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Cellular Senescence: Physiological Roles, Pathological Consequences and Its Contribution to Age-Related Lens Degeneration- A review.

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Abstract:

Background: Cellular senescence is a state of irreversible cell-cycle arrest that acts as a key regulator of tissue homeostasis, organismal aging, and many diseases. Transient senescence supports normal development, wound repair, and tumour suppression, whereas persistent senescent cells promote chronic inflammation, tissue dysfunction, and age-related disorders such as cataracts. Lens epithelial cells (LECs), which are crucial for maintaining lens transparency and metabolic balance, are highly susceptible to oxidative-stress–induced senescence, thereby accelerating lens aging and cataractogenesis. This review explores the dual role of senescence in LEC biology and its contribution to age-related cataract formation, while also considering emerging senescence-targeted therapies. **Methods:** This narrative review integrates current evidence on the molecular drivers of cellular senescence, with particular emphasis on oxidative stress, mitochondrial dysfunction and the senescence-associated secretory phenotype (SASP). It compiles experimental and clinical studies that link LEC senescence to cataract development, focusing on stress-response signalling, DNA damage pathways and antioxidant defence systems. In addition, it critically examines recent advances in senotherapeutic approaches—including senolytics and senomorphics—for their capacity to attenuate LEC senescence and retard cataract progression. **Conclusions:** LEC senescence is primarily triggered by cumulative oxidative injury, mitochondrial impairment, and disturbed redox homeostasis, which converge on canonical p53/p21 and p16/Rb pathways to enforce permanent cell-cycle arrest and induce a pro-inflammatory SASP. The progressive accumulation of senescent LECs diminishes the regenerative pool, disrupts lens homeostasis, and drives structural and functional changes characteristic of cataractogenesis. Emerging senotherapeutic agents such as dasatinib, quercetin and metformin show promise in selectively reducing senescent cell burden or modulating SASP signalling, offering a potential strategy to preserve lens clarity and delay age-related cataract formation.

Keywords: Cellular senescence, lens epithelial cells, oxidative stress, senescence-associated secretory phenotype, cataractogenesis, senotherapeutics.

Introduction:

The life cycle of a cell is a dynamic, tightly regulated sequence of events controlled by complex molecular signalling networks that govern transitions between proliferation, quiescence, repair, and death.[1] Cellular senescence is a distinctive state within this continuum, characterized by irreversible arrest of the cell cycle and clearly differentiated from temporary, reversible growth arrest.[2] Senescence functions as a protective mechanism that prevents replication of cells

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harbouring genomic damage, thereby limiting malignant transformation.[3] Despite their loss of proliferative capacity, senescent cells remain metabolically active and develop a characteristic senescence-associated secretory phenotype (SASP), through which they release cytokines, growth factors, and proteolytic enzymes that can modulate the surrounding microenvironment by supporting tissue repair and regeneration.[3,4] When senescent cells are efficiently cleared, this response is largely beneficial; however, persistent or excessive accumulation of senescent cells transforms the SASP into a driver of chronic inflammation, matrix degradation, and functional decline,[5] thereby contributing to aging and a range of degenerative pathologies. Understanding both senescence and the SASP is therefore essential for appreciating their paradoxical roles in preserving tissue integrity while also promoting age-related disease.[6]

The Tai Chi (Yin–Yang) symbol provides a useful conceptual framework for this balance of opposing cellular forces.[7] In the context of the cell cycle, the Yang (white) component represents phases of active growth and division. Proliferating cells traverse the G1, S, G2, and M phases to duplicate their genome and divide, enabling tissue expansion and regeneration;[8] stem cells, with their self-renewal and differentiation potential, also reside predominantly in this Yang domain. In contrast, the Yin (black) component embodies the counter-regulatory forces that restrain unchecked growth. Quiescent cells in G0 are metabolically active but non-proliferative, poised to re-enter the cycle in response to appropriate cues.[9] Programmed cell death, or apoptosis, exemplifies controlled cellular elimination, removing damaged or superfluous cells to maintain tissue homeostasis.[10] At the pathological extreme, necrosis reflects uncontrolled cell death associated with loss of membrane integrity and inflammatory damage, signalling a breakdown of normal regulatory mechanisms.[11] Together, these Yin–Yang states illustrate how cellular proliferation, arrest, and death must remain in dynamic equilibrium to support organismal health.

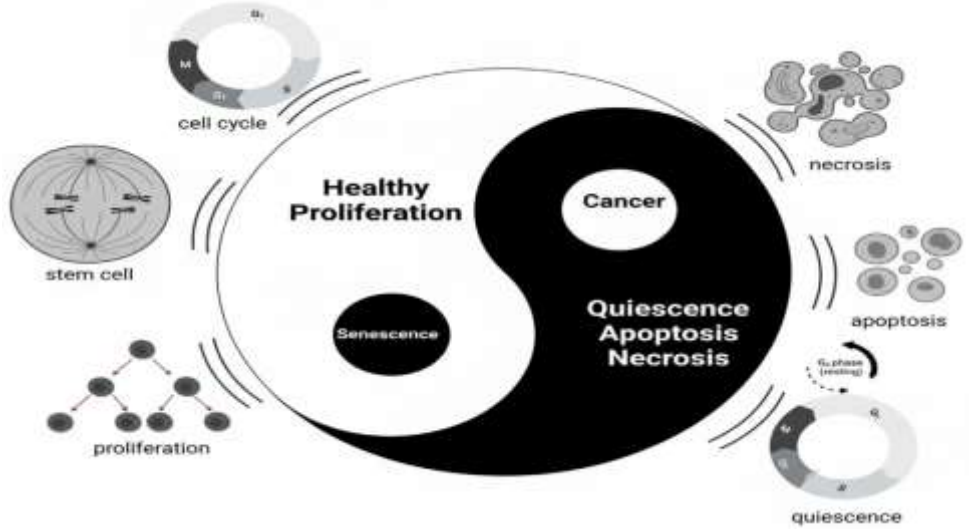

Fig 1*: The Tai Chi symbol is used to depict how proliferation, quiescence, death, and senescence interact to maintain cellular balance, while illustrating how misregulated senescence and cancer can shift this equilibrium toward disease.*

Within this conceptual model, cancer cells are represented by the white dot e
black (Yin) region, signifying their emergence from an otherwise g
environment into a state of uncontrolled proliferation that disrupts normal regulatory balance.[12] These cells evade canonical checkpoints and cell-cycle arrest mechanisms, converting what should be a quiescent or protective context into one dominated by malignant expansion.[13]

