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Review

Chronic Inflammation and Aging in Rheumatic Diseases

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ABSTRACT: Cellular senescence and immunosenescence drive chronic tissue damage via persistent senescence-associated secretory phenotype (SASP)-mediated inflammation, particularly through pro-inflammatory cytokines, including interleukin-6 (IL-6), interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α). In osteoarthritis (OA), senescent chondrocytes promote cartilage degradation, while in rheumatoid arthritis (RA), aged immune cells impair self-tolerance. Emerging therapies targeting these mechanisms - including senolytics and cytokine inhibitors-demonstrate potential to break this pathological cycle. These findings emphasize the necessity of combined anti-inflammatory and anti-aging approaches for managing age-related rheumatic diseases.

Keywords: chronic inflammation, aging, rheumatic diseases

INTRODUCTION

Inflammation is a defensive response mounted by the organism against the invasion of harmful agents, marked by the activation of immune and non-immune cells. This process serves to protect the host from pathogens such as bacteria, viruses, and toxins, as well as from infections, by eliminating harmful agents and facilitating tissue repair. A well-regulated inflammatory response is typically self-limiting, persisting only as long as the threat remains and resolving once the threat is neutralized. In contrast, chronic inflammation represents a maladaptive, nonspecific reaction to sustained pathological stimuli, characterized by the prolonged activation of inflammatory cells and mediators [1]. During childhood and adulthood, inflammation helps maintain a stable internal environment. However, chronic inflammation is now recognized as a common pathological basis for various age-related diseases, such as cardiovascular disease, diabetes, and cancer. It may also be a significant contributor to the increased morbidity and mortality of most degenerative diseases [2].

Aging represents an inescapable biological phenomenon intrinsic to all living organisms. The World Health Organization defines it as "the gradual accumulation of various molecular and cellular damages in the body over time." Aging is both an independent state and interdependent with disease. It is the process of permanent changes in the structure and function of cells and tissues caused by prolonged exposure of an organism to external or internal harmful factors [3]. Aging is usually accompanied by physiological and biochemical changes, such as functional decline, weakened immunity, and organ damage in the organism. In the face of global population aging, understanding the interplay between chronic inflammation, aging, and rheumatic diseases is crucial for improving health outcomes in the elderly.

Rheumatic diseases, as a group of diseases characterized by chronic inflammation and autoimmune responses, include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's syndrome and

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osteoarthritis (OA). These diseases usually involve joints, skin, and internal organs, seriously affecting patients' quality of life and health status. Aging, as one of the factors in the development and exacerbation of rheumatic diseases, leads to a gradual decline in the functioning of joints, the immune system, and the metabolic system, increasing the risk of disease and exacerbating symptoms [4, 5]. A deeper understanding of how chronic inflammation and aging affect the development and clinical manifestations of rheumatic diseases is essential to improve patient treatment and management strategies. diseases.

The aim of this article is to explore the mechanisms of chronic inflammation and aging in rheumatic diseases and to provide a scientific basis for future clinical practice and treatment (Fig. 1). As illustrated in Figure 1, chronic inflammation and cellular senescence interact through multiple feedback loops. Senescent cells release SASP factors that recruit immune cells and amplify inflammatory signaling, whereas chronic inflammation induces further DNA damage and senescence. This bidirectional process forms a pathogenic cycle contributing to the onset and progression of rheumatic

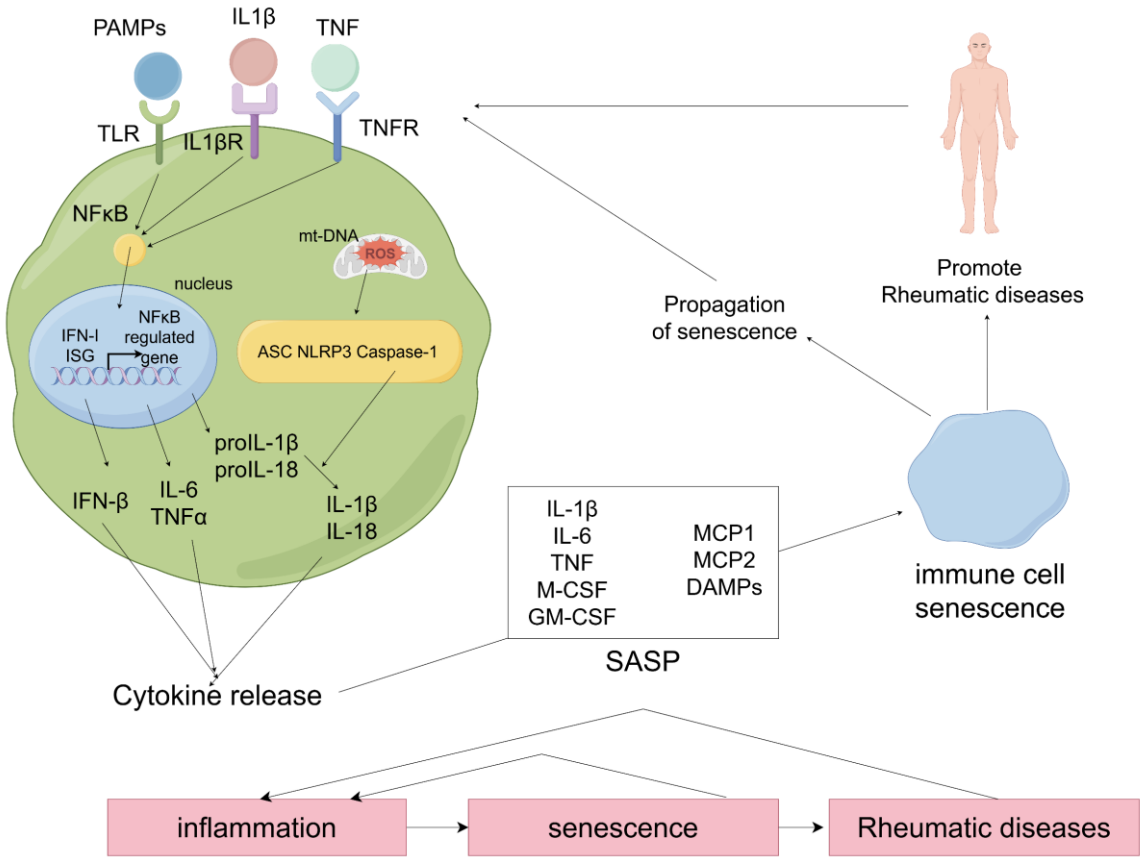

Figure 1. The interrelationship between rheumatic diseases and inflammation and senescence.

