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Review

Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!)

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SUMMARY

Osteoarthritis (OA) has long been considered a “wear and tear” disease leading to loss of cartilage. OA used to be considered the sole consequence of any process leading to increased pressure on one particular joint or fragility of cartilage matrix. Progress in molecular biology in the 1990s has profoundly modified this paradigm. The discovery that many soluble mediators such as cytokines or prostaglandins can increase the production of matrix metalloproteinases by chondrocytes led to the first steps of an “inflammatory” theory. However, it took a decade before synovitis was accepted as a critical feature of OA, and some studies are now opening the way to consider the condition a driver of the OA process. Recent experimental data have shown that subchondral bone may have a substantial role in the OA process, as a mechanical damper, as well as a source of inflammatory mediators implicated in the OA pain process and in the degradation of the deep layer of cartilage. Thus, initially considered cartilage driven, OA is a much more complex disease with inflammatory mediators released by cartilage, bone and synovium. Low-grade inflammation induced by the metabolic syndrome, innate immunity and inflammaging are some of the more recent arguments in favor of the inflammatory theory of OA and highlighted in this review.

Osteoarthritis (OA) has long been considered a “wear and tear” disease leading to loss of cartilage. OA used to be considered the sole consequence of any process leading to increased pressure on one particular joint (e.g., overload on weight-bearing joints, anatomical joint incongruency) or fragility of cartilage matrix (genetic alterations of matrix components). This paradigm was mainly based on the observation that chondrocytes, the only cell type present in cartilage, have very low metabolism activity with no ability to repair cartilage. Moreover, unlike all other tissues, articular cartilage, once damaged, cannot respond by a usual inflammatory response because it is non-vascularized and non-innervated.

Progress in molecular biology in the 1990s has profoundly modified this paradigm. The discovery that many soluble mediators such as cytokines or prostaglandins can increase the production of matrix metalloproteinases (MMPs) by chondrocytes led to the first steps of an “inflammatory” theory. However, it took a decade before synovitis was accepted as a critical feature of OA, and some studies are now opening the way to consider the condition a driver of the OA process. Recent experimental data have shown that subchondral bone may have a substantial role in the OA process, as a mechanical damper, as well as, as a source of inflammatory mediators implicated in the OA pain process and in the degradation of the deep layer of cartilage. Thus, initially considered cartilage driven, OA is a much more complex disease with inflammatory mediators released by cartilage, bone and synovium[1–3] (Fig. 1). Interestingly, the source and type of inflammatory mediators may differ by OA phenotype[4].

Synovitis (local inflammation) in OA

Joint swelling is one clinical feature of OA attributed to inflammation and reflecting the presence of synovitis due to thickening of the synovium or to effusion. When patients experience OA flares (night pain, morning stiffness), they usually exhibit in parallel joint effusion, as is seen in classical inflammatory arthropathies such as rheumatoid arthritis (RA)[5]. Pannus-like synovitis may occur, although much more rarely than in RA[6]. Gadolinium-enhanced MRI and ultrasonography are reliable, valid tools for showing OA synovitis[7]. Many studies suggest that the presence of synovitis seen by arthroscopy, magnetic resonance imaging (MRI) or ultrasonography may be a surrogate marker of severity and associated with increased risk of radiographic evidence of disease progression[8,9]. Systemic high-sensitivity C-reactive protein levels reflect synovial inflammation in

