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Osteoarthritis as an aging-driven multi-tissue disorder: genomic instability, cellular senescence, and emerging gerotherapeutic strategies

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Abstract
Background. Osteoarthritis (OA) is the most common musculoskeletal disorder and a major cause of disability in older adults. Once considered primarily a consequence of mechanical wear, OA is now recognized as an aging-driven, multi-tissue degenerative disease. Processes such as genomic instability, mitochondrial dysfunction, and cellular senescence play central roles in disease initiation and progression.
Objective and methods. This review synthesizes mechanistic evidence linking biological aging to OA pathogenesis and evaluates emerging senescence-targeted therapies. A PRISMA-informed narrative search of PubMed, Embase, Cochrane Central, and Google Scholar identified 86 relevant clinical and preclinical studies from 360 screened records.
Results. Aging chondrocytes accumulate DNA damage, telomere shortening, and metabolic dysfunction, leading to persistent senescence and a pro-inflammatory SASP. Senescent cells across cartilage, synovium, subchondral bone, and adipose tissue interact via paracrine and extracellular vesicle signaling, driving chronic inflammation and matrix degradation. Preclinical data show that interventions targeting aging hallmarks – including senolytics, senomorphics, autophagy activation, NAD^+ restoration, stem cell-based therapies, and lifestyle modification–can reduce senescence burden and slow structural decline, though human evidence remains limited.
Conclusion. OA should be reframed as an aging-mediated systemic joint disorder rather than isolated cartilage failure. Therapies addressing upstream mechanisms of cellular aging offer realistic potential for disease modification, but successful translation will require age-adapted clinical strategies and biomarker-guided patient selection.
Keywords: osteoarthritis, aging, genomic instability, chondrocyte senescence, SASP.
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Остеоартроз как возрастное заболевание, поражающее различные ткани: геномная нестабильность, старение клеток и новые геротерапевтические стратегии

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Аннотация
Введение. Остеоартроз (ОА) – это наиболее распространенное заболевание опорно-двигательного аппарата и основная причина инвалидизации лиц пожилого возраста. ОА, который первоначально считали следствием механического износа, в настоящее время признан возрастным дегенеративным заболеванием, поражающим различные ткани. Такие процессы, как геномная нестабильность, митохондриальная дисфункция и старение клеток, играют важнейшую роль в развитии и прогрессировании заболевания.
Цель и методы. В настоящем обзоре обобщены данные о механизмах, связывающих биологическое старение с патогенезом ОА, оценены новые методы лечения, направленные на борьбу со старением. В ходе поиска в базах данных PubMed, Embase, Cochrane Central и Google Scholar в соответствии с протоколом PRISMA среди 360 просмотренных записей идентифицированы 86 подходящих клинических и доклинических исследований.
Результаты. С возрастом в хондроцитах накапливаются повреждения ДНК, укорачиваются теломеры, возникают метаболические нарушения, приводящие к старению и формированию провоспалительного SASP-фенотипа. Стареющие клетки хрящевой ткани, синовиальной оболочки, субхондральной кости и жировой ткани взаимодействуют через паракринную сигнализацию и внеклеточные везикулы, вызывая хроническое воспаление и деградацию матрикса. Данные доклинических исследований показывают, что вмешательства, предполагающие воздействие на главные признаки старения, а именно применение сенолитиков и сеноморфиков, активация аутофагии, восстановление $НАД^+$, терапия стволовыми клетками и изменение образа жизни, могут снизить бремя старения и замедлить развитие структурных нарушений, однако данных исследований на человеке по-прежнему недостаточно.
Выводы. Взгляды на ОА следует пересмотреть – это возрастное системное заболевание суставов, а не просто повреждение хряща. Терапия, воздействующая на механизмы старения клеток на ранних стадиях, обладает реальным потенциалом с точки зрения изменения течения заболевания, однако для успешного внедрения в клиническую практику потребуются адаптированные к возрасту клинические стратегии и отбор пациентов по результатам анализа биомаркеров.
Ключевые слова: остеоартроз, старение, геномная нестабильность, старение хондроцитов, SASP-фенотип.
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Introduction

Osteoarthritis (OA) is the most prevalent musculoskeletal disorder and a leading cause of disability worldwide, with a rapidly increasing burden in aging populations [1]. Although genetics, obesity, sex, and joint injury contribute to risk, aging remains the strongest and most consistent determinant of OA development [2]. Epidemiological and experimental data indicate that biological aging processes – rather than mechanical wear alone – are central to disease initiation and progression [1, 3]. Modern concepts now recognize OA as a multi-tissue disorder involving cartilage, synovium, subchondral bone, and periarticular structures, all of which undergo age-related dysfunction [4].

Current OA therapies are largely palliative, focusing on pain control and functional support, with no approved disease-modifying treatments [5, 6]. This therapeutic gap reflects an incomplete targeting of upstream mechanisms. The geroscience framework proposes that conserved aging pathways drive chronic diseases, including OA [7]. Among these, cellular senescence has emerged as a key mechanism: senescent joint cells acquire a pro-inflammatory SASP that promotes matrix degradation, chronic inflammation, and secondary senescence across tissues [7–9]. While transient senescence can be beneficial, its persistent accumulation in aging joints becomes pathogenic [10].