Search strategy

A comprehensive literature search was conducted using PubMed and Web of Science databases to identify relevant studies published between 2000 and 2024. The following keywords and their combinations were used: "chronic inflammation," "aging," "immunosenescence," "senescence-associated secretory phenotype (SASP)," "rheumatic diseases," "osteoarthritis," "rheumatoid arthritis," "systemic lupus erythematosus," and "Sjögren's syndrome." Filters were applied to include only English-language articles involving human or animal models. Reference lists of key studies were also screened to identify additional relevant publications.

The relationship between chronic inflammation and aging

Inflammation, as part of the body's defense mechanism, is triggered when the immune system recognizes and eliminates internal or external harmful stimuli and initiates repair. Aging is a universal and complex natural phenomenon. Chronic inflammation, one of the twelve hallmarks of aging [6], is inextricably linked to aging,

with the two influencing and largely exacerbating each other's processes . It has been noted that chronic inflammation is closely linked to inappropriate activation and dysfunction of the immune system. [2]. With age, the immune system undergoes changes that lead to immunosenescence, the characteristic hallmark of which is the low activation of the immune system, the presence of a chronic inflammatory state [7–9]. A senescent immune system further contributes to solid organ senescence.

A study found that reduced expression of ERCC1-XPF endonuclease, a key DNA repair protein encoded by the Ercc1 gene, impaired endogenous DNA damage repair and accelerated the accumulation of endogenous oxidative damage and senescent cells in multiple tissues, leading to premature development of senescence-associated diseases and pathological features in mice [10]. In this study, the researchers found that knockout mice exhibited premature aging of the immune system in adulthood; transplantation of aged spleen cells into young mice accelerated the latter's aging, whereas transplantation of spleen cells from young mice into knockout mice alleviated their aging process. This further demonstrates that senescent immune cells promote systemic senescence, whereas transplantation of young immune cells delays senescence.

Meanwhile, chronic inflammation produces a series of inflammatory mediators that not only affect the function of the immune system but also further influence or accelerate cell and tissue senescence. On the other hand, the SASP, consisting of a series of biologically active molecules secreted by senescent cells, includes pro-inflammatory cytokines, chemokines, matrix metalloproteinases, and growth factors. SASP can alter the surrounding microenvironment, trigger inflammatory responses, and play an important role in senescence and disease progression [11]. SASP is inherently both autocrine and paracrine in nature and may trigger secondary senescence in neighboring cells [12]. For example, transplantation of senescent cells into the knee joints of mice induced an osteoarthritis-like phenotype, whereas localized removal of senescent cells attenuated osteoarthritis symptoms in mice [13]. Therefore, a bidirectional, self-perpetuating relationship exists between chronic inflammation and cellular senescence. Cai et.al. developed a compound called SSK1 that selectively kills senescent cells. The drug effectively removed senescent cells from various tissues in aged mice, significantly improved several aging-related functional degenerations, reduced both local and systemic inflammation levels, and restored physical function [14]. In summary, the interplay between chronic inflammation and aging forms a vicious cycle that significantly impacts organismal health and the progression of age-related diseases.

The role of chronic inflammation in rheumatic diseases

Osteoarthritis

Osteoarthritis (OA) was long regarded as a simple degenerative joint disease, but growing evidence suggests that low-grade inflammation plays a key role in its pathogenesis [15]. OA symptoms are typically progressive and may initially affect only one or a few joints, but can progress to involve multiple joints as the disease advances. How does crosstalk occur between different joints, and what mechanisms are involved? Answering these questions could provide crucial insights for preventing, delaying, or reversing OA. Many OA patients initially present with symptoms such as pain, morning stiffness, and low-grade fever, consistent with joint inflammation. This synovial inflammation involves inflammatory cell infiltration at the synovial site. Recent studies have demonstrated that cellular senescence is a major driver of local inflammation in osteoarthritis. Senescent chondrocytes accumulate within the cartilage matrix and secrete a wide array of SASP factors, including IL-6, IL-1β, TNF-α, and matrix metalloproteinases. These molecules promote chronic low-grade inflammation and matrix degradation. Selective elimination of senescent chondrocytes in post-traumatic OA mouse models has been shown to attenuate cartilage degeneration, whereas intra-articular injection of senescent cells can induce OA-like pathology. Moreover, synovial macrophages, fibroblasts, and osteoclasts in the senescent microenvironment amplify SASP production, alter subchondral bone remodeling, and aggravate disease progression. The accumulation of senescent chondrocytes disrupts extracellular matrix organization, increases mechanical stress, and accelerates biomechanical dysfunction, further predisposing the joint to degeneration. [16, 17] From early observations of elevated inflammatory plasma proteins and synovial fluid to current findings of multiple cytokines, complement components, and various inflammatory factors, such as IL-1β, TNF-α, nitric oxide [NO]), evidence consistently suggests that inflammation plays an important role in OA pathogenesis [18]. These key mediators and their actions are summarized in Table 1.

Rheumatoid Arthritis

While OA primarily involves degenerative and mechanical components, rheumatoid arthritis (RA) represents a systemic autoimmune condition in which

chronic inflammation is driven by adaptive immune dysfunction. Chronic inflammation plays an equally important role in the pathogenesis of RA, another rheumatic disease characterized by small joint inflammation. As a systemic chronic inflammatory disease, RA manifests as recurrent and sustained activation of both the innate and adaptive immune systems. Over time, this leads to immune tolerance failure, autoantibody production, and excessive inflammatory cytokine production [19].

