Journal of Inflammation Research

Dovepress
Taylor & Francis Group

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REVIEW

The Interplay of Aging and PANoptosis in Osteoarthritis Pathogenesis: Implications for Novel Therapeutic Strategies

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Abstract: Osteoarthritis (OA) is a common degenerative joint disease characterized by the progressive degradation of articular cartilage, synovial inflammation, and subchondral bone remodeling. This review explores the interplay between aging, PANoptosis, and inflammation in OA progression. Age-related cellular and immune dysfunctions, including cellular senescence, senescence-associated secretory phenotypes (SASPs), and immunosenescence, significantly contribute to joint degeneration. In OA, dysregulated apoptosis, necroptosis, and pyroptosis, particularly in chondrocytes, exacerbate cartilage damage. Apoptosis, mediated by the JNK pathway, reduces chondrocyte density, while necroptosis and pyroptosis, involving RIPK-1/RIPK-3 and the NLRP3 inflammasome, respectively, amplify inflammation and cartilage destruction. Inflammatory cytokines and damage-associated molecular patterns (DAMPs) further enhance these PANoptotic pathways. Current therapeutic strategies primarily focus on anti-inflammatory agents such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, with growing interest in anti-senescence drugs targeting cellular senescence and SASP. Additionally, exploring PANoptosis mechanisms offers potential for innovative OA treatments.

Keywords: osteoarthritis, aging, senescence, PANoptosis, inflammation, therapeutic strategies

Introduction

Osteoarthritis (OA) is a chronic, debilitatingly progressive disease that involves all structures of the affected joint.[1] It is one of the most prevalent chronic musculoskeletal disorders, impacting over 250 million individuals worldwide.[2] Aging and obesity are two major contributors to OA.[3–5] In the United States alone, more than 32 million people are affected by OA, making it the leading cause of activity limitation among adults.[6] OA primarily affects the elderly, with aging being the most significant risk factor. The disease often manifests with chronic pain and motor impairment, which can range from intermittent to persistent discomfort, and it leads to a decline in physical function.[7,8] OA's harmful effects extend far beyond mere pain and mobility issues, affecting numerous dimensions of life quality, from mental health and sleep quality to work participation and even life expectancy.[9] Given the high incidence of falls among older adults and the substantial burden of OA on individuals and healthcare systems, effective management strategies for OA should be taken into account.

In recent years, the interplay of aging and PANoptosis in OA pathogenesis has emerged as a critical area of research, particularly in light of the globally aging population. Cellular senescence, a hallmark of aging defined as a state of virtually irreversible cell cycle arrest triggered by various stressors,[10] is increasingly recognized as a key biological mechanism in OA. Senescent cells can contribute to OA progression by secreting pro-inflammatory factors (known as the senescence-associated secretory phenotype [SASP] factors), which exacerbate local inflammation. They also alter the

Received: 1 August 2024
Accepted: 22 January 2025
Published: 10 February 2025

surrounding microenvironment, leading to cartilage degradation. As senescent cells accumulate in the joint, they drive chronic low-grade inflammation, which accelerates the disease's progression.[11]

At the same time, emerging evidence suggests that PANoptosis, a collective concept of programmed cell death (PCD) forms including apoptosis, necrosis, and pyroptosis, may also play a significant role in OA pathophysiology. PANoptosis is a complex cellular death process regulated by a variety of internal and external signals, involving immune cell activation, heightened inflammation, and cross-talk between different cell death mechanisms. In addition, there is evidence showing that PANoptosis can influence the immune response by releasing pro-inflammatory cytokines and damage-associated molecular patterns (DAMPs), thereby aggravating the inflammatory cascade.[12–14] The activation of PANoptosis could result in the release of pro-inflammatory cytokines, thus accelerating cartilage damage and disease progression.[15]

This literature review aims to integrate insights from biological and mechanical aging, cell death pathways, and the progression of chronic orthopedic diseases, with the goal of proposing potential therapeutic targets. These findings could inform strategies to modify disease progression and alleviate the symptoms of OA, ultimately improving the quality of life for affected individuals.

Pathophysiology of OA

OA is a complex orthopedic disorder characterized by cellular, molecular, and tissue interactions that lead to the progressive degeneration of joint structures. Degeneration impacts all tissues forming the synovial joint, encompassing the subchondral and metaphyseal bones, synovium, ligaments, joint capsules, and the muscles functioning across the joint.[1]

At the tissue level, changes in subchondral bone play a critical role, with early stages characterized by increased porosity, accelerated remodeling, and reduced bone mineralization. These changes, which often precede or coincide with cartilage degradation, are potentially driven by cartilage-bone crosstalk through subchondral pores and vascular invasion. In late-stage OA, subchondral bone sclerosis becomes evident, with reduced remodeling and increased bone density.[16] Significant pathological changes in the subchondral bone can impact the mechanical properties of the bone and can lead to the development of subchondral cysts and bone marrow lesions, which are closely associated with OA pain.[17,18]

Similarly, the synovium undergoes significant alterations early in OA, including hypertrophy, hyperplasia, angiogenesis, low-grade inflammation, and fibrosis. Synovitis, which intensifies in late-stage OA with macrophage infiltration, contributes to cartilage degradation through the release of pro-inflammatory factors. Adipose tissue, particularly local fat depots such as the infrapatellar fat pad, also plays a crucial role in OA development by interacting with other synovial tissues and releasing adipokines that exacerbate joint damage.[16]

At the cellular level, the loss of chondrocytes, a major contributor to the degradation of articular cartilage, emerges as a critical factor in OA. Chondrocytes, along with the extracellular matrix (ECM), constitute the primary components of articular cartilage, which accounts for 10–20% of its thickness.[19] Notably, articular cartilage is devoid of blood vessels and nerves. The chondrocytes in the middle and deep layers are relatively sparse. These cells demonstrate an increased rate of apoptosis in OA. Chondrogenic progenitor cells (CPCs), also referred to as cartilage precursor cells, originate from bone marrow-derived mesenchymal stem cells (BMSCs) and have the capability to differentiate into chondrocytes[20] (Figure 1).

