HHS Public Access

Author manuscript

Curr Opin Rheumatol. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

Curr Opin Rheumatol. 2015 May ; 27(3): 289–294. doi:10.1097/BOR.0000000000000162.

The Biological Basis of Osteoarthritis: State of the Evidence

Charles J. Malemud[1]

Arthritis Research Laboratory, Department of Medicine, Division of Rheumatic Diseases, Case Western Reserve University School of Medicine and University Hospitals Case Medical Center, Cleveland, Ohio USA

Abstract

Purpose of Review—Evidence accumulated since 2010 indicates that human osteoarthritis should now be reclassified as a systemic musculoskeletal disease rather than a focal disorder of synovial joints.

Recent Findings—Inflammation was seen as the key component promoting synovitis as well as progression of cartilage and bone destruction in osteoarthritis. Thus, metabolic-triggered inflammation involving cytokines, adipokines, abnormal metabolites, acute phase reactants and even complement, all appear to play major roles in OA pathophysiology. Immune-mediated inflammation involving T- and B-cells as well as macrophages is now considered a common finding in OA synovial tissue. Many experimental and clinical analyses showed that the pro-inflammatory cytokines which stimulate matrix metalloproteinase and a disintegrin and metalloproteinase with thrombospondin motif gene transcription in normal and OA human chondrocyte cultures are also present at significantly elevated levels in the synovial fluid of OA patients compared to non-arthritic synovial fluids.

Summary—Human osteoarthritis is a systemic musculoskeletal disorder involving activation of innate and adaptive immune systems accompanied by inflammation exemplified by the elevated production of pro-inflammatory cytokines which play a significant role in the progression of the disease. The future of novel therapies for osteoarthritis should consider developing drug development strategies designed to inhibit pro-inflammatory cytokine-induced signal transduction. These strategies have been successful in the development of drugs for the treatment of rheumatoid arthritis.

Keywords

A disintegrin and metalloproteinase with thrombospondin motif; adipokines; cytokines; innate and adaptive immunity; matrix metalloproteinases

[1]Corresponding Author's Address and Contact Information: Charles J. Malemud, Ph.D., Department of Medicine, Division of Rheumatic Disease, University Hospitals Case Medical Center, Foley Medical Building, 2061 Cornell Road, Room 207, Cleveland, Ohio 44106-5076 USA, Telephone: (216) 844-7846; Mobile Phone: (216) 536-1945 (Preferred), Fax: (216) 844-2288, cjm4@cwru.edu.

Conflicts of Interest: None

Introduction

The pathogenesis of human osteoarthritis (OA) was, for most of the 20th century, characterized merely as a “wear-and-tear” mechanically-driven focal musculoskeletal disorder associated with the ageing process [1] for which no medical intervention besides joint replacement surgery would “cure.” It was only a little more than 10 years ago when Pelletier, Martel-Pelletier and Abramson “re-conceptualized” human OA as an inflammatory disease of diarthrodial synovial joints for which the inflammation characterized as “non-classical” [2]. Thus, they Pelletier et al. [2] contended that “non-classical” inflammation contributed to OA synovitis [3–6] and its pathology, but more importantly inflammation was viewed as the key component in promoting the progression of OA cartilage and bone destruction. In fact, Berenbaum noted [7] that, in addition to inflammatory changes which clearly alter articular cartilage homeostasis, subchondral bone may also play substantial role in the OA process, not only by acting to dampen mechanical responses but also serving as a primary source and reservoir for inflammatory mediators implicated in both the pain pathways associated with OA as well as in the degradation of the deep layer of articular cartilage.

More recently, Cicuttini and Wluka [8] proposed that OA also be reclassified as a systemic disease rather than a focal disease of the joints. Thus metabolic-triggered inflammation involving cytokines, adipokines, abnormal metabolites, acute phase reactants, Vitamin D deficiency and dysregulated microRNA metabolism all appear to play major roles in OA pathophysiology [9].

As we enter the middle of the second decade of the 21st century, this novel and seminal contra point to reclassify OA as an inflammatory, systemic disease with abnormal metabolic overtones has been confirmed through many systematic analyses of sera, synovial tissue, synovial fluid, articular cartilage and subchondral bone. Even more than inflammation simply contributing to OA, OA also appears to involve altered innate and adaptive immunity which was totally unforeseen until activated T-cells were immunolocalized to the synovial tissue of human OA joint specimens [10]. In fact, immune-mediated inflammation is now considered to be a common finding in OA synovial tissue where immune cell infiltration and cytokine secretion is a prominent finding [11].