Table 1. Major Inflammatory Factors and Their Roles in the Pathogenesis of Osteoarthritis.

Inflammatory Factor	Source Cell Type	Major Signaling Pathways	Effect on OA Pathogenesis
IL-1β	Chondrocytes, macrophages	NF-κB, MAPK	Promotes MMP expression and cartilage degradation
IL-6	Chondrocytes, fibroblasts	JAK/STAT3	Induces inflammation and osteoclast activation
TNF-α	Synovial macrophages	MAPK, PI3K/Akt	Enhances synovial inflammation and cartilage loss
MMP-13	Senescent chondrocytes	p53/p21	Degrades collagen II and extracellular matrix

This in turn triggers joint inflammation and ultimately permanent and limited bone and cartilage damage. Prior to the appearance of autoantibodies, the earliest changes are alterations in inflammatory cytokines, including IL-1, IL-6, and IL-10. IL-6 predominantly activates the Janus kinase/signal transducer protein and activator of JAK/STAT pathway, which is a key regulator of downstream signaling for many inflammatory cytokines [20] and interacts with other immune related pathways, such as the phosphatidylinositol-3-kinase (PI3K)/Akt/ mammalian target of rapamycin (mTOR) pathway [21]. It is well known that IL-1 and IL-6 act as pro-inflammatory agents, while IL-10 acts as an inhibitor of inflammation. These chronic inflammatory responses lead to the emergence of impaired T and B cell immune tolerance, which promotes an autoimmune response [22]. Tumor necrosis factor-alpha (TNF-α) is one of the key cytokines involved in the pathogenesis of RA [23]. TNF-α is produced by a wide range of cells and is critical in influencing the immune cascade response. In addition to primarily driving the SAPK/MAPK pathway, it activates JAK/STAT signaling and is one of the major triggers of inflammation and joint damage in RA [20]. Dendritic cells (DC) release many cytokines including TNF-α, which initiates the differentiation of T and B cells [24, 25]. B cells differentiate into plasma cells and plasmacytoid cells, which produce anti-cyclic citrullinated peptide antibodies (ACPA), rheumatoid factor (RF), and immune complement to promote autoimmune responses. Stimulated by inflammatory factors such as transforming growth factor-beta (TGF-β), interferon-gamma (IFN-γ), IL-2, IL-12, and IL-21, T cells differentiate into Th1 and Th17 cells and release inflammatory cytokines in large quantities. Although Treg and Th2 release large amounts of anti-inflammatory cytokines (IL-2, IL-4, and IL-10), this anti-inflammatory response is far from sufficient in RA. Additional cytokines released by Th1 and Th17 cells trigger immune responses in macrophages and synovial fibroblasts through signaling molecules, such as Receptor Activator of Nuclear Factor-κB Ligand (RANKL) and CD40L. RANKL and NF-κB-related cell signaling pathways are considered one of the major validation pathways for RA [26]. Activated macrophages secrete large amounts of inflammatory cytokines, which are effected by T cells, osteoclasts and chondrocytes, which together maintain the inflammatory environment. At this point the synovium is in a highly immunoreactive environment, and other cells such as mast cells and neutrophils are subsequently activated. Neutrophils produce a variety of cytokines, proteases, reactive oxygen species (ROS), and neutrophil extracellular trapping networks Neutrophil Extracellular Traps (NETs), which ultimately lead to the destruction of bone and cartilage tissue [27–30]. At the same time, synovial fibroblasts are subjected to a variety of inflammatory stimuli and produce a variety of metalloproteinases, Cyclooxygenase-2 (COX2), ProstaglandinE2 (PGE2), and Cadherin-11, which promote inflammation and tissue damage. Given the complexity of RA pathogenesis, its corresponding therapeutic tools are diverse, and many treatments targeting chronic inflammation have shown quite remarkable therapeutic results [23]. In particular, TNF-α inhibitors have become a new cornerstone in the treatment of RA, and their application significantly reduces TNF-α levels and the ensuing damage. Another type of disease-modifying antirheumatic drugs DMARDs (JAK inhibitors) interferes with downstream signaling of pro-inflammatory factors such as IL-6, thereby reducing the inflammatory cascade response. Furthermore, the B-cell-depleting monoclonal antibody rituximab has also shown efficacy in the treatment of RA [31]; it reduces circulating B-cell levels and indirectly inhibits T-cell activation, leading to decreased cytokine production [22]. The

complex network of inflammatory factors and pathways driving RA pathology is outlined in Table 2.

Table 2. Major Inflammatory Factors and Signaling Pathways Involved in Rheumatoid Arthritis.

Inflammatory Factor	Source Cell Type	Major Signaling Pathways	Pathophysiological Effect in RA
TNF-α	Macrophages, dendritic cells, synovial fibroblasts	NF-κB, MAPK, JAK/STAT	Promotes synovial inflammation, bone erosion, and cartilage destruction; activates T cells and osteoclasts
IL-6	T cells, B cells, macrophages, fibroblast-like synoviocytes	JAK/STAT3, PI3K/Akt/mTOR	Induces acute-phase response, B-cell differentiation, and joint inflammation
IL-1β	Monocytes, macrophages, fibroblasts	NF-κB, MAPK	Stimulates MMPs and COX2 expression; enhances cartilage degradation
IL-17	Th17 cells	NF-κB, MAPK, STAT3	Amplifies cytokine cascade, recruits neutrophils, promotes bone resorption
IFN-γ	Th1 cells, NK cells	JAK/STAT1	Enhances macrophage activation and antigen presentation; contributes to chronic inflammation
BAFF	B cells, dendritic cells	NF-κB	Promotes B-cell survival and autoantibody production
RANKL	T cells, synovial fibroblasts	NF-κB, MAPK	Stimulates osteoclast differentiation and bone erosion

