Osteoarthritis and Cartilage

Review

Osteoarthritis year in review 2013: biology

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A R T I C L E   I N F O

Article history:
Received 25 April 2013
Accepted 27 May 2013

Keywords:
Inflammation
Signaling
Growth factors
Bone
Cartilage
Meniscus
Synovium

S U M M A R Y

The purpose of this review was to present highlights from the published literature on the topic of the biology of osteoarthritis (OA). A PubMed search was conducted in order to locate original research manuscripts published since the last OARSI meeting in 2012. From review of the published literature, common themes emerged as active areas of research over the past year including studies in the areas of epigenetics, Wnt signaling, the role of inflammatory pathways in OA, lubricin, fibroblast growth factor signaling, and studies on OA biology in bone. Key findings in these areas were summarized and implications for future therapies were discussed.

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Introduction

Research into the basic biology of osteoarthritis (OA) continues to grow with many investigators focused on elucidating mechanisms relevant to cartilage matrix destruction. However, an accumulating number of studies have reported findings in other joint tissues affected by OA including bone, synovium, ligaments, and the menisci. Since OA is a disease of the joint as an organ, knowledge of how these tissues interact to result in OA will be important and could lead to new approaches for the treatment. This review attempts to capture and summarize key findings in the biology of OA published since the last OARSI meeting in April 2012 up to the end of March 2013.

A PubMed search of English language articles from April 1, 2012 to March 24, 2013 under the search term of osteoarthritis with MESH terms of embryology, enzymology, etiology, immunology, metabolism, pathology, physiology, and physiopathology returned 843 published articles. The titles and selected abstracts from this list were reviewed and publications relevant to the biology of OA were collected. In addition, selected journals in the field were cross-checked for additional articles of interest that were not picked up in the PubMed search. Articles more relevant to cartilage tissue engineering were not included in the review in order to focus on the biology of OA.

Many of the topic areas covered by Peter van der Kraan in the 2012 review1, such as epigenetics (in particular micro-RNA), Wnt signaling, autophagy, inflammation, obesity/metabolic syndrome, aging, and the concept of OA as a disease of the joint as an organ, continued to be active areas of investigation over the past year. From these topic areas, epigenetics and Wnt signaling were particularly active areas and so these will be discussed. In addition, the role of inflammatory pathways in OA, including those involved in innate immune responses, was chosen to highlight along with selected publications on lubricin, fibroblast growth factor (FGF) signaling, and studies on OA biology in bone (Table I). It is not possible to cover all of the excellent work being done in the field and so apologies to those whose work was not included.

Epigenetics

Epigenetic regulation of gene transcription allows cells to alter and fine tune gene expression in response to external cues. Unlike genetic modifications which require very long periods of evolutionary pressure to occur, organisms can use epigenetic modifications to more rapidly respond to changes in the environment. Individual cells and tissues can likewise use epigenetic modifications to alter gene expression to respond to changes in their microenvironment. Many epigenetic modifications can be maintained in cultured cells. It has been observed for quite some time that chondrocytes removed from an osteoarthritic joint and placed in culture will maintain an OA-like phenotype for a week or more, expressing genes seen in OA despite the fact that the cells are no
Epigenetics

† Methylation of MMP-13, IL-1β, and INOS promoters.
† Methylation of Sox-9 promoter.
Altered histone acetylation and differential miRNA expression in OA chondrocytes.
† Dkk-1 promoter.
† WISP-3/CCL6 promoter.

Therapeutic implications
HDAC inhibitors decrease OA in a mouse model of OA. DNA methylation and miRNA expression will be much more difficult to target for therapy.

Wnt signaling
Sclerostin present in articular cartilage.
† Dkk-1 in OA cartilage and synovium.
† WISP-3/CCL6 in OA cartilage.

Sclerostin inhibition/deletion did not affect the development of OA in rat or mouse models. Inconclusive results with Dkk-1 inhibition/overexpression or manipulation of Wnt/β-catenin activity.