Recently, Haseeb and Haqqi [12] proposed a model of OA pathogenesis in which multiple aberrations in genetic, homeostatic and/or mechanical factors described by earlier investigators were incorporated. These abnormalities could include genetic mutations, a skewed balance between anabolic and catabolic cytokines and growth factors as well as evidence for subtle anatomic joint dysplasias contributing to the mechanical abnormalities associated with OA. Taken together these factors would then cause cartilage injury and as a result destroy the integrity of articular cartilage that would potentially expose sequestered cartilage-specific autoantigens to the immune system. Thus, newly produced cartilage autoantigens would then have the capacity to promote immune activation resulting in the migration, adhesion and retention of T-cells, B- cells and macrophages in joint synovial tissue. In this fashion, cytokines and chemokines would be secreted from activated immune cells which, in all likelihood, also involve activated complement components as well.

Now we know that in addition to T-cells, B-cells and macrophages, the degradation of the articular cartilage extracellular matrix proteins in OA is brought about by the concerted activity of several matrix metalloproteinases (MMPs), but most prominently, MMP-1 (collagenase-1), MMP-3 (stromelysin-1), MMP-2, (72kDa gelatinase), MMP-9 (92kDa gelatinase) and MMP-13 (collagenase-3) [13, 14] as well as another class of enzymes, a disintegrin and metalloproteinase (ADAMS) and a disintegrin and metalloproteinase with thrombospondin motif (ADAMTS) [15] of which ADAMTS-4 and ADAMTS-5 appear to be the most critical of the ADAMTS family for initiating the degradation of the large aggregating proteoglycan, aggrecan, in early OA [16, 17].

Importantly results from many experimental and clinically-based studies demonstrated that the pro-inflammatory cytokines which were shown to stimulate MMP and ADAMTS gene transcription in normal and OA human chondrocyte cultures [18, 19] were also found at significantly elevated levels in the synovial fluid of patients with OA compared synovial fluids from to non-arthritic patients. Thus, these studies also provided compelling evidence that the pro- and anti-inflammatory cytokines, tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-4, IL-6, IL-15, IL-10, IL-13, IL-15, IL-17, IL-18, IL-21, as well as chemokines, such as monocyte chemotactic protein-1 (MCP-1), fractalkine and IL-8, transcription factors, such as NF-κB and NFAT1, members of the bone morphogenetic protein family including the *BMP*, *WNT*, *GREM1*, *FRZB and DKK1* genes, growth factors, such as transforming growth factor-β, vascular endothelial growth factor, and epidermal growth factor [20, 21], leukemia inhibitory factor [22, 23], hormonally-stimulated pain pathways, and OA susceptibility genes, such as *GDF5*, all appear to be vital components germane to the OA process [24–38]. Thus, it is likely that further understanding of how a balance between the pro-inflammatory and anti-inflammatory cytokine repertoire is maintained will not only reveal the complexity inherent in regulating the destruction of synovial joints in OA, but will also be instructive for designing interventional strategies that would have been completely ignored 20 or more years ago. These interventional strategies should now include ways to therapeutically limit synovial tissue inflammation and therefore the joint destruction of OA whilst also potentially stimulating articular cartilage repair.

The cytokine repertoire in synovial fluid and serum reflects their presumed role in OA

The cytokine repertoire in serum and synovial fluid from OA patients has been employed to determine the extent to which they reflect their role in OA [39]. In that regard, the results from a few studies indicated that that increased levels of serum IL-6 and CRP were consistently higher in individuals diagnosed with radiographic knee OA than in a control group [40]. In addition, Moktar et al [41] found that 57.1% of the cartilages obtained from OA patients who underwent total knee replacement contained elevated levels of IL-6 compared to normal cartilage. Furthermore, serum levels of IL-6 and TNF-α were associated with cartilage loss (measured by joint space narrowing) in older adults with radiographic evidence of OA [42]. However, whereas baseline serum levels of IL-6 predicted loss of medial and lateral tibial plateau cartilage volume, this finding was independent of TNF-α. Most importantly, the TNF-α concentration in knee synovial tissue from OA subjects did not correlate with Kellgren-Lawrence (K-L) grading score, whereas IL-6 had a significantly negative relationship with K-L scores [43].

Whilst differences were detected in IL-6 and TNF-α using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) an instrument to measure pain, stiffness and physical function in OA, this finding suggested that IL-6 and TNF-α played a role in synovial inflammation in OA, but in opposite directions; thus increased levels of TNF-α levels were associated with pain, whereas increased IL-6 levels were associated with joint function. Of note, Abe et al [44] concluded from their recently published study that elevated levels of IL-6 and TNF-α were highly predictive of the rate of ongoing joint destruction in OA.