Other rheumatic diseases

Beyond rheumatoid arthritis, other autoimmune rheumatic diseases such as systemic lupus erythematosus and Sjögren's syndrome share similar inflammatory mechanisms mediated by aberrant cytokine networks. Chronic inflammation plays an important role in other rheumatic diseases. The pathogenesis of SLE, an autoimmune disease, involves a variety of factors, among which aberrant B cell activation is common and is involved in the release of T-cell antigen presentation and cytokines (IL-6, IL10, TNF-α, and B-cell Activating factor of the TNF family [BAFF]), as well as the formation of autoantibodies [32]. Excessive release of inflammatory mediators and abnormal activation of the immune system exacerbate the autoimmune response and organ damage, which in turn leads to the onset and progression of SLE; SS is an autoimmune disease characterized by dryness symptoms, and its pathological features include inflammation and hypoplasia of the salivary and lacrimal glands, and abnormal activation of the innate immune system plays a key role in the pathogenesis of SS, particularly through the IFN and NF-κB pathways, CXCR5-mediated atypical recruitment of lymphoid follicles, and T-cell activation, leading to salivary and lacrimal gland destruction and dysfunction, which in turn triggers symptoms of desiccation [33]; Ankylosing spondylitis (AS), as a chronic inflammatory arthropathy, is characterized by inflammation and bony cribriform formation of spinal and pelvic joints, and studies have shown that chronic inflammation plays an important role in the pathologic process of AS, leading to bone destruction and joint deformity, which aggravate patients' symptoms and dysfunction [34]. These studies provide ample evidence that chronic inflammation plays a central role in the pathogenesis of specific rheumatic diseases. An in-depth understanding of the role of inflammation in these diseases can help develop more effective therapeutic strategies and improve the quality of life of patients. Key inflammatory mediators and molecular pathways in these diseases are summarized in Table 3.

The role of aging in rheumatic diseases

The Hallmarks of Aging represent one of the most significant conceptual frameworks in contemporary biomedical research. As organisms age, core biological pathways exhibit progressive functional deterioration. The scientific community has established twelve fundamental mechanisms collectively termed the hallmarks of aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, impaired macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and microbial dysbiosis [6]. These markers of aging are not diseases per se, but are present in the development and physiologic dysregulation of age-related diseases (ARDs). For example, loss of protein homeostasis plays an important role in neurodegenerative diseases such as Alzheimer's and Parkinson's [35]; genetic instability and epigenetic changes, on the other hand, often lead to breast and bowel cancer. The association between single markers of aging and disease has also been much studied [36].

Table 3. Key Inflammatory Mediators and Molecular Pathways in Other Rheumatic Diseases.

Disease	Major Inflammatory Factors	Source Cell Types	Key Signaling Pathways	Main Pathophysiological Effects
Systemic Lupus Erythematosus (SLE)	IL-6, TNF-α, IFN-α, IFN-γ, BAFF	Dendritic cells, B cells, T cells, monocytes	JAK/STAT, NF-κB, IRF7	Promote autoantibody production and immune complex deposition; trigger systemic inflammation and organ damage, particularly in lupus nephritis
Sjögren's Syndrome (SS)	IL-1β, IL-6, IFN-γ, TNF-α, BAFF, CXCL13	Epithelial cells, T cells, B cells, macrophages, dendritic cells	NF-κB, JAK/STAT, IFN pathway	Drive glandular inflammation and apoptosis, leading to salivary and lacrimal gland dysfunction (xerostomia and keratoconjunctivitis sicca)
Ankylosing Spondylitis (AS)	TNF-α, IL-17, IL-23, IL-22, GM-CSF	T cells, macrophages, neutrophils, innate lymphoid cells	NF-κB, STAT3, MAPK	Induce osteoclast activation, bone erosion, and pathological new bone formation in the axial skeleton

As a representative of age-related degenerative diseases, cartilage loss in OA is an important pathological feature. In the United States, more than 80% of people over 65 years of age suffer from OA, resulting in disability and imposing a heavy burden on patients and society [37]. Chondrocyte senescence is one of the major risk factors for OA. As OA disease progresses, senescent chondrocytes begin to secrete matrix metalloproteinases 13 (MMP13) and a disintegrin and metallo-proteinases (ADAMs) to degrade collagen, ultimately leading to cartilage calcification. There is evidence of senescent chondrocytes in joint specimens obtained during total joint replacement surgery [38] and the number of senescent chondrocytes in articular cartilage increases with age [39, 40]. OA may also be associated with telomere depletion, with an increase in the number of ultrashort telomeres at the site of the lesion, and a significant correlation with the severity of OA [40, 41]. Oxidative stress causes an imbalance between catabolism and anabolism of articular cartilage, which leads to loss of joint matrix. Oxidative stress that accumulates with aging decreases chondrocyte viability and growth factor sensitivity. Reactive oxygen species (ROS) induce apoptosis and inflammatory responses in cells by activating the MAPK and PI3K/Akt signaling pathways and upregulating p53 and p21 protein levels in chondrocytes [42]. Mitochondrial dysfunction in chondrocytes may be one of the pathogenic mechanisms of OA, in which the number of mitochondria is reduced and the integrity of the mitochondrial membrane is impaired in chondrocytes from OA patients. Impaired mitochondria promote ROS production and MMP13 expression, leading to disease progression in OA patients [43]. Senescent chondrocytes induce peripheral chondrocyte senescence by releasing SASP factors (IL-6, IL-1β, and monocyte chemotactic protein 1 [MCP1]). SASP recruits macrophages, which activate an inflammatory response that leads to synovitis and impairs the stability of the extracellular matrix (ECM), inducing the development of OA [44]. The ECM is a complex network of proteoglycans, collagen, water, minerals and fibrous proteins that confer biodynamic properties to articular cartilage. In healthy individuals, some limited defects in the articular surfaces are capable of spontaneous repair, but often damage accumulates with age, and this, together with loss of cellular function, reduced water content in the tissues and changes in matrix composition, combine to lead to the development of OA [45]. Currently, the mainstay of treatment for OA remains pain management and joint replacement for critically ill patients, but studies have found that the osteoporosis drug Forteo can increase proteoglycan content and inhibit cartilage degeneration in mouse models of OA [46]; Johnson et al. found that the application of kartogenin also promotes cartilage regeneration through modulation of CBF/RUNX1. cartilage regeneration [47]. These experimental studies demonstrate that treatment can promote the repair of damaged cartilage. In addition, the application of natural or synthetic antioxidants can also alleviate cartilage breakdown [48, 49], and caspase inhibitors to enhance mitochondrial activity and reduce apoptosis have also been suggested as possible therapeutic interventions for OA [50].