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Senescent cells occupy the opposite niche, depicted as the black dot within the white (Yang) region, functioning as a suppressive influence within a predominantly proliferative milieu. Although permanently withdrawn from the cell cycle and unresponsive to mitogenic cues, they remain metabolically active and exert substantial paracrine effects through the senescence-associated secretory phenotype, promoting tissue remodelling, fibrosis, chronic inflammation, and, in some settings, tumour promotion. This dual positioning emphasizes senescence as a pivotal determinant of cellular destiny with profound implications for both physiological aging and disease.[14]

Throughout daily life, cells are continuously exposed to exogenous insults—such as ultraviolet radiation, environmental pollutants, and toxic chemicals—as well as endogenous stressors including normal metabolism and reactive oxygen species.[15] Under ideal circumstances, DNA damage and macromolecular lesions are corrected by intrinsic repair pathways, preserving structural integrity and metabolic competence.[16] When injury is severe or irreparable, cells frequently undergo apoptosis, a highly regulated form of programmed cell death that prevents compromised cells from jeopardizing tissue function.[17] In many instances, however, damaged cells instead enter a state of permanent growth arrest and become refractory to proliferative signals, a condition termed cellular senescence.[18] This complex response can be triggered by telomere attrition, genotoxic stress, oncogene activation, or other forms of cellular stress and has both protective and pathological dimensions.[19] Acute, transient senescence contributes to embryonic morphogenesis, wound repair, tissue remodelling, and tumour suppression, thereby supporting homeostasis and preventing unchecked expansion of damaged cells.[20] Conversely, chronic accumulation of senescent cells in response to persistent stress leads to sustained SASP production, characterized by pro-inflammatory cytokines, growth factors, and proteases that disrupt tissue architecture.[21] This maladaptive state is now implicated in the pathogenesis of cardiovascular disease, multiple cancers, type 2 diabetes, neurodegenerative disorders, and age-related ocular conditions, underscoring senescence as both a guardian and a driver of pathology depending on context. [22]

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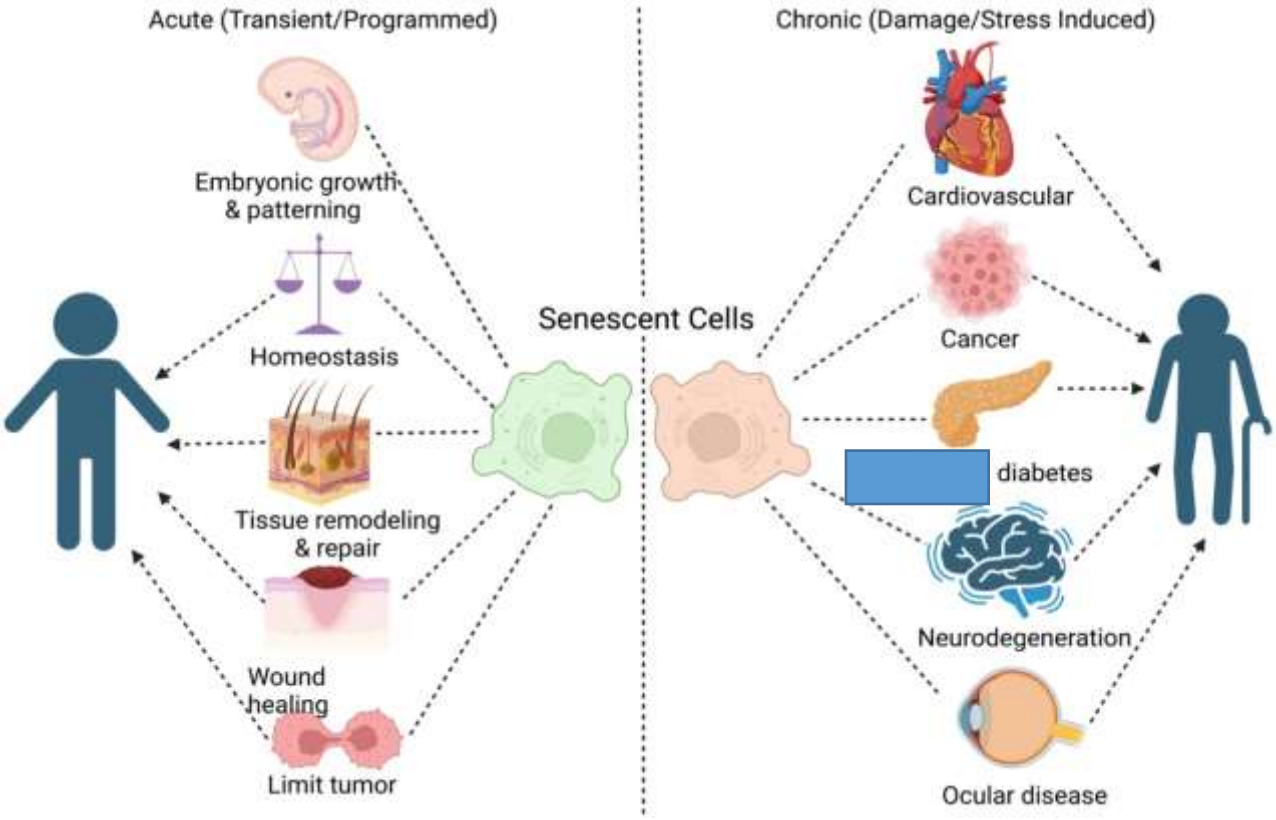

Fig 2: *Senescent cells support development, repair, and tumor limitation when activated transiently, but when chronically induced by damage or stress they accumulate, fuelling inflammation, aging, and diverse age-related diseases across multiple organ systems.*

Multiple epidemiological and experimental studies identify aging, ultraviolet radiation, tobacco use, diabetes, and socioeconomic determinants as key contributors to cataract development, with advancing age emerging as the dominant risk factor across cataract subtypes.[23] Despite this strong association, the mechanistic link between cellular senescence and lens opacification is still incompletely defined, and dedicated research remains relatively sparse.[24]

The present review aims to delineate how senescence of lens cells, particularly lens epithelial cells, perturbs lens homeostasis and promotes cataractogenesis, while also evaluating emerging therapeutic strategies that target senescent cells to support ocular longevity.[25] By clarifying these cellular and molecular pathways, such work may identify novel interventions to delay or prevent age-related cataracts and thereby preserve visual function in aging populations. [26]