With respect to other cytokines involved in the OA process, Barker et al [45] showed that evidence of early knee OA as measured by radiography, pain and muscle weakness parameters was associated with increased serum levels of TNF-α as expected, but also these patients had increased levels of IL-5, IL-6, IL-12, IL-13 compared to patients with late OA. This was also the case for serum and synovial fluid levels of IL-17 which was higher in OA patients compared with controls where synovial fluid IL-17 was increased in association with the higher K-L grade and the Lequesne index [46], the latter a scoring system for determining the severity of hip OA which has also been employed to assess the effectiveness of therapies for hip OA.

Studies which measured the concentration of IL-2, IL-5, MCP-1 and macrophage inhibitory protein-1 (MIF-1) in OA synovial fluid also showed a marked elevation in these parameters compared to synovial fluid from those subjects with little or no arthritis, indicative that IL-5 and these other cytokines were likely to play a role in OA progression [47]. Moreover, elevated levels of MIF-1 in the serum and synovial of OA patients with a K-L cartilage grade of 4 showed that MIF-1 levels were associated with the radiographic severity of OA [48].

IL-1β levels are generally elevated in OA synovial fluid. Thus IL-1β was considered to be an important component in OA pathogenesis and progression [49]. However, the median synovial fluid concentration of IL-1α was shown to be increased when subjects with “mild” OA were compared to subjects with “moderate” OA, which was not the case with IL-1β [50]. However, this finding was re-examined by Tsuchida et al [51] who found that IL-1α and IL-1β was markedly higher in OA cartilage than in OA synovial fluid. In addition, IL-6, IL-13, interferon-α and OSM levels in synovial fluid were higher in subjects with cartilage pathology compared to non-pathologic synovial fluids. Thus, the overall cytokine repertoire, including IL-1β, of OA synovial fluid was primarily dependent on the extent of OA pathology. Importantly, human chondrocytes cultures derived from these pathologic cartilage samples produced a cytokine repertoire reminiscent of the very same cytokines that are elevated in OA synovial fluid.

Adipokines are a family of cytokines with a prominent role in OA

Adiponectin, a member of the adipokine family was shown to be a mediator of cartilage extracellular matrix protein degradation through its capacity to increase MMP and inducible nitric oxide synthase-II (iNOS-II) gene expression [52, 53]. Induction of MMP and iNOS-II by adiponectin also required activation of human chondrocyte adenosine monophosphate protein kinase and c-Jun-amino-terminal kinase signaling [53].

Other analyses of adipokine-induced changes associated with OA showed that 1) although adipokine levels were higher in sera from OA subjects compared to sera from non-OA subjects, there was no association between adipokine levels in OA sera and damage to articular cartilage determined by proteoglycan content and histochemical analysis of cartilage specimens [54]. However, a weak, but positive correlation, between adiponectin (as well as IL-1β) was found with respect to the inflammatory state of OA synovial tissue; 2) Resistin, another member of the adipokine family, was found at elevated levels in OA synovial fluid [55]. Furthermore, resistin levels in OA synovial fluid correlated with the level of IL-6, MMP-1 and MMP-3. Furthermore, resistin levels in OA plasma were positively correlated with resistin levels in OA synovial fluid; 3) Nefastin-1, another member of the adipokine family, was elevated in the sera of patients with OA of the knee, but nefastin-1 levels in OA sera exceeded that of OA synovial fluid [56]. Of note, serum nefastin-1 levels were positively correlated with high-sensitivity CRP and IL-18, suggesting a relationship between nefastin-1, inflammation and OA pathology; 4) Visfatin/Nampt, another member of the adipokine family, was found to be released into the culture medium by OA synovial tissue *ex vivo* [57]. Moreover, visfatin significantly increased IL-6, keratinocyte chemoattraction factor, and MCP-1 levels by cultured chondrocytes and osteoblasts. All 3 of these molecules were decreased by adding APO866 (Daporinad) an inhibitor of Nampt enzyme activity to the culture medium. Thus, Nampt activity appeared to be involved in chondrocyte and osteoblast activation and, as such, Nampt may be another suitable target for OA by determining the extent to which inhibition of Nampt enzyme activity alters OA progression. Additional weight was added to this possibility because Yang et al [58] had previously shown that Nampt protein increased MMP-1, -12 and -13 as well as hypoxia-inducible factor-1α mRNA in articular chondrocytes and in OA cartilage explants *in vitro*, suggesting that Nampt was likely a strong catabolic factor in determining the extent of OA cartilage damage.