Aging significantly influences rheumatic diseases by increasing susceptibility, exacerbating disease severity through heightened inflammation and impaired repair mechanisms, and complicating clinical management due to multi-morbidity and reduced physiological reserve. During aging, the immune system declines and the autoimmune response tends to become dysregulated, in part due to impaired lymphocyte production, making rheumatic diseases more likely to occur [51–53]. Aging reduces the patient's ability to tolerate rheumatic diseases, leading to exacerbation and complicating the clinical picture. Elderly patients often have multiple chronic diseases and multi-system involvement, and these factors affect the outcome and prognosis of rheumatic diseases. Thus, aging profoundly impacts both the onset and

clinical course of rheumatic diseases. With the increasing trend of population aging, preventing and managing the progression and severity of rheumatic diseases in the elderly population has become particularly important. Early intervention, individualized treatment and comprehensive management modalities are essential to improve the quality of life and health status of elderly patients, and more comprehensive and individualized treatment plans for elderly patients are needed to improve outcomes and quality of life.

At the molecular and cellular level, the interplay between inflammation and aging is evident. Chronic inflammation and aging are inextricably linked. At the molecular level, cellular SASPs, which promote chronic inflammation and push normal cells into the senescence process. SASPs can be regarded as inflammation at the molecular level, which mainly include cytokines, chemokines, and growth factors. From the cellular level, immune cells are the key regulators of senescent cells, shouldering the heavy responsibility of removing senescent cells, and have always been the focus and hotspot of aging research. Specifically, immune cells are differentiated from bone marrow hematopoietic stem cells, and when hematopoietic stem cells become senescent, immune cells become dysfunctional, exacerbating immune system aging [54]. Moreover, with the passage of life, most immune cells exhibit senescence characteristics, which are manifested internally as a decrease in the ability to clear senescent or damaged cells and externally as a weakening of the body's resistance. The concept of inflammatory senescence inflamm-aging also emerged. When the immune system is senescent, it is unable to remove senescent cells and pro-inflammatory factors, and the level of inflammation will rise accordingly; and when the low level of chronic inflammation accumulates gradually, it further accelerates senescence, forming a vicious cycle [55, 56]. If the above inflamm-aging at the molecular and cellular level continues to accumulate, it may lead to pathologic aging of the organ, where inflammation levels remain high, repair becomes difficult and ultimately leads to disease.

In fact, in healthy individuals, a mild inflammatory response is beneficial in maintaining the stability of the organism. However, in the process of aging, inflammatory factors gradually accumulate in the body, exceeding 2 to 4 times the normal level and breaking through the homeostatic threshold, which leads to a vicious cycle of aging and inflammation, developing into inflamm-aging [57]. Studies have shown that inflamm-aging is a key contributing factor to the development of age-related diseases, whether acute infections or chronic diseases. [58–61].

Rheumatology is an emerging clinical discipline. Its progress is closely related to the development of immunology, genetics, cell biology and other disciplines. Rheumatic diseases refer to a group of diseases that affect bones, joints and their surrounding soft tissues, muscles, bursae, tendons, fascia, and the immune system, etc. Their pathogenesis can be infectious Lyme disease, gonococcal arthritis, immunologic, and metabolic gout, pseudogout, degenerativ or hereditary.

Recent studies have shown that chronic inflammation plays an important role in the pathogenesis of arthritis in the elderly and may accelerate the degeneration of articular cartilage and bone and promote the development of arthritis [62, 63]. The levels of senescence-related cytokines (IL-6 and IL-1β) correlate with the development and severity of rheumatic diseases such as RA and C-reactive protein (CRP) [64–68]. And inflammatory markers play an important role in rheumatic diseases, for example, inflammatory markers such as CRP play an important role in the diagnosis, assessment of disease activity, and prognosis prediction of rheumatoid arthritis and other rheumatic diseases [69–71].

In recent years, researchers have developed a series of therapeutic strategies to address the role of chronic inflammation and aging in rheumatic diseases, such as targeted therapy for inflammatory mediators, immunomodulatory therapy, and the use of biologics, which have significantly improved the symptoms and quality of life of patients. Overall, an in-depth understanding of the relationship between chronic inflammation, aging, and rheumatic diseases will help develop more individualized treatment strategies; further discover new biomarkers and diagnostic techniques that will facilitate the diagnosis of early rheumatic diseases and improve the quality of patients' survival; and discover new therapeutic targets and monitoring indicators that will help assess the effectiveness of treatments and predict the prognosis of patients, and help physicians to better adjust their treatment regimens to improve efficacy; and through the continuous development of new therapeutic strategies, we will be able to improve the quality of life of patients by improving the quality of life. The discovery of new therapeutic targets and monitoring indicators to assess treatment effects and predict patients' prognosis, helping doctors to better adjust treatment programs to improve therapeutic efficacy; through the continuous revelation of the complex relationship between the three, it is conducive to an in-depth understanding of the pathogenic mechanisms of rheumatic diseases, and provides new ideas and directions for future research. It can provide new ideas and methods for individualized treatment, early diagnosis and prevention, treatment effect monitoring and prognosis prediction, which can help to improve the treatment effect and survival quality of patients.

