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Inflammaging and Osteoarthritis

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Abstract
Osteoarthritis is a highly prevalent disease particularly in subjects over 65 years of age worldwide. While in the past it was considered a mere consequence of cartilage degradation leading to anatomical and functional joint impairment, in recent decades, there has been a more dynamic view with the synovium, the cartilage, and the subchondral bone producing inflammatory mediators which ultimately lead to cartilage damage. Inflammaging is defined as a chronic, sterile, low-grade inflammation state driven by endogenous signals in the absence of infections, occurring with aging. This chronic status is linked to the production of reactive oxygen species and molecules involved in the development of age-related disease such as cancer, diabetes, and cardiovascular and neurodegenerative diseases. Inflammaging contributes to osteoarthritis development where both the innate and the adaptive immune response are involved. Elevated systemic and local inflammatory cytokines and senescent molecules promote cartilage degradation, and antigens derived from damaged joints further trigger inflammation through inflammasome activation. B and T lymphocyte populations also change with inflammaging and OA, with reduced regulatory functions, thus implicating self-reactivity as an additional mechanism of joint damage. The discovery of the underlying pathogenic pathways may help to identify potential therapeutic targets for the management or the prevention of osteoarthritis. We will provide a comprehensive evaluation of the current literature on the role of inflammaging in osteoarthritis and discuss the emerging therapeutic strategies.

Keywords Degenerative joint pain · Senior · Cartilage failure · Frailty

Introduction

Osteoarthritis (OA) is a slowly progressing joint disease that predominantly affects the elderly population, affecting mobility, quality of life, and increasing mortality. Historically, it was thought to be a consequence of degenerative alterations leading to anatomical remodeling of the joints [1]. In the past decades, it has become increasingly clear that other factors are involved in the etiopathogenesis of OA and that the immune response to stressors plays a key role. In this review, the role of inflammation in OA will be elucidated, in particular in light of new evidence related to the condition referred to as "inflammaging."

The Burden of Osteoarthritis

OA is the most common form of joint disease. It involves the cartilage and other surrounding tissues, leading, in the advanced stages of the disease, to damage and loss of articular cartilage, remodeling of the subchondral bone with osteophyte formation, ligamentous laxity, and weakening of periarticular muscles [2]. OA predominantly affects the hands, hips, knees, feet, and cervical and lumbar spine while being less common in other joints. Pain is the typical symptom that leads people to present to healthcare providers and subsequently to receive a diagnosis of OA. Other primary symptoms include joint stiffness and limitation of movements. Progression is usually indolent and can eventually lead to complete joint impairment with pain and disability [3].

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OA can be defined as a clinical or radiological entity. Clinical OA is defined by features in the history and in the medical examination, requiring invariably the presence of joint pain [3]. Some of the used standards for the diagnosis of clinical OA are the American College of Rheumatology (ACR) criteria which have been developed for hip [4], knee [5], and hand [6] OA.

Radiographic OA diagnosis and severity grade are often assessed in studies using the Kellgren and Lawrence score [3]. The overall grades of severity are determined from 0 to 4 and are related to the presumed sequential appearance of joint space loss, osteophytes, sclerosis, and cysts [7]. Magnetic resonance imaging (MRI) detects the disease earlier and provides evidence of matrix changes in cartilage, synovitis, bone marrow lesions, and degenerative changes in soft-tissue structures beyond the cartilage, including ligaments and the knee menisci [8, 9].

Epidemiology

The number of people affected by OA is constantly rising worldwide, and OA is currently one of the major causes of disability in older adults [10]. As it is primarily related to aging, the prevalence of OA will increase and is expected to be the single greatest cause of disability in the general population by 2030 [2]. The prevalence of OA varies according to the definition of OA, the specific joint considered, and the features of the population studied. Incidence rates of symptomatic hand, hip, and knee OA increase rapidly around 50 years of age reaching a plateau after 70 years of age [11].

The prevalence of hand OA at imaging varies greatly and has been reported to range from 27 to over 80% [12]. Data from the Framingham Cohort demonstrated a prevalence of 13.2% in men and 26.2% in women aged 70 or more years with at least one hand joint with symptomatic OA [13]. Knee involvement occurs less frequently than hand OA, although both are more common in women. Among participants older than 45 years in the Framingham Study, the prevalence of radiographic knee OA was 19.2%, and in those over 80 years, it rose to 43.7%. Hip OA is the most unfrequently kind [3]. In addition, OA leads to a substantial amount of healthcare costs and resource use. In the USA, the estimated total annual average direct per-patient cost varied from $1,442 to $21,335 (adjusted to 2015 US$ equivalent) [14]. The indirect costs on working activity have also to be taken into account. In a Swedish population-based study, the risk for sick leave or disability was more frequent among workers affected by knee OA [15].

OA is one of the major causes of disability around the globe [16] that invalidates an elevated number of everyday living activities [17], and years lived with disability were exceptionally high among elderly people with OA [18]. Furthermore, OA may also negatively impact mental health, with higher probability to manifest depressive symptoms in patients with lower limb OA than those without the disease [19]. OA is also associated with greater odds of suicidal ideation [20]. A strong relationship between OA and perceived memory loss due to sleep and mood impairment was demonstrated [21]. There is also evidence that OA is a risk factor for cardiovascular disease (CVD) development, with a significant increase of the risk of myocardial infarction in patients having OA or other types of arthritis [22–24]. In the Chingford Cohort study, an increased risk of CVD-specific and all-cause mortality among women with symptomatic knee OA compared with an healthy group was found, while notably no relationship was found between hand OA and mortality risk [24, 25]. OA may impair the ability of people with cardio-metabolic conditions to exercise and lose weight, which is the core of the management of these conditions [26]. Among people with symptomatic hip and/or knee OA and concomitant diabetes, difficulty in walking predicts higher risk of serious complications related to diabetes [27] and an increased risk for diabetes in those who did not have diabetes at baseline [28]. Potential explanations include the influence of OA-related low-grade systemic inflammation on insulin resistance, the use of non-steroidal anti-inflammatory drugs (NSAIDs) for OA pain and weight gain for sedentary behavior [26, 29–31].