History of Senescence

In 1961, Leonard Hayflick and Paul Moorhead made a seminal observation while culturing normal human fibroblasts. They noticed that these cells did not divide indefinitely, but instead underwent only a finite number of population doublings before permanently stopping proliferation.[27] This finding overturned the prevailing assumption that somatic cells were capable of limitless replication.[28,29,30] The phenomenon was later termed the Hayflick limit (or Hayflick phenomenon) and established that normal human somatic cells possess an intrinsic ceiling to their replicative capacity.[31] After approaching this limit—typically on the order of

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several dozen divisions—cells exit the cell cycle and enter a state now recognized as cellular senescence.[32]

Causes of Cellular Senescence

The major inducers of senescence are summarized as several interconnected stress signals, one of the best-characterized being telomere shortening, which underlies replicative senescence. Telomeres are repetitive nucleotide sequences at chromosome ends that shield genomic DNA from degradation and inappropriate repair.[33] With each round of DNA replication, the end-replication problem causes progressive loss of approximately 50–200 base pairs of telomeric DNA, gradually eroding this protective cap.[34] When telomeres become critically short, they are sensed as DNA damage, activating a canonical DNA damage response that drives the cell into a senescent growth-arrested state.[35] This telomere-dependent checkpoint functions as a molecular clock that limits the proliferative lifespan of normal somatic cells, thereby helping to maintain genomic stability and reduce malignant transformation.[36]

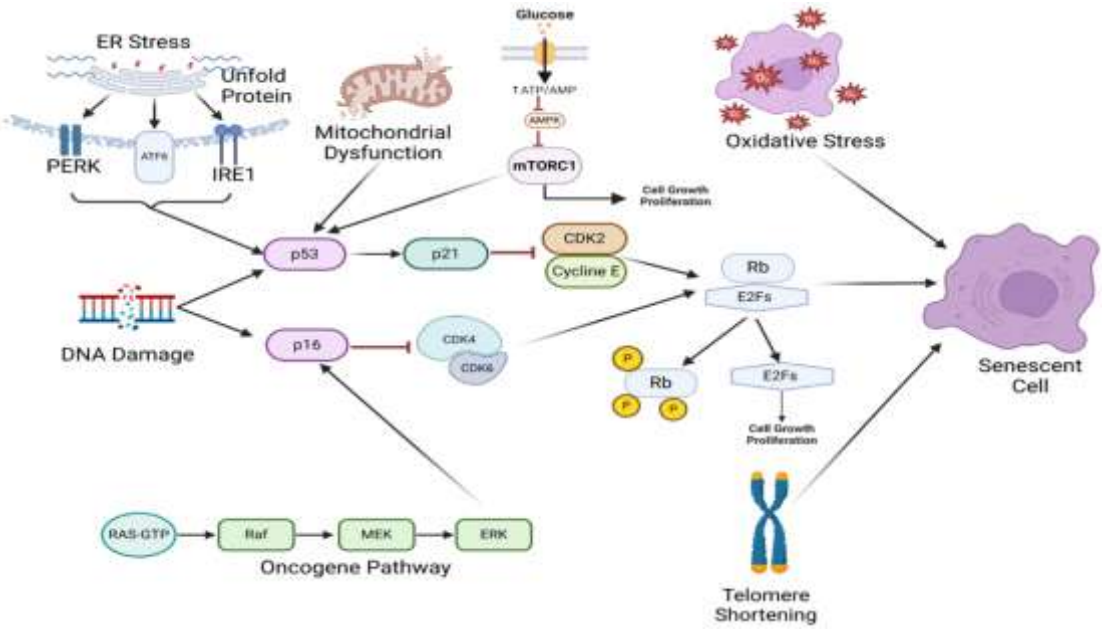

Fig 3: *Multiple stresses—including DNA damage, oxidative and mitochondrial dysfunction, oncogene activation, and telomere erosion—converge on p53/p21 and p16/Rb signaling to block CDK activity, enforce G1/S arrest, and establish senescence, preventing cancer yet promoting age-related pathology.*

DNA damage and genotoxic stress are major inducers of cellular senescence that function as key safeguards to preserve genomic integrity.[37] Such insults arise from ultraviolet and ionizing radiation, oxidative stress, and numerous chemotherapeutic agents, each capable of generating lesions such as base modifications and DNA double-strand breaks.[38] In response, cells activate DNA damage–response networks in which the tumor suppressors p53, p21, and p16 are central mediators of cell-cycle arrest. p53 upregulates p21, a cyclin-dependent kinase (CDK) inhibitor that transiently halts the cell cycle to allow repair; when damage is irreparable, this axis can commit cells to permanent senescence or apoptosis.[39] In parallel, p16 blocks CDK activity to reinforce arrest, with p21 largely initiating and p16 maintaining the senescent state. This robust

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antiproliferative program effectively suppresses oncogenic transformation but, as senescent cells accumulate, can impair tissue function and promote age-related disease.[40]

Oxidative stress, defined as an imbalance between reactive oxygen species (ROS) generation and antioxidant defenses, also drives senescence by damaging lipids, proteins, and DNA. [41]Under physiological conditions, the Nrf2 pathway induces antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase to detoxify ROS and maintain redox homeostasis.[42] Chronic or excessive ROS exposure—for example from UV light or dysfunctional mitochondria—overwhelms these defenses, leading to persistent macromolecular damage and activation of senescence-inducing signaling cascades. With aging or sustained stress, Nrf2 activity often declines, further diminishing antioxidant capacity and predisposing cells to senescence. Senescent cells then develop a senescence-associated secretory phenotype (SASP) that amplifies oxidative and inflammatory stress within the tissue microenvironment.[43]

Mitochondrial dysfunction–associated senescence (MiDAS) arises when impaired mitochondria disrupt energy metabolism and enhance ROS production.[44] Defects in the electron transport chain, particularly at Complexes I and III, cause electron leakage and partial oxygen reduction, generating excess ROS. While low-level ROS participate in signaling, sustained overproduction damages nuclear and mitochondrial DNA, proteins, and lipids, activating DNA-damage responses and stabilizing p53.[45] This leads to induction of p21 and other CDK inhibitors, culminating in irreversible growth arrest and a senescent phenotype. MiDAS cells typically show reduced oxidative phosphorylation, altered mitochondrial biogenesis, and a shift toward glycolysis, changes that fuel the SASP and drive chronic inflammation, tissue dysfunction, and aging. [46]

Metabolic stress—whether nutrient deprivation or chronic nutrient excess—also contributes to senescence by perturbing intracellular signaling.[47] Senescent cells display reprogrammed metabolism, with increased glycolysis and impaired mitochondrial respiration. Nutrient-sensing pathways involving mTOR and AMPK are key regulators: sustained mTOR activation tends to promote senescence, whereas AMPK activation and caloric restriction–like interventions can delay its onset.[48] Experimental and clinical data indicate that modulating these pathways can slow senescence-associated metabolic remodelling and extend cellular health span.