Conclusions

The role of cytokines as orchestrators of OA pathogenesis and progression has been a focus of attention by basic and clinical investigators for many years. However, despite the fact that a pro-inflammatory cytokine, such as IL-1β, was implicated in OA pathology, OA clinical trials employing several anti-IL-1 strategies have generally been disappointing because they lacked significant clinical efficacy [49, 59–61].

Unfortunately at present there are no novel US Federal Drug Administration approved anti-cytokine therapies for OA. However, recent developments have implicated other cytokines besides IL-1 in the OA process, including IL-6. In addition, showing that IL-17, IL-18, [62], IL-15 and TNF-α correlate with OA pathology has provided the impetus for focusing some attention on these cytokines as potential targets for OA therapeutic intervention. Moreover, identifying cytokines belonging to the adipokine family of proteins such as adiponectin [52, 53] and OSM [63] as mediators of OA cartilage and subchondral bone abnormalities has also been advanced due, in part, to the role that adipokines play in promoting the expression of MMP genes by chondrocytes. These findings have implicated adipokines as playing an important role in the degradation of articular cartilage extracellular matrix proteins. This advance in our knowledge base is particularly important because MMP inhibitor strategies

exploiting paradigms of medicinal chemistry [64] which were essentially designed to directly inhibit MMP activity by articular chondrocytes in OA cartilage have been unsuccessful when these MMP inhibitors were employed in OA clinical trials [65]. Because of these failures novel approaches may have to be employed to take advantage of those signal transduction pathways that are likely to govern gene expression in OA and, therefore specifically to dampen MMP gene expression [14]. However, despite failed opportunities, new tactics to develop “selective” proteinase inhibitors for ameliorating OA progression does not seem beyond the realm of possibility [66]. Therefore, the next period of basic and clinical OA research will be forced to take into account the mounting evidence which points to a targeted genomic approach to limit pro-inflammatory cytokine-induced changes in synovial joint immune-mediated inflammation. This could also include the “fine-tuning” of the chondrocyte reactive oxygen species responses which has been shown to alter chondrocyte mitochondrial function [67].

Finally, the future of OA therapeutic drug development will likely require the use of biologic approaches designed to alter the pathologic responses and activities of chondrocytes, synoviocytes and macrophages. Thus, drug development strategies such as those employed to successfully treat RA may also have to be aligned with those strategies that analyze the effects of these biologic drugs as inhibitors of OA chondrocyte, macrophage and synoviocyte MMPs [68–75]. These agents will also have to be assessed for their ability to ameliorate OA in pre-clinical animal models and then going forward tested to determine their clinical efficacy in OA clinical trials as was shown to be the case for biologic drugs in use for the treatment of RA.

Acknowledgements

None

Financial support and sponsorship: From 2010–2014 the Arthritis Research Laboratory was supported by a contract (#ACT-077) between Charles J. Malemud, Ph.D. (Principal Investigator)/Case Western Reserve University School of Medicine and Genentech/Roche Group (South San Francisco, CA, USA).

The Arthritis Research Laboratory is supported, in part, by the Case Western Reserve University Visual Sciences Core Center Grant (P30-EY11373) from the National Eye Institute (Bethesda, MD, USA)

References

1. Hügle T, Geurts J, Nüesch C, et al. Aging and osteoarthritis: an inevitable encounter? J Aging Res. 2012; 2012:950192. [PubMed: 22720159]
2. Pelletier J-P, Martel-Pelletier J, Abramson SB. Osteoarthritis, an inflammatory disease: potential implications for the selection of new therapeutic targets. Arthritis Rheum. 2001; 44:1237–1247. [PubMed: 11407681]
3. Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nat Rev Rheumatol. 2010; 6:625–635. [PubMed: 20924410]
4. Mueller MB, Tuan RS. Anabolic/Catabolic balance in the pathogenesis of osteoarthritis: identifying molecular targets. PM R. 2011; 3(6 Suppl 1):S3–S11. [PubMed: 21703577]
5. Goldring MB, Otero M. Inflammation in osteoarthritis. Curr Opin Rheumatol. 2011; 23:471–478. [PubMed: 21788902]
6. Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. Bone. 2012; 51:249–257. [PubMed: 22387238]

7. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage. 2013; 21:16–21. [PubMed: 23194896] At one time OA was considered to be driven only by the altered structure of articular cartilage. Now OA must be reevaluated and characterized as a complex disease orchestrated by inflammatory mediators produced by cartilage, bone and synovium.
8. Cicuttini FM, Wluka AE. Osteoarthritis: Is OA a mechanical or systemic disease? Nat Rev Rheumatol. 2014; 10:515–516. [PubMed: 25023454]
9. Wang X, Hunter D, Xu J, et al. Metabolic triggered inflammation in osteoarthritis. Osteoarthritis Cartilage. 2015; 23:22–30. [PubMed: 25452156] Complement components are abundant in OA joints and may be a causative component of pathology.
10. Sakkas LI, Platsoucas CD. The role of T cells in the pathogenesis of osteoarthritis. Arthritis Rheum. 2007; 56:409–424. [PubMed: 17265476]
11. de Lange-Brokaar BJ, Ioan-Facsinay A, van Osch GJ, et al. Synovial inflammation, immune cells and their cytokines in osteoarthritis: a review. Osteoarthritis Cartilage. 2012; 20:1484–1499. [PubMed: 22960092]
12. Haseeb A, Haqqi TM. Immunopathogenesis of osteoarthritis. Clin Immunol. 2013; 146:185–196. [PubMed: 23360836] Cartilage-specific auto-antigens trigger an immune response resulting in immune cell activation, migration and retention in OA synovial tissue where these cells establish a state of inflammation.
13. Meszaros E, Malemud CJ. Prospects for treating osteoarthritis: enzyme-protein interactions regulating matrix metalloproteinase activity. Therapeut Adv Chronic Dis. 2012; 3:219–229.
14. Malemud, CJ. Regulation of chondrocyte matrix metalloproteinase gene expression. In: Dhalla, NS.; Chakraborti, S., editors. Role of Proteases in Cellular Dysfunction. United Kingdom: Springer Science; 2013. p. 63-77.
15. Gargiulo S, Gamba P, Poli G, et al. Metalloproteinases and metalloproteinase inhibitors in age-related diseases. Curr Pharm Des. 2014; 20:2993–3018. [PubMed: 24079771]
16. Verma P, Dalal K. ADAMTS-4 and ADAMTS-5: key enzymes in osteoarthritis. J Cell Biochem. 2011; 112:3507–3514. [PubMed: 21815191]
17. Zhang E, Yan X, Zhang M, et al. Aggrecanases in the human synovial fluid at different stages of osteoarthritis. Clin Rheumatol. 2013; 32:797–803. [PubMed: 23370724] ADAMTS-4 is likely to be the principal aggrecanase in OA cartilage responsible for the degradation of the large aggregating proteoglycan, aggrecan.
18. Sylvester J, El Mabrouk M, Ahmad R, et al. Interleukin-1 induction of aggrecanase gene expression in human articular chondrocytes is mediated by mitogen-activated protein kinases. Cell Physiol. Biochem. 2012; 30:563–574. [PubMed: 22832115]
19. Xue J, Wang J, Liu Q, et al. Tumor necrosis factor-α induces ADAMTS-4 expression in human osteoarthritis chondrocytes. Mol Med Rep. 2013; 8:1755–1760. [PubMed: 24126638] This study demonstrated that TNF-α induces ADAMTS-4 gene expression in human osteoarthritis chondrocytes which involves a p38 MAPK-dependent mechanism.
20. Wu L, Huang X, Li L, et al. Insights on biology and pathology of HIF-1α/-2α, TGFβ/BMP, Wnt/β-catenin and NF-κB pathways in osteoarthritis. Curr Pharm Des. 2012; 18:3293–3312. [PubMed: 22646092]
21. Melas IN, Chairakaki AD, Chatzopoulou EI, et al. Modeling of signaling pathways in chondrocytes based on phosphoproteomics and cytokine release data. Osteoarthritis Cartilage. 2014; 22:509–518. [PubMed: 24457104]
22. Kapoor M, Martel-Pelletier J, Lajeunesse D, et al. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. Nat Rev Rheumatol. 2011; 7:33–42. [PubMed: 21119608]
23. Jiang Y, Xiao Q, Hu Z, et al. Tissue levels of leukemia inhibitory factor vary by osteoarthritis grade. Orthopedics. 2014; 37:e460–e464. [PubMed: 24810823]
24. Funck-Brentano T, Cohen-Solal M. Crosstalk between cartilage and bone: when bone cytokines matter. Cytokine Growth Factor Rev. 2011; 22:91–97. [PubMed: 21596615]
25. Wang M, Shen J, Jin H, et al. Recent progress in understanding molecular mechanisms of cartilage degeneration during osteoarthritis. Ann N Y Acad Sci. 2011; 1240:61–69. [PubMed: 22172041]

