

International Journal of Advanced Biochemistry Research



ISSN Print: 2617-4693
ISSN Online: 2617-4707
NAAS Rating (2026): 5.29
IJABR 2026; 10(7): 391-396
www.biochemjournal.com
Received: 01-04-2026
Accepted: 05-05-2026

SK Jadhav

Assistant Professor, Department of Veterinary Pathology, Shourabh College of Veterinary Science, Rajasthan University of Veterinary and Animal Sciences, Bikaner, Rajasthan, India

Dr. AB Patil

Assistant Professor, Department of Animal Nutrition, Shourabh College of Veterinary Science, Rajasthan University of Veterinary and Animal Sciences, Bikaner, Rajasthan, India

SD Nagre

Assistant Professor, Department of Animal Nutrition, Shourabh College of Veterinary Science, Rajasthan University of Veterinary and Animal Sciences, Bikaner, Rajasthan, India

AA Gurde

Assistant Professor, Department of Animal Nutrition, Shourabh College of Veterinary Science, Rajasthan University of Veterinary and Animal Sciences, Bikaner, Rajasthan, India

PN Patel

Assistant Professor, Department of Veterinary Gynecology and Obstetrics, Shourabh College of Veterinary Science, Rajasthan University of Veterinary and Animal Sciences, Bikaner, Rajasthan, India

SV Bhusse

Assistant Professor, Department of Livestock Products and Technology, Shourabh College of Veterinary Science, Rajasthan University of Veterinary and Animal Sciences, Bikaner, Rajasthan, India

Corresponding Author:**Dr. AB Patil**

Assistant Professor, Department of Animal Nutrition, Shourabh College of Veterinary Science, Rajasthan University of Veterinary and Animal Sciences, Bikaner, Rajasthan, India

Cellular senescence: Role in ageing, diseases and therapeutics: A review

SK Jadhav, AB Patil, SD Nagre, AA Gurde, PN Patel and SV Bhusse

DOI: <https://www.doi.org/10.33545/26174693.2026.v10.i7f.9032>

Abstract

Cellular senescence is a state of stable, irreversible proliferative arrest in which damaged cells exit the cell cycle while retaining metabolic activity and actively resisting apoptosis. Since its initial description by Hayflick and Moorhead in 1961, senescence has emerged as a pivotal biological process with wide-ranging consequences for tissue homeostasis, aging, and disease. Senescent cells are distinguished by persistent cell cycle arrest, nuclear chromatin reorganization, and the senescence-associated secretory phenotype (SASP)—a collection of pro-inflammatory cytokines, proteases, and growth factors that profoundly alters the tissue microenvironment. Their progressive accumulation with age drives chronic low-grade inflammation, disrupts stem cell niches, and impairs organ function. Senescence is initiated by diverse stimuli including telomere attrition, oncogene activation, genotoxic and oxidative stress, and mitochondrial dysfunction, converging on the p53/p21 and p16INK4A/pRb tumor suppressor pathways. Pathologically, senescent cell burden underpins major age-related conditions such as osteoarthritis, idiopathic pulmonary fibrosis, atherosclerosis, and cancer — where it plays a paradoxical dual role as both a tumor suppressor and a promoter of malignancy. Established biomarkers including SA- β -galactosidase activity, p16INK4A expression, phosphorylated p53, and Lamin B1 downregulation enable identification of senescent cells in experimental and clinical contexts. Senotherapy-comprising senolytics that selectively eliminate senescent cells and senomorphics that attenuate SASP offers transformative potential for healthspan extension and disease modification. This review integrates current mechanistic understanding with translational perspectives on cellular senescence in aging and disease.

Keywords: Cellular senescence, SASP, p16INK4A, senolytics, aging, age-related diseases, senotherapy

1. Introduction

More than six decades ago, Hayflick and Moorhead documented a phenomenon that would reshape cell biology: normal human fibroblasts maintained in culture could divide only a finite number of times before entering a state of permanent, non-proliferative viability^[1]. Once dismissed as an *in vitro* artifact, this phenomenon—cellular senescence—is now understood as a fundamental biological program with profound consequences for tissue health, organismal aging, and susceptibility to disease^[2]. Senescent cells are not simply dormant; they maintain vigorous metabolic activity, resist apoptotic signals, and engage extensively with neighboring cells and the extracellular environment through the senescence-associated secretory phenotype (SASP)^[3].