Risk Factors for OA

There are several risk factors for OA. First, there are strong genetic bases causing the susceptibility to OA. Genetics accounts for 40–65% of OA risk [32], with a non-Mendelian manner inheritance, as OA is a multifactorial disease. Genetics alone is unlikely to identify individuals who will develop disease, but it might reveal new biological insights into disease pathogenesis for individual joints [33]. The genetic bases are stronger for hand and hip OA compared to knee OA [32, 34, 35]. The Arthritis Research UK Osteoarthritis Genetics (arcOGEN) Consortium has identified 11 loci associated with OA [36]. Genome-wide association studies (GWAS) have identified 90 independent susceptibility loci for OA [37]. In addition, single-nucleotide polymorphisms have been associated with several known risk factors, including hip shape, body mass index, and bone mineral density [38]. Several inflammation-related genes are involved in OA susceptibility (summarized in Table 1) reinforcing the concept that OA has an inflammatory component [39, 40]. Nonetheless, the OA loci discovered explain only a small fraction of OA heritability estimated by epidemiological studies.

Table 1 The major inflammation-related genes involved in osteoarthritis [40]

Genes	Genetic loci	Normal function	Dysregulation in OA
SMAD3	15q22.33	It is an intracellular mediator of TGF-β signaling which is involved in regulating chondrocyte proliferation, differentiation, and matrix mineralization	The shift from ALK5-SMAD2/3 dependent to AL1-SMAD1/5/8 dependent signaling leads to loss of chondrocyte homeostasis and to development of OA
RUNX2	6P21.1	It is essential in endochondral ossification but has to be suppressed to allow formation and maintenance of permanent cartilage	Its alteration leads to chondrocyte hypertrophy, cartilage destruction, and osteophyte development
PTHLH	12p11.22	It encodes the parathyroid hormone-related protein (PTHrP), and it is involved in chondrocyte differentiation rate control and in cartilage homeostasis in postnatal life	Its alteration leads to the reduction of PTHrP/PTH signaling
GDF5	20q11.22	It signals through SMAD1/5/8 pathway, enhancing mesenchymal stem cell differentiation to the chondrogenic lineage and promoting chondrocyte hypertrophy during endochondral ossification. It has important function in postnatal joint homeostasis and repair	It is overexpressed in osteophytic cartilage
CHST11	12q23.3	It encodes for carbohydrate sulfotransferase 1, a Golgi membrane enzyme that catalyzes the transfer of sulfate groups to chondroitin, a disaccharide covalently linked to the aggrecan core protein, forming the highly abundant extracellular matrix glycoprotein aggrecan	Gene knockout in mice led to fibrillation of the cartilage, similar to that seen in OA cartilage

New evidences show that part of the risk may be due to epigenetic modifications of genomic DNA [41–44], illustrated in Table 2. This is of particularly interest since aging-related DNA methylation involves different genome portions according to gender: less than 5% of DNA methylation changes are common between males and females [45].

Age is the strongest risk factor for OA [12], since it leads to reduction in regenerative capacity and accumulation of risk factors. Compared to other races, African-Americans are also more likely to develop symptomatic knee and hip OA, with ethnic differences in radiographic OA features [11, 46]. Another risk factor is sex, since OA is more common in women than in men, even if the underlying mechanism remains unclear [47].

Congenital anatomical factors (hip dysplasia [33], femoroacetabular impingement [48], tibial and femoral bone abnormal morphology [49], varus or valgus knee alignment [50, 51], and leg length inequality [52]) and functional factors like a poor quadriceps function [53], sporting activity [54], and a high-intensity activity [55] may all promote the development of OA. Despite these strong associations, individuals with abnormal joint biomechanics may never develop OA, as susceptibility is partly determined by other factors [48]. Specific bone properties could confer some susceptibility, as high bone mineral density seems to increase the risk of incident OA but not disease progression [56]. Injuries can cause bone or cartilage damage that makes the

Table 2 Proposed epigenetic modifications in OA [44]

Gene	Epigenetic alteration	Effects
P65 activation	DNA methylation	Potentiation of inflammatory response
Col10a1 expression	Hypomethylation	Increased expression during chondrocyte hypertrophy and maturation
MMP2, MMP9, MMP13, ADAMTS4	Hypomethylation	ECM degradation
COL9A1	Hypermethylation	Attenuates SOX9 (a transcription factor essential for differentiation of precursor cells into chondrocytes) binding to the COL9A1 promoter
IL-8	Hypomethylation	Increased expression
IL-1alfa and TNF	Hypomethylation	Increased MMP13 expression
COL2A1	Histone deacetylation	Gene expression suppression
MMP	Histone deacetylation	Induction of gene expressions
SIRT1	Histone deacetylation	Reduced expression in OA (this gene has a chondroprotective effect)
miR-146a	Decreased expression in human last stage OA cartilage while their levels raise in early stage OA	It is a regulator of inflammatory mediators: it directly targets Irak1 (IL-1 receptor-associated kinase 1) and Traf6 (TNF receptor-associated factor 6) which are regulators of NF-kB
miR-140	Loss of miR-140	Accelerated OA following aging or surgical destabilization

joint more susceptible to further insults and damage to ligaments or meniscus, adversely affecting joint biomechanics [57].

Obesity increases the risk of knee OA more than threefold and accelerates disease progression by loading the weight-bearing joints and increasing joint susceptibility through the action of inflammatory adipokines [58, 59]. An independent association between weight gain and hip OA diagnosis has been shown [60]. Conversely, weight loss has been consistently associated with improvement of arthritis symptoms and slower knee cartilage degeneration [61, 62]. It has also been demonstrated that hyperlipidemia is an independent risk factor for new onset of hand OA [63], and higher levels of high-density lipoprotein cholesterol are protective against the incidence of radiographic hand OA [64]. In parallel, use of an antilipemic agent like ezetimibe is associated with fewer structural and better knee pain changes [65]. An association between higher systolic blood pressure and increased incidence of radiographic knee OA has been reported [66], while no data support an association between diabetes mellitus and hand/knee OA [67–69]. As vitamin D plays a major role in cartilage and bone metabolism, it has been hypothesized that low levels may increase OA risk. The VIDEO study, a randomized double-blind trial comparing a group of patients receiving placebo with a group of patients receiving vitamin D, showed that after 2 years of treatment, synovitis (as measured by MRI) remained stable among patients taking vitamin D, while it increased in the placebo group [70].