Inflammatory factors
Production of multiple pro-inflammatory mediators by the injured meniscus.
S100A8 and S100A9 present in OA synovium.
Plasma proteins and soluble CD14 present in SF which activate TLRs.
CCL2 → CCR2 involved in pain in OA.

Overexpression of lubricin reduces OA severity in mouse models of OA.

Lubricin (PRG4)
Important boundary lubricant that protects articular surface.

Overexpression of lubricin reduces OA severity in mouse models of OA.

FGF signaling
Balance of FGFR1 to FGFR3 mediated signaling determines catabolic vs anabolic activity of FGFs.

Activation of FGFR3 by FGF-18 more likely to reduce OA than FGFR1 activation by FGF-2.

Bone
Correlation between cartilage and bone changes in OA varies by model system studied, particularly when osteophytes are examined.

Overexpression of lubricin reduces OA severity in mouse models of OA.

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longer in the presence of the altered milieu of the OA joint. This phenomenon could be explained by epigenetic changes in the cell, including DNA methylation, histone methylation and acetylation, and micro (mi)RNAs, which regulate expression of the genes related to the OA-phenotype.

MMP-13 is a critical enzyme that mediates cartilage matrix destruction in OA and which appears to be under epigenetic regulation. Increased MMP-13 expression by human OA chondrocytes was associated with demethylation of CpG sites in the MMP-13 promoter. A site at −104 bp was studied further and found to be a site for binding of the CAMP response element-binding (CREB) when the site was demethylated. In another MMP-13 promoter study, demethylation at −110 bp and −299 bp in human chondrocytes was associated with increased levels of MMP-13 gene expression. The same study found similar sites in the IL-1β promoter. Interestingly, binding of HIF-2α, which was recently implicated in promoting OA in mice, to the MMP-13 but not IL-1β promoter, was greater when the two sites were demethylated. CREB was not tested but RUNX2, AP-1, and ELF3 regulation of MMP-13 expression was not altered by methylation status.

Another gene associated with catabolic activity in cartilage is the inducible nitric oxide synthase (iNOS). A site in the NF-κB enhancer region was found to be demethylated in human OA chondrocytes relative to controls and methylation of this region was associated with decreased iNOS expression. On the anabolic side, methylation of the SOX-9 promoter was found to be increased rather than decreased in human OA cartilage relative to normal controls. The demethylating agent 5-azacytidine was able to increase SOX-9 expression demonstrating that methylation was inhibitory and this appeared to be mediated by altered binding of the CCAAT-binding factor/nuclear factor-Y and a CREB factor. Histone methylation and acetylation may also regulate SOX-9 promoter activity and an increase in H3K9 and H3K27 trimethylation and a decrease in acetylation at H3K9, K18, 18, 23, and 27 at the SOX-9 promoter was found.

Histone modifications can also regulate catabolic mediators in cartilage. Human chondrocytes induced to express RUNX-2, MMP-3 and ADAMTS-5 by mechanical stress were treated with histone deacetylase (HDAC) inhibitors MS-275 or trichostatin A (TSA). The HDAC inhibitors reduced expression of all three genes. Likewise, IL-1-induced expression of MMP-1, MMP-3, and MMP-13 was reduced by treatment of human articular chondrocytes with TSA, MS-275, or valproic acid. In further support for an in vivo role for histone acetylation in OA, TSA treatment of mice reduced the severity of cartilage damage in the destabilized medial meniscus (DMM) model of OA. Thus, studies to date strongly implicate a number of catabolic and anabolic factors in OA chondrocytes which are regulated by both methylation and histone modifications.

In addition to studies in cartilage, differences in DNA methylation in OA vs osteoporotic bone, taken from the central part of the femoral head, have been examined. Out of 241 sites in 228 genes that were differentially methylated, the vast majority (217) were found to have reduced methylation in osteoporotic bone. When these genes were annotated for function, the homeobox superfamily of transcription factors was found to be significantly different between OA and osteoporotic bone. This is of interest given the important role of this family of transcription factors in bone and joint development.