The SASP encompassing pro-inflammatory interleukins, chemokines, growth factors, and matrix-remodeling enzymes exerts both protective and detrimental paracrine effects depending on context^[3]. In the short term, SASP facilitates immune-mediated clearance of senescent cells and supports tissue repair. Over time, however, persistent SASP signaling from accumulating senescent cells engenders chronic sterile inflammation termed 'inflammaging' that progressively erodes tissue architecture and function^[4, 5]. This shift from adaptive to maladaptive senescence underpins a growing number of age-associated pathologies.

A transformative development in the field has been the emergence of senotherapeutics—pharmacological agents capable of selectively eliminating or modulating senescent cells—which have demonstrated the ability to delay, attenuate, or even reverse aging phenotypes in animal models^[6].

These advances have repositioned cellular senescence as an actively modifiable driver of disease rather than a passive hallmark of aging. This review provides a comprehensive account of senescence triggers, molecular mechanisms, biomarker detection, pathological roles in key age-related diseases, and the therapeutic landscape of senotherapy.

2. Triggers of Cellular Senescence

Senescence is triggered not by a single stimulus but by a diverse array of cellular insults that signal sufficient damage or unacceptable proliferative risk. The resulting senescent state, while mechanistically varied, converges on common downstream effector pathways.

2.1 Telomere Shortening

With each round of DNA replication, 50-200 base pairs are lost from telomeric ends owing to the inability of DNA polymerase to replicate the terminal portion of linear chromosomes [4]. Human telomeres span roughly 8-12 kilobases at birth; upon reaching a critically short length after sufficient cell divisions, dysfunctional telomeres are recognized as DNA damage, activating ATM/ATR kinase signaling and upregulating p21CIP1 and p16INK4A to enforce replicative senescence [7]. This telomere-based mitotic clock serves as an evolutionary compromise limiting somatic cell proliferation to suppress tumorigenesis while inevitably constraining tissue regenerative capacity with age.

2.2 Oncogene Activation

Activating mutations in proto-oncogenes such as RAS, BRAF, and cyclin-E, or loss-of-function alterations in tumor suppressors including PTEN and NF-1, paradoxically provoke senescence rather than sustained proliferation [8]. This oncogene-induced senescence (OIS) is mediated by excessive replication fork activity, attendant ROS generation, and consequent DNA damage signaling. OIS represents a critical intrinsic anti-cancer barrier halting the expansion of incipient neoplastic clones before full transformation and constituting one of the most frequently bypassed tumor-suppressive mechanisms in human cancer.

2.3 Oxidative Stress and Mitochondrial Dysfunction

Reactive oxygen species, generated as byproducts of mitochondrial respiration, are normally neutralized by enzymatic antioxidant systems including superoxide dismutase and catalase [9]. Mitochondrial dysfunction whether from aging, environmental toxins, or bioenergetic failure overwhelms these defenses, producing oxidative lesions in nuclear and mitochondrial DNA that trigger DDR-mediated senescence [9]. A distinct subtype, mitochondrial dysfunction-associated senescence (MiDAS), is characterized by a SASP enriched in IL-6 and IL-8 but lacking IL-1-driven components, reflecting the specific inflammatory consequences of mitochondrial impairment.

2.4 Additional Triggers

Numerous other stimuli converge on senescence pathways. Therapy-induced senescence (TIS) arises when cancer cells treated with cytotoxic agents or radiation enter growth arrest rather than apoptosis an outcome with complex implications for disease recurrence and the tumor microenvironment [4]. Epigenetic deregulation, proteostasis perturbation, and paracrine signals from neighboring senescent cells

(bystander senescence) further amplify senescent cell accumulation in aged tissues [3].

3. Mechanisms and Pathways of Cellular Senescence

The sustained cell cycle arrest central to senescence is enforced through two major tumor suppressor cascades: the p53/p21 pathway and the p16INK4A/pRB pathway. Though mechanistically distinct, these pathways are deeply interconnected and ultimately converge on the retinoblastoma protein to repress E2F-dependent transcription of genes required for cell cycle progression [10].

3.1 The p53/p21 Axis

DNA damage arising from telomere dysfunction, oxidative insult, or oncogenic stress activates the ATM and ATR kinases, which stabilize and post-translationally modify p53 through phosphorylation, acetylation, and ubiquitination [11]. Activated p53 transcriptionally induces p21CIP1, which inhibits cyclin-CDK complex activity, prevents pRB phosphorylation, and promotes formation of the repressive DREAM complex-collectively enforcing durable G1 arrest [12, 13]. The p53/p21 axis is engaged early upon senescence entry, providing the initial proliferative brake before longer-lasting p16INK4A-mediated mechanisms consolidate the phenotype.