Typically, chondrocytes maintain a low rate of collagen turnover and do not engage in mitosis under normal conditions.[21] However, aging, mechanical stress, and conditions like diabetes and hypertension can enhance collagen turnover. This leads to alterations in the composition and structure of the cartilage matrix, ultimately causing the formation of fibrous tissue, development of deep fissures, and the eventual delamination and exposure of underlying calcified cartilage and bone.[2] In the early stages, chondrocyte surface receptors employ integrins among other factors to sustain low rates of collagen turnover.

Apoptosis, one of the earliest reported forms of cell death, is significantly intensified in OA. This process is primarily influenced by death receptors such as FAS and TNFR,[22,23] as well as cytokines like TNF-α and IL-1β, among other stress factors.[20,24,25] As the pathological process advances, there is an uptick in chondrocyte activity, which significantly contributes to the disruption and subsequent repair of the collagen network within the perichondrial matrix, signifying the irreversible progression of OA. This increased activity of chondrocytes is also associated with elevated production of inflammatory proteins such as IL-1β, IL-6, TNF-α, and matrix metalloproteinases (MMPs, MMP-1, MMP-3, and MMP-13).[26] The pathways involved in inducing apoptosis in OA encompass mitochondrial-mediated caspase-dependent

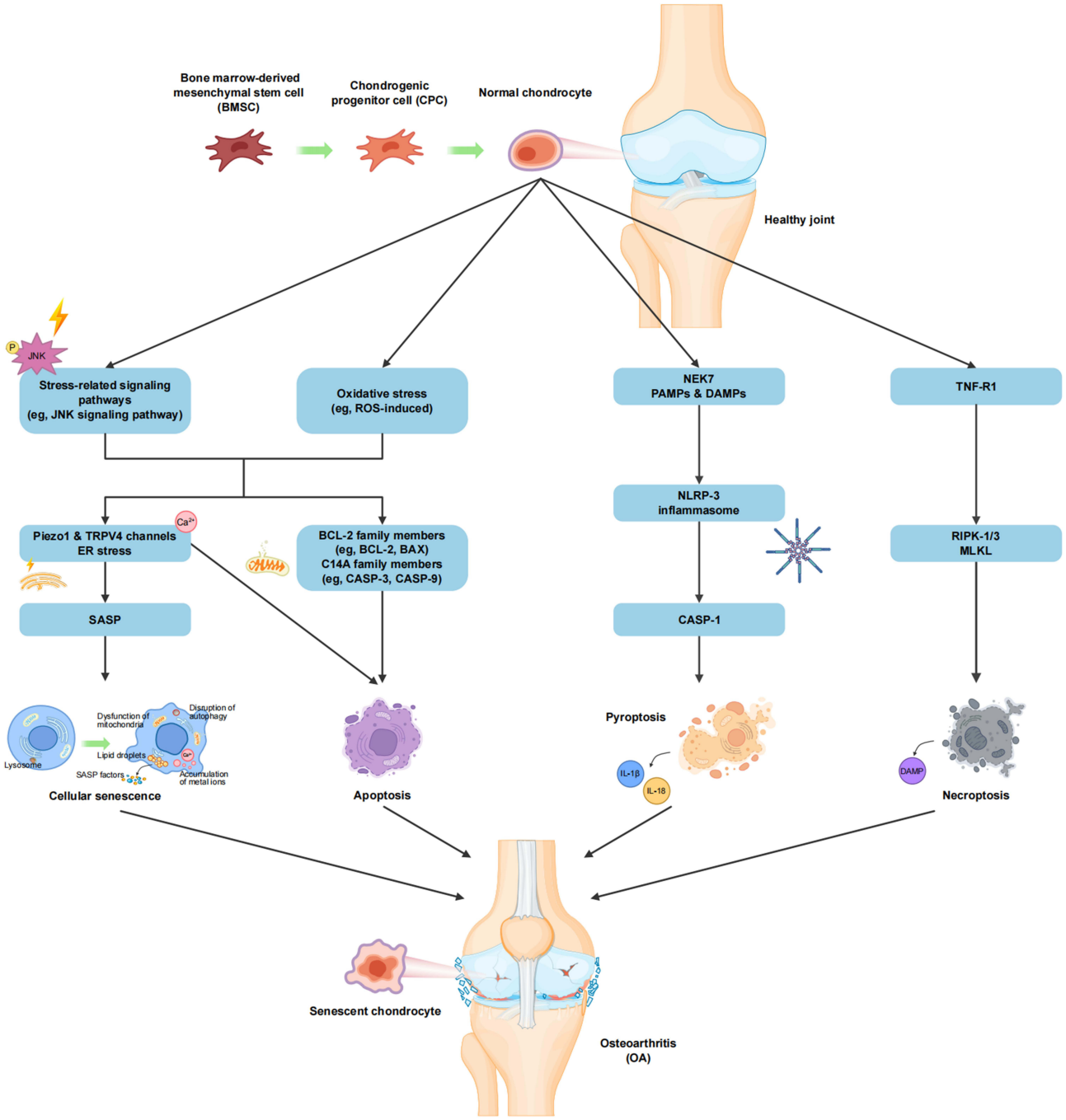

Figure 1 The interplay between chondrocyte senescence and PANoptosis in osteoarthritis (OA) progression. The transition from a healthy joint to OA through cellular mechanisms includes mitochondrial dysfunction, oxidative stress, and the accumulation of metal ions like calcium and zinc. Chondrocyte senescence is characterized by senescence-associated secretory phenotype (SASP) secretion, disrupted autophagy, and permeable lysosomal. PANoptosis, encompassing apoptosis, necroptosis, and pyroptosis, involves key molecular players like NLRP3 inflammasomes, CASP-1, and RIPK-1/3. Stress-related pathways, such as JNK signaling, further exacerbate cellular senescence and PANoptosis, contributing to OA pathogenesis and joint degradation.