Endoplasmic reticulum (ER) stress is another important driver of senescence. When misfolded or unfolded proteins accumulate, the unfolded protein response (UPR) is engaged to restore proteostasis by enhancing folding capacity and degrading aberrant proteins.[49] If ER stress persists, chronic UPR signaling through PERK, ATF6, and IRE1 transitions from adaptive to pro-senescent, converging on p53 and p21 pathways to impose lasting cell-cycle arrest. These signals integrate with other stress responses to establish a stable senescent state.[50]

Aberrant oncogene activation can provoke oncogene-induced senescence (OIS), a potent intrinsic barrier to malignant transformation. Hyperactivation of pathways such as RAS–RAF–MEK–ERK generates excessive proliferative and replication stress that, paradoxically, triggers senescence as a fail-safe mechanism.[51,52] OIS is enforced through upregulation of p16 and ARF, which inhibit CDKs and stabilize p53, respectively, thereby locking cells in permanent arrest. Yet, as senescent cells persist, their SASP can remodel the microenvironment, fostering

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angiogenesis, epithelial–mesenchymal transition, and chronic inflammation that, in some settings, promote tumor progression and metastasis. Thus, while these stress-responsive pathways make senescence a powerful tumor-suppressive program, the long-term accumulation of senescent cells links them directly to tissue aging and age-associated pathology.

Senescence Markers:

Because no single feature uniquely identifies a senescent cell, their detection relies on a combination of complementary biomarkers. Estela González-Gualda and colleagues highlight that confirming a senescent phenotype generally requires demonstrating at least three independent hallmarks: sustained cell-cycle arrest, characteristic structural or morphological alterations, and a third readout tailored to the specific senescence subtype under study.[53] This third criterion may include evidence of DNA-damage signaling, increased reactive oxygen species, or elevated expression of selected SASP components, as summarized schematically below.

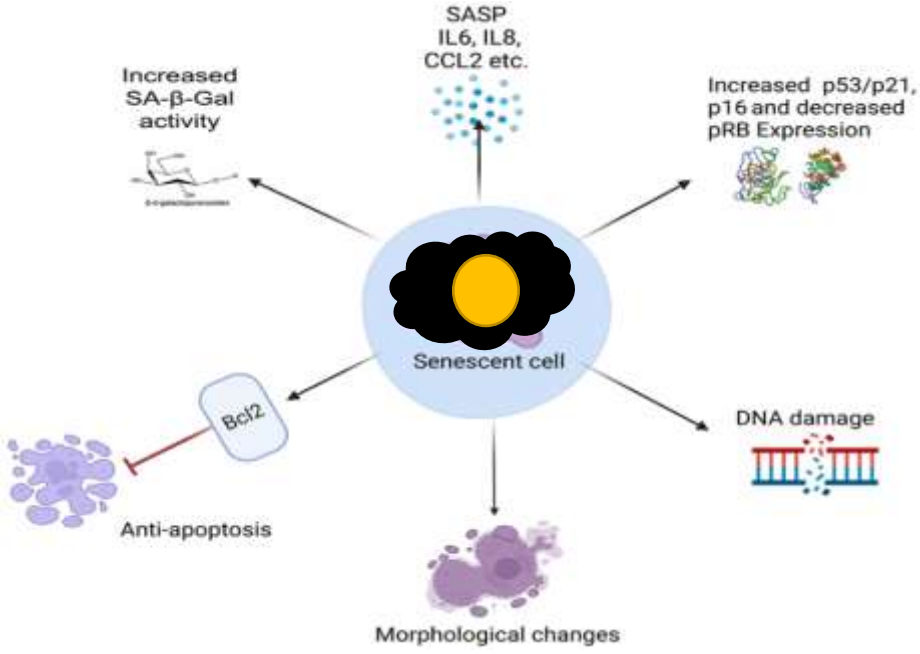

Fig 4: *Senescent cells show SA-β-Gal activity, SASP secretion, p53–p21–p16 activation with reduced pRB, chronic DNA damage, enlarged and misshapen morphology, and apoptosis resistance via increased anti-apoptotic proteins such as Bcl-2.*

Elevated senescence-associated β-galactosidase (SA-β-gal) activity is the most widely used readout for identifying senescent cells and reflects their enlarged lysosomal compartment and increased expression of the GLB1 gene,[54] which encodes β-galactosidase. In standard assays, cells are incubated with the chromogenic substrate X-gal, leading to a blue precipitate in SA-β-gal-positive cells; however, because this enzyme is not entirely specific to senescence, SA-β-gal staining must be interpreted together with additional markers such as p16, p21, or DNA-damage indicators. The assay is performed at pH 6.0, a suboptimal condition that suppresses most endogenous lysosomal β-galactosidase activity in proliferating cells, and staining times are typically restricted to about 6–12 hours to avoid nonspecific background signal.[55]

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Cell-cycle arrest constitutes another core hallmark of senescence and is characterized by upregulation of p16, p21 and p53, accompanied by reduced levels of phosphorylated retinoblastoma protein (pRB). Two main tumor-suppressor cascades enforce this arrest: the p16/RB pathway, which inhibits CDK4/6 and thereby prevents RB phosphorylation so that active RB can sequester E2F transcription factors, and the p53/p21 pathway, in which stress-activated p53 induces p21 to block CDKs and keep RB in its growth-suppressive form.[56] Together, these mechanisms lock cells in a stable G1 arrest and prevent further proliferation.