3.2 The p16INK4A/pRB Axis

p16INK4A, encoded within the CDKN2A locus, directly inhibits CDK4 and CDK6, preventing cyclin D-CDK4/6 complex formation and thereby blocking pRB phosphorylation [14]. Hypophosphorylated pRB sequesters E2F transcription factors and represses S-phase gene expression, locking cells in G1 [15]. The critical importance of this axis is illustrated by the fact that CDKN2A deletion or methylation is among the most common molecular events in human cancer. Experimental overexpression of any one of the four core components-p53, pRB, p16INK4A, or p21 is sufficient to impose a senescence-like state [16].

3.3 DNA Damage Response

DNA double-strand breaks potently trigger senescence through sustained activation of the DDR cascade. ATM kinase phosphorylates histone H2AX at Ser139 (γ H2AX), nucleating cytologically visible repair foci that serve as signal amplification platforms [17]. When damage is irreparable as at critically short telomeres-DDR signaling persists indefinitely, preventing checkpoint resolution and establishing permanent senescence. CHK1 and CHK2 downstream kinases further amplify p53 stabilization; p16INK4A is subsequently engaged to maintain the senescence barrier against potential bypass mechanisms [18].

3.4 SASP: Biology and Regulation

The SASP comprising IL-1 α , IL-1 β , IL-6, IL-8, CXCL1, VEGF, HGF, and multiple MMPs fundamentally reshapes the tissue microenvironment through autocrine and paracrine signaling [3]. SASP transcription is primarily driven by NF- κ B and C/EBP β , with upstream engagement from the cGAS-STING pathway activated by cytoplasmic chromatin fragments released from senescent cells experiencing nuclear Lamin B1 loss [3, 19]. While acute SASP facilitates immune clearance and wound repair, chronic SASP underlies inflammaging, promotes fibrosis, and paradoxically can foster tumor-permissive

microenvironments when senescent cells escape immune surveillance.

4. Cellular Senescence and Organismal Ageing

While senescence serves adaptive roles in acute contexts limiting malignant transformation and supporting embryonic patterning the progressive accumulation of senescent cells in aging tissues is fundamentally detrimental [5]. Two interconnected mechanisms account for this: senescent cells directly impair tissue function through ECM remodeling and parenchymal cell displacement, and their SASP progressively disrupts stem cell niches, impairing the regenerative responses needed to counteract normal tissue attrition [20].

Senescent cells evade elimination by upregulating Senescence-Associated Antiapoptotic Pathways (SCAPs), including the BCL-2 family members BCL-2, BCL-XL, and BCL-W, rendering them resistant to both intrinsic and extrinsic apoptotic signals [6]. Landmark genetic experiments demonstrated that selective elimination of p16INK4A-expressing cells from middle-aged mice delayed multiple aging phenotypes — including skeletal muscle weakness, cardiac dysfunction, and adipose tissue loss — providing definitive causal evidence that senescent cell accumulation actively drives biological aging [21].

The context-dependency of senescence is perhaps most clearly illustrated in wound healing: acutely senescent cells at injury sites transiently support ECM remodeling and epithelial regeneration; however, when these cells persist beyond their window of utility due to impaired immune clearance, their SASP drives pathological fibrosis in which normal tissue is progressively replaced by disorganized scar [5]. This dual temporal behavior transiently beneficial, chronically harmful encapsulates the central biological tension in senescence and motivates the development of time-targeted therapeutic interventions.

5. Diseases Associated with Cellular Senescence

Pathological accumulation of senescent cells has been documented across numerous organ systems. The following sections examine four conditions where mechanistic evidence for a senescence-driven component is particularly well established.

5.1 Osteoarthritis

Osteoarthritis is the most prevalent musculoskeletal disease globally and a leading cause of disability in older adults. Its core pathology progressive articular cartilage loss is driven substantially by senescence of chondrocytes, the sole cellular custodians of cartilage matrix [22]. Senescent chondrocytes in OA tissue express p16INK4A and p21, exhibit SA- β -gal activity, and elaborate a catabolic SASP encompassing IL-1 α , IL-6, IL-8, and MMP-3 that degrades ECM components, inhibits chondrocyte anabolic activity, and propagates senescence to neighboring cells [22].