26. Li H, Li L, Min J, et al. Levels of metalloproteinase (MMP-3, MMP-9), NF-kappaB ligand (RANKL), and nitric oxide (NO) in peripheral blood of osteoarthritis (OA) patients. Clin Lab. 2012; 58:755–762. [PubMed: 22997976]
27. Leijten JC, Bos SD, Landman EB, et al. GREM1, FRZB and DKK1 mRNA levels correlate with osteoarthritis and are regulated by osteoarthritis-related factors. Arthritis Res Ther. 2013; 15:R126. [PubMed: 24286177]
28. Rigoglou S, Papavassiliou AG. The NF-κB signalling pathway in osteoarthritis. Int J Biochem Cell Biol. 2013; 45:2580–2584. [PubMed: 24004831] Strategies targeted to inhibit the activity of NF-κB signaling could offer a therapeutic option for OA.
29. Houard X, Goldring MB, Berenbaum F. Homeostatic mechanisms in articular cartilage and role of inflammation in osteoarthritis. Curr Rheumatol Rep. 2013; 15:375. [PubMed: 24072604]
30. Sun R, Zhang B, Chen L, et al. Role of nuclear factor of activated T cells in the pathogenesis of osteoarthritis. Exp Ther Med. 2014; 7:195–198. [PubMed: 24348789] Nuclear factor of activated T-cells-1 (NFAT-1), IL-1β and TNF-α gene expression in OA cartilage exceeded these genes expressed by control cartilage. TNF-α, MMP-1, -3-and -9 gene expression induced by IL-1β was decreased in NFAT-1-silenced human chondrocytes.
31. Miller RE, Miller RJ, Malfait AM. Osteoarthritis joint pain: the cytokine connection. Cytokine. 2014; 70:185–193. [PubMed: 25066335]
32. Bevill SL, Boyer KA, Andriacchi TP. The regional sensitivity of chondrocyte gene expression to coactive mechanical load and exogenous TNF-α stimuli. J Biomech Eng. 2014; 136:091005. [PubMed: 24976081]
33. Hermann J, Lipp RW, Dunzinger A, et al. Anti-TNF scintigraphy to assess TNF-α-associated joint inflammation in rheumatoid arthritis and osteoarthritis. Clin Exp Rheumatol. 2014; 32:614. [PubMed: 24959905]
34. Wojdasiewicz P, Poniatowski LA, Szukiewicz D. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. Mediators Inflamm. 2014; 2014:561459. [PubMed: 24876674] IL-1β, TNF-α, IL-6, IL-15, IL-17 and IL-18 appear to be the controlling cytokine repertoire in OA.
35. Blasioli DJ, Kaplan DL. The roles of catabolic factors in the development of osteoarthritis. Tissue Eng Part B Rev. 2014; 20:355–363. [PubMed: 24172137]
36. Remst DF, Blom AB, Vitters EL, et al. Gene expression analysis of murine and human osteoarthritis synovium revelas expression of transforming growth factor β-responsive genes in osteoarthritis-related fibrosis. Arthritis Rheumatol. 2014; 66:647–656. [PubMed: 24574225]
37. Muoh O, Malemud CJ, Askari AD. Clinical significance and implications of genetic and genomic studies in patients with osteoarthritis. Adv Genomics Genetics. 2014; 4:193–206.
38. Ratnayake M, Ploger F, Santibanez-Koref M, et al. Human chondrocytes respond discordantly to the protein encoded by the osteoarthritis susceptibility gene GDF5. PLoS One. 2014; 9:e86590. [PubMed: 24466161]
39. Kokebie R, Aggarwal R, Lidder S, et al. The role of synovial fluid markers of catabolism and anabolism in osteoarthritis, rheumatoid arthritis and asymptomatic organ donors. Arthritis Res Ther. 2011; 13:R50. [PubMed: 21435227]
40. Livshits G, Zhai G, Hart DJ, et al. Interleukin-6 is a significant predictor of radiographic knee osteoarthritis: The Chingford study. Arthritis Rheum. 2009; 60:2037–2045. [PubMed: 19565477]
41. Moktar NM, Yusof HM, Yahaya NH, et al. The transcript level of interleukin-6 in the cartilage of idiopathic osteoarthritis of knee. Clin Ter. 2010; 161:25–28. [PubMed: 20393674]
42. Stannus O, Jones G, Cicuttini F, et al. Circulating levels of IL-6 and TNF-α are associated with knee radiographic osteoarthritis and knee cartilage loss in older adults. Osteoarthritis Cartilage. 2010; 18:1441–1447. [PubMed: 20816981]
43. Orita S, Koshi T, Mitsuka T, et al. Associations between proinflammatory cytokines in the synovial fluid and radiographic grading and pain-related scores in 47 consecutive patients with osteoarthritis of the knee. BMC Musculoskelet Disord. 2011; 12:144. [PubMed: 21714933]
44. Abe H, Sakai T, Ando W, et al. Synovial joint fluid cytokine levels in hip disease. Rheumatology (Oxford). 2014; 53:165–172. [PubMed: 24136066]