Abbreviations: DAMPs, damage-associated molecular patterns; ER, endoplasmic reticulum; PAMPs, pathogen-associated molecular patterns; ROS, reactive oxygen species.

pathways, death receptor signaling, and endoplasmic reticulum (ER) stress-induced unfolded protein response (UPR) pathways.[16] Moreover, autophagy, initially a mechanism promoting cell survival, eventually contributes to cell death in advanced OA stages.[27] Additionally, other forms of cell death, including ferroptosis and pyroptosis, are also implicated in the progression of OA.[16]

https://doi.org/10.2147/JIR.S489613

OA is marked by the production of ECM-degrading enzymes and cartilage destruction, a process similar to endochondral ossification. Chondrocyte hypertrophic differentiation, driven by various systemic and local signaling factors, is a key factor in OA onset and progression. Metabolic abnormalities in chondrocytes also contribute to OA, with accelerated catabolism leading to ECM degradation. The interplay of low-grade inflammation in the synovial membrane, abnormal blood vessel invasion, and changing stress levels in chondrocytes and synovial cells underlines the complexity of OA pathogenesis.[16]

Newly identified mechanisms contributing to OA also include diminished responsiveness of chondrocytes to growth factors, mitochondrial dysfunction, oxidative stress, and abnormal accumulation of advanced glycation end products (AGEs).[28] The progression of OA involves multiple molecular pathways and cellular dysfunctions. Mitochondrial dysfunction, identified as one of the earliest pathogenic mechanisms, impairs chondrocyte function by disrupting mitochondrial structure, leading to decreased adenosine triphosphate (ATP) production and increased oxidative stress. This contributes to chondrocyte apoptosis and articular structure degradation. Chondrocytes also show diminished responsiveness to growth factors, exacerbating mitochondrial dysfunction and oxidative stress, resulting in further oxidative damage from an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, promoting cellular senescence and cartilage breakdown.[28] Elevated ROS levels are associated with increased chondrocyte apoptosis and inflammatory responses. Additionally, the abnormal accumulation of AGEs in cartilage exacerbates OA progression by stiffening the cartilage.[29,30]

Although OA was traditionally considered a prototypical non-inflammatory arthropathy,[31] it is now acknowledged that synovitis occurs in a substantial number of cases, contributing to joint pain and swelling and furthering the progression of cartilage damage.[17] The formation of osteophytes or bone spurs at joint margins is another hallmark of OA, representing the body's attempt to stabilize the deteriorating joint. However, these growths can restrict joint movement and are a source of pain.[18]

The Association Between Aging and OA

Aging, a physiological process governed by numerous biological and genetic pathways, is intrinsically linked to lifespan and contributes to the development of many age-related diseases.[32] Apart from physiological aging, age-related cellular and immune dysfunctions, including cellular senescence and immunosenescence, significantly contribute to both the onset and progression of the disease through various mechanisms.

Physiological Aging in OA

As individuals age, the cumulative effects of wear and tear on joint tissues become increasingly evident, and the regenerative capacity of cartilage diminishes. This is primarily due to the age-related decline in the quality and quantity of chondrocytes, the cells responsible for maintaining cartilage integrity. Aging can lead to a decrease in the cell density and proliferative capacity of articular chondrocytes, and cartilage cell density further declines in post-traumatic osteoarthritis.[33]

Physiological aging significantly influences the pathogenesis of OA through various factors, including genetic predisposition, mechanical stress, obesity, and biological processes such as inflammation and mitochondrial dysfunction.[9] These age-related changes impair the cells' ability to maintain tissue homeostasis, leading to the degradation of the ECM, a hallmark of OA.[34]

Aging can also induce changes in the mechanical properties of joint tissues, making them more prone to damage even under normal loads. Additionally, the aging process is associated with alterations in the molecular and cellular environment of joint tissues. This includes an increase in oxidative stress and the production of AGEs, both of which can adversely affect the health of the cartilage.[17,35] During aging and in response to injuries, cartilage and bone cells face increased levels of ROS, leading to oxidative stress. This stress contributes to diseases like osteoporosis and osteoarthritis by causing cellular dysfunction and impairing the cells' ability to regenerate. Although cells have defense mechanisms against ROS, these defenses can be overwhelmed, resulting in further damage, such as incorrect cell differentiation and cell death.[36]

Cellular Senescence in OA

Senescent cells can drive physiological aging and limit both health span and median lifespan.[37,38] During cellular senescence, lipid droplets increase due to enhanced incorporation of exogenous lipids into triacylglycerols and elevated levels of free polyunsaturated fatty acids (PUFAs), driven by p38-dependent PLA2G1B activation. These lipids

accumulate in droplets within senescent cells, with notable effects observed in models of obesity where senescent cells and lipid droplets are abundant. Clearance of senescent cells or reducing exogenous lipid levels prevents both lipid droplet accumulation and the up-regulation of SASP factors, indicating that lipid droplets or lipids are critical for certain aspects of senescence and SASP regulation. Furthermore, lysosomes of senescent cells can become permeable, resulting in cytosol acidification. Some forms of autophagy may also be disrupted, which may further induce cellular senescence by destabilizing cellular homeostasis. In senescent cells, macroautophagy activity is reduced, while specific factors undergo selective microautophagic degradation. Inhibiting key autophagy components such as ATG7, ATG12, or LAMP2 has been shown to trigger senescence, suggesting that loss of autophagic balance reinforces the maintenance of the senescent state (Figure 1).[39]

Senescent cells accumulate in various tissues and organs as part of the aging process, and their presence in articular cartilage is closely linked to the pathogenesis of OA. One significant impact of cellular senescence in OA is through the SASP. SASP factors include pro-inflammatory cytokines, chemokines, and proteases, which can exacerbate the local inflammatory environment within the joint, further driving the degenerative processes associated with OA, including cartilage breakdown and synovial inflammation.[30,40] The production of SASP factors can be influenced by various regulatory pathways including the DNA damage response (DDR) signaling, NF-κB signaling pathway, p38/MAPK pathway, mTOR pathway, JAK/STAT3 pathway, IL-1α pathway, and cGAS-STING pathway.[41]

MSCs can regulate intercellular communication and target senescent cells and the SASP.[42] MSCs exhibit immunomodulatory effects by secreting anti-inflammatory factors, promoting chondrocyte proliferation, and enhancing ECM synthesis, aiding in cartilage and bone repair.[43,44] MSC senescence negatively impacts OA progression, as aging MSCs exhibit reduced differentiation and proliferation capacities and contribute to the apoptosis of senescent chondrocytes, further promoting OA.[11]