A very active area of epigenetics research in the past year has been the study of miRNAs although which ones might be important in the biology of OA is not completely clear. A microarray analysis of miRNAs present in cultured human normal and OA chondrocytes found seven miRNAs differentially expressed. Only one, miR483-5p was increased in OA cells while the others (miR-149, miR-582-3p, miR-1227, miR-634, miR576-5p, and miR-641) were at higher levels in normal chondrocytes. Functional studies were not performed and so it was not clear what role if any these have in OA. Another study using human cartilage noted an age-related increase in miR-199a-3p and miR193b. In contrast, IL-1β treated human chondrocytes had decreased levels of miR-199a and this was associated with increased expression of cyclooxygenase-2 and subsequent PGE-2 production. Treatment of the immortalized C28/I2 chondrocyte line with HDAC inhibitors decreased OA in a mouse model of OA. DNA methylation and miRNA expression will be much more difficult to target for therapy.

Wnt signaling and OA

Wnt signaling plays a key role in the development of the joint and recent work supports a role in OA as well. Because Wnt pathways are involved in both cartilage and bone formation that include
a role in regulation of chondrocyte hypertrophy in the growth plate, dysregulation of Wnt pathways in adult tissues could contribute to the chondrocyte hypertrophy seen in OA and pathologic changes in cartilage and bone. Sclerostin serves as an inhibitor of Wnt signaling in bone and loss of function mutations in sclerostin or inhibition through the use of neutralizing antibodies result in increased bone mass. In addition to bone, Roudier et al.14 confirmed earlier reports demonstrating sclerostin was also expressed in articular cartilage, albeit at similar levels in normal and OA human cartilage. However, neither genetic deletion of sclerostin in mice or antibody inhibition in rats altered the development of naturally occurring OA in mice or surgically-induced OA in rats. Interestingly, sclerostin knock-out mice at 12 and 16 months of age did not have more severe cartilage lesions compared to age-matched controls despite significantly increased subchondral bone mass. This finding either argues against a direct effect of increased subchondral bone mass on the overlying cartilage or suggests loss of sclerostin in cartilage might have counter-acted the effect of increased bone.

Dkk1-4 are also Wnt antagonists and Dkk-1 and -2 were reported to be present in articular cartilage with Dkk-1 also found in human OA synovium15,16. Dkk-1 was increased while Dkk-2 was decreased in OA cartilage when compared to normal15. In another study, Dkk-1 and two other Wnt antagonists, Gremlin 1 and Frizzled-related protein, were found to be expressed at higher levels in articular cartilage when compared to growth plate17. These Wnt antagonists were shown to inhibit chondrocyte hypertrophy in vitro suggesting the higher levels in articular cartilage might serve to inhibit hypertrophy. Dkk-1 overexpression in the mouse joint by adenovalinjection or by transgenic overexpression resulted in reduced OA severity in the DMM model15. However, the opposite effect of Dkk-1 on OA was seen in the rat anterior cruciate ligament transection (ACLT) model where intra-peritoneal injection of Dkk-1 antisense oligonucleotides sufficient to reduce the number of Dkk-1 positive cells in the synovium reduced the severity of OA rather than increasing it16. Dkk-1 was shown to inhibit MMP-13 and ADAMTS-4 expression in chondrocytes in response to the Wnt pathway activator Wnt-3a15 while it promoted the opposite effect of Dkk-1 on OA was seen in the rat anterior cruciate ligament transection (ACLT) model where intra-peritoneal injection of Dkk-1 antisense oligonucleotides sufficient to reduce the number of Dkk-1 positive cells in the synovium reduced the severity of OA rather than increasing it16. Dkk-1 was shown to inhibit MMP-13 and ADAMTS-4 expression in chondrocytes in response to the Wnt pathway activator Wnt-3a15 while it promoted production of pro-angiogenic factors and proteinases (ADAMTS-5 and MMP-3) produced by synovial fibroblasts16. If these findings of opposite effects in cartilage and synovium are confirmed, it would suggest that Dkk-1 would not serve as a very good target for treatment of OA when both tissues are affected. Adding to the complexity of the role of Wnt signaling in OA, a study of the Wnt-1-inducible signaling protein 3/CCN6 found that it was highly expressed in human OA cartilage compared to normal cartilage and in vitro experiments found that it down-regulated ADAMTS-5 expression while up-regulating MMP-1018. Activation of Wnt/β-catenin signaling in primary human chondrocytes inhibited basal and IL-1β stimulated MMP-1, -3, and -13, possibly through inhibition of NFκB19. However, another in vitro study found that Hedgehog proteins stimulated accumulation of superficial zone protein (lubricin) while antagonists of Wnt/β-catenin also stimulated lubricin accumulation in explants. Indian hedgehog, which can regulate Wnt signaling as well as PTHrP, was found to be increased in human OA cartilage and synovium and promote chondrocyte hypertrophy including increasing MMP-1320. These studies suggest that a much more complete understanding of Wnt signaling pathways in cartilage and related joint tissues will be needed before rational therapeutic interventions can be designed.