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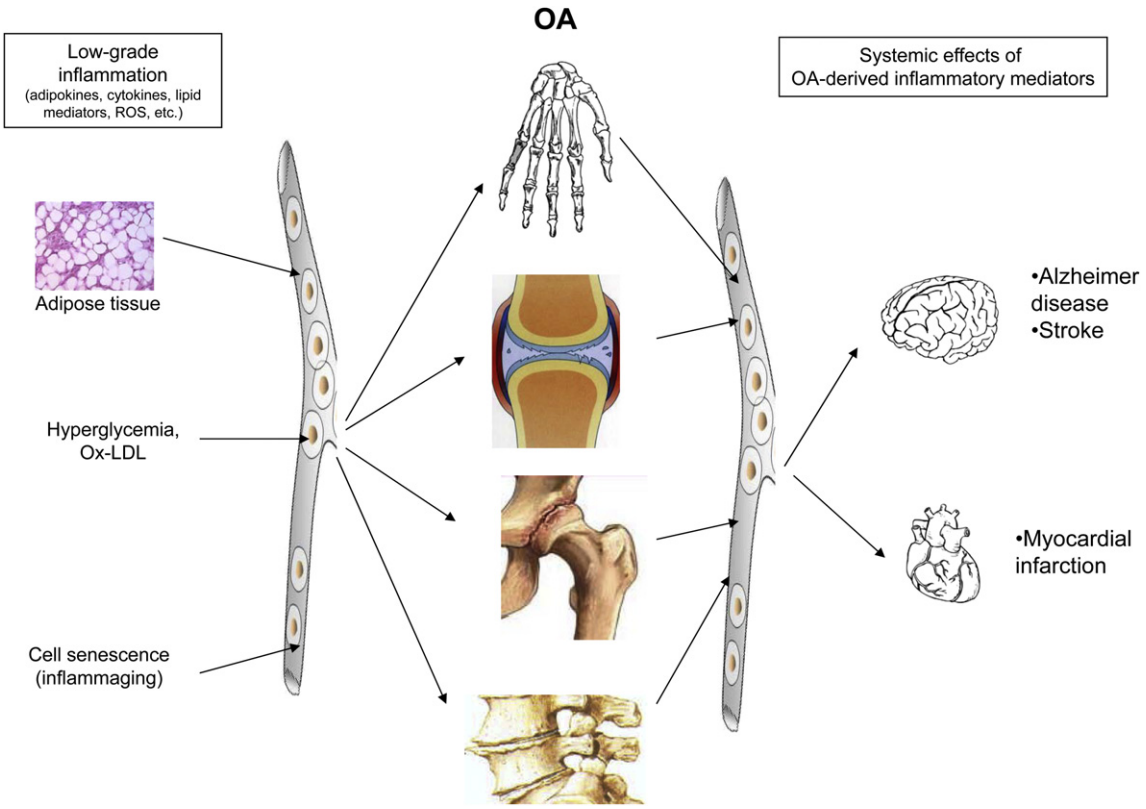

Fig. 1. Systemic effects and potential consequences of OA-derived inflammatory mediators. A proposed novel paradigm for the role of low-grade inflammation in OA. Low-grade inflammation is characterized by the release of inflammatory mediators into the blood during MetS (obesity, insulin resistance, lipid abnormalities, hypertension) or aging (secretory senescence, see text). These inflammatory mediators are deleterious for joint tissues, thus initiating and/or perpetuating the OA process. Once activated, OA joint cells in turn release inflammatory mediators into the joint cavity and eventually into the blood. The mediators amplify the low-grade inflammation, which may induce or accelerate other chronic diseases affected by systemic low-grade inflammation.

OA patients and are associated with level of pain[10,11]. Interestingly, synovial inflammation frequently occurs in traumatic meniscal injury and is associated with increased pain and dysfunction[12].

Why the synovium becomes inflamed in OA remains controversial[13]. The most accepted hypothesis is that, once degraded, cartilage fragments fall into the joint and contact the synovium. Considered foreign bodies, synovial cells react by producing inflammatory mediators, found in synovial fluid. These mediators can activate chondrocytes present in the superficial layer of cartilage, which leads to metalloproteinase synthesis and, eventually, increase cartilage degradation. The mediators can also induce synovial angiogenesis and increase the synthesis of inflammatory cytokines and MMPs by synovial cells themselves (vicious circle). Thus, OA synovitis perpetuates the cartilage degradation.

More recently, another theory involves synovial tissue as a primary trigger of the OA process. Indeed, many cell types usually present in immunological processes have been described in OA, as bystanders and as actors[14]. Depleting synovial macrophages with clodronate liposome before inducing a collagenase-induced instability model of OA in mice prevented the generation of MMP-induced neoepitopes into cartilage[15,16], which indicates an important role for synovial macrophages in MMP-mediated cartilage damage. Moreover, osteophyte formation was decreased, which suggests that these cells are pivotal for this feature[16]. Synovial Inflammation may drive synovial angiogenesis, linked to OA pain, through macrophage activation[17,18]. Molecular markers for dendritic cells were detected in the synovium in a post-traumatic rabbit OA model. Interestingly, large numbers of such cells were observed in the early stages after surgery, which suggested their participation in the early stages of OA[19]. Suurmond *et al.* showed an increased expression of interleukin 17 (IL-17) in OA synovial tissue, synovial mast cells being the main IL-17-positive cells[20].