New Insights into OA Pathogenesis and the Role of Inflammation

OA has historically been considered a "wear and tear" disease, where weight overload, anatomical alterations, or other mechanical triggers induced loss of cartilage, particularly in genetically susceptible individuals, with subsequent bone reparative attempt. Chondrocytes were the only cell type considered in OA etiopathogenesis, and as cartilage is not vascularized, local or systemic inflammation was not taken into account. In the last decades, new evidence has led to the insight that other tissues are involved in OA development, as synovium and subchondral bone, both able to produce inflammatory mediators and to induce cartilage degradation (Fig. 1 illustrates the main actors of OA pathogenesis) [71]. Cartilage destruction and loss of chondrocytes are the peculiar starting features of OA, and cartilage plays an active role in disease pathogenesis. In fact, the function of chondrocytes is crucial in maintaining the production and the homeostasis of the extracellular matrix (ECM), and although it is not clear which the first event is, chondrocytes death and matrix loss may form a vicious cycle, with the onset of one inducing the other [72]. In addition, the ECM can promote the development of OA, in particular the region immediately surrounding and enclosing the chondrocytes, named "chondron." It can act as a transducer of biochemical and biomechanical signals for the chondrocyte, regulating its metabolic activity in response to environmental signals. Chondron alterations could serve as a driver of OA [73].

The subchondral bone is also an active player in the development of OA. Imaging studies have demonstrated that bone changes can be observed even before cartilage lesions, and an association between subchondral bone mineral density and osteoarthritis has been shown [74]. Cartilage and subchondral bone are linked by regulatory pathways, which can be disrupted in OA. Among them, the Wnt and the OPG-RANKL-RANK systems contribute to the regulation of bone remodeling and are impaired in OA. The resulting imbalance between subchondral bone osteoblasts and osteoclasts leads to altered bone deposition and late formation of osteophytes [75, 76].

The synovium, constituting the cellular lining of the joint and producing the synovial fluid, is another tissue implicated in OA that becomes inflamed and hypertrophic. Despite its degree of inflammation does not reach that of rheumatoid arthritis, synovitis is present in all stages of OA, is related to pain, is a marker of severity, and can predict structural progression [77]. Imaging allows to detect synovial alterations in patients with OA. A large meta-analysis described that people with knee OA or knee pain had high prevalence of ultrasound-detected effusion, synovial hypertrophy, and power Doppler signals [78]. At MRI, synovitis correlated with radiographic OA severity in patients with all degree of knee OA [79]. Moreover, synovitis detected at MRI was a risk factor for OA even when adjusting for confounding pathologies [80].

Immune Mechanisms

Histologically, the synovium may show significant alterations, even before cartilage degeneration. Synovial lining hyperplasia, sublining fibrosis, and stromal vascularization are the typically patterns found. Early events, as release of debris after cartilage damage, induce the production of pro-inflammatory cytokines by synoviocytes, which leads to recruitment of leukocytes from the vascular compartment. The balance between anabolic and catabolic cytokines, which allow a proper turnover of cartilage, is impaired in OA. The cytokines upregulated in OA include interleukin-1 beta (IL-1β), tumor necrosis factor (TNF)-α, IL-6, IL-15, IL-17, and IL-18. IL-1β and TNF-α are the most deeply studied and are elevated in OA synovial fluid, synovial membrane, cartilage, and subchondral bone and have an effect in inducing further inflammation and cartilage degradation.