Role of inflammatory factors in OA

Studies of pro-inflammatory mediators found in the OA joint support the paradigm that although OA may be largely a biomechanical disease, its manifestations at the tissue level are mediated by the activity of inflammatory factors. In addition, post-traumatic OA is an example of a form of OA where both acute inflammation induced by joint injury and abnormal biomechanics resulting from joint instability likely work in concert to promote joint tissue destruction. Meniscal injury, either alone or in combination with an ACL tear, is an important risk factor for knee OA. A study of meniscal tissue removed during partial meniscectomy in patients with a meniscal tear, with or without a concomitant ACL tear, provided evidence that the injured meniscus can be a source of inflammatory mediators in the joint21. Numerous cytokines, chemokines, and matrix degrading proteinases were found to be expressed in the meniscus samples including IL-1α and β, IL-6, TNF-α, CCL3, CXCL1, CXCL3, ADAMTS-4 and -5, MMP-1, MMP-9, and MMP-13.

In a post-traumatic OA model in mice that involves fracture of the lateral tibial plateau, the role of inflammation was studied by measuring inflammatory mediators in the synovial fluid and expression in the synovium in two different strains of mice22. Male MRL/MpJ mice developed less severe OA than C57BL/6 mice despite having a similar joint injury. The C57BL/6 mice were found to have higher levels of IL-1α and IL-β in the synovial fluid and greater expression of TNF-α and IL-1β as well as the chemokine CCL22 in synovial tissue where a greater infiltration of macrophages was also found. These findings support the hypothesis that a more active inflammatory response contributed to more severe OA in these mice. In addition to cytokines and chemokines, many other pro-inflammatory factors have been studied for their potential involvement in OA including the S100 proteins. S100A8 and S100A9 are referred to as alarmins or as damage-associated molecular patterns (DAMPs) since they are released in response to tissue injury and their presence alarms the innate immune system that tissue damage has occurred. Both proteins were found to be present in human synovial tissue removed by biopsy of patients with early symptomatic OA23. Macrophages are one potential source of S100 proteins in the joint and in vitro treatment of macrophages with basic calcium phosphate crystals, which can be involved in OA, stimulated production of S100A824. Two mouse models of OA with different levels of synovial inflammation were compared using S100A9 knockout mice (S100A8 knockouts are not viable and so were not tested). In the less inflammatory DMM model, S100A9 knockout did not protect the articular cartilage while in the collagenase-induced OA model, where much more synovitis was noted, knockout mice had less severe synovitis and cartilage destruction21. In further studies, S100A8 and A9 were identified in human OA cartilage and stimulation of chondrocytes in vitro resulted in increased production of IL-6, IL-8, and MCP-125. S100A8 and A9 can induce production of pro-inflammatory mediators through Toll-like receptors (TLRs) which are gaining attention for their role in OA. Inhibition of TLR-4 inhibited catabolic effects of S100A8 and A9 when chondrocytes were stimulated25. Additional pro-inflammatory mediators, some of which also activate TLRs, were identified in human OA synovial fluid using a proteomics approach26. These included plasma proteins such as Gc-globulin, x1-microglobulin, and x2-microglobulin. Of interest, this study also measured the amounts of several cytokines in OA synovial fluids and compared the levels to those in serum. Two widely studied cytokines, IL-1β and TNF-α, were present at very low levels in synovial fluid while IL-6, VEGF, MCP-1, IP-10, and MIG were all present at higher levels with IP-10 and MIG levels over 1,000-fold higher than IL-1β27. Another study looked for TLR activators in synovial fluid from patients with early cartilage damage who were undergoing arthroscopy to treat a meniscal injury28. This strategy resulted in the discovery of a TLR co-receptor, soluble CD14, which augmented the ability of TLR-2 and -4 ligands to stimulate IL-8 release from synovial fibroblasts.
In addition to promoting joint tissue destruction, inflammatory mediators may also contribute to pain in people with OA. Using the mouse DMM model of OA, Miller et al. showed that the mice exhibit alldynia and discovered that the chemokine MCP-1 (CCL2) and its receptor CCR2 were increased in the dorsal root ganglia. CCR2 knockouts exhibited similar cartilage damage to wild type mice after DMM surgery but had reduced movement-evoked pain behavior and some resolution of alldynia. A possible role for macrophages in this process was indicated by the finding of macrophages in the dorsal root ganglia of the DMM mice which were reduced in the CCR2 knockouts. These studies support an important role for macrophages and inflammation in OA but suggest that different factors may contribute to macrophage infiltration that contributes to pain and infiltration in the synovium that contributes to joint tissue destruction.