Mechanistic experiments have clarified the causal relationship: intra-articular injection of senescent cells in mice reproduces OA hallmarks including cartilage erosion and pain behavior, whereas senolytic clearance of senescent chondrocytes markedly attenuates disease severity in preclinical models [22]. These findings have prompted early-phase clinical investigations of senolytic therapy for human OA, representing a potential paradigm shift toward disease-modifying rather than purely symptomatic treatment.

5.2 Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is a progressive, invariably fatal interstitial lung disease whose peak incidence in individuals over 60 years implicitly suggests aging-related pathomechanisms [23]. Senescent alveolar type 2 cells (AT2Cs), endothelial cells, and fibroblasts have all been identified in IPF lung tissue, each contributing distinct pathogenic effects: AT2C senescence impairs progenitor-mediated epithelial repair; senescent endothelial cells disrupt alveolar-capillary barrier function; and senescent fibroblasts, through SASP-mediated paracrine activation of myofibroblasts, directly amplify collagen deposition and fibrotic remodeling [23].

Dasatinib plus quercetin has demonstrated measurable reductions in fibrosis burden and improvements in lung mechanics in murine IPF models, providing proof-of-concept for senolytic intervention in fibrotic lung disease [23]. These results have supported the initiation of early-phase human clinical trials, the outcomes of which are eagerly anticipated.

5.3 Atherosclerosis

Atherosclerosis the underlying cause of most myocardial infarctions and ischemic strokes — is fundamentally an inflammatory disease of the arterial wall. Senescence of vascular endothelial cells (ECs) and smooth muscle cells (SMCs) critically shapes both atherogenesis and plaque vulnerability [24]. Senescent ECs exhibit markedly reduced eNOS-mediated NO bioavailability abrogating vasodilatory, anti-thrombotic, and anti-inflammatory endothelial functions while their SASP recruits monocytes and perpetuates subendothelial inflammation [24].

Within atherosclerotic plaques, senescent SMCs show impaired proliferative repair capacity and heightened apoptosis susceptibility, compromising fibrous cap integrity and predisposing plaques to rupture. SASP-derived MMPs—MMP-1, MMP-3, and MMP-9 actively degrade fibrous cap collagen while pro-inflammatory cytokines promote necrotic core expansion and calcification, collectively shifting plaques toward an unstable, rupture-prone phenotype [24].

5.4 Cancer

Cancer remains the second leading cause of death globally, with approximately 9.6 million fatalities annually [25]. Cellular senescence engages a complex, context-dependent relationship with malignancy, functioning as a potent tumor suppressor under some circumstances and as a facilitator of tumor progression under others.

5.4.1 Tumor Suppressive Role

In the earliest stages of carcinogenesis, cells acquiring oncogenic mutations typically encounter OIS a robust anti-proliferative response that limits clonal expansion [8]. SASP-derived paracrine signals including IL-1, IL-6, and TGF- β can extend senescence to adjacent pre-malignant cells. Crucially, the SASP also orchestrates immune surveillance by recruiting cytotoxic T lymphocytes and NK cells that recognize and clear senescent cells, maintaining tissue integrity against early neoplastic progression [19].

5.4.2 Tumor Promoting Role

When immune clearance is impaired or senescent cell burdens exceed clearance capacity, chronic SASP remodels

the microenvironment in pro-tumorigenic ways [26]. Sustained cytokine and growth factor secretion creates a permissive niche for pre-cancerous cell proliferation, while SASP-derived TGF- β can drive epithelial-to-mesenchymal transition in neighboring epithelial cells, enhancing invasive and metastatic potential. Senescence-associated transcriptional reprogramming has further been shown to confer cancer stem-like properties, potentially seeding more aggressive tumor variants [26]. These observations highlight that efficient immune clearance of senescent cells is as critical as their initial induction in maintaining anti-tumor defense.

6. Biomarkers of Cellular Senescence

Given the heterogeneity of senescent cells across tissues, cell types, and induction contexts, no single marker is universally sufficient for their accurate identification [3]. Multi-parameter detection strategies combining complementary biomarkers are increasingly recommended for reliable senescence quantification in experimental and clinical settings.