Recognition of OA as an aging-driven condition has stimulated interest in therapies that target fundamental aging processes, including senolytics, senomorphics, and metabolic modulators [11]. This review integrates current evidence across joint compartments to clarify how genomic instability and cellular senescence orchestrate OA pathogenesis and to evaluate emerging anti-aging strategies with true disease-modifying potential.

Methods

This review followed a structured search strategy to identify evidence on aging, cellular senescence, and OA. Peer-reviewed studies published up to 2025 were retrieved from PubMed, Scopus, Web of Science, and Google Scholar using keywords including “osteoarthritis”, “aging”, “senescence”, “chondrocytes”, “SASP”, “DNA damage” and “disease-modifying therapies.”

Included were English-language studies examining age-related mechanisms in OA, biomarkers of senescence in joint tissues, and preclinical or clinical interventions targeting aging pathways. Studies focused on non-OA disorders, non–peer-reviewed sources, or reports lacking experimental or clinical data were excluded.

Findings were synthesized across molecular, preclinical, and clinical evidence to define shared biological patterns and therapeutic opportunities. This approach emphasized the multi-tissue, aging-driven nature of OA and integrated mechanistic insights with translational relevance.

Aging and Genomic Instability in Chondrocytes

DNA damage and oxidative stress. Aging and OA chondrocytes show increased DNA lesions and impaired repair capacity [12, 13]. Reactive oxygen species (ROS) accelerate telomere erosion and mitochondrial dysfunction, linking oxidative stress to senescence and matrix failure [8, 14, 15]. Persistent DNA damage activates the DNA damage response (DDR), favoring p53–p21–p16–mediated senescence rather than apoptosis, thereby promoting chronic tissue dysfunction [16–18].

Signaling pathways and organellar stress. The IKKα–NF-κB axis modulates oxidative damage responses; its suppression enhances DNA repair and limits senescence, positioning it as a therapeutic target [19, 20]. Mitochondrial DNA damage and defective mitophagy amplify ROS production, creating a self-reinforcing cycle of genomic and metabolic stress [21, 22]. Parallel lysosomal and endoplasmic reticulum stress further compromise proteostasis and cartilage integrity [21, 23].

DNA damage-induced senescence. Genomic instability drives irreversible chondrocyte senescence and acquisition of a pro-inflammatory SASP. Experimental DNA damage reproduces OA-like senescence features and SASP activation [24]. Together, these mechanisms converge on persistent senescence as the central cellular outcome that reshapes the joint microenvironment [9, 14].

Cellular senescence in the osteoarthritis joint: a multi-tissue perspective

Cartilage. Senescent chondrocytes accumulate with age and disease severity and causally drive degeneration [25, 28]. Their SASP suppresses collagen II and aggrecan synthesis while inducing matrix metalloproteinases; mTOR signaling regulates this output [29, 30]. Paracrine IL-6 signaling and EV-mediated microRNA transfer propagate senescence to neighboring cells [31–34]. Mechanical overload triggers senescence via Piezo1-mediated calcium influx and nuclear envelope stress, integrating biomechanical risk with aging biology [35–37]. Metabolic redox imbalance, circadian disruption (BMAL1 loss), and impaired FOXO–SIRT–AMPK signaling further promote chondrocyte aging [37–45].

Synovium. Senescent synovial fibroblasts accumulate through hypoxia/reoxygenation and inflammatory signaling, releasing SASP factors that intensify synovitis and cartilage damage [19, 46, 47]. Immune surveillance declines with age, enabling persistence of senescent cells through decoy receptor–mediated immune evasion [48–51].

Infrapatellar fat pad. The fat pad acts as a local senescence hub, secreting pro-inflammatory extracellular vesicles that induce chondrocyte dysfunction, paralleling systemic adipose tissue aging mechanisms [52, 53].

Subchondral bone. Senescent osteoblasts, osteocytes, and mesenchymal stromal cells disrupt bone remodeling and repair capacity; their clearance prevents age-related bone loss and OA progression [32, 54]. Stem cell exhaustion and metabolic reprogramming further accelerate sclerosis and joint degeneration [54].

Integrated mechanisms. Mechanical stress, oxidative injury, and inflammation induce senescence across joint tissues [14]. Once established, SASP signaling and extracellular vesicles create a bystander effect that spreads dysfunction [19, 55]. This self-propagating cycle represents a maladaptive “remodeling activation” program that explains disease persistence and the limited success of single-target therapies [56].

Overall, cellular senescence unifies genomic instability, metabolic failure, immune dysregulation, and biomechanical stress into a coherent model of OA pathogenesis, providing a strong rationale for senotherapeutic strategies aimed at disease modification rather than symptom control.