45. Barker T, Rogers VE, Henriksen VT, et al. Serum cytokines are increased and circulating micronutrients are not altered in subjects with early compared to advanced knee osteoarthritis. Cytokine. 2014; 68:133–136. [PubMed: 24787465]
46. Chen B, Deng Y, Tan Y, et al. Association between severity of knee osteoarthritis and serum and synovial fluid interleukin 17 concentrations. J Int Med Res. 2014; 42:138–144. [PubMed: 24319050] The concentration of IL-17 in OA sera was significantly greater than in control sera. The concentration of IL-7 increased significantly as a function of K-L grade and also was significantly correlated with the Lesquesne index.
47. Vangsness CT Jr, Burke Ws, Narvy SJ, et al. Human knee synovial fluid cytokines with grade of knee osteoarthritis—a pilot study. Bull NYU Hosp Jt Dis. 2011; 69:122–127. [PubMed: 22035391]
48. Liu M, Hu C. Association of MIF in serum and synovial fluid with severity of osteoarthritis. Clin Biochem. 2012; 45:737–739. [PubMed: 22449335]
49. Malemud CJ. Anticytokine therapy for osteoarthritis: evidence to date. Drugs Aging. 2010; 27:95–115. [PubMed: 20104937]
50. McNulty AL, Rothfusz NE, Leddy HA, Guilak F. Synovial fluid concentrations and relative potency of interleukin-1 alpha and beta in cartilage and meniscus degeneration. J Orthop Res. 2013; 31:1039–1045. [PubMed: 23483596]
51. Tsuchida AI, Beekhuizen MT, Hart MC, et al. Cytokine profiles in the joint depend on pathology, but are different between synovial fluid, cartilage tissue and cultured chondrocytes. Arthritis Res Ther. 2014; 16:441. [PubMed: 25256035] Several pro-inflammatory, pro-angiogenic and pro-repair cytokines are elevated in the joints from patients with symptomatic cartilage defects and/OA.
52. Lago R, Gomez R, Otero M, et al. A new player in cartilage homeostasis: adiponectin induces nitric oxide synthase II and pro-inflammatory cytokines in chondrocytes. Osteoarthritis Cartilage. 2008; 16:1101–1109. [PubMed: 18261936]
53. Kang EH, Lee YJ, Kim TK, et al. Adiponectin is a potential catabolic mediator in osteoarthritis cartilage. Arthritis Res Ther. 2010; 12:R231. [PubMed: 21194467]
54. de Boer TN, van Spil WE, Huisman AM, et al. Serum adipokines in osteoarthritis: comparison with controls and relationship with local parameters of synovial inflammation and cartilage damage. Osteoarthritis Cartilage. 2012; 20:846–853. [PubMed: 22595228]
55. Koskinen A, Vuolteenaho K, Moilanen T, et al. Resistin as a factor in osteoarthritis: synovial fluid resistin concentrations correlate positively with interleukin 6 and matrix metalloproteinases MMP-1 and MMP-3. Scand J Rheumatol. 2014; 43:249–253. [PubMed: 24780007] Resistin levels in OA synovial fluid and were positively correlated with IL-6, MMP-1 and MMP-3. Resistin levels in plasma were positively correlated with resistin in synovial fluid.
56. Jiang L, Bao J, Zhou X, et al. Increased serum levels and chondrocyte expression of nesfatin-1 in patients with osteoarthritis and its relation with BMI, hsCRP and IL-18. Mediators Inflamm. 2013; 2013:631251. [PubMed: 24259949]
57. Laiguillon MC, Huard X, Bougault C, et al. Expression and function of visfatin (Nampt), an adipokine-enzyme involved in inflammatory pathways in osteoarthritis. Arthritis Res Ther. 2014; 16:R38. [PubMed: 24479481] The Nampt activity of visfatin is involved in chondrocyte and osteoblast activation in OA.
58. Yang S, Ryu JH, Oh H, et al. NAMPT (visfatin), a direct target of hypoxia-inducible factor-2α, is an essential catabolic regulator of osteoarthritis. Ann Rheum Dis. 2013 Dec 17. [Epub ahead of print].
59. Malemud CJ, Schulte ME. Is there a final common pathway for arthritis? Future Rheumatol. 2008; 3:253–268.
60. Chevalier X, Goupille P, Beaulieu AD, et al. Intrarticular injection of anakinra in osteoarthritis of the knee: a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2009; 61:344–352. [PubMed: 19248129]
61. Jotanovic Z, Mihelic R, Sestan B, et al. Role of interleukin-1 inhibitors in osteoarthritis: an evidence-based review. Drugs Aging. 2012; 29:343–358. [PubMed: 22550965]

