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Review

Osteoarthritis year in review 2015: biology

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SUMMARY

This review highlights a selection of recently published literature in the area of osteoarthritis biology. Major themes transpiring from a PubMed search covering the year between the 2014 and the 2015 Osteoarthritis Research Society International (OARSI) World Congress are explored. Inflammation emerged as a significant theme, revealing complex pathways that drive dramatic changes in cartilage homeostasis and in the synovium. Highlights include a homeostatic role for CXC chemokines in cartilage, identification of the zinc-ZIP8-MTF1 axis as an essential regulator of cartilage catabolism, and the discovery that a small aggrecan fragment can have catabolic and pro-inflammatory effects through Toll-like receptor 2. Synovitis can promote joint damage, partly through alarmins such as S100A8. Synovitis and synovial expression of the pro-algesic neurotrophin, Nerve Growth Factor, are associated with pain. Increasingly, researchers are considering specific pathogenic pathways that may operate in distinct subsets of osteoarthritis associated with distinct risk factors, including obesity, age, and joint injury. In obesity, the contribution of metabolic factors and diet is under intense investigation. The role of autophagy and oxidative stress in age-related osteoarthritis has been further explored. This approach may open avenues for targeted treatment of distinct phenotypes of osteoarthritis. Finally, a small selection of novel analgesic targets in the periphery is briefly discussed, including calcitonin gene-related peptide and the neuronal sodium voltage-gated channels, Nav1.7 and Nav1.8.

Search criteria and selection process

Papers published online between February 2014 and April 2015 were identified by performing a PubMed search using the following terms: “osteoarthritis”, “animal models”, “joint”, “cartilage”, “chondrocytes”, “synovium”, “subchondral bone”, “risk factors”, “ageing”, “obesity”, “post-traumatic”, and “pain”. From this search, papers were selected in order to illustrate active research topics. The papers included below are a personal selection and by no means capture the wealth of meritorious studies published in the past year. Rather, they were chosen because they exemplify some overarching themes that are emerging in the field, and it is hoped that this selection will entice the reader to conduct a more in-depth exploration of these themes. In addition, reference is made to several recent review articles that provide background information to these main themes.

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Mechanisms of inflammation in cartilage and synovium that drive joint organ failure

All articular tissues – including cartilage, subchondral bone (SCB), synovium, intra-articular fat, meniscus, ligaments, and periarticular muscles – can be affected by osteoarthritis (OA) pathology. Individual tissues and the crosstalk between them likely contribute to disease progression and pain (reviewed in Refs. [1,2]). Emphasis in the past year was on complex pathways, especially in articular cartilage and synovium, that drive catabolism and low-grade inflammation and how these processes affect global joint metabolism (for review, see Ref. [3]).

Altered cartilage homeostasis

In the course of OA, articular chondrocytes are exposed to a range of insults, including aberrant biomechanical stresses, pro-inflammatory cytokines and chemokines and extensive changes in the extracellular matrix (ECM). This provokes a phenotypic shift in chondrocytes and disturbs cartilage homeostasis[4]. Several novel

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pathways that contribute to and perpetuate these dramatic phenotypic changes were uncovered in the past year.

mRNA decay in healthy vs OA chondrocytes

mRNA levels are not just controlled by the rate of synthesis but also by the rate of degradation (i.e., "post-transcriptional regulation"). Tew and colleagues examined mRNA decay in the transcriptome of healthy and OA human chondrocytes, by microarray analysis following an actinomycin D chase[5]. They reported that the majority of chondrocyte-expressed transcripts were stable, but a subset exhibited rapid decay with, interestingly, a clear bias toward shortening of mRNA half-life in OA chondrocytes. Short-lived transcripts included genes involved in transcriptional regulation, localized to the nucleus, or involved in the regulation of programmed cell death. Additionally, the study identified genes related to ECM turnover, such as ADAMTS-1, ADAMTS-5, ADAMTS-9, the hyaluronic acid synthase, HAS2, the heparan sulfate sulfotransferase, HS3ST3A1, and also the NFκB complex component, RELA. These short-lived transcripts were overall more highly expressed in OA chondrocytes, which may mean that they are associated with processes that rely on rapid and flexible gene responses in OA[5]. This first-of-its-kind study adds a new dimension to the regulation of chondrocyte phenotypic stability.

A homeostatic role for CXCR2 signaling in articular cartilage

CXC chemokines with an ELR motif are heparin-binding chemokines that signal through CXCR1 and CXCR2 and have been targeted in inflammatory arthritis because of their chemotactic properties. However, an unexpected homeostatic role for CXCR2 signaling in articular cartilage was revealed by Sherwood and coworkers[6], who found that the CXCR1/2 ligand, CXCL6, was present in the territorial matrix of healthy human cartilage, bound to heparan sulfate proteoglycans. In contrast, in early human or murine OA, CXCL6 was no longer detected. CXCR2-deficient mice showed more severe cartilage damage 8 weeks after destabilization of the medical meniscus (DMM) than wild types, while *in vitro* disruption of CXCR2 signaling resulted in loss of mRNA for the transcription factor, SOX9, COL2A1 mRNA and aggrecan mRNA in primary human chondrocytes. The authors concluded that CXCL6 may support chondrocyte phenotypic stability through SOX9 and that the loss of CXCL6 from degrading cartilage may contribute to the characteristic changes in the phenotype of the OA chondrocyte.