Senescent synovial cells also play a significant role in OA pathology, with SASP factors from synovial fibroblasts driving joint inflammation, cartilage degeneration, and ECM breakdown.[11] Cytokines such as IL-1, IL-6, and IL-17, induced by various stressors, promote synovial fibroblast senescence and joint degeneration.[45] Senescent cells in the synovium can lead to fibrous synovitis, ECM degradation, and cartilage damage, altering the joint microenvironment and contributing to OA.[45] This ECM degradation is primarily mediated by SASP-released cytokines and MMPs such as MMP-13 and ADAMTS-5, which are associated with chondrocyte senescence and OA progression.[46]

Mechanical stress and oxidative stress are also significant drivers of cellular senescence in chondrocytes, the cells within cartilage that maintain the ECM. Mechanical overloading, for example, can induce cellular senescence by reducing the expression of protective proteins like FBXW7, which normally help mitigate stress responses within the cell. This reduction leads to increased activity of stress-related signaling pathways such as the JNK signaling pathway, promoting senescence and contributing to cartilage catabolism.[30]

Additionally, fragments of type II collagen (COL2A1), generated due to catabolic enzymes in response to inflammatory mediators,[47] act as DAMPs in the synovial cavity and are recognized by macrophages through pattern recognition receptors.[48] This interaction leads to M1 polarization of the macrophages, which then release a variety of inflammatory mediators, notably IL-1 and TNF-α.[49] This mechanism is essential for initiating the inflammatory response associated with the onset of OA. The synovium of OA patients contains a large number of M1-type macrophages, which secrete inflammatory factors such as TNF-α and IL-1β. These factors induce aging and apoptosis in chondrocytes and fibroblast-like synoviocytes (FLSs) by activating inflammatory signaling pathways.[50] Additionally, this activity promotes autosecretion of IL-1β and TNF-α, leading to the production of NO, PGE2, and MMPs, which further degrade the ECM of chondrocytes.[51]

Metal ion accumulation, particularly calcium, plays a crucial role in cellular senescence and the progression of OA. The senescence of chondrocytes is strongly associated with orthopedic degenerative diseases such as OA. In senescent cells, calcium ion (Ca^{2+}) accumulation is a common phenomenon that can accelerate the senescence process. Additionally, calcium ions, through mechanosensitive ion channels such as Piezo1 and TRPV4 channels, can trigger ER stress and mitochondrial dysfunction, leading to ROS accumulation, DNA damage, and ultimately promoting cellular senescence and OA development.[30,52]

 https://doi.org/10.2147/JIR.S489613

Immunosenescence in OA

Age-related changes in the immune system, termed immunosenescence, significantly affect the development of OA. Immunosenescence arises from genetic, environmental, and immune factors and is characterized by impairments in innate and adaptive immunity.[53] Innate immune dysfunction involves reduced phagocytosis and superoxide production in monocytes and neutrophils, as well as impaired natural killer and dendritic cell functions. Adaptive immunity is marked by thymic atrophy, increased proinflammatory cytokines, and autoreactivity.[54] These changes contribute to chronic low-grade inflammation, activating signaling pathways such as NF-κB, TOR, and JAK/STAT, which exacerbate joint degeneration and cartilage breakdown.[55]

The accumulation of senescent cells, a hallmark of aging, plays a crucial role in OA progression. The number of senescent cells increases with age due to either excessive production or incomplete clearance, with an estimated presence of 1% to 15% in aged tissues.[56] In vivo studies have confirmed the presence of senescent cells in OA-affected tissues, establishing their direct link to the disease.[57,58]

Additionally, telomere shortening and DNA damage response (DDR) mechanisms play a pivotal role in the relationship between immunosenescence and OA. DDR promotes a proinflammatory state by influencing stem cells, fibroblasts, and macrophages, thereby exacerbating inflammaging and tissue degradation.[59,60] This chronic inflammatory environment, coupled with the reduced regenerative capacity of aging stem cells.

The Association Between PANoptosis and OA

PANoptosis is a recently identified form of PCD that integrates aspects of pyroptosis, apoptosis, and necroptosis. This intricate form of cell death is facilitated through a multi-protein complex known as the PANoptosome. Unlike the individual processes of apoptosis, necroptosis, and pyroptosis, PANoptosis can be initiated through various triggers and involves a coordinated response that includes elements from all three cell death pathways. The concept of PANoptosis is pivotal in understanding cell death mechanisms, as it provides insights into how cells respond to various physiological and pathological stimuli with a multifaceted cell death process.[61,62]

Apoptosis in OA

The degradation process of articular cartilage is influenced by various factors, including mechanical stress and inflammatory cytokines, leading to an imbalance in the cellular environment of chondrocytes.[63] The apoptosis of these cells can be interpreted as a response to the damaged ECM and an effort to eliminate cell debris and dysfunctional components. However, this also leads to a reduction in cell density and the ability of the cartilage to repair itself, exacerbating the condition of the joint.[64]

The inducible nitric oxide synthase (iNOS) enzyme is up-regulated in OA chondrocytes, resulting in excessive nitric oxide (NO) production. This overproduction of NO induces apoptosis via a mitochondria-dependent mechanism, which involves the inhibition of mitochondrial respiration and the release of cytochrome C (cyto C) and CASP-9. Furthermore, mitochondrial dysfunction—characterized by increased mitochondrial membrane permeability and reduced mitochondrial membrane potential—facilitates the translocation of cyto C from the mitochondrial matrix to the cytoplasm. This process triggers apoptosis through caspase activation and an elevated BAX/BCL-2 ratio. Elevated levels of ROS can further contribute to apoptosis by inducing the opening of the mitochondrial permeability transition pore (PTP). Additionally, STING expression is significantly upregulated in both human and mouse OA tissues, as well as in chondrocytes exposed to IL-1β, further promoting apoptosis in these cells. Collectively, these mechanisms drive cartilage degradation in OA.[65]