**Protective role of lubricin (PGR4) in OA**

Changes in lubrication at the surface of articular cartilage in response to injury and altered mechanics have emerged as important in the biology of OA. Much of the recent attention in this area has been on lubricin which is also known as superficial zone protein or as proteoglycan protein 4 (PRG4). When compared to normal synovial fluid, synovial fluid from human OA joints that had reduced lubricin levels was found to have reduced cartilage boundary-lubricating ability when tested in a friction test. Supplementing these samples with lubricin restored the lubricating ability. Testing done in lubricin knockout mice demonstrated increases in joint friction and chondrocyte apoptosis in the superficial cartilage that appeared to be related. Loss of lubricin from the articular surface was seen in the rat ACLT model. Supplementation with lubricin by intra-articular injection improved weight bearing in a measurement of hind limb force and reduced the level of urinary CTX-II but did not alter the OARSI score.

Finally, in a very exciting study over-expression of lubricin in transgenic mice reduced the severity of both age-related OA (tested at 10 months of age) as well as in a cruciate ligament transection model of OA. The severity of post-traumatic OA was also reduced by expressing lubricin in the mouse knee joint using intra-articular injection of adeno-associated virus, even when injected 2 weeks after the joint injury. The study went on to examine how lubricin affected gene transcription using superficial chondrocytes for RNA isolation and analysis by microarrays. It was discovered that expression of lubricin inhibited expression of genes involved in cartilage catabolism and chondrocyte hypertrophy in association with an up-regulation of HIF-3α, a negative regulator of HIF-1α and HIF-2α. The authors proposed that the increase in HIF-3α may correct the imbalance in catabolic and anabolic activity that promotes OA through down-regulation of HIF-1α and HIF-2α. These studies support further investigation of lubricin (PRG4, S2P) as a therapeutic agent for human OA, perhaps given as soon as possible after an acute joint injury to prevent post-traumatic OA.

