways and OA tissues [26]. Nociceptive input from the joint is processed via different spinal cord pathways, and inflammation may potentially reduce the threshold for nociceptive stimulus. These triggers are transmitted through the DRG, where they then travel up the spinothalamic tract to cortical centers for processing. The relative contribution of these processes into peripheral and central pathways appears to be strongly segmented, with intra-articular anesthetic studies in hip and knee OA suggestive of a peripheral drive to pain in approximately 60% to 80% of patients, depending on the affected joint [6, 27]. In some individuals, however, central mechanisms such as dysfunction of descending inhibitory control or altered cortical processing of noxious information, may play a greater role [28]. Therefore, research and pharmacotherapy for OA pain need to investigate two broad classes: central sensitization and peripheral sensitization, both leading to one final outcome: pain in a patient with OA.

Current “central” targets of pharmacotherapy for OA pain are numerous and include opioids, kinins, cannabinoids, and their respective receptors, in addition to adrenergic receptors, glutamate receptors, specific ion channels, and neurotrophins. The literature is replete with data on the alteration of pain pathways via inhibition of central processes [27]. By contrast, the peripheral processes linking pain with OA are lesser-known, and a better understanding of causative pro-inflammatory signaling that links OA with pain may allow clinicians to develop localized therapeutic regimens to treat OA symptoms via intraarticular injections [29]. Currently, there is a lack of a ‘gold standard’ to relieve pain caused by OA, prompting recent research to focus more on understanding the pathophysiological mechanisms leading to joint degeneration and pain symptoms, with the aim of developing more long-term solutions via prevention and/or reversal of OA in the future [5, 14–15, 19, 30–34]. While much of this research is pre-translational, the potential for an injection of a particular mediator to induce anabolic, anti-catabolic, anti-inflammatory, and anti-pain effects in an arthritic joint via peripheral application is promising. Here, we will focus on select pro-inflammatory cytokines and mediators known to play a peripheral role in both cartilage degradation and pain processing, and briefly discuss two mediators with exciting therapeutic

potential in the treatment of OA in the future, resveratrol (RSV) [35] and bovine lactoferricin (LfcinB) [36].

Catabolic & Pain Mediators in Osteoarthritis

Numerous mediators contribute to both degradative and nociceptive pathways associated with the progression of OA. Inflammatory stimuli initiate a cascade of events, including the release of cytokines by chondrocytes, leading to complex biochemical and mechanical interplay with other biological mediators to induce OA and promote pain [27, 37]. Particular mediators then stimulate hyperalgesia by a number of direct and indirect actions, including the sensitization of primary afferent fibers for mechanical stimuli. Examples include pro-inflammatory members from the interleukin family (IL-1, IL-6, and IL-17), tumor necrosis factor- α (TNF- α), and prostaglandin E2 (PGE2) (Figure 2). Each of these mediators not only stimulates the production of cartilage-degrading proteases to induce ECM degradation, but also contributes to OA-associated pain pathways. While many of the specific mechanisms involved in nociceptive sensitization by peripheral mediators remain largely unknown, the available literature demonstrates that these factors may be potential targets for novel biological therapies that may be used for prevention of OA and pain in the future [10, 13, 21, 37].

Interleukin-1

One of the most well-studied cytokines involved in OA, IL-1, has been shown to play a prominent role in both cartilage degradation and stimulation of nociceptive pathways [38–39]. IL-1 demonstrates potent bioactivities in inhibiting ECM synthesis and promoting cartilage breakdown, represses the expression of essential ECM components (ie. aggrecan and collagen type II) in chondrocytes [40–42], and induces a spectrum of proteolytic enzymes such as collagenases (MMP-1 and MMP-13) and ADAMTS-4, in both chondrocytes and synovial fibroblasts. Aside from these direct effects, IL-1 β also induces a variety of other cytokines, including IL-6, IL-8, and leukemia inducing factor (LIF), which interact to induce additive or synergistic effects in the catabolic cascade. IL-1 β has also been shown to activate nociceptors directly via intracellular kinase activation, and may also induce indirect nociceptive sensitization via the production of kinins and prostanoids [43]. This relationship is relevant to clinicians, as studies have demonstrated the possibility of associating patient cytokine levels with subjective outcome, pain perception, and radiographic findings of knee OA patients [44].