The JNK pathway can be triggered by various stress stimuli and is essential in regulating cellular processes, including apoptosis, differentiation, and immune responses.[66] This pathway orchestrates a series of complex processes in which the JNK isoforms (ie, JNK-1, JNK-2, and JNK-3), via phosphorylation events, regulate a myriad of cellular functions such as cell death, survival, and inflammation. JNK activity exacerbates these pathological developments (joint inflammation, erosion of articular cartilage, and osteophyte formation).[67] For instance, upon activation by the pro-inflammatory cytokine TNF-α, JNK promotes the degradation of cartilage. Specifically, active JNK phosphorylates c-Jun, which

then enhances the transcription and expression of MMP-13, a key enzyme involved in cartilage breakdown. This results in reduced proteoglycan synthesis, further impairing cartilage integrity.[68,69] Furthermore, increased levels of CXCL8 (IL-8) and CXCL11 in synovial fluids exacerbate OA by activating the JNK signaling pathway, resulting in chondrocyte apoptosis.[70]

In OA, the JNK signaling pathway can promote chondrocyte apoptosis. Stimulation with CXCL8 and CXCL11 increases the expression of phosphorylated JNK, which leads to reduced proliferation and increased apoptosis of chondrocytes. This process is associated with elevated levels of proinflammatory cytokines and MMPs, contributing to cartilage destruction and OA progression.[70]

TRPV4 is up-regulated under mechanical stress conditions, and its activation leads to increased intracellular Ca^{2+} levels, triggering the apoptotic pathways in chondrocytes through up-regulation of apoptosis-related proteins like caspases.[71] On the other hand, Piezo1 is activated by mechanical stress as well, and its activity is intricately regulated by GPER. GPER modulation influences the actin cytoskeleton dynamics and YAP localization, ultimately leading to the inhibition of Piezo1-mediated effects on chondrocyte viability.[72]

Furthermore, apoptosis-related genes have been identified as potential predictors of the onset of OA. These genes are involved in the regulation of immune responses and cellular stress pathways, which are activated in the articular cartilage of individuals with OA. For instance, genes like GDF-15 and KLF9 are involved in the regulation of chondrocyte apoptosis and have been linked to variations in the severity and progression of OA.[73]

Apoptosis not only contributes directly to cartilage deterioration but is also intricately linked with other cell death processes and inflammatory mechanisms that further exacerbate the disease. This highlights the potential of targeting apoptotic pathways and related mechanisms as therapeutic strategies to modulate disease progression and alleviate symptoms.[73]

Necroptosis in OA

Necroptosis is a distinct PCD process that deviates from apoptosis, primarily in its mechanism and morphological outcomes. Unlike apoptosis, which is caspase-dependent and generally non-inflammatory, necroptosis is characterized by cell membrane rupture and the subsequent release of cellular contents, leading to a significant inflammatory response. This form of cell death resembles necrosis, involving the swelling of organelles and a translucent cytoplasm before the membrane ruptures.[74,75]

In OA, elevated levels of inflammatory mediators in the joints trigger necroptosis through the activation of the TNF receptor 1 (TNF-R1), which in turn recruits key necroptosis proteins such as RIPK-1, RIPK-3, and MLKL.[76–78] This process contributes to cartilage matrix degradation via the release of DAMPs. These DAMPs not only exacerbate inflammation and increase the activity of MMPs but also stimulate chondrocytes to release pro-inflammatory cytokines, further damaging joint tissue.[78–80]

Despite advancements in understanding OA, current treatments like non-steroidal anti-inflammatory drugs (NSAIDs) and opioids primarily offer symptomatic relief. As OA progresses, surgical interventions often become necessary.[81,82] The complex nature of OA underscores the urgent need for innovative therapies that can halt disease progression and effectively treat early-stage OA.[83,84] In this context, inhibitors targeting RIPK-1 and RIPK-3 show promise in preclinical models, as they have been found to reduce chondrocyte death and preserve cartilage integrity.[85,86]

Pyroptosis in OA

Pyroptosis, a form of PCD associated with inflammation, plays a significant role in the progression of OA. This process is triggered by inflammatory signals and is characterized by the formation of pores in the cell membrane, leading to cell lysis and the release of pro-inflammatory cytokines such as IL-1β and IL-18, which exacerbate joint inflammation and cartilage degradation.

A key aspect of pyroptosis in OA is the involvement of the NLRP3 inflammasome, which is triggered by various cellular stress signals, including mitochondrial dysfunction, ROS production, and ion fluxes. NEK7 is also critical in this process, as it interacts with the NLRP3 inflammasome complex, facilitating cellular potassium efflux. This interaction is

vital for the NLRP3 inflammasome to cleave pro-CASP-1 into active CASP-1. The active CASP-1 then processes pro-inflammatory cytokines and cleaves GSDMD, a protein essential for executing pyroptosis.[87,88]

Interplay of Aging, PANoptosis, and Inflammation in OA

As individuals age, cellular mechanisms slow down, and immune system efficacy declines, increasing vulnerability to inflammatory conditions.[89,90] Inflammation has been considered as a predictor of senescence. It also actively promotes it through various molecular pathways.[11] Inflammatory factors, such as IL-1β and TNF-α, synergize with ROS to induce DNA damage and telomere attrition, accelerating the onset of cellular senescence. Furthermore, lipid metabolism dysregulation is closely linked to inflammation and senescence, particularly in obese individuals, where inflammatory phenotypes of adipose tissue exacerbate immune senescence. As such, inflammation may impact senescence not only through direct pathways but also via cascades of inflammatory signaling that further propagate senescence.[91–93]

Senescent chondrocytes, the cells accumulated in degenerated cartilage present in joints affected by osteoarthritis, can induce senescence and apoptosis in BMSCs, while also inhibiting these stem cells' proliferation and chondrogenic differentiation abilities. Moreover, although BMSCs were able to induce apoptosis and reduce the proportion of senescent chondrocytes, their positive effects were significantly inhibited in the intra-articular senescent microenvironment, leading to impaired survival, proliferation, and proper differentiation of the transplanted BMSCs, which in turn affected cartilage regeneration.[94]

Pyroptosis occurring in chondrocytes with markers such as elevated cytokine levels and lactate dehydrogenase leakage has been observed in OA cases.[95] This may lead to excessive cellular lysis and cytosolic contents release to the extracellular environment.[96] Necroptosis is notably more immunogenic than apoptosis, primarily due to its robust inflammatory response driven by the release of DAMPs, which in turn accelerates ECM degradation.[97] The elevated expression of RIPK-3 observed in OA patients confirms the significant influence of this pathway on disease progression, with necroptosis exhibiting a tissue-destructive potential that surpasses that of apoptosis.[98,99]