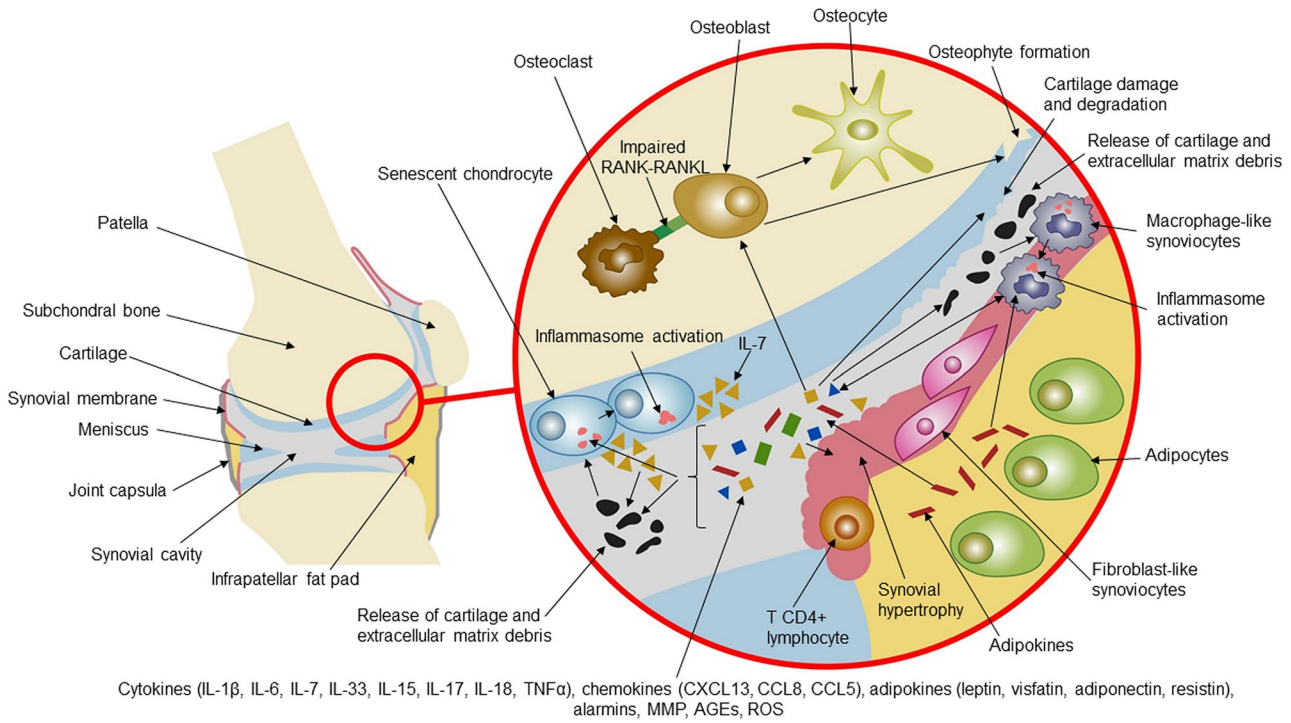

Fig. 1 Schematic representation of a knee (on the left) and of the main actors and inflammaging-related pathways involved in OA pathogenesis described in the text (on the right). Senescent joint tissues release pro-inflammatory mediators; among them, chondrocytes release IL-7, which induces cartilage degradation and the release of debris and extracellular matrix fragments. They induce inflammasome activation in chondrocytes and macrophage-like synoviocytes, with further release of cytokine and chemokines in the synovial fluid. In addition, biomechanical stress or catabolic activity further stimulates synovial cells. This process is enhanced by adipokines released by fat pads, in a vicious circle. These pro-inflammatory mediators induce synovial hypertrophy, neoangiogenesis, and infiltration by lymphocytes, in particular CD4 + T cells, which can induce self-reactivity. The subchondral bone activity is dysregulated by the inflammatory environment, with impaired RANK-RANKL signaling and ectopic bone deposition and formation of osteophytes. Legend: RANK, receptor activator of nuclear factor kappa-B; RANKL, RANK ligand; IL, interleukin; CXCL, C-X-C motif chemokine ligand; CCL, C–C motif ligand; MMP, metalloproteinase; AGEs, advanced glycation end products; ROS, reactive oxygen species

The predominant cells observed in the OA synovium are T lymphocytes and macrophages, responsible, with activated synoviocytes, for further cytokine production and for the increased angiogenesis, leading to a vicious cycle which induces secretion of metalloproteinase and proteolytic enzymes, with perpetuation of cartilage degradation [81–84]. Of note, synovial fibroblasts undergo a transition process to activated and pro-inflammatory synoviocytes that is similar for OA and rheumatoid arthritis, although it is much more intense in the latter [85].

The local articular inflammation can be mirrored by plasmatic increase of inflammatory markers. Increased IL-6 and C-reactive protein levels have been detected in blood of individuals with OA compared with healthy controls and may predict the progression of the disease [86–89].

Adipokines are also involved in the pathogenesis of OA. In fact, despite obesity is a well-recognized risk factor for OA in relation to weight overload, adipose tissue and in particular infiltrated macrophages produce and secrete adipokines, proteins involved in modulation of inflammation, angiogenesis, and glucose and lipid metabolism. Evidence suggests that chronically elevated local or systemic concentrations of adipokines have an important role in obesity-associated metabolic complications [90]. Elevated levels of adipokines have been detected in the infrapatellar fat pad, synovial fluid, and serum of patients with OA, with different levels detected in relation to the specific adipokine, the biological sample analyzed, and the clinical features of the patients [83, 91–93]. Studies on non-weight-bearing joints have been performed to distinguish the metabolic from the mechanical effect of fat excess and the relationship between OA and adipokines. They demonstrated that obesity is significantly associated with the development of clinical and radiological hand OA and that adipokine levels correlated with hand OA severity [94]. Distinct adipokines have been found to modulate bone remodeling and inflammatory responses, and their effects can change in relation to the stage of the disease. Leptin seems involved in inflammation, destruction of cartilage, and osteogenesis, as its serum levels have been correlated with presence of synovitis, cartilage defects, bone

marrow lesions, and osteophytes. Adiponectin can enhance the matrix metalloproteinase (MMP)-mediated destruction of cartilage and bone, the osteogenic differentiation, and the capacity of osteoblasts to mineralize bone. It can also induce pro-inflammatory cytokines and can reduce osteoclastogenesis and osteoclast-mediated resorption activity. Resistin and visfatin seem involved in the production of pro-inflammatory cytokines and degradative enzymes [95, 96]. Interestingly, visfatin is related to the NAMPT/SIRT1 pathway, involved in metabolic redox reactions and in the modulation of inflammation. Nicotinamide phosphoribosyltransferase (NAMPT) is an intracellular key enzyme involved in nicotinamide adenine dinucleotide (NAD) salvage pathway. NAD, besides being an essential coenzyme involved in cellular redox reactions, also promotes the activation of sirtuin-1 (SIRT1), a histone deacetylase [97]. SIRT1-mediated histone deacetylation regulates gene expression, proteostasis, cell differentiation, and inflammation, also by inducing the release of myeloid suppressor-derived cells from the bone marrow [98, 99]. In cartilage, SIRT1 promotes the expression of protective genes, such as aggrecan and type II collagen, and inhibits chondrocyte apoptosis [100]. With aging, the expression levels of SIRT1 are reduced [101], and this might be deleterious both systemically and locally. Visfatin is the extracellular deacetylated form of NAMPT and plays a role in enhancing inflammatory pathways and in osteogenesis [95, 97]. Visfatin also enhances vascular endothelial growth factor (VEGF) expression in synovial fibroblasts, inducing neovascularization and OA progression [102]. The dual function of the intracellular and extracellular forms of NAMPT/visfatin, one with a protective role and the other with pro-inflammatory activity, has yet to be fully elucidated.

Another mechanism involves advanced glycation end products (AGEs), formed by a non-enzymatic process in aging tissues, often induced by environmental factors such as cigarette smoke. This process leads to the irreversible glycation of proteins and lipids, which undergo structural changes and the formation of cross-linkages. The modifications result in change of enzymatic functions, in accumulation and in damage of tissues. AGEs can accumulate in the cartilage and trigger chondrocyte activation by binding to their receptors (RAGEs). RAGEs are transmembrane receptors belonging to the immunoglobulin gene superfamily and can bind several AGEs and other several DAMPs as HMGB1 and amyloid-β and induce inflammation by activation of the NF-κB and MAPK pathways [71, 103–105].