Anti-aging therapeutic strategies targeting osteoarthritis

Senolytic and senomorphic therapies. Senolytics aim to eliminate senescent chondrocytes, whereas senomorphics suppress SASP without inducing cell death. Dasatinib plus quercetin clears senescent cells and partially restores anabolic markers, with dasatinib providing the dominant effect [57]. Fisetin reduces chondrocyte senescence through SIRT6 pathways and slows OA progression [58]. Navitoclax shows senolytic activity but is limited by toxicity and inconsistent benefits [59]. Senomorphics such as rapamycin, resveratrol, and metformin reduce SASP and enhance autophagy, though systemic adverse effects restrict translation [14, 60, 61]. Even intra-articular hyaluronic acid exhibits senomorphic actions via SIRT1 activation and oxidative stress reduction [62].

Clinical evidence remains limited. Trials often exclude very old patients, and UBX0101 failed to meet primary endpoints in OA [39, 63, 64]. Safety concerns include transient inflammation after senescent cell clearance and drug-specific toxicities such as myelosuppression with navitoclax and dasatinib [57, 60]. Glucosamine is being reconsidered as a potential geroprotective agent through AMPK activation and autophagy enhancement, with improved delivery systems proposed to increase efficacy [65, 66]. Immunotherapeutic approaches – including CAR-T cells targeting senescent markers – represent emerging alternatives to small-molecule senolytics [67, 68].

Autophagy activation and mTOR inhibition. Enhancing autophagy offers an integrative strategy to restore cellular resilience. mTOR inhibition with rapamycin preserves chondrocyte viability, reduces synovitis, and limits cartilage loss in experimental OA [30, 69]. Activation of AMPK further supports metabolic homeostasis and suppresses senescence-associated inflammation [70]. Regenerative approaches such as autologous chondrocyte implantation and mesenchymal stem cell (MSC) therapies provide structural repair potential, with platelet-rich plasma enhancing MSC expansion and chondrogenesis [14].

Metabolic, anti-inflammaging, and regenerative strategies. Restoring NAD^+ levels using nicotinamide riboside or nicotinamide mononucleotide improves mitochondrial function and protects cartilage in aging models, offering disease-modifying potential [71, 72]. Targeting inflammaging with metformin or low-dose cytokine inhibition can reduce SASP activity, while microRNA modulation represents an additional regulatory approach [73–75]. MSC-based therapies–particularly exosome and secretome preparations–suppress inflammation, enhance autophagy, and reduce chondrocyte senescence [76, 77]. Short-term safety appears acceptable, but long-term efficacy and durability require further study [78, 79].

Lifestyle and nutritional modulation of aging pathways in osteoarthritis

Nutrition influences OA primarily by regulating core aging mechanisms. Caloric restriction and intermittent fasting reduce senescence burden, suppress SASP mediators, and activate AMPK–sirtuin pathways while inhibiting mTOR, thereby enhancing autophagy and mitochondrial quality control in chondrocytes [23, 32, 80]. Mediterranean-style diets similarly reduce inflammation and metabolic stress, converging on pathways that delay chondrocyte senescence [81]. Caloric restriction mimetics such as resveratrol, quercetin, curcumin, metformin, and rapamycin replicate these molecular effects by suppressing NF-κB signaling and limiting cartilage catabolism [63, 82].

Physical activity functions as a systemic anti-senescence intervention. Physiological mechanical loading promotes chondrocyte autophagy, improves metabolic efficiency, and reduces inflammatory signaling, while exercise-induced myokines such as irisin inhibit NF-κB and Wnt/β-catenin pathways, protecting cartilage and subchondral bone [83, 84]. Even modest levels of regular activity are sufficient to reduce disability and preserve function in older adults with OA [85].

Circadian rhythm alignment represents an additional modifiable regulator of joint aging. Disruption of clock genes, particularly BMAL1, impairs DNA repair and autophagy and accelerates senescence in cartilage [41, 86]. Lifestyle measures that maintain circadian integrity therefore offer a practical, non-pharmacologic strategy to counteract inflammaging and slow OA progression.

Limitations, future perspectives, and conclusions

OA is a heterogeneous, aging-driven condition encompassing multiple phenotypes shaped by joint site, metabolic status, mechanical loading, and inflammatory burden. These differences lead to distinct senescence profiles and SASP signatures, limiting the universal applicability of current anti-aging strategies and complicating therapeutic translation across OA subtypes.

Clinical advancement is further constrained by the predominance of preclinical evidence, which inadequately reflects the complexity of aged human joints, comorbidities, and lifelong biomechanical stress. Additional challenges include potential off-target effects of senotherapeutics, uncertain dosing and durability, and a lack of long-term, age-stratified human trials.

Future progress depends on defining OA subtypes based on senescence burden, developing robust biomarkers for patient stratification and monitoring, and testing combination therapies that target multiple aging hallmarks. Integrating geroscience with precision medicine offers a pathway to shift OA management from symptomatic relief toward mechanism-based, disease-modifying interventions that improve joint health across the aging lifespan.

Conflict of interests. The author declares that there is not conflict of interests.

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