Mitochondrial dysfunction, which is an important factor in PANoptosis, significantly influences OA progression through impaired energy production and heightened oxidative stress. Mitochondria are indispensable in cellular homeostasis, generating ATP via oxidative phosphorylation (OXPHOS) and participating in apoptosis, calcium signaling, and ROS production.[45–47] The reduction in chondrocyte population due to apoptosis leads to diminished production of ECM components, including collagen and proteoglycans, ultimately resulting in cartilage degradation.[100] This degradation contributes to the progression of OA and is evidenced by a decrease in cell density within the cartilage, a process often accompanied by the formation of empty lacunae (spaces formerly occupied by chondrocytes).[101] On the other hand, certain mitochondrial DNA (mtDNA) haplogroups, such as the European mtDNA haplogroup cluster TJ, are associated with reduced OA risk and slower radiographic progression. For example, haplogroups J and T exhibit protective effects against knee and hip OA.[102] However, specific mtDNA variants can elevate ROS levels, suppress mitochondrial fission-related genes, and impair autophagy, emphasizing mitochondrial dysregulation's role in OA.[34] The crosstalk between chondrocyte senescence and PANoptosis in OA progression is illustrated in Figure 1.

Therapeutic Strategies for OA

Anti-Inflammatory Agents

The treatment of OA, particularly knee osteoarthritis, involves a variety of pharmacological strategies, primarily focusing on symptom management given the progressive nature of the disease. One of the most commonly used treatment categories is anti-inflammatory agents, which include NSAIDs and corticosteroids.

Most clinical guidelines for OA recommend using NSAIDs as the next step after the failure of acetaminophen for managing mild to moderate symptoms of OA and as the first-line treatment for severe symptoms.[103] However, their use must be carefully managed due to potential adverse effects, particularly gastrointestinal issues, cardiovascular risks, and kidney problems. For this reason, it is often recommended to use the lowest effective dose and to consider the patient's overall health profile when prescribing these medications.[104] UBX0101, shows promise in treating OA by selectively eliminating senescent chondrocytes. This action reduces SASP and NF-κB activity, enhances matrix synthesis, and

mitigates pain in the anterior cruciate ligament transection mouse model.[105] UBX0101 may also improve joint degeneration by promoting the apoptotic pathway, reducing inflammatory markers, and fostering cartilage regeneration. Despite its short half-life, it effectively reduces senescent cell formation and suppresses SASP factors, demonstrating potential in alleviating post-traumatic OA symptoms and improving joint function.[105]

Recent studies also suggest potential benefits from combining NSAIDs with glucosamine sulfate (GS), a supplement often used in the management of joint pain. Some evidence indicates that this combination can provide greater symptomatic relief compared to either treatment alone. This synergistic effect could be particularly beneficial in managing pain and improving joint function in OA patients.[106]

Corticosteroids and hyaluronic acid injections are other common treatments, providing temporary relief from pain and inflammation. These treatments are typically used when oral medications are ineffective or unsuitable There's ongoing debate and varying recommendations about their effectiveness from different professional societies, reflecting the need for personalized treatment plans based on individual patient needs.[107]

Glucocorticoids (eg, dexamethasone)[108–111] and sivelestat sodium hydrate[112] have been explored for their anti-inflammatory effects in different tissues and their ability to suppress inflammatory cytokines and attenuate osteoarthritic changes in animal models. Additionally, compounds like JQ-1 and flavopiridol have shown efficacy in suppressing inflammatory pathways and joint degeneration through inhibition of key enzymes like BRD-4 and CDK-9 in both in vitro and in vivo models.[113]

Methylene blue (MB), a potent antioxidant, shows therapeutic potential for OA by protecting cartilage, reducing synovitis, and alleviating pain through the regulation of Nrf2 and PRDX1 pathways. Additionally, MB inhibits CGRP expression in rats, mitigating neural inflammation associated with oxidative stress in OA.[114]

Anti-Senescence Drugs

Experimental evidence suggests that targeting cellular senescence may offer novel therapeutic strategies for treating or managing OA. Anti-senescence drugs have demonstrated potential in preclinical studies. These strategies aim to alleviate OA symptoms and possibly reverse some joint tissue damage by addressing one of the disease's root causes: the accumulation of senescent cells that promote chronic inflammation and tissue degeneration.[40]

The senolytic combination therapy of dasatinib (D) and quercetin (Q) presents a promising approach in treating OA by targeting the root cause of cellular senescence.[115] This therapy effectively eliminates senescent cells and reduces inflammatory factors (SASP) associated with OA, while simultaneously promoting cartilage repair through increased expression of key chondrogenic genes like COL2A1, ACAN, and SOX9. The treatment also enhances the production of growth factors such as FGF18, IGF1, and TGFB2, fostering an environment conducive to cartilage regeneration. Notably, dasatinib is identified as the primary contributor to these beneficial effects, suggesting its pivotal role in the therapeutic efficacy of the D+Q combination. This approach not only mitigates the symptoms of OA but also addresses underlying cellular mechanisms, making it a significant candidate for further research as a disease modifying OA drug (DMOAD).

Senomorphics, another category of anti-cellular senescence drugs, can reduce the harmful effects of SnCs by inhibiting SASP (senescence-associated secretory phenotype) factors without inducing SnC apoptosis.[116] Intra-articular hyaluronic acid (IAHA) has potential as a senomorphic agent in treating knee osteoarthritis (KOA). IAHA can modulate the function and morphology of senescent cells, potentially delaying their progression to a senescent state or rejuvenating them. This action, along with its ability to inhibit MMP-13, suggests that IAHA may have additional benefits beyond its lubricating and shock-absorbing properties.[117]

PANoptosis-Based Therapies

Despite advancements in understanding OA's complex nature, current treatments primarily focus on symptom management through anti-inflammatory drugs and physical therapy, with joint replacement surgeries often being the last resort.[18] Continued research into OA's PANoptosis pathways may provide new perspective. Promising PANoptosis-based OA therapies are listed in Table 1.