Toll-like receptors (TLRs) are involved in OA pathogenesis being expressed by immune cells, chondrocytes, osteoblasts, and synoviocytes. Their expression is upregulated in the OA synovium, and high-soluble TLR levels have been found in OA synovial fluid, as well as several damage-associated molecular patterns (DAMPs) able to induce inflammation [105].

Inflammaging in Clinics

Inflammaging is defined as a chronic, sterile, low-grade inflammation state, primarily driven by endogenous signals in absence of infection and involving self-reactivity, occurring during aging, leading to increased levels of pro-inflammatory mediators compared to younger individuals [106, 107]. Inflammaging has been proposed as a relevant risk factor for morbidity and mortality in the elderly population, as many age-related diseases share an inflammatory pathogenesis [108]. In the large scale, there is an increasing incidence worldwide of chronic age-related diseases, including obesity, metabolic syndrome, type 2 diabetes mellitus, and CVD, reflecting the growing aging population. Statistics show a raise of new cancer cases, attributed to increased risk factors as well as to the growth of the aging population [109]. There is a large overlap between the mechanisms driving aging and age-related diseases: common "pillars" are adaptation to stress, epigenetics, inflammation, macromolecular damage, metabolism, proteostasis, stem cells, and regeneration, which operate in an interconnected way, influencing and modulating each other to the constitution of an integrated network [110, 111]. Of major note, these pillars converge on chronic inflammation, and an impairment of any one fuels inflammation, which subsequently affects all the other pillars. Inflammation leads to increased levels of reactive oxygen species (ROS) inducing oxidative stress, which is a key component in the pathogenesis of chronic inflammation. Aging cells have increased levels of oxidant-damaged DNA [112], and oxidative stress can lead to the activation of systemic pro-inflammatory pathways [113], contributing to the pathogenesis of many age-related diseases. This has serious implication in tumorigenesis [114], development of diabetes [115], CVD [116], cognitive dysfunction and neurodegenerative diseases such as Alzheimer's and Parkinson's disease [117, 118], chronic obstructive pulmonary disease [119], and rheumatic diseases such as rheumatoid arthritis [120, 121].

One major characteristic of inflammaging is the chronic activation of the immune system [122]. Several cellular and molecular mechanisms are involved in inflammaging, including cellular senescence, mitochondrial dysfunction, defective autophagy, activation of the inflammasome, dysregulation of the ubiquitin–proteasome system, activation of the DNA damage response, and dysbiosis [123]. Senescent immune cells can acquire a pro-inflammatory phenotype since misplaced nucleic acids can accumulate and trigger an immune response, self-reactive T-cells can be released, while infections or gut dysbiosis can promote and modulate the inflammatory state. During life, chronic diseases, physical activity, stressors, infections, and nutrition may play a role in this process, contributing to the development of different phenotypes. Essentially, inflammaging can be considered the consequence of a dysregulated immune response [124].

Causes of Inflammaging

Inflammaging was originally attributed to somatic cell senescence-associated secretory phenotype (SASP) and chronic innate immune activation [125–128]. In recent years, contribution of aged adaptive immune components, particularly self-reactive T lymphocytes, has been proposed as a probable contributor to the age-related development of subclinical autoimmune predisposition [124, 129]. In fact, in elderly, thymic involution reduces the capacity to maintain central tolerance, allowing escaping of self-reactive T cells, which participate in the process of inflammaging [130]. Other major contributors are persistent viral [131] and bacterial [132] infections, cell debris, misplaced self-molecules, and misfolded and oxidized proteins [108, 133]. Persistent infections by viruses such as cytomegalovirus may lead to chronic immune activation through persistent production of low levels of pro-inflammatory cytokines, such as IFNγ and TNFα. In fact, the virus is found in a latent state in myeloid progenitor cells and monocytes, but also in epithelial cells of salivary glands and in the kidney, leading to chronic cytokine release; in addition, due to a severe impairment of the T cell system, highly differentiated exhausted CD28- CD4 + and CD8 + T cells accumulate [129]. Furthermore, the alternation between reactivation and latency can alter lipid and glucose metabolism; in fact, cytomegalovirus infection restructures lipid rafts and has a deleterious effect on pancreatic β-cells, and the infection-related pro-inflammatory state may lead to type 2 diabetes [134–138].

Another factor linked to the activation of the immune response is nutrition, as food and water are contaminated by microbial stimuli. There is evidence that innate immunity is stimulated when food is ingested, starting "postprandial inflammation" that is part of the response to meals, as inflammatory markers increase after ingestion of food through several molecular mechanisms [139, 140]. The gut microbiota represents the boundary between diet, the host metabolism, and the innate immune response [141] and may also undergo profound remodeling with aging [142–145]. Its composition depends on several factors such as individual-based (age, gender, genetics, lifestyle, method of childbirth, and whether one was breastfed or formula fed), population-based (ethnicity, cultural habits, nutrition, population genetic structure, and ancestry), and environment-based (climate, use of antibiotics, and lifelong immunological stimuli) factors, constituting a sort of biography of each person [146]. The adaptive and plastic nature of the gut microbiota allows it to adjust the host's immune and metabolic pathways in response to dietary habits and energy requirements having a profound effect on health and disease. The age-related remodeling of gut microbiota might contribute to systemic inflammaging, which can directly or indirectly affect its composition, in a self-sustaining loop [147, 148]. Changes in the gut microbiota profile in centenarians by an enrichment of Proteobacteria and a decrease in butyrate-producing bacteria are correlated with a systemic increase in levels of the pro-inflammatory cytokines IL-6 and IL-8 [149].