The zinc-ZIP8-MTF1 axis is an essential regulator of the catabolic cascade in cartilage

Kim *et al.* reported that the zinc (Zn^{2+}) importer, ZIP8, was increased in human and murine OA cartilage, raising intracellular Zn^{2+} in chondrocytes[7]. ZIP8-mediated Zn^{2+} influx upregulated chondrocyte expression of catabolic enzymes, including MMP3, MMP9, MMP12, MMP-13, and ADAMTS-5. Chondrocyte-specific ZIP8 overexpression in mice (using a Col2a1 promoter) resulted in cartilage damage and SCB sclerosis without overt synovitis. After DMM surgery, these mice developed accelerated cartilage destruction and SCB changes, while there was no effect on synovitis and osteophytes. Conversely, chondrocyte-specific conditional *Zip8* knock-out mice showed less cartilage damage and SCB sclerosis 8 weeks after DMM, without protection from synovitis and osteophyte growth. Further, the transcription factor, MTF1, was identified as an essential mediator of Zn^{2+}/ZIP8-induced catabolism. This study establishes the zinc-ZIP8-MTF1 axis as a novel therapeutic target in OA. It also substantiates the notion that cartilage damage can drive changes in other joint tissues, in this case the SCB – but remarkably, there was no effect on synovium or osteophytes.

Catabolic and pro-inflammatory effects of an aggrecan fragment mediated through TLR2

It has long been recognized that matrix molecules and fragments thereof, including fibronectin, tenascin C, and hyaluronan fragments, can act as Damage Associated Molecular Patterns (DAMPs). These DAMPs activate Pattern Recognition Receptors (PRR) such as Toll-like receptors (TLR) and Receptor for Advanced Glycation Endproducts (RAGE) that are locally expressed in the joint, initiating a cascade of inflammatory cytokine production[3]. Lees and co-workers investigated bio-activity of an aggrecan fragment that is generated when ADAMTS-4/5 cleave the interglobular domain of the aggrecan core protein at the ^{374}ARGS cleavage site and the remaining G1-EGE^{373} stub is subsequently cleaved by MMPs at DIPEN^{341}, resulting in a 32-amino acid fragment[8]. A synthetic 32-mer peptide caused a pro-catabolic, anti-anabolic, and pro-inflammatory response *in vitro* in murine and human chondrocytes, increasing mRNA expression for several proteases, including MMP-13 and ADAMTS-5, and decreasing mRNA for matrix molecules, including Col2A1 and aggrecan. These effects are mediated through TLR2 and are NFκB-dependent. It was confirmed that the native, glycosylated 32-mer also has biological activity. This is the first demonstration that a TLR ligand can be derived from one of the major cartilage macromolecules. This aggrecan fragment adds to the pool of DAMPs that can originate from degrading cartilage and amplify the pro-inflammatory and catabolic network in the OA joint. The specific role of the 32-mer aggrecan fragment within the innate immune network *in vivo* needs to be determined.

The pathogenic role of synovium

Clinical and imaging studies provide substantial evidence that low-grade synovitis is associated with accelerated cartilage loss as well as with symptoms (reviewed in Ref. [9]). The recent studies discussed below shed light on synovial pathways that may contribute to OA disease.

The role of the alarmins, S100A8 and S100A9, in OA with pronounced synovitis

S100A8 and S100A9 are abundantly present in OA joints. A few years ago, it was reported that these alarmins have pro-catabolic effects on chondrocytes *via* TLR4, and that they contribute to OA pathogenesis in collagenase-induced OA (CIOA), a model with pronounced synovial inflammation, but not in the DMM model, which exhibits low-grade synovitis[10]. The same authors now reported that intra-articularly (IA) deposited adipose-derived stem cells were efficacious in reducing cartilage damage and osteophytes in CIOA but not after DMM – indicating that synovial activation drives the protective effects of locally administered adipose-derived stem cells[11]. Efficacy in CIOA was related to rapid suppression of synovial activation, suppression of S100A8/A9 and IL-1 in the joint and of S100A8/A9 serum levels[11]. These findings further reinforce the concept that these alarmins may contribute to OA progression in subsets with a high degree of synovitis, and this could be therapeutically exploited. OA joints may, of course, contain a variety of DAMPs in addition to S100 proteins, including ECM degradation products that signal through various PRRs. Hence, it is of interest that female TLR1, TLR2, TLR4, TLR6, or MyD88 deficient mice were not protected from cartilage damage or synovial inflammation 8 weeks after partial removal of the medial meniscus[12]. These paradoxical findings further illustrate the need for careful assessment of the role of the innate immune network in different subsets of OA and at different stages of disease.