Table 1 Promising PANoptosis-Based Osteoarthritis (OA) Therapies

Compound	Type of Compound	Mechanism	Application Context	Type of Experiment
N-acetyl cysteine[118]	Antioxidant	Reducing oxidative stress and preserving chondrocytes	Chondroprotection	In vitro human model (human cartilage trauma-model)
Mn(III)–porphyrin (MnP)[119]				In vitro animal model (Bovine articular cartilage disks)
Vitamin E[120]				In vitro human model (human articular cartilage)
Navitoclax (ABT-263)[94]	Anti-senescence agent	Reducing the induction of cellular apoptosis and senescence in bone marrow-derived mesenchymal stem cells (BMSCs) and lessening the inhibition of their chondrogenic differentiation	Senescent chondrocyte removal	In vitro human model (rat BMSCs) and in vivo animal model (rat cartilage defect model)
SS-31[121]	Caspase inhibitor	Preventing chondrocyte death and cartilage degeneration by reducing cell membrane damage	Post-traumatic osteoarthritis (PTOA)	In vitro animal model (bovine knee joints)
Icariin (ICA)[95]	NLRP3 inflammasome inhibitor	Inhibiting LPS-induced activation of NLRP3 inflammasome and pyroptosis-related CASP-1 signaling pathway	OA management	In vitro animal model (Rat chondrocytes) and in vivo animal model (OA rat model)
AZD8330[122]	RIPK-3 inhibitor	Inhibiting RIPK1-associated necrosis	OA management	In vitro animal model (mouse chondrocytes of the ADTC5 cell line)
AZ-628[123]	RIPK-3 and MLKL inhibitor	Reducing osteoarthritis pathogenesis by inhibiting RIPK3	OA management	In vitro animal model (mouse chondrocytes of the ADTC5 cell line)
VX-11e[86]	Extracellular signal-regulated kinase (ERK) inhibitor	Protecting articular cartilage and subchondral bone by regulating the RIP1/RIPK-3/MLKL and MAPK signaling pathways	OA management	In vivo animal model (OA mice)
Celecoxib and glucosamine sulfate (GS)[124]	Celecoxib: analgesic and anti-inflammatory GS: amino-monosaccharide	Mitigating oxidative stress and apoptosis	OA management	In vitro human model (human chondrocytes)

Targeting apoptosis for the treatment of OA holds promise, particularly by addressing mitochondrial dysfunction, a critical early pathogenic mechanism in OA progression.[125] Mitochondrial damage in the sub-acute phase post-injury promotes chondrocyte apoptosis and articular degeneration, as evidenced by reduced respiratory function, decreased proteoglycan content, and disrupted ECM homeostasis, including up-regulated MMP-13 expression in a DMM mouse model.[121,126] Therapeutic strategies targeting mitochondrial pathways, such as the electron transport chain and BAX/BAK pathways, aim to mitigate apoptosis by neutralizing oxidative stress and inhibiting caspase activation. The use of antioxidants like N-acetyl cysteine,[118] Mn(III)–porphyrin (MnP),[119] and vitamin E[120] has shown significant chondroprotective effects in ex vivo studies.

Both in vitro and in vivo experiments have shown that using the anti-senescence agent navitoclax (ABT-263) to clear senescent chondrocytes can mitigate their harmful effects on BMSCs.[94] Specifically, ABT-263 helps reduce the induction of cellular apoptosis and senescence in BMSCs and lessens the inhibition of their chondrogenic differentiation. This suggests that ABT-263 is effective in counteracting the negative impact of senescent cells in osteoarthritis, potentially improving the environment for cartilage regeneration.

Caspase inhibitors have also been investigated to prevent chondrocyte from apoptosis in preclinical studies, even though the efficacy of these drugs in human bodies remains unverified.[127] SS-31, a mito-protective peptide, has proven to effectively prevent chondrocyte death, apoptosis, and cartilage matrix degeneration in post-traumatic osteoarthritis (PTOA). When administered immediately or up to 12 hours after cartilage injury, SS-31 sustains chondrocyte viability, reduces cell membrane damage, and prevents glycosaminoglycan loss for up to a week in culture.[121] However, targeting mitochondrial-associated pathways presents challenges due to non-tissue-specific effects, despite the reported safety of SS-31 in human studies.[128]

Moreover, the development of drugs based on the regulation of pyroptosis has attracted the attention of researchers. FOXQ1 serves as a protector in OA by inhibiting NLRP3-induced pyroptosis. It is down-regulated in OA, and its overexpression promotes chondrocyte proliferation while suppressing apoptosis. Additionally, FOXQ1 reduces the expression of pyroptosis-related proteins (eg, NLRP3, CASP-1, GSDMD) and inflammatory cytokines (eg, IL-6, IL-18, TNF-α). Conversely, silencing FOXQ1 exacerbates these processes, suggesting that FOXQ1 may mitigate OA progression by regulating inflammation and pyroptosis.[129]

Icariin (ICA), derived from *Epimedium*, exhibits potential therapeutic effects on OA by targeting inflammation and cartilage degradation.[95] Specifically, ICA suppresses lipopolysaccharide (LPS)-induced inflammation and collagen degradation in chondrocytes, and alleviates pyroptosis by inhibiting the NLRP3 inflammasome-mediated CASP-1 signaling pathway. These effects were confirmed in both in vitro and in vivo OA models.

Meanwhile, the inhibition of specific proteins that facilitate necroptosis process has also become a molecular novel target for the treatment of osteoarthritis. Among these developments, inhibitors like AZD8330 have shown promise. AZD8330 works by activating cIAP1, which subsequently inhibits RIPK1-associated necrosis in OA, suggesting a novel approach to managing this condition.[122] Furthermore, AZ-628, an inhibitor of RIPK-3 and MLKL, has been found to significantly stabilize the chondrocyte microenvironment, alleviate inflammation, and reduce OA pathogenesis.[123]

VX-11e, an ERK inhibitor, has shown protective effects in OA.84 In a mouse OA model, VX-11e mitigated cartilage and subchondral bone loss by inhibiting the expression and phosphorylation of RIPK3 and MLKL, thus promoting ECM synthesis in chondrocytes. Additionally, VX-11e suppressed RANKL-induced osteoclast differentiation by targeting the ERK/RSK signaling pathway, without affecting the NF-κB pathway. These findings suggest that VX-11e protects articular cartilage and subchondral bone during OA progression by regulating the RIP1/RIPK3/MLKL and MAPK signaling pathways.