On the other hand, a low-calorie diet activates pathways stimulating autophagy, stress defense mechanisms, and survival pathways acting like a mild stressor that promotes hormetic responses [149, 150], leading to a general reduction of inflammation in the body with many effects on aging mechanisms including insulin resistance, adult neurogenesis and neuronal plasticity, autophagy, and mitochondrial biogenesis [151, 152]. Reduction of specific dietary proteins and amino acids without the restriction of calories currently seems to be the most effective dietary intervention for promoting longevity [149, 153].

Role of Inflammaging in OA

Considered that OA is an age-related disease and that inflammation is strictly involved in its pathogenesis, inflammaging may play a relevant role in the development and in the evolution of the disease. Evidence suggests that OA is associated with low-grade systemic and local inflammation, and both the innate and the adaptive immune response are involved.

With aging, joints can release pro-inflammatory mediators; in mouse models, a different genetic expression in joint tissues has been described with aging, with an upregulation of pro-inflammatory cytokines and chemokines, in particular of IL-33, CXCL13, CCL8, and CCL5 [154]. Human chondrocyte cultures derived from elderly release higher levels of IL-7 compared to cultures from young subjects. Moreover, chondrocytes from patients with OA release more IL-7 than age-matched subject without OA, and IL-7 leads to increase of metalloproteinases and proteoglycan release from cartilage [155]. The term "chondrosenescence" has been coined to include the age-related alterations of chondrocytes, due to systemic or local stimuli, as increased levels of ROS and pro-inflammatory cytokines, fluctuating oxygen and nutrient supply due to vascular impairment, reduced cartilage water content and elasticity, and increased advanced glycation end products [156].

This process can trigger the inflammasome, via the pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). In OA, the principal DAMPs include hydroxyapatite, basic calcium phosphate, calcium pyrophosphate dihydrate, or uric acid crystals. These are capable to activate intracellular NLRP3, a major component of the inflammasome, highly expressed in macrophages, chondrocytes, synoviocytes, and osteoblasts [157]. Subjects with innate genetic-related reduced capacity to produce IL-1β and IL-6 are protected from OA in old age, while no impact was found for TNFα and IL-10 [158]. IL-1β, produced by the inflammasome, is involved in the link between inflammaging and OA, as IL-1β expression is increased in OA [159] and synovial fibroblasts stimulated with IL-1β induce OA-like modifications in the joint

[160, 161]. IL-6 levels are associated with the risk of OA progression [88], and in chondrocytes, IL-6 appears to interact with basic calcium phosphate to promote cartilage degradation and OA [162]. An association between pro-inflammatory cytokines and articular functionality or level of pain has also been demonstrated [156]. The age-related increase in fat mass could contribute to the increased levels of adipokines and cytokines involved in OA pathogenesis. This can occur both systemically, given the increment of the visceral fat, and locally, due to the increase in fat pad volume into the knee joints [163]. Evidence also shows that senescent cells accumulate in degenerated tissues and induce the expression of senescent markers. Cartilage and synovium are the sites where senescent cells localize in experimental OA and secrete matrix degrading proteins and cytokines, thus inducing chronic inflammation. The molecules released exacerbate the disease and seem to affect the subchondral bone, with dysregulation of bone remodeling and osteophyte formation [157].

Autophagy, the homeostatic mechanism of removal of macromolecules or dysfunctional organelles as inflammasomes through lysosome degradation, is reduced in OA [156, 164], and animal models have shown that autophagy activation can prevent OA damage [165]. The adaptive immune response may connect inflammaging and OA. An analysis of blood lymphocyte composition in OA patients and healthy controls showed that T and B cell function was compromised, with CD4, T regulatory, and B-cell decreased in OA, while CD8 increased in OA compared to controls, possibly reflecting inflammation and autoreactivity [166]. In other studies, T and B cell profiles in OA patients were proved altered compared to healthy controls, although with different features among reports. Nevertheless, they all suggest that the acquired immune system is impaired in OA and may play a relevant role in the pathogenesis of OA [167, 168]. Locally, an increased infiltrate of T lymphocytes has been shown in OA synovium compared to healthy synovium [169], accounting for up to 25% of inflammatory cells [170]. Moreover, an increased CD4 + /CD8 + ratio has been reported in synovium from OA patients compared to controls [171], and the number of synovial CD4 + lymphocytes has been associated with the pain visual analog scale [83]. Other lymphocytes, including B and NK, and plasma cells have been detected in synovial tissue from OA patients, although their precise role still has to be elucidated [172].

The alterations due to systemic and local factors lead to an inflammatory environment, with increased cytokines, ROS, adipokines, proteinases, and self-reactive lymphocytes; in joints, this ultimately results in chondrosenescence and degenerative modifications, which further enhance inflammation and autoimmunity, in a vicious circle. One hypothesis is based on the existence of a spectrum of OA phenotypes, with a portion of subject in whom inflammaging is the primary driver, as identified with imaging and serum biomarkers, and who may benefit from anti-inflammatory treatments [173]. In this context, the concept of frailty can be introduced as its definition, and implementation in clinical practice can help in the management of patients with OA. Frailty is a clinical syndrome characterized by physiological changes across multiple systems and organs, resulting in a progressive loss of internal homeostasis, reduced physiological reserves, loss of function, reduced resilience, compromised ability to cope with everyday or acute stressors, and increased vulnerability to internal and external stressors [174, 175].

The pathogenesis of frailty is related to multiple factors. Polymorphisms in genes involved in inflammation, metabolism, endocrine system, and homeostasis have been proposed, although acquired and environmental factors appear to be predominant. Inflammaging plays a role in accelerated aging in individuals with chronic diseases and multimorbidity, mediates the development of functional limitations and disability, impairs the mechanisms of homeostasis and repair that occur in healthy and damaged tissue, and can therefore have detrimental effects and contribute to frailty. Chronic low-grade inflammation in inflammaging leads to sarcopenia, loss of strength, increased risk of falls, reduced physical activity, anemia, cardiovascular diseases, and poor nutrition, all features well described in frailty syndrome. Moreover, in the frail syndrome, low-grade inflammation persists after removal of the trigger, and the immune system is hyperresponsive to further stimuli; acute illness or exacerbation of chronic conditions may further worsen the clinical scenario. Inflammaging and frailty are thus closely related, and ultimately frailty has been regarded as an inflammaging-related disease [124, 176] or the clinical counterpart of inflammaging. OA appears to be closely related to inflammaging and frailty, with high prevalence of frailty in patients with OA since low-grade systemic inflammation, pain, impaired joint function, and disability due to OA contribute to reduced movement autonomy and decreased resilience typical of frailty [177]. Of clinical relevance, frailty predicts mortality in patients with OA [178], and this suggests that targeting inflammaging would affect not only the mechanism involved in the development and worsening of OA, but also the complex pathways involved in homeostasis and in inflammaging-related diseases, thus potentially reducing vulnerability to stressors and increasing survival.