6.1 Senescence-Associated β -Galactosidase (SA- β -gal)

SA- β -gal activity, detectable histochemically at pH 6 using the chromogenic substrate X-Gal, remains the most widely applied senescence marker owing to its technical simplicity and applicability across diverse tissue types [27]. The assay exploits the greatly expanded lysosomal content of senescent cells, which elevates β -galactosidase activity above the threshold detectable at sub-optimal pH. While false positives can arise in confluent or serum-deprived cultures, combination with proliferation markers substantially improves diagnostic specificity.

6.2 p16INK4A Expression

Progressive tissue accumulation of p16INK4A is among the most robust molecular correlates of biological aging in mammals and serves as a widely used surrogate of senescent cell burden in human studies [28]. Its detection by immunohistochemistry, Western blotting, or quantitative PCR has proven informative across multiple tissue contexts. Clinical studies have established that p16INK4A expression in peripheral blood T-lymphocytes correlates with frailty, cancer risk, and adverse outcomes following cytotoxic chemotherapy, underscoring its practical utility as a non-invasive aging biomarker [28].

6.3 p53 and Phosphorylated p53

Phosphorylation of p53 at Ser15 by ATM kinase and Ser46 by HIPK2 marks its activation in DNA damage-driven senescence [11]. Immunofluorescence detection of phospho-p53, particularly when co-localizing with γ H2AX foci at persistent DNA damage sites, provides spatially resolved evidence of senescent cells within tissue sections. Because p53 is also transiently activated during apoptosis and acute genotoxic responses, its co-detection with other established senescence markers is essential for confident attribution to the senescent state.

6.4 Lamin B1 Downregulation

Lamin B1, a type B nuclear lamin essential for nuclear envelope integrity and heterochromatin organization, is markedly and specifically downregulated during senescence across virtually all cell types examined to date [29]. Its loss

promotes nuclear blebbing and release of cytoplasmic chromatin fragments (CCFs) that activate the cGAS-STING innate immune pathway, sustaining SASP-driving inflammatory signaling. The relative specificity of Lamin B1 downregulation for senescence compared to other growth arrest states makes it a particularly valuable complement in multi-parameter senescence detection [29].

6.5 Emerging and Multi-Parameter Approaches

The field is rapidly advancing beyond individual biomarkers toward comprehensive detection frameworks. γ H2AX nuclear foci indicate persistent DSBs; telomere dysfunction-induced foci (TIFs) co-localizing γ H2AX with telomeric sequences mark telomere-driven senescence specifically [3]. Circulating SASP components (IL-6, IL-8, MMP-3) offer non-invasive systemic surrogates of senescent cell burden. Single-cell RNA sequencing and multiplex immunofluorescence platforms now enable high-resolution characterization of tissue-specific senescence heterogeneity, facilitating discovery of disease-relevant senescence subtypes with distinct therapeutic implications.

7. Senotherapy: Targeting Senescent Cells

The recognition that senescent cells actively drive aging and disease rather than merely reflecting it — has catalyzed intense pharmacological interest in strategies to eliminate or modulate them. Two broad classes of agents have emerged: senolytics, which trigger selective death of senescent cells, and senomorphics (senostatics), which suppress SASP without inducing cell death [6].

7.1 Senolytics

Senolytics exploit the dependency of senescent cells on pro-survival Senescence-Associated Antiapoptotic Pathways (SCAPs) to selectively induce their apoptosis while sparing normal cells [30]. The first characterized senolytic combination dasatinib plus quercetin — demonstrated striking selective clearance of senescent cells in fat, liver, and lung tissues of aged mice, accompanied by improved locomotor function and reduced physical frailty. Since this seminal finding, an expanding pharmacological toolkit has emerged: BCL-2/BCL-XL inhibitors (navitoclax/ABT-263, venetoclax) target anti-apoptotic proteins overexpressed in senescent cells; FOXO4-DRI, a modified interfering peptide, disrupts the FOXO4-p53 interaction required for senescent cell survival; and HSP90 inhibitors such as 17-DMAG exploit heat shock protein dependency in senescent cells [30].

Early-phase clinical trials evaluating dasatinib plus quercetin in diabetic kidney disease and pulmonary fibrosis have demonstrated measurable reductions in skin biopsy senescent cell markers and exploratory improvements in physical function — the first human evidence that senolytics can reduce tissue senescent cell burden *in vivo* [30]. Key translational challenges include achieving adequate tissue penetration, managing off-target effects (notably thrombocytopenia with navitoclax), and defining optimal dosing schedules that maximize senescent cell clearance without disrupting beneficial senescence in wound healing or tumor suppression.