Persistent DNA damage is a further defining feature of senescent cells. Phosphorylated H2AX (γ-H2AX) accumulates as discrete nuclear foci at double-strand breaks, often co-localizing with the DNA-damage mediator 53BP1, and these structures are readily visualized by immunofluorescence.[57] Chronic γ-H2AX and 53BP1 foci, along with telomere-associated DNA-damage foci (TAF), indicate defective resolution of lesions and are particularly prominent in replicative senescence driven by telomere attrition. Such markers help distinguish truly senescent cells from those undergoing transient, repairable cell-cycle arrest. [58]

Senescent cells also adopt a distinctly anti-apoptotic phenotype. They resist programmed cell death by engaging multiple survival pathways, including upregulation of anti-apoptotic Bcl-2 family members and sustained expression of cell-cycle inhibitors like p21 and p16 that can also have pro-survival functions.[59] This resistance allows senescent cells to persist in tissues, where their long-term accumulation is linked to chronic inflammation and functional decline.

Characteristic morphological changes provide additional, though non-exclusive, clues to senescence. Under light microscopy, senescent cells typically appear enlarged, flattened and more granular, often containing numerous cytoplasmic vacuoles that reflect altered metabolism and accumulation of lysosomal contents, including SA-β-gal.[60] These structural alterations, when combined with molecular markers, help differentiate senescent cells from normal proliferating counterparts. Lastly, components of the senescence-associated secretory phenotype (SASP) serve as powerful functional markers. Senescent cells secrete high levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8), matrix metalloproteinases (for example MMP-1 and MMP-3), growth factors including VEGF and various IGFBPs, and chemokines like CCL2 and CXCL1 that recruit immune cells.[61] They also release proteases, reactive oxygen species and signaling molecules such as amphiregulin, collectively reshaping the tissue microenvironment, driving extracellular-matrix remodelling, and modulating the behavior of neighbouring cells; this complex secretory profile therefore provides a rich, multiparametric signature for defining and studying the senescent state.

Human Eye and the lens

The human crystalline lens focuses incoming light onto the retina, enabling sharp vision across different distances. At birth it weighs roughly 65 mg, increases to about 160 mg by 10 years of age, and then continues to grow more slowly, reaching approximately 250 mg by around 90 years.[62] Lens transparency is maintained by a combination of specialized structure and tightly regulated physiology. Structurally, the lens is avascular and consists of a capsule, a monolayer of lens epithelial cells (LECs), and underlying lens fiber cells (LFCs).[63] The capsule is a transparent, elastic basement-membrane–like envelope that functions as a selective barrier, supporting nutrient and waste exchange while preserving a stable internal milieu. LECs are metabolically active, synthesize ATP and lens proteins, and progressively migrate toward the

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equator where they differentiate into LFCs. During this differentiation, LFCs elongate extensively and degrade their nuclei and other organelles to generate an organelle-free zone (OFZ) that minimizes light scattering. High concentrations of tightly packed crystalline proteins in both LECs and LFCs, together with an organized actin cytoskeleton that supports cell shape and alignment, further enhance optical clarity by promoting a uniform refractive index and reducing internal diffraction.[64]

Physiological mechanisms are equally critical for transparency. Na^+/K^+-ATPase pumps in LECs and LFCs maintain ionic homeostasis by extruding sodium and importing potassium, thereby keeping intracellular Na^+ low and generating an osmotic gradient that drives water out of the lens.[65] This regulated fluid movement prevents swelling and is essential for maintaining the precise protein density required for transparency. Aquaporin-0, the predominant water channel in lens fiber cell membranes, facilitates controlled water flux and contributes to the characteristic dehydrated, compact state of the lens fibers.[66] Together, these structural and physiological adaptations allow light to traverse the lens with minimal absorption or scattering, preserving clear vision throughout life.

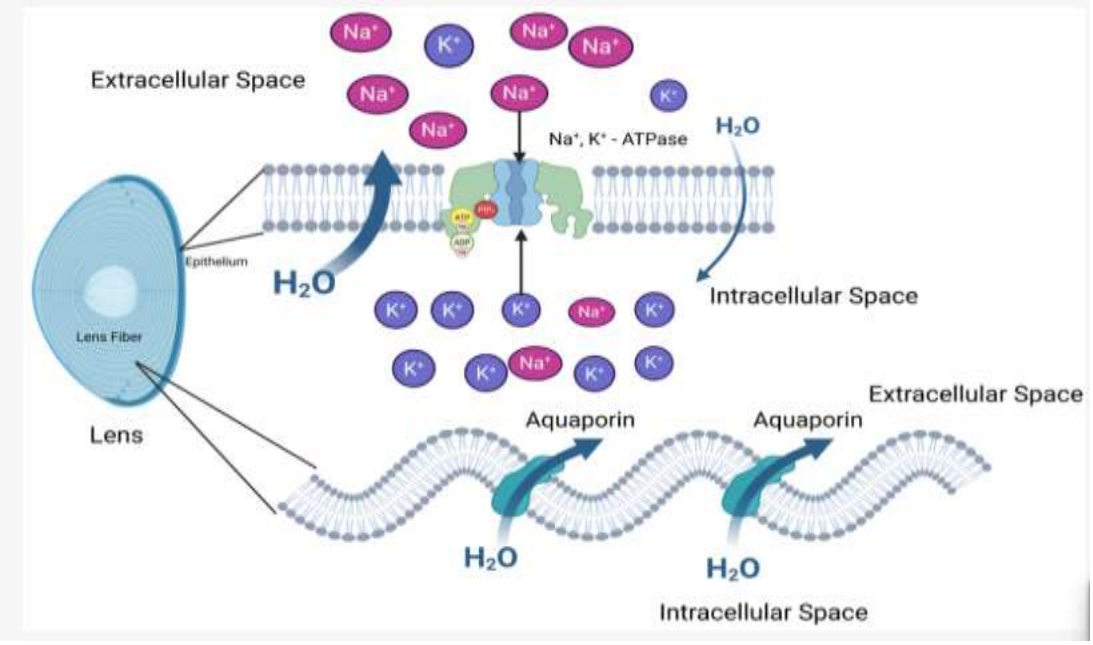

Fig 5: *Lens epithelial cells regulate ion (Na^+/K^+ via Na^+/K^+-ATPase) and water (aquaporins) homeostasis, maintaining lens transparency and preventing cataracts.*

The lens employs a robust antioxidative system, featuring small molecules like reduced glutathione (GSH) to scavenge reactive oxygen species (ROS), with enzymatic regeneration sustaining its efficacy. Complementary enzymes—catalase, superoxide dismutase (SOD), glutaredoxin (Grx), and thioredoxin (Trx)—detoxify peroxides and superoxide radicals, shielding lens proteins from oxidative damage amid UV exposure and thereby upholding transparency. [67]