The significance of IL-1 in OA was further corroborated by *in vivo* studies and pharmaceutical efforts using IL-1 receptor antagonist (IL-1ra) as a potential therapeutic factor to prevent cartilage degeneration. As an inhibitory molecule of IL-1 β , IL-1ra not only showed efficacy in OA animal models, but also improved clinical outcomes [45]. Both gene delivery and IL-1ra intra-articular injection models have been shown to impede OA progression, indicating anti-IL-1 therapy may be a viable option in OA disease modification [45–46].

IL-6

IL-6, another familiar pro-inflammatory cytokine with known involvement in cartilage degradation, has also been associated with hyperalgesia and hypersensitivity in joint tissues [47]. IL-6 plays an important role in the pathogenesis of rheumatoid arthritis, and its concentration is elevated in the serum and synovial fluid of arthritic patients [48–49]. Interestingly, primary afferent neurons also respond to IL-6 [50], suggesting a role of IL-6 in pain propagation in arthritic states. Indeed, more studies are warranted to elucidate the potential role of IL-6 in pain pathways associated with OA.

TNF- α

In addition to its potent catabolic effects in the pathophysiology of OA, TNF- α activates sensory neurons directly via the receptors TNFR1 and TNFR2, and initiates a cascade of inflammatory reactions via the production of IL-1, IL-6 and IL-8 [43, 51]. Direct TNF- α application in the periphery induces neuropathic pain, and this pain may be blocked by anti-inflammatory medications such as ibuprofen and celecoxib [52]. Anti-TNF- α treatment with a TNF antibody produces a prolonged reduction of pain symptoms in OA [53], and neutralization of TNF- α in mice rescues both mechanical hyperalgesia (testing of withdrawal responses in behavioral experiments) and the inflammatory process [54]. Taken together, TNF- α induces an analgesic effect, at least in part, via both neuronal and inflammatory stimulation. Antagonists to TNF- α , such as etanercept or infliximab, may serve as a potential therapeutic strategy to decrease OA pain clinically [27]. Further well-designed and controlled studies will help substantiate these promising preliminary data on TNF inhibitors in OA.

Prostanoids and PGE2

During pro-inflammatory states in articular cartilage, numerous prostanoid cyclooxygenase (COX) enzyme products are produced and released, including PGE2, PGD2, PGF2a, thromboxane, and PGI2 [27]. These factors serve as the premise for blocking the major synthetic enzymes COX-1 and COX-2 with either selective or non-selective COX-inhibitor medications (ie. NSAIDs, dexamethasone, or selective COX-2 inhibitors) [55]. COX activation has been shown to enhance production of matrix metalloproteinase-3, inhibit PG and collagen synthesis, and stimulate chondrocyte apoptosis.

Of these mediators, PGE2 is considered to be the major contributor to inflammatory pain in arthritic conditions. PGE2 exerts its effects via a variety of E prostanoid (EP) receptors (EP1, EP2, EP3, EP4), which are present in both peripheral sensory neurons and the spinal cord [27]. Activation of these receptors induces a variety of effects, ranging from calcium influx to cAMP activation or inhibition. Peripherally, sensitization of nociceptors by PGE2 is caused by the cAMP-mediated enhancement of sodium currents after ion channel phosphorylation [56]. However, in the spinal cord, PGE2 acts via different receptors than peripherally, suggesting further complexity in the prostanoid regulation of pain [57]. Several studies [58–59] have analyzed chondrocytes derived from tissue obtained during joint replacement surgery to understand the pathway of PGE2 synthesis. IL-1 β has shown to stimulate and produce high levels of PGE2 that may induce pain and the degeneration with OA. Biochemically, IL-1 β is noted to enhance the expression of COX-2 and microsomal prostaglandin E synthase-1 (mPGES-1) at the mRNA and protein levels [59]. It has been shown that increased production of PGE2 is concurrently accompanied by increases in mPGES-1 and COX-2 derived from OA chondrocytes stimulated with as IL-1 β [59].