7.2 Senomorphics

Senomorphics modulate rather than eliminate senescent cells, pharmacologically suppressing SASP while preserving

cell viability a strategy advantageous where beneficial senescence must be maintained [31]. Rapamycin, a well-characterized mTOR inhibitor, reduces SASP by suppressing translational output of IL-1 α and dampening NF- κ B signaling, and has consistently extended healthy lifespan across diverse murine models when given intermittently [31]. JAK1/2 inhibitors such as ruxolitinib attenuate cytokine receptor signaling downstream of SASP, reducing systemic inflammatory burden. NAD⁺ precursors including nicotinamide riboside and NMN support mitochondrial bioenergetics and sirtuin activity, indirectly suppressing SASP through improved mitochondrial function and reduced ROS production.

An increasingly favored clinical strategy combines senolytics and senomorphics in intermittent regimens: periodic senolytic pulses to clear accumulated senescent cells, interspersed with continuous senomorphic therapy to suppress SASP from residual or newly arising senescent populations [31]. This integrated approach may offer superior efficacy compared to either modality alone and is currently being explored in early-phase clinical investigations.

8. Conclusion

Cellular senescence has evolved from a descriptive observation in cultured fibroblasts into a mechanistically understood and therapeutically actionable program at the heart of aging biology. Its dual identity as an indispensable guardian against malignancy and a chronic driver of tissue dysfunction when unresolved reflects the deep evolutionary trade-offs that have shaped multicellular life. The realization that senescent cells actively reshape tissue environments through the SASP, rather than passively accumulating as inert cellular debris, has fundamentally reframed how we understand the biology of aging.

Pathological consequences of unchecked senescent cell accumulation span a remarkable range of conditions from cartilage destruction in osteoarthritis to vascular wall dysfunction in atherosclerosis, fibrotic lung remodeling in IPF, and the paradoxical tumor-suppressive and tumor-promoting influences on cancer progression. Concurrently, validated biomarker panels and robust animal models have provided the experimental infrastructure needed to transition from observational correlation to mechanistic causation and, critically, toward clinical intervention.

Senotherapy stands at a pivotal translational juncture. Early clinical data with senolytic and senomorphic agents are emerging, but significant work remains to optimize delivery, dosing, and patient stratification. Future priorities should include developing non-invasive *in vivo* senescence imaging tools, characterizing tissue- and disease-specific SASP diversity, refining combinatorial therapeutic regimens, and leveraging artificial intelligence for biomarker discovery and personalized treatment targeting. Addressing these challenges will determine whether the fundamental biological insights accumulated over decades of senescence research can ultimately translate into meaningful improvements in human healthspan and quality of life.

9. Acknowledgement

I would like to express my sincere gratitude to all the researchers whose work has been reviewed in this article, as their valuable contributions form the foundation of this study. I am deeply thankful to my colleagues and peers for

their insightful discussions and constructive feedback, which greatly enhanced the quality of this work.