**The role of altered FGF signaling in OA**

Unlike the consistent pro-anabolic effects observed with FGF-18, FGF-2 effects in adult articular cartilage have been less clear. Previous in vitro experiments found FGF-2 stimulated chondrocyte proliferation, inhibited matrix synthesis, and promoted MMP-13 production. FGF-2 released when cartilage is cut with a scalpel (or a proposed model of cartilage injury) resulted in activation of MAP kinases and IKKβ that might be expected to promote pro-inflammatory gene expression. However, FGF-2 knockout mice were found to develop accelerated OA with aging and more severe OA in the DMM model. Experiments showing differences in the response of human and mouse cartilage to FGF-2 suggested that differences in expression of FGF receptors (FGFR-1 and FGFR-3 might be to blame for the inconsistent findings. Earlier studies had shown deletion of FGFR-3 in mice resulted in spontaneous OA suggesting FGF-2 activation of FGFR-3 might be chondroprotective while FGFR-1 was proposed to mediate catabolic effects of FGF-2 based on in vitro experiments. In support of catabolic activity in response to FGFR-1 activation, Weng et al. found that FGFR-1 deficient mice developed less severe age-related aggrecan loss at 12 months and less severe OA in younger mice using the DMM model that was associated with decreased expression of MMP-13 and interestingly higher expression of FGFR-3.

Taken together, these studies suggest that the ratio of FGFR-1 and FGFR-3 in articular cartilage determines the response of chondrocytes to FGF stimulation such that an excess of FGFR-1 stimulation relative to FGFR-3 would promote cartilage catabolism and the development of OA. Previous work had demonstrated the ratio of FGFR-3 to FGFR-1 was reduced in OA. This is similar to the finding that the ratio of the TGF-β receptors Alk-1 and Alk-5 determine the response to TGF-β stimulation such that an increased Alk-1 to Alk-5 ratio in OA is pro-catabolic. Since FGF-2 can stimulate either FGFR-1 or FGFR-3 and TGF-β can stimulate either Alk-1 or Alk-5, they would be unlikely to be of much benefit in treating OA when the relative receptors levels favor catabolic over anabolic activity. However, FGF-18 primarily stimulates FGFR-3 and so would be expected to promote anabolic over catabolic activity making it a better choice for treating OA. Currently, intra-articular FGF-18 is in early phase studies as an anabolic agent to promote cartilage repair and to treat OA.

**Bone**

The role of bone in the biology of OA has been an active area of investigation. Although OA changes in the articular cartilage in some humans and animal models (see above studies on the DMM model in mice) can be seen in the absence of significant synovitis, involvement of bone proximate to the affected joint seems to be universal during at least some stage of OA. However, various studies reported during the last year that used either human tissue or animal models found both a good correlation between changes occurring in bone and in the overlying articular cartilage or a poor correlation between the two. Human osteochondral plugs taken from tibial plateaus with a range of cartilage damage were found by micro-CT to have changes in subchondral bone mineralization and bone volume underneath the samples with the most severe cartilage changes. The same group published a second study investigating the contribution of excessive loading and endochondral ossification to the subchondral bone changes seen in OA and concluded that both processes were responsible.

Studies in various mouse models of OA noted both a good and poor correlation between cartilage and bone changes. A study using the DMM model to compare OA severity in a strain of mice (LGXSM-6) noted to be “super healers” and a strain (LGXSM-33) noted to be “poor healers” of cartilage and ear punch lesions found that the more severe cartilage lesions in the poor healer strain correlated with more severe bone changes measured by micro-CT. Likewise, bone targeted overexpression of EphB4 resulted in reduced cartilage damage in the DMM model that correlated with a reduction in subchondral sclerosis and bone volume as well as the number of tartrate-resistant acid phosphatase-positive osteoclasts. In contrast to these studies, compared to wild-type controls, Col6a1−/− mice surprisingly had less knee joint cartilage loss at 15 months of age despite large osteophytes which appeared as early as 2 months of age. As noted above, sclerostin knockouts did not exhibit age-related OA at 12 or 16 months of age despite a
significant increase in subchondral bone mass. A time course study of the DMM model in 12 week old C57BL/6 mice found significant osteophyte (chondrophyte) formation at 2 weeks after DMM surgery which was a time point when the articular cartilage damage was minimal. In that study, the size of the medial abaxial osteophyses did not progress from 2 to 16 weeks while the cartilage damage and subchondral bone thickening did progress.