Previously in our laboratory, we have studied the role of PGE2 in human adult articular cartilage homeostasis and its relation to possible pain pathways [60]. PGE2 utilizes the EP2 and EP4 receptors to induce its downstream catabolic effects, and PGE2 may mediate pain pathways in articular cartilage via its stimulatory effect on the pain-associated factors IL-6 [47] and inducible nitric oxide synthase (iNOS) [58]. Further, when combined with the catabolic cytokine IL-1, PGE2 synergistically upregulates both IL-6 and iNOS mRNA levels *in vitro* [60]. Similar synergistic results were found with iNOS expression as well. Therefore, the EP2/4 receptor may be an important signaling initiator of the PGE2-signaling cascade and a potential target for therapeutic strategies aimed at preventing progression of arthritic disease and pain in the future.

As opposed to PGE2 EP receptor blockade, an alternative route of PGE2 inhibition is via the blockade of PGE synthase (PGES), a major route of conversion of prostaglandin H2 to PGE2 [27]. Two isoforms of the enzyme have been identified, membrane or microsomal associated (mPGES-1) and cytosolic (cPGES/p23), which are respectively linked with COX-2 and COX-1 dependent PGE2 production [61]. Both isoforms are upregulated by inflammatory mediators, and gene deletion studies in mice indicate an important role for mPGES in acute and chronic inflammation and inflammatory pain, revealing a potential target for pain treatment in OA [27,62].

FGF-2 and PKC δ

A consecutive line of evidence from our laboratory has demonstrated a potent catabolic and anti-anabolic role of FGF-2 in human cartilage homeostasis [63]. FGF-2 is released in supraphysiological amounts during loading and/or injury of the cartilage matrix and activates multiple transduction signal pathways (MAPKs), such as ERK, p38, and JNK [33]. These kinases in turn phosphorylate a set of transcription factors to regulate gene expression and modify cellular function, resulting in a decrease in PG synthesis and antagonism against anabolic growth factors, such as insulin-like growth factor 1 (IGF-1) and bone morphogenetic protein (BMP-7) in articular cartilage [33]. FGF-2 potently stimulates MMP-13 expression, which is the major type II collagen-degrading enzyme [33]. The FGFR1-Ras/PKC δ -Raf-MEK1/2-ERK1/2 signaling pathway is activated after FGF-2 stimulation, which mediates upregulation of matrix-degrading enzyme expression (ADAMTS-5 and MMP-13), as well as downregulation of aggrecan expression (Figure 4). Correspondingly, PKC δ inhibition significantly impairs these detrimental effects mediated by FGF-2 [19, 34, 63–64].

It is worth noting that controversy over the role of FGF-2 in joint homeostasis does exist. Anabolic activity of FGF-2 in articular cartilage has been reported [19]. For example, unlike in human articular cartilage, intraarticular administration of FGF-2 demonstrates protective effects on cartilage in a murine OA animal model [63]. Such an apparent discrepancy can be explained by our recent finding that human and murine articular cartilage bear distinct FGFR expression profiles, where FGF-2 appeared to differentially regulate the expression of FGFR subtypes between human and murine cartilage. Further, despite the successful regeneration of cartilage in the murine model, FGF-2 fails to relieve symptomatic joint pain *in vivo* as determined by behavioral tests, perhaps due to FGF-2-promoted angiogenesis and inflammation in murine synovium [63]. These findings suggest that there are fundamental differences in cellular responses between human and murine tissues that eventually determine biological outcomes of FGF-2, possibly due to the complex interplay of FGFRs and their downstream signaling cascades. Our data pertaining to FGF-2 in human cartilage should add caution to the use of this particular growth factor for biological therapy in the future.

Multiple studies have implicated PKC δ as the rate-limiting factor in which PKC δ is situated at the convergent point of multiple signaling inputs, including FGF-2, substance P (SP), TNF- α , IL-1, and fibronectin fragment (Fn-f). PKC δ activation can lead to NF κ B activation in addition to MAPK activation, and these pathways work in concert to inhibit anabolic signaling and stimulate ECM degeneration (Figure 5). Recently, PKC δ has also been shown to play a nociceptive role as a regulator of both peripheral knee joint tissues (cartilage, synovium, meniscus, subchondral bone) and spinal glial activity. Utilizing an established *in vivo* model for OA, research has shown glial activity may be controlled by the PKC δ axis which integrates key nociceptive signals that promote central knee OA pain [34]. While many of these concepts are novel and pre-translational in nature, they provide deeper insights into the feasibility of utilizing downstream FGF-2 pathway-specific inhibitors in prevention and/or treatment of degenerative joint diseases and OA-associated pain. Future

focuses may be toward elucidating pharmacological interventions that have a high translational potential and may establish the potential efficacy of a PKC δ peptide inhibitor in the treatment of symptomatic OA.