Despite these safeguards, aging erodes lens defenses, allowing cumulative oxidative stress and protein alterations to trigger opacification and cataractogenesis. Cataracts arise as lens fibers and crystalline aggregate, scattering light akin to fogged glass; though often insidious, progression impairs vision severely and may shorten lifespan if unmanaged. Globally, cataracts

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dominate as the primary blindness cause per CDC data. NIH 2014 data indicate 24 million U.S. adults over 40 (17.2%) harbour cataracts, with 6.1 million (5.1%) post-surgery; by 65, over 90% of Americans and 50% worldwide are affected. Cataracts classify chiefly as nuclear sclerotic, cortical, and posterior subcapsular.[68] Nuclear sclerotic variants target the lens nucleus, inducing myopia, blur, and yellow-brown discoloration. Cortical forms manifest as peripheral spokes encroaching centrally, diabetes-linked, provoking glare and scotopic deficits. Posterior subcapsular cataracts, at the posterior cortex and tied to steroids, diabetes, or irradiation, rapidly degrade near acuity and heighten photic glare, underscoring vigilant screening.[69]

LEC Senescence in Cataractogenesis

Human tissue studies from cataract patients link LEC senescence to cataract development. Yao et al. analyzed lens capsules across age groups, revealing age-dependent declines in progenitor markers (Sox2, Abcg2, Ki67)—nearly absent beyond age 60—coupled with rising SA-β-gal staining, especially in cortical cataracts.[70] This underscores senescence-driven loss of regenerative capacity as a key driver of cortical opacification. Extracellular matrix alterations further promote LEC senescence by disrupting signaling and integrity. In age-related cataracts, matrix imbalances heighten oxidative stress, inducing senescent morphology (enlarged, flattened cells) and elevated SA-β-gal in cultured LECs, akin to in vivo findings. Targeting matrix homeostasis and stress pathways may thus mitigate senescence and preserve LEC function. Zhou et al. correlated cataract severity with LEC senescence in human lenses, observing graded increases in SA-β-gal-positive cells paralleling opacity progression. Senescent LECs not only forfeit regeneration but actively contribute to lens clouding, suggesting early anti-senescence interventions could halt cataract advancement.[71]

Drivers of LEC Senescence

Lens epithelial cells (LECs) are vital for lens homeostasis, fuelling transparency and acuity through multifaceted roles. Metabolically dynamic, they generate ATP and biomolecules essential for lens function.[72] As progenitors, LECs migrate equatorially, differentiating into lens fiber cells (LFCs) while shedding organelles to form an organelle-free zone that curbs light scattering. They drive regeneration/repair, synthesize refractive crystalline, manage nutrient/waste flux, and bolster antioxidative defenses against oxidative insults.[73] Yet, LECs succumb to age-related senescence, impairing these functions. As depicted in the figure, oxidative damage predominates—driven by chronic UV exposure and endogenous mitochondrial ROS. Cumulative ROS/RNS overloads redox homeostasis, igniting senescence-associated molecular cascades.

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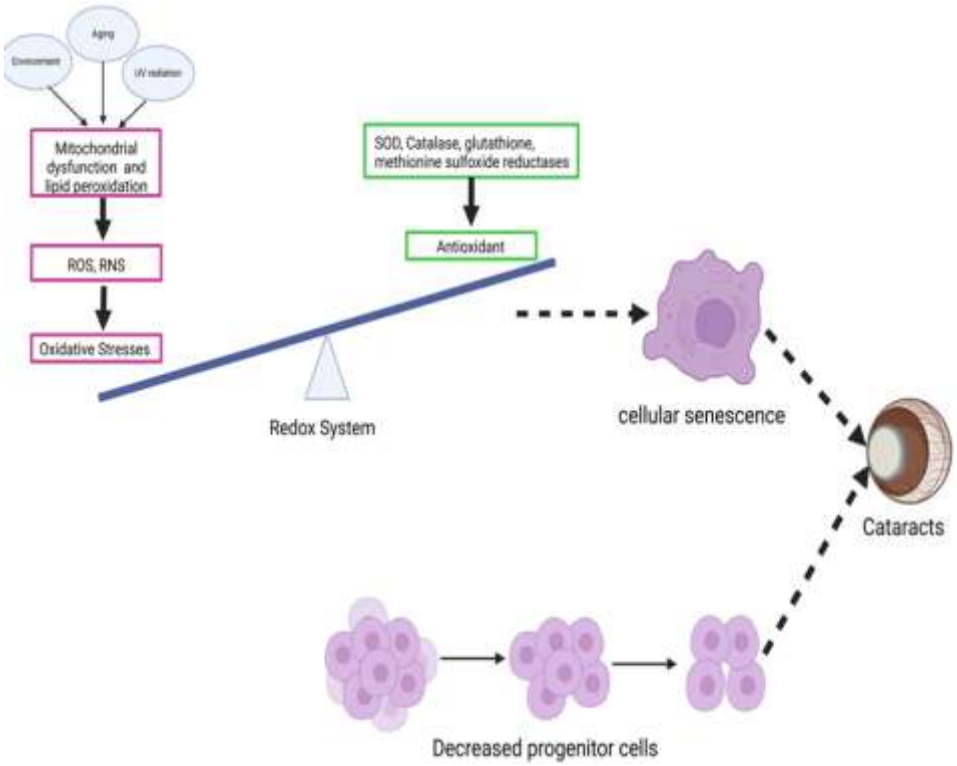

Fig 6: *Lens epithelial cells regulate ion (Na^+/K^+ via Na^+/K^+-ATPase) and water (aquaporins) homeostasis, maintaining lens transparency and preventing cataracts.*

Oxidative modifications of DNA, proteins, and lipids drive LEC senescence. Nuclear/mitochondrial DNA damage impairs repair, activating DNA damage response (DDR) via γ-H2AX and p53 upregulation, enforcing cell cycle arrest through p16/Rb and p21/CDK inhibition.[73,74] Mitochondrial dysfunction amplifies this via excess ROS production and ATP deficits, creating a vicious oxidative feedback loop. Declining antioxidants (SOD, catalase, Grx, GSH) heighten, while impaired methionine sulfoxide reductase activity promotes protein misfolding/aggregation.[76] Notably, Grx1/Grx2 double-knockout LECs exhibit premature senescence versus wild-type controls, underscoring cytosolic/mitochondrial Grx in repairing oxidized cysteines and preserving redox homeostasis.