Innate immunity as a trigger of local inflammation in OA

The innate immune system, also known as non-specific immune system, comprises the cells and mechanisms that defend the host from infection by other organisms in a non-specific manner. This system is triggered after the binding of pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) on pattern-recognition receptors (PRRs)[21,22]. Thus, these responses have been studied as predominant features in multiple non-infectious diseases with tissue injury and/or defective repair. PRRs include membrane-associated PRRs (Toll-like receptors [TLRs], the basic signaling receptors of the innate immune system), cytoplasmic PRRs (nucleotide-binding oligomerization domains [NODs], NALPs, RNA helicases) and secreted PRRs (complement receptors, collectins). PAMPs include bacterial and viral ligands and also extracellular matrix molecules. PAMPs are recognized by TLRs and other PRRs. A pioneer study showed that TLRs are increased in level in OA cartilage lesions[23]. TLR-2 and TLR-4 ligands such as low-molecular-weight hyaluronic acid, fibronectin, tenascin-C and alarmins (S100 proteins, high-mobility group protein B1 [HMGB1]) have been found in OA synovial fluid[24–26]. These factors can induce catabolic responses in chondrocytes and/or inflammatory responses in synoviocytes. For example, S100A8 and S100A9 proteins are involved in synovial activation and cartilage destruction, and high levels may predict joint destruction in OA[27]. These results are corroborated by a proteomic analysis revealing that proteins from OA synovial fluid can induce macrophage production of inflammatory

cytokines *via* TLR-4 signaling[28]. Interestingly, recent data suggest that these events may occur early in the disease, so innate immunity may be a driver of the OA process. Synovial fluid from patients with early OA cartilage damage showed increased fibroblast-like synoviocyte responses to TLR-2 and TLR-4 ligands[28]. Increased levels of interleukin-15 (IL-15) protein are found in the synovial fluid of early knee OA patients when compared to end-stage OA, and numbers of CD8 cells within the synovial membrane is correlated with MMP-1[29].

Another group of proteins involved in innate immunity has recently been highlighted in the context of OA. With proteomic and transcriptomic analyses of synovial fluids and synovial membranes from subjects with OA, Qiang *et al.* found that the expression and activation of complement is abnormally high in human OA joints[30]. Moreover, with experimental OA-induced in mice genetically deficient in different complement factors or by using specific pharmacological inhibitors, the authors showed that dysregulation of complement in synovial joints may have a key role in OA pathogenesis.

Innate immunity responses may be triggered by crystals[31]. Calcium pyrophosphate dihydrate and basic calcium phosphate crystals are common in OA joint fluids and tissues[32]. These crystals, along with uric acid, can interact with the NALP-3 inflammasome, an intracellular protein complex involved in IL-1β and IL-18 activation by cleaving pro-caspase-1 to caspase-1[33,34]. These processes have been well described in gout, but whether they occur in OA remains debatable[35].

Low-grade systemic inflammation in OA

Local production of inflammatory mediators are well known to contribute to cartilage degradation and synovial cell activation, but additional data may link these events to a more systemic pathway. In other words, inflammatory events occurring within joint tissues could be reflected outside the joint in plasma and peripheral blood leukocytes (PBLs) of patients with OA. Levels of several inflammatory mediators are higher in OA than healthy sera[27,36,37]. A remarkable study assessed gene expression profiles in PBLs from patients with OA and found a subset with activated PBLs[38]. Interestingly, cluster analysis revealed two distinct subgroups: one with increased level of IL-1β and one with normal expression. Patients with the inflammatory "IL-1β signature" had higher pain scores and decreased function and were at higher risk of radiographic progression of OA.