Potential Biological Treatments: The Future

In addition to the development of pharmacologic inhibitors of key catabolic mediators discussed above, recent research has elucidated several compounds that may also play a key role in the future treatment of symptomatic OA. Two of these compounds, resveratrol (RSV) and bovine lactoferricin (LfcinB), have been extensively studied in our laboratory and show considerable promise as an additional potential biological treatment strategy for OA in the coming years.

Resveratrol

The phytoestrogen resveratrol (trans-3,4',5-trihydroxystilbene; RSV) is a natural polyphenol compound found in peanuts, cranberries, and the skin of red grapes, and is thought to be one of the compounds responsible for the health benefits of moderate red wine consumption [65–66]. The anti-inflammatory, anti-oxidant, cardioprotective, and anti-tumor properties of RSV have been well-documented in a variety of tissues [66–74], with recent studies beginning to analyze the effects of RSV on cartilage homeostasis. Elmali *et al* first reported a significant protective effect of RSV injections on articular cartilage degradation in rabbit models for OA and RA via histological analysis *in vivo* [75–76]. In human articular chondrocytes, Shakibaei [77] and Czaki [78] elucidated both anti-apoptotic and anti-inflammatory regulatory mechanisms mediated by RSV.

In our laboratory, we have demonstrated potent anabolic and anti-catabolic potential of RSV in bovine spine nucleus pulposus IVD tissue [32] and human adult articular chondrocytes [35] via inhibition of matrix-degrading enzyme expression at the transcriptional and translational level. Further, combination therapy of RSV with BMP-7 induces synergistic effects on PG accumulation, and RSV reverses the catabolic effects of FGF-2 and IL-1 on matrix-degrading enzyme expression, PG accumulation, and the expression of factors (iNOS, IL-1, IL-6) associated with oxidative stress and inflammatory states [32]. Future studies are needed to assess the role of RSV in nociceptive stimulation with OA, as well as its role *in-vivo* before its use in a clinical setting, but these findings reveal considerable promise for use of RSV as a unique biological therapy for treatment of cartilage degenerative diseases.

Lactoferricin

Bovine lactoferricin (LfcinB) is a 25-amino acid cationic peptide with an amphipathic, anti-parallel β -sheet structure that is obtained by acid-pepsin hydrolysis of the N-terminal region of lactoferrin (Lf) found in cow's milk [79–80]. Similar to RSV, the anti-inflammatory, anti-viral, anti-bacterial, anti-oxidant, anti-pain, and anti-cancer properties of LfcinB have been reported in a variety of tissues [81–82]. The natural anti-oxidative effect of LfcinB has also been reported, suggesting a possible chondroprotective biological role in articular cartilage [83], and recent studies have attempted to unravel the role of LfcinB in musculoskeletal disease. In a mouse collagen-induced and septic arthritis model, periarticular injection of human Lf substantially suppresses local inflammation [84]. Further, in a rat adjuvant arthritis model, oral administration of bovine Lf suppresses the development of arthritis and hyperalgesia in the adjuvant-injected paw, suggesting Lf has preventative and therapeutic effects on the adjuvant-induced inflammation and pain [85].

In our laboratory, LfcinB was found to exert potent anabolic and anti-catabolic effects in bovine nucleus pulposus matrix homeostasis in the IVD [36]. Further, we found similar

anabolic and anti-catabolic effects of LfcinB in human articular cartilage (Im et al, unpublished data). LfcinB reverses the catabolic effects of FGF-2 and IL-1 on matrix-degrading enzyme production, PG accumulation, and expression of factors associated with oxidative stress and inflammation, suggesting the promise of LfcinB as an anti-catabolic and anti-inflammatory molecule in human articular cartilage. To date, the anti-pain potential of LfcinB has yet to be studied, and caution must be advised as further studies are warranted to determine, among other things, possible detrimental effects of the use of LfcinB (and RSV) *in vivo*.