Celecoxib is a commonly used selective NSAID for the treatment of OA.98 In contrast, glucosamine sulfate (GS) or chondroitin sulfate (CS) are considered first-line long-term treatments for OA. The study by Cheleschi, et al[124] demonstrated the promising therapeutic potential of combining celecoxib and GS for OA treatment through anti-inflammatory and anti-apoptotic mechanisms. This combination significantly reduces the expression and release of pro-inflammatory mediators such as COX-2, PGE2, IL-1β, IL-6, and TNF-α, as well as matrix-degrading enzymes like MMPs, while promoting the synthesis of COL2A1. Furthermore, it effectively mitigates oxidative stress and apoptosis by modulating antioxidant enzyme activity, enhancing anti-apoptotic protein expression (eg, BCL-2), and downregulating NF-κB subunits (p50 and p65).[103]

Dietary Interventions

Omega-3 fatty acids (ω-3 PUFAs) demonstrate significant therapeutic potential in managing OA by influencing bone and joint health through various mechanisms. These bioactive compounds exhibit an inhibitory effect on osteoclastogenesis, thereby helping to preserve bone mineral mass and promoting osteoblastogenesis.[130] They regulate musculoskeletal growth and bone homeostasis by reducing bone resorption while maintaining consistent bone formation.[131,132] ω-3 PUFAs improve bone strength by enhancing microarchitecture, increasing trabecular network density, and reducing trabecular space and bone surface density.[133,134] Studies in ovariectomized animal models have shown that fish oil supplementation reduces bone

mineral density loss[135] and positively correlates with femur bone mineral content.[136] Moreover, docosahexaenoic acid (DHA), a key ω-3 PUFA, accumulates in bone periosteum and marrow, enhancing bone mineral content.[137] During skeletal growth, ω-3 PUFAs promote chondrocyte proliferation, differentiation, and bone growth, resulting in superior bone structure and quality, as demonstrated in fat-1 mice.[138] However, further large-scale RCTs are needed to establish the optimal dose, treatment duration, and molecular pathways involved, as well as to address heterogeneity across studies.[139]

A recent single-arm feasibility trial[140] designed an anti-inflammatory diet intervention aimed at alleviating symptoms of knee osteoarthritis, focusing on reducing inflammation. The diet emphasized nutrient-dense whole foods, minimally processed anti-inflammatory foods (such as omega-3 rich fish and antioxidant-rich vegetables), and the avoidance of pro-inflammatory processed foods (like refined sugars and fats). The diet led to improvements in all five subscales (pain, symptoms, activities of daily living, sport/recreation, quality of life), with changes falling within the minimal detectable change for each subscale. The anti-inflammatory diet was effective in managing knee osteoarthritis symptoms and improving overall health, demonstrating its potential as a viable non-pharmacological treatment.

Future Research Directions

Future research directions in the field of OA should aim to address the disease's complex pathophysiology, influenced by aging, cellular senescence, immunosenescence, and PANoptosis. A crucial area of focus is gaining a deeper understanding of the molecular mechanisms involved in OA progression. Detailed studies on signaling pathways such as NF-κB, JAK/STAT, and the JNK pathway in chondrocytes and joint tissues will provide insights into the fundamental processes driving OA. Additionally, exploring metabolic homeostasis and its disruption in OA can uncover novel therapeutic targets aimed at restoring balance and mitigating symptoms.

The role of PANoptosis, which integrates apoptosis, necroptosis, and pyroptosis pathways, is increasingly recognized in OA research. Understanding how these cell death mechanisms interact and contribute to joint degradation will be vital. Developing specific inhibitors that can block PANoptosis-related pathways without disrupting normal cellular functions could revolutionize OA treatment. Additionally, advancing mitochondrial research is critical, as mitochondrial dysfunction is a key factor in OA pathogenesis. Protective compounds and gene therapy approaches targeting mitochondrial defects hold promise for enhancing cellular energy production and reducing oxidative stress in chondrocytes.

Advancements in genomics and personalized medicine offer exciting possibilities for OA treatment. Genetic profiling to identify susceptibility genes and variants associated with OA can lead to personalized therapeutic strategies. Exploring the impact of mitochondrial haplotypes and gene-gene interactions on OA progression will further refine these approaches, allowing for tailored interventions based on individual genetic makeup.

Innovative therapeutic modalities, including regenerative medicine, are also essential. Research on stem cell therapy, tissue engineering, and biomaterials aims to repair and regenerate damaged joint tissues. Targeting cellular senescence and immunosenescence presents another promising research direction. Senolytics and senomorphics, drugs developed to eliminate or mitigate the effects of senescent cells, have demonstrated promising potential in ex vivo studies.[105,115,117] Evaluating the efficacy and safety of these drugs in clinical trials will be essential to determine their viability as OA treatments. Moreover, strategies to rejuvenate the aging immune system through immunomodulatory therapies could enhance tissue repair and reduce chronic inflammation, providing a dual approach to tackling OA.

Finally, lifestyle and preventive strategies play a significant role in managing OA. Research should continue to focus on the impact of diet, exercise, and weight management on OA progression. Public health interventions to raise awareness about OA prevention and early management, along with community-based programs, can significantly improve patient outcomes. By addressing these multifaceted research directions, the scientific community can develop comprehensive, effective, and personalized therapeutic strategies to improve the quality of life for individuals suffering from OA.

Conclusion

The pathophysiology of OA involves a complex interplay between cellular senescence and PANoptosis, including apoptosis, necroptosis, and pyroptosis. These mechanisms drive cartilage degradation, subchondral bone remodeling,

and synovial inflammation, contributing to the pain and functional limitations associated with OA. Current treatments primarily focus on symptom management; however, emerging strategies that target cellular senescence and PANoptosis hold promising potential for halting or even reversing the progression of OA, especially in aging populations. Further research and clinical trials are essential to translate these findings into effective therapies for OA patients.

Funding

This study was supported by Shandong Traditional Chinese Medicine Science and Technology Project (M-2023159); Shandong Province Medical and Health Science and Technology Development Programme (202204070834); Shandong Geriatrics Society Science and Technology Tackling Programme Project (LKJGG2021Y030).

Disclosure

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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