Potential Therapeutic Targets and Biomarkers

Currently, there is no effective treatment to prevent or reverse OA short of prosthetic surgery, despite several molecules, even with anti-inflammatory properties, have been studied based on basic science.

Based on the unique OA characteristics, the use of intra-articular injection of platelet-rich plasma (PRP) has been

proposed. PRP is an autologous serum containing high concentrations of platelets and growth factors, obtained by centrifugation of blood. Growth factors and cytokines are released after degranulation of platelet alpha-granules. In vitro experiments have demonstrated that they can increase the synthetic capacity of chondrocytes through upregulation of gene expression, proteoglycan production, and type II collagen deposition, thereby accelerating cartilage matrix synthesis, promoting cartilage healing, and reducing synovial inflammation. Many studies have shown great pain relief and improved patient-reported outcomes with PRP injection into the knee compared with other intra-articular injections, such as corticosteroid or hyaluronic acid, or oral medications. There is less evidence on the efficacy of PRP injection into the hip compared with hyaluronic acid. No differences in side effects have been found between PRP, hyaluronic acid, and placebo [179–186].

Drugs targeting IL-6, IL-1, and TNF-α have demonstrated no effect. On the other hand, antagonists of colony-stimulating factors (CSFs), molecules which increase the myeloid population during an inflammatory response, showed beneficial effects in preventing disease development and pain in experimental preliminary analyses [187, 188]. Blocking granulocyte macrophage CSF (GM-CSF) receptor prevents and reverses arthritic pain and is able to modulate the degree of osteoarthritic changes by reducing osteophyte formation in the joint of OA-induced murine experimental models. There is now ongoing a phase II trial in hand OA exploring potential of one of this molecule (GSK3196165) in the future for the prevention of OA damage and OA-related pain [187, 189].

As high levels of IL-4R and IL-10R have been described in the knee of patients with OA compared with healthy controls, drugs targeting these molecules with anti-inflammatory properties have been studied [190]. IL4-10FP in vitro can reduce release of inflammatory, catabolic, and pain-related mediators from human OA cartilage and synovial tissue, and it beneficially affects proteoglycan turnover. According to these data, IL4-10FP reduces pain in animal models [190]. A recent study by van Helvoort et al. demonstrated for the first time that in rats, repeated intra-articular injections of rIL4-10 FP, compared to saline solution injections, resulted in preventing/reducing joint damage in early OA stages, as well as relieving OA-induced pain [191].

More subtle and inflammaging-targeted treatments are now under investigation, and promising results are expected. In particular, recent research focuses on pattern recognition receptors (PRRs), which bind PAMPs and DAMPs and trigger inflammation. Among them, TLRs and RAGEs appear as promising targets. TLRs can be blocked by high-molecular weight hyaluronic acid, Pep-1 and a 12-mer peptide, which prevent the binding of DAMPs as short hyaluronic acid oligosaccharides. The activation of TLR antagonist pathways can be induced by prostaglandin 2, vasoactive intestinal peptide, adenosine 2A receptor, bone morphogenic protein 7, and peroxisome proliferator-activated receptor γ (PPARγ). The latter is activated by rosiglitazone and pioglitazone, commonly used for type 2 diabetes, which are now under evaluation as they inhibit TLR stimulation in OA synoviocytes and chondrocytes and reduce inflammatory response in vitro [105, 192–194]. In animal experiments, pioglitazone arrests and reverses AGE-induced arthritis by reducing inflammation and cartilage damage by MAPKs and NF-kB signaling inhibition. All these evidences suggest the potential of this drug in early treatment of OA, especially among diabetic patients [193, 195–197].

RAGEs can also be targeted by its soluble receptor, sRAGE. In OA plasmatic levels of sRAGE are significantly lower compared to those in healthy controls [198]. sRAGE acts as a competitive inhibitor of RAGE, scavenges DAMP/PAMP ligands, and reduces inflammatory signals. It can modulate the chronic low-grade inflammation occurring in elderly and has been proposed as anti-inflammaging-related disease molecule [199].

Since many infectious agents are recognized by the same PRRs as DAMPs, directly blocking TLRs or RAGEs could impair the host immune defense against pathogens. Therefore, specifically addressing DAMPs as alarmins S100 and HMGB1 might be a safer approach. Alarmins are secreted by alternative pathways not involving the endoplasmic reticulum or the Golgi complex; therefore, inhibiting these pathways could block the release of multiple alarmins. Glycyrrhizin and ethyl pyruvate act on these mechanisms. In OA rat models, treatment with glycyrrhizin led to hyperalgesia and joint edema improvement, with suppression of serum levels of cartilage catabolic markers and decreased serum and intra-articular levels of IL-1β, IL-6, TNFα, and inducible nitric oxide synthase (iNOS) [200]. Furthermore, ethyl pyruvate blocks the NLRP3 inflammasome involved in the release of both IL-1 and alarmins [201].

Individual alarmins can also be blocked: antibodies against HMGB1 and S100A8/A9 have been studied, and recently identified epitopes of the S100A8/A9 complex capable of activating TLRs could further guide the production of specific antibodies. Natural or synthetic small molecules can target alarmins, and among them, the S100A9 inhibitor paquinimod proved effective to reduce synovial inflammation, Wnt signaling, osteophyte formation, and cartilage damage in a preclinical model of OA [105, 202–209]. The potential therapeutic targets in OA, considered an inflammaging-related disease, are summarized in Table 3.