The risk of hand OA is increased two-fold in obese patients[39]. This increased risk cannot be explained by the mechanical effect of overload but can certainly be explained by systemic factors released mainly by abdominal adipose tissue and able to reach and then activate joint cells[40]. These systemic factors, called adipokines, have been extensively studied in OA. Among them, leptin, adiponectin, resistin and visfatin/NAMPT have pro- and/or anti-inflammatory properties in OA[41–43]. Interestingly, recent epidemiological and clinical data have highlighted that a metabolic syndrome (MetS) rather than obesity itself has the greatest impact on the initiation and severity of OA[44–46]. In that context, it is noteworthy that there is an independent association between carotid intima medial thickness with the prevalence of knee OA (OR 1.7, 1.1–2.7), and carotid plaque with distal interphalangeal OA (OR 1.4, 1.2–1.7)[47]. The reasons why there is such a link between atherosclerosis and OA remains elusive. One hypothesis relies on the inflammatory theory of atherosclerosis. Several lines of evidence support the hypothesis that oxidized lipids, including oxidized low-density lipoprotein (ox-LDL), are the most likely triggering factors for cytokine production[48]. All these data give strength to the "adipokines theory," because the concentration of plasma adipokines is known to be associated with MetS[49]. Not unsurprisingly, a study showed an association of serum adipokine concentration and OA severity[50,51]. Moreover, systemic adipokines were found associated with local synovial tissue inflammation[52]. Recently, the infrapatellar fat pad, an adipose tissue localized in the knee, was found to be a potential source of adipokines such as IL-6[53,54]. Whether these discoveries would lead to "anti-adipokine" therapies remain hypothetical since these molecules participate into many other physiological processes. However, some data coming from pre-clinical studies could open opportunities. An inhibitor of visfatin/nicotinamide phosphoribosyltransferase (NAMPT), FK866, has recently demonstrated anti-arthritic properties[55]. Another result supporting the role of adipokines relates on the clinical efficacy of a dramatic weight loss by bariatric surgery of obese patients on knee OA that parallels a decrease of low-grade inflammatory systemic markers[56].

A unique study could change the paradigm of the role of inflammation in OA in the near future. Kyrkanides *et al.* induced OA in mice genetically at risk of Alzheimer disease[57]. OA exacerbated and accelerated the development of neuroinflammation as assessed by glial cell activation and quantification of inflammation-related mRNAs, as well as Aβ pathology, assessed by the number and size of amyloid plaques. A likely scenario is that circulating cytokines contribute to brain inflammation and may exacerbate it in the context of Alzheimer disease.

Thus, OA could be initiated and/or aggravated by the presence of a systemic low-grade inflammation but this study supports also the hypothesis that OA could be at the initiation of distant age-related diseases *via* a joint release of inflammatory mediators into the blood stream (Fig. 1). Further experimental and epidemiological studies are needed to confirm this provocative hypothesis.

Aging, inflammation and OA

Inflammation is triggered by external mediators such as cytokines and proteases, as well as internal cellular mechanisms leading to increased production of inflammatory mediators and lack of elimination of oxidated proteins. These proteins will in turn increase the concentration of reactive oxygen species (ROS) in cells, further adding to the oxidative damage triggering the inflammation[58]. Interestingly, oxidative stress can promote cell senescence, and in particular chondrocyte senescence[59].

Although OA is a prototypic age-related disease, the specific mechanisms underlying the process remain largely unknown. At the cellular level, senescence can be divided into two main categories: replicative and secretory. Many human cells in culture have a limited proliferative capacity. After a period of vigorous proliferation, the rate of cell division declines (replicative senescence). However, other cell types like chondrocytes have a lower capacity to divide, which leaves little room for replicative senescence. But these cells have high capacity to synthesize soluble mediators. So, secretory senescence should be predominant with aging. This condition has been called the senescence-associated secretory phenotype (SASP) that includes several inflammatory and prodegradative mediators driven by oxidative stress[60]. Interestingly, the SASP is primarily a delayed response to (epi)genomic damage[61]. Indeed, IL-1β-stimulated MMP-13 chondrocyte production increases with age, suggesting that aging chondrocytes acquire a SASP[62].