Senescent LECs accumulate, forfeiting proliferation and inducing morphological/functional shifts that erode transparency. Progenitor depletion—via redox imbalance and senescence—curtails regeneration, forming a self-perpetuating cycle of repair failure, inflammation and opacification.[57,92]

In essence, oxidative stress, DDR activation, mitochondrial failure, and antioxidative decline converge to impair LEC/progenitor function, driving cataractogenesis. Targeting these axes holds therapeutic promise

Apoptosis vs. Senescence in LEC Fate?

Elucidating LEC death dynamics is crucial for age-related cataractogenesis. Early work (Li et al.) implicated apoptosis as primary, revealing elevated TUNEL-positive cells and DNA laddering in human/animal lens which is having or diagnosed with cataract, inspiring anti-apoptotic therapeutic strategies. Beebe et al. challenged this through comprehensive human lens analyses—integrating TUNEL, proliferation markers, and density quantification.[77] True apoptosis proved negligible; TUNEL signals likely signified necrosis from surgical/oxidative artefacts. Notably, lens having cataract exhibited stable LEC density sans proliferative

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rebound, negating substantial cell loss. We propose senescence as the prevailing trajectory: senescent LECs resist apoptosis via Bcl-2 upregulation and caspase-3 suppression, preserving density while accruing dysfunction.[78] This paradigm reconciles persistent, damaged cells driving opacification. Refocusing from apoptosis inhibition to senescence clearance—via senolytics or SASP modulators—unlocks novel interventions. Validating LEC senescence markers and SASP contributions in cataract progression remains imperative.[79]

Senotherapeutics

Key senotherapeutics targeting senescent cells are outlined in the figure below. Cellular senescence drives aging and age-related pathologies, with senescent cell accumulation evident at disease foci in cataracts, Alzheimer's, cardiovascular disease, osteoporosis, diabetes, CKD, and cirrhosis.[80] These cells perpetuate damage via senescence-associated secretory phenotype (SASP)[80,81]—a cocktail of pro-inflammatory cytokines, chemokines, and proteases—fostering a chronic inflammatory milieu that propagates senescence to bystander cells, rendering aging "contagious" Senotherapeutics counter this burden, classifying into senolytics (selectively eliminating senescent cells) and senomorphics (suppressing SASP/toxicity without cytotoxicity).[81] These strategies hold promise for health span extension and cataract delay.

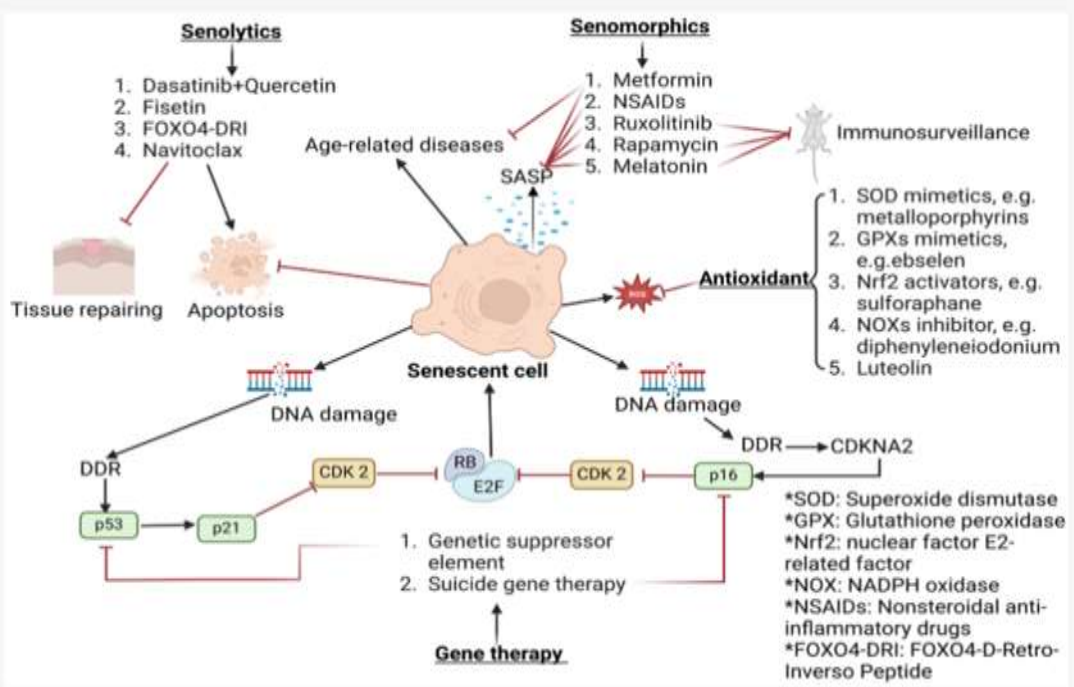

Fig 7: *Senotherapeutics target senescence: senolytics (Dasatinib+Quercetin, Fisetin) eliminate cells; senomorphics (Rapamycin, Metformin) suppress SASP; antioxidants/gene therapies aid repair.*

Senescent cells evade apoptosis via upregulated anti-apoptotic pathways (e.g., Bcl-2 family), persisting to drive tissue dysfunction and inflammation through SASP. Senolytics counter this by selectively triggering apoptosis in senescent cells while sparing healthy ones. Kirkland et al. pioneered multi-pathway targeting: dasatinib + quercetin (D+Q) effectively clears senescent cells across tissues. Fisetin, another flavonoid, disrupts senescent anti-apoptotic networks. FOXO4-DRI, a synthetic peptide, liberates nuclear-sequestered p53 by competitively disrupting FOXO4-p53 binding, activating apoptosis[82] selectively in senescent