References

- Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. *Experimental Cell Research*. 1961;25(3):585-621.
- Campisi J, d'Adda di Fagagna F. Cellular senescence: when bad things happen to good cells. *Nature Reviews Molecular Cell Biology*. 2007;8(9):729-740.
- Gorgoulis V, Adams PD, Alimonti A, Bennett DC, Bischof O, Bishop C, *et al.* Cellular senescence: defining a path forward. *Cell*. 2019;179(4):813-827.
- Mikuła-Pietrasik J, Niklas A, Uruski P, Tykarski A, Książek K. Mechanisms and significance of therapy-induced and spontaneous senescence of cancer cells. *Cellular and Molecular Life Sciences*. 2020;77(2):213-229.
- Van Deursen JM. The role of senescent cells in ageing. *Nature*. 2014;509(7501):439-446.
- Zhu YI, Tchkonja T, Pirtskhalava T, Gower AC, Ding H, Giorgadze N, *et al.* The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. *Aging Cell*. 2015;14(4):644-658.
- Di Micco R, Krizhanovsky V, Baker D, d'Adda di Fagagna F. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. *Nature Reviews Molecular Cell Biology*. 2021;22(2):75-95.
- Lee S, Schmitt CA. The dynamic nature of senescence in cancer. *Nature Cell Biology*. 2019;21(1):94-101.
- Martini H, Passos JF. Cellular senescence: all roads lead to mitochondria. *The FEBS Journal*. 2023;290(5):1186-1202.
- Liu X, Wan M. A tale of the good and bad: Cell senescence in bone homeostasis and disease. *International Review of Cell and Molecular Biology*. 2019;346:97-128.
- Kastenhuber ER, Lowe SW. Putting p53 in context. *Cell*. 2017;170(6):1062-1078.
- Wiedemeyer WR. Resistance mechanisms to cyclin-dependent kinase inhibitors. In: *Resistance to Anti-Cancer Therapeutics Targeting Receptor Tyrosine Kinases and Downstream Pathways*. Cham: Springer International Publishing; 2018. p.181-210.
- Fischer M, Müller GA. Cell cycle transcription control: DREAM/MuvB and RB-E2F complexes. *Critical Reviews in Biochemistry and Molecular Biology*. 2017;52(6):638-662.
- Serrano M, Hannon GJ, Beach D. A new regulatory motif in cell-cycle control causing specific inhibition of cyclin D/CDK4. *Nature*. 1993;366(6456):704-707.
- Gil J, Peters G. Regulation of the INK4b-ARF-INK4a tumour suppressor locus: all for one or one for all. *Nature Reviews Molecular Cell Biology*. 2006;7(9):667-677.
- McConnell BB, Starborg M, Brookes S, Peters G. Inhibitors of cyclin-dependent kinases induce features of replicative senescence in early passage human diploid fibroblasts. *Current Biology*. 1998;8(6):351-354.
- Fagagna FD, Reaper PM, Clay-Farrace L, Fiegler H, Carr P, Von Zglinicki T, *et al.* A DNA damage checkpoint response in telomere-initiated senescence. *Nature*. 2003;426(6963):194-198.

18. Mallette FA, Ferbeyre G. The DNA damage signaling pathway connects oncogenic stress to cellular senescence. *Cell Cycle*. 2007;6(15):1831-1836.
19. Fane M, Weeraratna AT. How the ageing microenvironment influences tumour progression. *Nature Reviews Cancer*. 2020;20(2):89-106.
20. Fafián-Labora JA, Rodríguez-Navarro JA, O'Loughlen A. Small extracellular vesicles have GST activity and ameliorate senescence-related tissue damage. *Cell Metabolism*. 2020;32(1):71-86.
21. Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, *et al*. Naturally occurring *p16Ink4a*-positive cells shorten healthy lifespan. *Nature*. 2016;530(7589):184-189.
22. Coryell PR, Diekman BO, Loeser RF. Mechanisms and therapeutic implications of cellular senescence in osteoarthritis. *Nature Reviews Rheumatology*. 2021;17(1):47-57.
23. Schneider JL, Rowe JH, Garcia-de-Alba C, Kim CF, Sharpe AH, Haigis MC. The aging lung: Physiology, disease, and immunity. *Cell*. 2021;184(8):1990-2019.
24. Milanovic M, Fan DN, Belenki D, Däbritz JH, Zhao Z, Yu Y, *et al*. Senescence-associated reprogramming promotes cancer stemness. *Nature*. 2018;553(7686):96-100.
25. World Health Organization. Global cancer statistics 2020 [Internet].. Geneva: World Health Organization; 2020 [cited 2024 Jan 15].. Available from: <https://www.who.int/news-room/fact-sheets/detail/cancer>
26. Leite de Oliveira R, Bernards R. Anti-cancer therapy: senescence is the new black. *The EMBO Journal*. 2018;37(10):e99386.
27. Hernandez-Segura A, Nehme J, Demaria M. Hallmarks of cellular senescence. *Trends in Cell Biology*. 2018;28(6):436-453.
28. He S, Sharpless NE. Senescence in health and disease. *Cell*. 2017;169(6):1000-1011.
29. Burd CE, Sorrentino JA, Clark KS, Darr DB, Krishnamurthy J, Deal AM, *et al*. Monitoring tumorigenesis and senescence *in vivo* with a *p16INK4a*-luciferase model. *Cell*. 2013;152(1-2):340-351.
30. Zhang L, Pitcher LE, Prahalad V, Niedernhofer LJ, Robbins PD. Targeting cellular senescence with senotherapeutics: senolytics and senomorphics. *The FEBS Journal*. 2023;290(5):1362-1383.
31. Zhu XY, Lerman LO. Senomorphic, senolytic, and rejuvenation therapies. In: *Regenerative Nephrology*. London: Academic Press; 2022. p.405-417.