Differences in osteophyte formation and cartilage damage were also noted in studies examining the effect of cathepsin K inhibition on the development of OA. Cathepsin K, a protease produced by osteoclasts and involved in bone resorption, has also been shown to be made by synovial fibroblasts and chondrocytes. A recent study found it can contribute to type II collagen cleavage seen with aging and in OA. Treatment of rabbits with a chemical inhibitor of cathepsin K (L-235) reduced cartilage damage measured by Mankin scoring in the ACLT model and cathepsin K knockout mice likewise had reduced cartilage damage after ACLT surgery. In both models, inhibition of cathepsin K protected the subchondral bone. However, a significant reduction in osteophytes was only seen in the rabbit ACLT model where the chemical inhibitor was only partially protective in terms of cartilage damage while in the cathepsin K−/− mice no reduction in osteophytes was seen despite a very significant reduction in the Mankin score.

Conclusions

The various tissues involved in the OA process and a host of potential mediators that contribute to the development of OA continue to be defined. The ultimate goal of research on the biology of OA is to discover new therapeutic targets based on a better understanding of disease mechanisms. Although epigenetic regulation of gene transcription and Wnt signaling both appear to contribute to the OA process, the complexity of the interacting systems involved and the difficulty in targeting one aspect of their activity, which might be beneficial in OA, without affecting another aspect that would be harmful, will make these areas difficult to translate to new therapeutics. It is not to say that they are not important areas for continued research but rather translation to the clinic will require more precisely defined targets and will be much slower than in other areas.

The knowledge of the role of inflammation in OA is rapidly expanding and there is evidence that pro-inflammatory mediators can be produced by all of the joint tissues affected by OA. The limitation in this area of research is that no single target stands out above the others. Unlike in RA, where targeting TNFα results in significant improvement in symptoms and disease progression in many patients, it appears that in OA there may be subsets of patients where inflammation is a driving force and within this subset more than one pro-inflammatory mediator may need to be inhibited. It is very possible, as noted by the work on the chemokine receptor CCR2, that pro-inflammatory mediators responsible for pain differ from those responsible for joint tissue destruction.

Closer to translation as new therapeutics for knee OA, intra-articular treatment with lubricin or with anabolic factors, such as FGF-18, is supported by recent work on the biology of OA. The finding that an injection of lubricin given 2 weeks after a joint injury can reduce the severity of subsequent OA in mice suggests that it could be a useful treatment to prevent post-traumatic OA. The ability of FGF-18 to activate FGFR3 and promote anabolic activity in joint tissues holds promise with the caveat that a loss of FGFR3 and gain of FGFR1 in OA cartilage could limit its effectiveness at more advanced stages of disease.

Finally, a review of the most recent literature on bone in OA supports the long-held belief that bone is involved in the OA disease process. However, the association between changes in bone and destruction of the overlying cartilage is not consistent, particularly in regards to osteophyte formation. This suggests that, similar to the role of inflammation, there are likely to be subsets of OA where bone is a driving factor in the disease process and osteophytes are not the best marker to define these subsets. Missing from this review is a discussion of the focal areas of bone remodeling that can be detected by imaging modalities such as CT and which may be important in pain and/or disease progression. Clearly the OA field is rapidly advancing but a better understanding of the biology of the disease that can translate to new therapeutics will require a division of OA into subsets of disease which will have different etiologies rather than lumping all of OA into a single disease process.

Author contribution

Richard F. Loeser searched the literature, summarized the results, and wrote the manuscript.

Conflict of interests

The author has no competing interests.

Acknowledgments

Dr Loeser’s work has been supported by grants from the NIH (R37 AR049003 and RO1 AG044034) and the Arthritis Foundation as well as the Dorothy Rhyne Kimbrell and Willard Duke Kimbrell Professorship.

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Fig. 1. Interactions among tissues and biological mediators that contribute to the biology of OA.
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