62. Fu Z, Liu P, Yang D, et al. Interleukin-18-induced inflammatory responses in synoviocytes and chondrocytes from osteoarthritic patients. Int J Mol Med. 2012; 30:805–810. [PubMed: 22825306]

63. Beekhuizen H, van Osch GJ, Bot AG, et al. Inhibition of oncostatin M in osteoarthritic synovial fluid enhances GAG production in osteoarthritic cartilage repair. Eur Cell Mater. 2013; 26:80–90. [PubMed: 24027021]

64. Tu G, Xu W, Huang H, et al. Progress in the development of matrix metalloproteinase inhibitors. Curr Med Chem. 2008; 15:1388–1395. [PubMed: 18537616]

65. Krzeski P, Buckland-Wright C, Bálint G, et al. Development of musculoskeletal toxicity without clear benefit after administration of PG-116800, a matrix metalloproteinase inhibitor, to patients with knee osteoarthritis: a randomized, 12-month, double-blind, placebo-controlled trial. Arthritis Res Ther. 2007; 9:R109. [PubMed: 17958901]

66. Flannery CR. Novel therapies in OA. Curr Drug Targets. 2010; 11:614–619. [PubMed: 20199389]

67. Wu L, Liu H, Li L, et al. Mitochondrial pathology in osteoarthritic chondrocytes. Curr Drug Targets. 2014; 15:710–719. [PubMed: 24745822]

68. Zhou M, Qin S, Chu Y, et al. Immunolocalization of MMP-2 and MMP-9 in human rheumatoid synovium. Int J Clin Exp Pathol. 2014; 7:3048–3056. [PubMed: 25031723]

69. Bondeson J. Activated synovial macrophages as targets for osteoarthritis drug therapy. Curr Drug Targets. 2010; 11:576–585. [PubMed: 20199392]

70. Wassilew GI, Lehnigk U, Duda GN, et al. The expression of proinflammatory cytokines and matrix metalloproteinases in the synovial membranes of patients with osteoarthritis compared with traumatic knee disorders. Arthroscopy. 2010; 26:1096–1104. [PubMed: 20678708]

71. Alcaraz MJ, Megias J, Garcia-Arnandis I, et al. New molecular targets for the treatment of osteoarthritis. Biochem Pharmacol. 2010; 80:13–21. [PubMed: 20206140]

72. Bondeson J. Are we moving in the right direction with osteoarthritis drug discovery? Expert Opin Ther Targets. 2011; 15:1355–1368. [PubMed: 22087738]

73. Chevalier X, Conrozier T, Richette P. Desperately looking for the right target in osteoarthritis : the anti-IL-1 strategy. Arthritis Res Ther. 2011; 13:124. [PubMed: 21888686]

74. Mobasheri A. The future of osteoarthritis therapeutics: emerging biological therapy. Curr Rheumatol Rep. 2013; 15:385. [PubMed: 24170255] This review article summarizes an overview of emerging biologic therapy for OA.

75. Chevalier X, Eymard F, Richette P. Biologic agents in osteoarthritis: hopes and disappointments. Nat Rev Rheumatol. 2013; 9:400–410. [PubMed: 23545735]

Key Points

- OA is reclassified as a systemic rather than a focal musculoskeletal disorder of synovial joints.
- Immune-mediated inflammation is now considered a common finding in OA synovial tissue where immune cell infiltration and cytokine secretion is a prominent finding.
- In addition to the changes in synovial joints orchestrated by T-cell, B-cell and macrophage infiltration of synovial tissue in OA, the degradation of articular cartilage extracellular matrix proteins is caused by the concerted activities of MMPs, ADAMS and ADAMTS.
- The repertoire of serum and synovial fluid cytokines reflect their role in the inflammatory response in OA patients. Elevated levels of these cytokines are associated with the severity of joint cartilage and subchondral bone damage.
- Adipokines are a class of pro-inflammatory cytokines that also mediate cartilage degradation in OA.