One more proposed therapeutic approach is based on the removal of senescent cells to prevent the secretion of pro-inflammatory factors produced by an impaired regulation of oxidative processes. Studies in vitro on chondrocytes from OA patients undergoing total knee replacement showed that removal of senescent cells reduced the expression of pro-inflammatory markers and improved the expression

Table 3 Potential therapeutic targets in inflammaging-related mechanisms of OA

Potential therapeutic molecule	Target	References
-Anti-colony-stimulating factors	Colony-stimulating factors	[187, 188]
-Fusion protein of IL-4 and IL-10 (IL4-10 FP)	IL-4 and IL-10	[190, 191]
-High-molecular weight hyaluronic acid -Pep-1 -12-mer peptide	TLR blockers	[105, 192, 194]
-Pioglitazone -Rosiglitazone	Activation of TLR antagonist pathways via PPARγ	[105, 193]
-Soluble RAGE	RAGEs	[199]
-Glycyrrhizin -Ethyl pyruvate	Alarmins, i.e., S100 and HMGB1	[202, 204]
-Ethyl pyruvate	NLRP3 inflammasome	[203]
-HMGB1 and S100A8/A9 blockers	HMGB1 and S100	[205, 209]
-Paquinimod	S100A9 inhibition	[206]

IL interleukin, *TLR* Toll-like receptor, *PPARγ* peroxisome proliferator-activated receptor γ, *RAGE* receptor for advanced glycation end products, *HMGB1* high mobility group box 1, *NLRP3* NLR family pyrin domain containing 3

of extracellular matrix proteins. In a mouse model of OA, removal of senescent cells accumulated in the cartilage and in the synovium attenuated the development of OA. In vitro studies on chondrocytes from patients with OA undergoing total knee replacement showed that removal of senescent cells reduced the expression of pro-inflammatory markers and improved the expression of extracellular matrix proteins. Senolytics as ABT-263 can inhibit the anti-apoptotic proteins belonging to the BCL2 family members, and after intra-articular injection, they can target senescent cells and prevent cartilage damage [157, 210]. The development of drugs to modify structural deterioration of the joint (disease-modifying OA drugs, DMOADs) requires measurable and universally applicable and accepted endpoints beyond traditional patient-reported outcomes [211].

Collagen is the main component of articular cartilage, and type II is the most represented. Many biomarkers are associated to type II collagen turnover, such as urinary C-telopeptide fragments of type II collagen (u-CTXII), serum (s) N-propeptide of collagen IIA (PIAANP), and serum N-propeptide of collagen IIB (PIIBNP or PRO-C2). The u-CTX II is a product of type II collagen degradation generated by MMPs, and high baseline levels of u-CTXII predict increased risk to undergo total joint replacement of hip or knee [211, 212]. Conversely, PIAANP and PIIBNP are two splice variants of N-terminal propeptide of type II collagen reflecting cartilage formation [213]. High serum PIIANP predicts reduced progression of clinically relevant knee OA over 4 years [212], and PIIANP and PIIBNP levels are lower in patients with established OA compared to controls [213, 214].

At the early OA stages, first changes appear in the subchondral bone rather than in cartilage, with horizontal trabeculae thickening followed by vertical trabeculae thinning in a second phase [212]. Bone biomarker abnormalities, as of urinary N-terminal telopeptide of type I collagen (uNTX-I), u-CTX-I, and serum CTX-I, are able to detect disease at early stages [215–217]. In the contest of inflammation, some synovial inflammatory fluid biomarkers specifically connected with macrophage and neutrophil activation have been demonstrated to be associated with synovitis and radiographic and symptom severity, i.e., metalloproteinase-3 (MMP3), soluble vascular cell adhesion molecule-1 (sVCAM1), soluble intercellular cell adhesion molecule-1 (sICAM1), VEGF, tissue inhibitor of metalloproteinases 1 (TIMP1), and monocyte chemoattractant protein 1 (MCP1) [218, 219]. As mentioned, reduced serum iNOS, MMPs, and TNFα levels have been described during experimental treatment with pioglitazone and glycyrrhizin [196, 200] and can be evaluated in future studies as biomarkers in OA patients.

S100A8/A9 are the best studied alarmins in the contest of OA, with high serum and synovial levels in the course of the disease, strongly related to synovitis and inflammation [220, 221]. Furthermore, their levels increase with aging, the principal risk factor for disease development [222], and they have been described as markers in many inflammatory arthritis [223–225]. The evaluation of their serum levels could be useful for monitoring specific target therapies, such as paquinimod treatment.

Conclusions and Future Perspectives

Despite being a condition affecting nearly a third of the world population and a growing amount of basic evidence on the mechanisms of disease, our therapeutic approach to OA is largely unsatisfactory. Recent research pointed out that several pathways and molecules in cartilage, subchondral bone,

adipose tissue, and synovium are involved and that inflammaging plays a major role. A hypothesis is that in patients with OA, mechanisms underlying the disease may differ. Therefore, beyond screening patients at risk to develop the disease by dosing bone biomarkers as serum or urinary CTX, research should focus on identifying and validating biomarkers to detect at early stages patients more at risk of developing severe OA, in order to stratify the population. To this regard, intriguing could be to study serum levels of alarmins and their modifications according to cartilage structural damage. Furthermore, their evaluation could be helpful to monitor the disease in future clinical trials, particularly if S100A8/A9 blockers such as paquinimod will be implemented in clinical practice. Similar strategies could be used to investigate the efficacy of molecules that currently appear promising in preventing or reversing OA early damage, such as IL4-10 FP and GSK3196165. Furthermore, patients affected by diabetes starting treatment with pioglitazone and rosiglitazone could be studied; understanding the impact of these drugs on joint damage could be relevant to define their role in the treatment of OA.

A deeper understanding of the key inflammatory pathways leading to OA could improve not only the treatment, but more importantly allow to early address target molecules and therefore prevent the disease, paving the way to a true personalized approach and reducing its high morbidity and mortality.

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