Another theory relating inflammation, aging and OA is based on the recent discovery that advanced glycation endproducts (AGEs), produced by a non-enzymatic process in aging tissues, weaken cartilage by modifying its mechanical properties. They can trigger chondrocyte activation by binding to specific receptors present at the surface of the chondrocytes, called RAGE (receptors for AGE). This process can lead to an overproduction of proinflammatory cytokines and MMPs[63–65].

Post-menopausal OA and inflammation

To understand why the incidence of OA increases greatly after menopause, some groups have investigated estrogen regulation. The estrogen receptor is present in chondrocytes, subchondral osteoblasts and synoviocytes[66]. Its activation by estrogen derivatives has led to controversial results, depending on their concentration. However, the overall effect predominantly leads to inhibition of the expression and secretion of proinflammatory cytokines such as IL-1 into the joint[67]. Moreover, decreased ovarian function is accompanied by a spontaneous increase in level of proinflammatory cytokines in plasma[68], which may participate in the low-grade inflammation mentioned here previously. However, this suggestion is speculative because the literature is poor on the topic.

A direct link between mechanics and inflammation: mechanoreceptor signaling

The controversy about the origin of the OA process, mechanics or inflammation, should be ended soon thanks to recent discoveries in mechanosignaling. Any abnormal mechanical stress applied on a joint (stretch, compression, shear stress, hydrostatic pressure) can be converted into activated intracellular signals in joint cells by mechanoreceptors present at the surface of joint cells (ion channels, integrins)[69]. These signals may eventually lead to the overexpression of inflammatory soluble mediators such as prostaglandins, chemokines and cytokines when a certain threshold is reached[70]. This is the case for chondrocytes and for subchondral bone cells present in subchondral bone[71–74]. Intracellularly, the conversion of a mechanical signal to the synthesis of inflammatory mediators is mediated by the activation of inducible signaling pathways. Among them, NF-κB and MAPK pathways seem predominant[75].

Therapeutical consequences

It is noteworthy that despite strong experimental studies described in this review and showing a central role of inflammation in OA, the anti-cytokine approach has not yet proven significative improvement in OA symptoms and structure modification. Pilot and controlled studies using anti-IL-1 and anti-TNF molecules have not been convincing yet[76,77]. However, a very recent open-labeled trial with etanercept is encouraging[78]. These disappointing results may be due to the heterogeneity of the OA patients included in these trials, including phenotypes that may have different pathophysiology (Fig. 2).

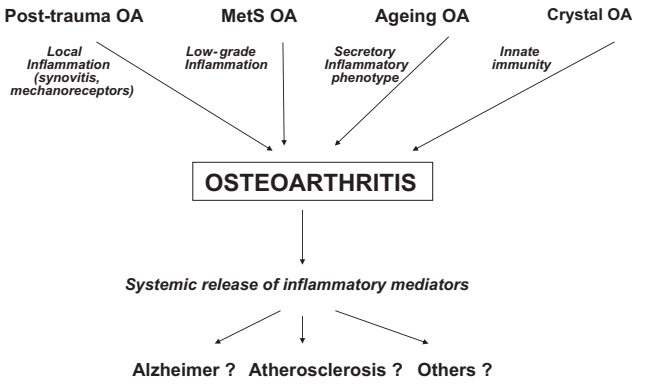

Fig. 2. An hypothesis for the role of inflammation in the pathogenesis of OA according to the phenotype. For each phenotype, the main pathway leading to the release of inflammatory mediators by the joint is highlighted. However, some pathways are shared between phenotypes.

Conclusions

The literature is rich in data suggesting that inflammatory mediators play a pivotal role in the initiation and perpetuation of the OA process. The source of such mediators would be local from joint cells and systemic from other tissues such as adipose tissue released in blood flow and then reaching the joint *via* the subchondral bone vasculature. These mediators then have a deleterious effect on cartilage, bone and synovium. By extrapolation, more recent data suggest that locally produced mediators may have an impact on the initiation and perpetuation of other age-related and metabolic diseases. Deciphering these inflammatory pathways is critical for the discovery of disease-modifying OA drugs in the future.

Author contribution

F. Berenbaum is the sole contributor to this review.

Conflict of interest

No.

Acknowledgments

No.

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