Conclusion

In summary, the literature reveals important roles of growth factors and cytokines in articular cartilage homeostasis and the development of OA and OA-associated pain. Upregulation of catabolic processes and/or downregulation of anabolic processes leads to disruption of equilibrium with subsequent cartilage degradation and OA, and several of these pathways are known to induce pain in OA as well. Currently, many of the underlying pathways remain unknown, but recent efforts have begun to increase our understanding. Catabolic factors involved in both cartilage degradation *in vitro* and nociceptive stimulation include IL-1, IL-6, TNF- α , PGE2, FGF-2 and PKC δ , and pharmacologic inhibitors to these mediators, as well as compounds such as RSV and LfcinB, may potentially be used as biological treatments in the future.

Despite a tremendous research effort in recent years to elucidate these processes, however, biologic therapy for OA remains experimental in nature, and several unknowns exist. Given the wide array of interactions of growth factors that are necessary for maintenance of cartilage homeostasis *in vivo*, it is unlikely that any single growth factor will lead to complete cartilage repair or affect the arthritic joint clinically, and rather a combination approach will be required [86]. Further, appropriate dosing, scaffolds, and routes of administration must be determined before biological factors play a beneficial role clinically. Nevertheless, this paper reviews several of the most well-studied biochemical mediators involved in OA and pain, and provides a framework for the understanding of potential biologic therapies in the treatment of degenerative joint disease in the future.

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Figure 1.

Complex cellular interplay in synovial joint. In osteoarthritic state, aberrantly activated chondrocytes produce ECM-degrading proteases (MMPs, aggrecanases), pro-inflammatory cytokines (eg. IL-1), and catabolic growth factors (eg. FGF-2). These proteins can be secreted into synovial fluid, and subsequently act upon synoviocytes. Fragments derived from ECM degradation (eg. Fn-f) are also present in the synovial fluid as catabolic inducers. In OA, a subpopulation of chondrocytes undergoes hypertrophic changes, as manifested by their expression of type X collagen. Chondrocytes may also upregulate apoptosis, resulting in diminished local cellularity. In response to cartilage loss, pathological remodeling of subchondral bone gives rise to sclerosis and osteophyte formation. Synoviocytes (fibroblasts and macrophages) also actively synthesize proteases and cytokines which can negatively effect on the articular cartilage and synovium. Pathophysiological changes in synoviocytes pave the way for angiogenesis and innervations, which may account for OA pain [adapted from S. B. Abramson & M. Attur, *Arthritis Res Ther* 2009;11(3):227].

Inflammatory mediators	Signaling Mediators	Proteases
<ul style="list-style-type: none">• TNF• IL-1β• IL-6• IL-8• IL-15• IL-17• IL-21• PGE2• Substance P• NGF• EGF• VEGF• FGF-2	<ul style="list-style-type: none">• NFκB• ERK1/2• p38• JNK• PKCδ• TLRs• β-catenin• Gli1• Ptch• HHIP• HIF-2α• iNOS• RUNX2	<ul style="list-style-type: none">• MMP-1• MMP-3• MMP-9• MMP-13• ADAMTS-4• ADAMTS-5• TACE

Figure 2.
Notable mediators in OA.

Figure 3.

Pathophysiological status of each component in synovial joint is linked to joint degeneration and related pain perception. Local homeostasis inside the joint can be perturbed by various factors, such as aging, injury, and genetic predisposition. Low grade chronic inflammation in the joint not only contributes to accelerated cartilage damage and synovitis, but also renders the joint susceptible to peripheral sensitization and, in some cases, central sensitization.

Figure 4.

Schematic model of FGF-2 signaling in articular chondrocytes. FGF-2 binds to FGFR1, which in turn activates both Ras and PKC δ . The signaling inputs then converge on the Raf1-MEK1/2-ERK1/2 axis. Activated ERK1/2 elicits transcription or repression of target genes mediated by a subset of transcription factors, including Elk-1 [adapted from D. Yan & H. J. Im et al., *J Cell Biochem* 2012].

Figure 5.

PKC δ functions as the signaling node of multiple pathways. Input from each illustrated ligand-receptor complex triggers PKC δ activation. PKC δ in turn activates MAP kinases (ERK1/2, p38, and JNK) and NF κ B, leading to inhibition of anabolic signaling (eg. IGF-1 and BMP7), suppression of PG production, and upregulation of catabolic proteases.