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cells—improving organ function in preclinical models. Caveat: repeated senolysis may accelerate new senescence formation, risking regenerative capacity. Senomorphics alternatively suppress SASP without cytotoxicity.[83] Metformin activates AMPK, inhibits mTOR, reduces oxidative stress/inflammation, and correlates with lower incidence of diabetes, CVD, neurodegeneration, and cancer. Ruxolitinib (JAK inhibitor) and rapamycin (mTORC1 inhibitor) dampen SASP cytokines; melatonin downregulates SASP genes. SASP duality (immune surveillance vs. pathology) necessitates cautious modulation. Antioxidants complement via SOD/GPx mimetics, Nrf2 activators (sulforaphane), and NOX inhibitors (diphenyleneiodonium), mitigating ROS-driven DNA damage and SASP. Gene therapy targets senescence axes: CDK2/RB modulation delays onset; suicide genes trigger selective apoptosis; suppressor elements repair DNA damage—offering precision against cataractogenic LEC senescence.[84] Senolytics selectively eliminate senescent LECs via apoptosis—sparing healthy cells—to curb oxidative stress and inflammation driving lens opacification. Dasatinib + quercetin (D+Q) shows broad tissue efficacy, potentially delaying cataract progression by reducing senescent burden.[85] Fisetin, a flavonoid, dual-targets senescent cells while quenching ROS, preserving clarity.[86] Navitoclax disrupts anti-apoptotic paths, clearing damaged LECs and mitigating risk. These agents address root cellular dysfunction, offering non-surgical strategies to maintain lens transparency.

Table 1. Overview of Lens-Targeted Senotherapeutics

Compound	Category	Mode of Action	Therapeutic Benefits
Dasatinib + Quercetin	Senolytics	Triggers apoptosis in senescent cells	Lowers senescent cell load in lens, postponing cataract development
Fisetin	Senolytics	Eliminates senescent cells and diminishes oxidative stress indicators	Improves lens transparency by alleviating oxidative damage and inflammation
Luteolin	Senolytics	Antioxidant, anti-apoptotic, calcium balance modulator	Preserves lens clarity, reinforces membrane stability, prevents LEC death

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Compound	Category	Mode of Action	Therapeutic Benefits
Metformin	Senomorphics	Stimulates AMPK, inhibits SASP, boosts autophagy	Decreases SASP components, strengthens cellular defence, counters oxidative stress, maintains lens clarity
Melatonin	Senomorphics	Antioxidant and anti-inflammatory	Blocks oxidative injury and ferroptosis, promoting lens integrity and transparency

Senomorphics complement senolytics by suppressing SASP toxicity without cell elimination—ideal for lens preservation where LEC numbers matter. They curb inflammation and oxidative damage, stabilizing transparency and slowing cataracts.[87,88] Metformin excels via AMPK activation, boosting autophagy to clear senescence markers (p21/p53) in aged LECs. Rapamycin inhibits mTOR/SASP, easing stress.[89,90] Preclinical D-galactose rat models show dasatinib+quercetin and rapamycin reduce early cataract/LEC senescence markers, though late-stage efficacy wanes—needing optimized timing.[91] Fisetin counters diabetic cataracts by scavenging ROS, blocking NF-κB inflammation, and clearing senescent cells.[93] Luteolin boosts antioxidants, stabilizes Ca^{2+}-ATPase/membranes, and inhibits caspase-3 in selenite models.[94] Melatonin activates SIRT6/p-Nrf2/GPX4 against UVB-ferroptosis, regulating NCOA4/FTH1 iron homeostasis to limit LEC senescence.[95]

Conclusion:

Cellular senescence serves dual functions: suppressing tumorigenesis while driving age-related diseases like cataracts through LEC dysfunction. Oxidative stress, mitochondrial impairment, and SASP-mediated inflammation converge to erode lens transparency, positioning LEC senescence as central to cataractogenesis. Senotherapeutics—senolytics (dasatinib+quercetin, fisetin, FOXO4-DRI) clearing senescent cells, and senomorphics (metformin, rapamycin, melatonin) suppressing SASP—offer targeted strategies to preserve LEC homeostasis and delay opacification. Natural flavonoids (fisetin, luteolin) and gene therapies further expand therapeutic horizons.

Future Directions:

- **Molecular Drivers**: Elucidate oxidative stress, mitochondrial dysfunction, and protein aggregation pathways in LEC senescence for precision targeting.
- **SASP Microenvironment**: Investigate SASP-lens matrix interactions driving chronic inflammation and accelerated cataractogenesis.

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- **High-Throughput Screening**: Identify novel senolytics/senomorphics from natural/synthetic libraries enhancing antioxidants or inhibiting misfolding.
- **Genetic/Epigenetic Biomarkers**: Uncover regulators for early LEC senescence detection and intervention.
- **Systemic Aging Links**: Explore connections between organismal senescence, metabolic dysregulation, and ocular pathologies.
- **Combination Therapies**: Optimize senolytic-senomorphic regimens with dosing/timing for stage-specific cataract prevention.
- **Translational Models**: Validate preclinical findings in humanized lens organoids and longitudinal cohorts.

Integrating these approaches promises transformative, non-surgical cataract interventions preserving vision healthspan.

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Abbreviations:

The following abbreviations are used in this manuscript:

AMPK	AMP-activated protein kinase
ARE	Antioxidant response element
ATF6	Activating transcription factor 6
Bcl-2	B-cell lymphoma 2
CDK	Cyclin-dependent kinase
CDKs	Cyclin-dependent kinases
DDR	DNA damage response
DRI	D-retro-inverso
ETC	Electron transport chain
FTH1	Ferritin heavy chain 1
FOXO4	Forkhead box O4
GSH	Glutathione

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GPx	Glutathione peroxidase
Grx	Glutaredoxin
IL-6	Interleukin-6
IL-8	Interleukin-8
LEC	Lens epithelial cell
LECs	Lens epithelial cells
MMPs	Matrix metalloproteinases
mTOR	Mechanistic target of rapamycin
MiDAS	Mitochondrial dysfunction-associated senescence
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
Nrf2	Nuclear factor erythroid 2-related factor 2
OFZ	Organelle-free zone
OIS	Oncogene-induced senescence
OXPHOS	Oxidative phosphorylation
p16	Cyclin-dependent kinase inhibitor 2A (CDKN2A)
p21	Cyclin-dependent kinase inhibitor 1A (CDKN1A)
p53	Tumor protein p53
PERK	Protein kinase R-like endoplasmic reticulum kinase
RB	Retinoblastoma protein
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SASP	Senescence-associated secretory phenotype

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SA-β-gal	Senescence-associated beta-galactosidase
SOD	Superoxide dismutase
TAF	Telomere-associated DNA damage foci
TUNEL	Terminal deoxynucleotidyl transferase dUTP nick end labelling
UPR	Unfolded protein response
UV	Ultraviolet
VEGF	Vascular endothelial growth factor
WT	Wild-type

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