Conclusion

Despite significant progress in this field, the current understanding of the interplay between chronic inflammation and aging in rheumatic diseases remains incomplete. Existing studies predominantly rely on cross-sectional designs or animal models, limiting the reliability of causal inference, while the heterogeneity of patient populations and disease phenotypes further complicates data interpretation. Therefore, future research should focus on longitudinal human cohort studies and multi-omics analyses to delineate causal pathways and identify therapeutic targets. Additionally, discrepancies in defining "inflamm-aging" and "immunosenescence" highlight the urgent need for unified conceptual frameworks and standardized biomarkers [72, 73]. Epidemiological and biological evidence indicates that there exists a mutually reinforcing pathological process between chronic inflammation and aging: chronic inflammation is a key feature of the aging process, while aging, in turn, exacerbates the onset and persistence of chronic inflammation. This cyclical interaction further drives the development and progression of rheumatic diseases [74].

Inflamm-aging leads to dysregulation of the immune system, making it susceptible to autoimmune reactions and abnormal inflammatory responses. This abnormal activation of the immune system is a key mechanism in the development of rheumatic diseases. Inflamm-aging further results in impaired tissue and organ function, accelerating degenerative changes and disease progression in joints, cartilage, bones, and other tissues. Such functional impairment, in turn, exacerbates the severity and progression of rheumatic diseases. Given the significant impact of chronic inflammation and aging on treatment strategies for rheumatic diseases, therapeutic approaches must comprehensively consider how chronic inflammation and aging influence disease progression. Appropriate medications and therapies should be selected to slow disease progression, alleviate symptoms, and improve patients' quality of life. In summary, there exists a complex interplay among chronic inflammation, aging, and rheumatic diseases, with each mutually influencing human health and disease development. A deeper understanding of their interrelationship will contribute to better prevention and treatment of rheumatic diseases and promote better patient quality of life. Future therapeutic strategies should focus on breaking the vicious cycle of inflamm-aging and cellular senescence. Emerging approaches, such as senolytics to selectively clear senescent cells and immunomodulators to recalibrate the dysregulated immune response, hold significant promises. Combining these with existing anti-cytokine therapies (IL-6, TNF-α inhibitors) may lead to more effective, multi-targeted treatment regimens for age-related rheumatic diseases.

Future research should be devoted to understanding the relationship between chronic inflammation, aging and rheumatic diseases. Uncovering the molecular mechanisms and cell signaling pathways of chronic inflammation and aging, exploring the association and impact between the two, and further in-depth research on this will help to discover new therapeutic targets and develop more effective treatments. Comprehensively utilize medication, rehabilitation training, nutritional conditioning, psychological support and other means to treat rheumatic diseases in an integrated manner and improve patients' quality of life and treatment outcomes. Develop individualized treatment strategies and strengthen prevention and health management to improve patients' quality of life and treatment outcomes.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Conceptualization, W.Z.W.; methodology, Z.L.Y; writing-original draft, W.Z.W.&L. J.X; writing - review and editing, L.R. S.Y.Z. L.Y. Z.H.J. & Z.L.; Both authors have read and agreed to the published version of the manuscript.

References

[1] Medzhitov R (2008). Origin and physiological roles of inflammation. Nature, 454:428–435.

[2] Kotas ME, Medzhitov R (2015). Homeostasis, inflammation, and disease susceptibility. Cell, 160:816–827.

[3] Rodier F, Campisi J (2011). Four faces of cellular senescence. J Cell Biol, 192:547–556.

[4] Ferrucci L, Fabbri E (2018). Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol, 15:505–522.

[5] Childs BG, Gluscevic M, Baker DJ, Laberge R-M, Marquess D, Dananberg J, et al. (2017). Senescent cells: an emerging target for diseases of ageing. Nat Rev Drug Discov, 16:718–735.

[6] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G (2023). Hallmarks of aging: An expanding universe. Cell, 186:243–278.

[7] Walford RL (1964). THE IMMUNOLOGIC THEORY OF AGING. Gerontologist, 4:195–197.

[8] Barbé-Tuana F, Funchal G, Schmitz CRR, Maurmann RM, Bauer ME (2020). The interplay between immunosenescence and age-related diseases. Semin Immunopathol, 42:545–557.

[9] Borgoni S, Kudryashova KS, Burka K, de Magalhães JP (2021). Targeting immune dysfunction in aging. Ageing Res Rev, 70:101410.
[10] Yousefzadeh MJ, Flores RR, Zhu Y, Schmiechen ZC, Brooks RW, Trussoni CE, et al. (2021). An aged immune system drives senescence and ageing of solid organs. Nature, 594:100–105.
[11] Gorgoulis V, Adams PD, Alimonti A, Bennett DC, Bischof O, Bishop C, et al. (2019). Cellular Senescence: Defining a Path Forward. Cell, 179:813–827.
[12] Nelson G, Wordsworth J, Wang C, Jurk D, Lawless C, Martin-Ruiz C, et al. (2012). A senescent cell bystander effect: senescence-induced senescence. Aging Cell, 11:345–349.
[13] Xu M, Bradley EW, Weivoda MM, Hwang SM, Pirtskhalava T, Decklever T, et al. (2017). Transplanted Senescent Cells Induce an Osteoarthritis-Like Condition in Mice. J Gerontol A Biol Sci Med Sci, 72:780–785.
[14] Cai Y, Zhou H, Zhu Y, Sun Q, Ji Y, Xue A, et al. (2020). Elimination of senescent cells by β-galactosidase-targeted prodrug attenuates inflammation and restores physical function in aged mice. Cell Res, 30:574–589.
[15] Loeser RF, Collins JA, Diekman BO (2016). Ageing and the pathogenesis of osteoarthritis. Nat Rev Rheumatol, 12:412–420.
[16] Liu Y, Zhang Z, Li T, Xu H, Zhang H (2022). Senescence in osteoarthritis: from mechanism to potential treatment. Arthritis Res Ther, 24:174.
[17] Falvino A, Gasperini B, Cariati I, Bonanni R, Chiavoghilefu A, Gasbarra E, et al. (2024). Cellular Senescence: The Driving Force of Musculoskeletal Diseases. Biomedicines, 12:1948.
[18] Shen J, Abu-Amer Y, O'Keefe RJ, McAlinden A (2017). Inflammation and epigenetic regulation in osteoarthritis. Connect Tissue Res, 58:49–63.
[19] Wright HL, Lyon M, Chapman EA, Moots RJ, Edwards SW (2020). Rheumatoid Arthritis Synovial Fluid Neutrophils Drive Inflammation Through Production of Chemokines, Reactive Oxygen Species, and Neutrophil Extracellular Traps. Front Immunol, 11:584116.
[20] Malemud CJ (2018). The role of the JAK/STAT signal pathway in rheumatoid arthritis. Ther Adv Musculoskelet Dis, 10:117–127.
[21] Cj M (2017). Negative Regulators of JAK/STAT Signaling in Rheumatoid Arthritis and Osteoarthritis. International journal of molecular sciences. doi: 10.3390/ijms18030484.
[22] Lund FE (2008). Cytokine-producing B lymphocytes-key regulators of immunity. Curr Opin Immunol, 20:332–338.
[23] Lin Y-J, Anzaghe M, Schülke S (2020). Update on the Pathomechanism, Diagnosis, and Treatment Options for Rheumatoid Arthritis. Cells, 9:880.
[24] Xx H, Yj W, J Z, W W (2019). T-cells interact with B cells, dendritic cells, and fibroblast-like synoviocytes as hub-like key cells in rheumatoid arthritis. International immunopharmacology. doi: 10.1016/j.intimp.2019.03.008.
[25] Ye BJ, Lee HH, Yoo EJ, Lee CY, Lee JH, Kang HJ, et al. (2020). TonEBP in dendritic cells mediates pro-inflammatory maturation and Th1/Th17 responses. Cell Death Dis, 11:421.
[26] Dd I, Dm B (2021). An Overview of the NF-kB mechanism of pathophysiology in rheumatoid arthritis, investigation of the NF-kB ligand RANKL and related nutritional interventions. Autoimmunity reviews. doi: 10.1016/j.autrev.2020.102741.
[27] Fearon U, Canavan M, Biniecka M, Veale DJ (2016). Hypoxia, mitochondrial dysfunction and synovial invasiveness in rheumatoid arthritis. Nat Rev Rheumatol, 12:385–397.
[28] Lin W, Shen P, Song Y, Huang Y, Tu S (2021). Reactive Oxygen Species in Autoimmune Cells: Function, Differentiation, and Metabolism. Front Immunol, 12:635021.
[29] Castanheira FVS, Kubes P (2019). Neutrophils and NETs in modulating acute and chronic inflammation. Blood, 133:2178–2185.
[30] Leopold J, Schiller J (2024). (Chemical) Roles of HOCl in Rheumatic Diseases. Antioxidants (Basel), 13:921.
[31] Vos K, Thurlings RM, Wijbrandts CA, van Schaardenburg D, Gerlag DM, Tak PP (2007). Early effects of rituximab on the synovial cell infiltrate in patients with rheumatoid arthritis. Arthritis Rheum, 56:772–778.
[32] Durcan L, O'Dwyer T, Petri M (2019). Management strategies and future directions for systemic lupus erythematosus in adults. Lancet, 393:2332–2343.
[33] Zhan Q, Zhang J, Lin Y, Chen W, Fan X, Zhang D (2023). Pathogenesis and treatment of Sjogren's syndrome: Review and update. Front Immunol, 14:1127417.
[34] Mauro D, Thomas R, Guggino G, Lories R, Brown MA, Ciccia F (2021). Ankylosing spondylitis: an autoimmune or autoinflammatory disease? Nat Rev Rheumatol, 17:387–404.
[35] Knopman DS, Amieva H, Petersen RC, Chételat G, Holtzman DM, Hyman BT, et al. (2021). Alzheimer disease. Nat Rev Dis Primers, 7:33.
[36] Fraser HC, Kuan V, Johnen R, Zwierzyna M, Hingorani AD, Beyer A, et al. (2022). Biological mechanisms of aging predict age-related disease co-occurrence in patients. Aging Cell, 21:e13524.
[37] Barbour KE, Helmick CG, Boring M, Brady TJ (2017). Vital Signs: Prevalence of Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation - United States, 2013-2015. MMWR Morb Mortal Wkly Rep, 66:246–253.
[38] Oh J, C K, Rm L, M D, S R, Ap V, et al. (2017). Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. Nature medicine. doi: 10.1038/nm.4324.
[39] Martin JA, Brown TD, Heiner AD, Buckwalter JA (2004). Chondrocyte senescence, joint loading and osteoarthritis. Clin Orthop Relat Res, S96-103.
[40] Price JS, Waters JG, Darrah C, Pennington C, Edwards DR, Donell ST, et al. (2002). The role of chondrocyte senescence in osteoarthritis. Aging Cell, 1:57–65.

[41] Harbo M, Bendix L, Bay-Jensen A-C, Graakjaer J, Søe K, Andersen TL, et al. (2012). The distribution pattern of critically short telomeres in human osteoarthritic knees. Arthritis Res Ther, 14:R12.

[42] Rim YA, Nam Y, Ju JH (2020). The Role of Chondrocyte Hypertrophy and Senescence in Osteoarthritis Initiation and Progression. Int J Mol Sci, 21:2358.

[43] Rego-Pérez I, Durán-Sotuela A, Ramos-Louro P, Blanco FJ (2019). Mitochondrial Genetics and Epigenetics in Osteoarthritis. Front Genet, 10:1335.

[44] McCulloch K, Litherland GJ, Rai TS (2017). Cellular senescence in osteoarthritis pathology. Aging Cell, 16:210–218.

[45] Rahmati M, Nalesso G, Mobasheri A, Mozafari M (2017). Aging and osteoarthritis: Central role of the extracellular matrix. Ageing Res Rev, 40:20–30.

[46] Sampson ER, Hilton MJ, Tian Y, Chen D, Schwarz EM, Mooney RA, et al. (2011). Teriparatide as a chondroregenerative therapy for injury-induced osteoarthritis. Sci Transl Med, 3:101ra93.

[47] Johnson K, Zhu S, Tremblay MS, Payette JN, Wang J, Bouchez LC, et al. (2012). A stem cell-based approach to cartilage repair. Science, 336:717–721.

[48] Elayyan J, Lee E-J, Gabay O, Smith CA, Qiq O, Reich E, et al. (2017). LEF1-mediated MMP13 gene expression is repressed by SIRT1 in human chondrocytes. FASEB J, 31:3116–3125.

[49] Gu H, Jiao Y, Yu X, Li X, Wang W, Ding L, et al. (2017). Resveratrol inhibits the IL-1β-induced expression of MMP-13 and IL-6 in human articular chondrocytes via TLR4/MyD88-dependent and -independent signaling cascades. Int J Mol Med, 39:734–740.

[50] Farnaghi S, Prasadam I, Cai G, Friis T, Du Z, Crawford R, et al. (2017). Protective effects of mitochondria-targeted antioxidants and statins on cholesterol-induced osteoarthritis. FASEB J, 31:356–367.

[51] Cancro MP (2020). Age-Associated B Cells. Annu Rev Immunol, 38:315–340.

[52] Zhao TV, Sato Y, Goronzy JJ, Weyand CM (2022). T-Cell Aging-Associated Phenotypes in Autoimmune Disease. Front Aging, 3:867950.

[53] Zheng Y, Liu Q, Goronzy JJ, Weyand CM (2023). Immune aging - A mechanism in autoimmune disease. Semin Immunol, 69:101814.

[54] Liggett LA, Sankaran VG (2020). Unraveling Hematopoiesis through the Lens of Genomics. Cell, 182:1384–1400.

[55] Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, et al. (2000). Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci, 908:244–254.

[56] Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES, et al. (2014). Geroscience: linking aging to chronic disease. Cell, 159:709–713.

[57] Giunta S, Wei Y, Xu K, Xia S (2022). Cold-inflammaging: When a state of homeostatic-imbalance associated with aging precedes the low-grade pro-inflammatory-state (inflammaging): Meaning, evolution, inflammaging phenotypes. Clin Exp Pharmacol Physiol, 49:925–934.

[58] Fülöp T, Dupuis G, Witkowski JM, Larbi A (2016). The Role of Immunosenescence in the Development of Age-Related Diseases. Rev Invest Clin, 68:84–91.

[59] Childs BG, Durik M, Baker DJ, van Deursen JM (2015). Cellular senescence in aging and age-related disease: from mechanisms to therapy. Nat Med, 21:1424–1435.

[60] Chen L, Wu B, Mo L, Chen H, Zhao Y, Tan T, et al. (2024). Associations between biological ageing and the risk of, genetic susceptibility to, and life expectancy associated with rheumatoid arthritis: a secondary analysis of two observational studies. Lancet Healthy Longev, 5:e45–e55.

[61] Torreggiani S, Castellan FS, Aksentijevich I, Beck DB (2024). Somatic mutations in autoinflammatory and autoimmune disease. Nat Rev Rheumatol, 20:683–698.

[62] Motta F, Barone E, Sica A, Selmi C (2023). Inflammaging and Osteoarthritis. Clin Rev Allergy Immunol, 64:222–238.

[63] Bi J, Zhang C, Lu C, Mo C, Zeng J, Yao M, et al. (2024). Age-related bone diseases: Role of inflammaging. J Autoimmun, 143:103169.

[64] Kim GW, Lee NR, Pi RH, Lim YS, Lee YM, Lee JM, et al. (2015). IL-6 inhibitors for treatment of rheumatoid arthritis: past, present, and future. Arch Pharm Res, 38:575–584.

[65] Grebenciucova E, VanHaerents S (2023). Interleukin 6: at the interface of human health and disease. Front Immunol, 14:1255533.

[66] Pandolfi F, Franza L, Carusi V, Altamura S, Andriollo G, Nucera E (2020). Interleukin-6 in Rheumatoid Arthritis. Int J Mol Sci, 21:5238.

[67] Yao X, Huang J, Zhong H, Shen N, Faggioni R, Fung M, et al. (2014). Targeting interleukin-6 in inflammatory autoimmune diseases and cancers. Pharmacol Ther, 141:125–139.

[68] Jing C, Castro-Dopico T, Richoz N, Tuong ZK, Ferdinand JR, Lok LSC, et al. (2020). Macrophage metabolic reprogramming presents a therapeutic target in lupus nephritis. Proc Natl Acad Sci U S A, 117:15160–15171.

[69] Rizo-Téllez SA, Sekheri M, Filep JG (2023). C-reactive protein: a target for therapy to reduce inflammation. Front Immunol, 14:1237729.

[70] Meyer O (2010). Anti-CRP antibodies in systemic lupus erythematosus. Joint Bone Spine, 77:384–389.

[71] Eklund CM (2009). Proinflammatory cytokines in CRP baseline regulation. Adv Clin Chem, 48:111–136.

[72] Franck M, Daunizeau C, Aronoff JE, Tanner K, Trumble BC, Franceschi C, et al. (2026). Inflamm-aging as a diverse and context-dependent process: From species and population differences to individual trajectories. Ageing Res Rev, 113:102880.

[73] Liu Z, Liang Q, Ren Y, Guo C, Ge X, Wang L, et al. (2023). Immunosenescence: molecular mechanisms and diseases. Sig Transduct Target Ther, 8:200.

[74] Ajoolabady A, Pratico D, Tang D, Zhou S, Franceschi C, Ren J (2024). Immunosenescence and inflammaging:

Mechanisms and role in diseases. Ageing Res Rev, 101:102540.