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Nucleus Pulposus Cell Senescence in IVDD: Mechanisms and Therapeutic Perspectives

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Abstract: Intervertebral disc degeneration (IVDD) is a common spinal pathological process that leads to the degeneration of the structure and function of the intervertebral disc, causing low back pain and nerve root compression. The molecular mechanism of intervertebral disc degeneration is not fully understood, but cellular senescence is an important factor. This article summarizes the characteristics, causes, signal transduction pathways and treatment methods of cellular senescence in intervertebral disc degeneration, including inhibiting the expression or activity of genes or signal pathways related to cellular senescence, increasing the number or function of intervertebral disc cells, and improving the microenvironment of the intervertebral disc. This article aims to provide new clues for the prevention and treatment of intervertebral disc degeneration.

Keywords: Intervertebral Disc Degeneration; Senescence; Mechanism; Nucleus Pulposus Cells.

1. Introduction

Intervertebral disc degeneration (IVDD), a principal contributor to cervical and lumbar spine pathologies, arises through a multifactorial and progressive deterioration of disc tissue. Its onset is closely linked to genetic predispositions, sustained biomechanical loading, inadequate nutrient supply, and elevated oxidative stress. These adverse stimuli collectively disrupt the cellular homeostasis of disc tissue, promoting senescence-like changes such as heightened inflammation, diminished cell proliferation, increased programmed cell death, and compromised autophagic mechanisms [1,2]. Senescent disc cells compromise tissue integrity not only by diminishing the population of metabolically active cells responsible for matrix production and hydration but also by releasing a complex array of pro-inflammatory mediators, matrix-degrading enzymes, and reactive oxygen species. This collective secretion profile, known as the senescence-associated secretory phenotype (SASP), accelerates extracellular matrix breakdown and exacerbates the degenerative cascade within the disc microenvironment [3,4]. Given its pivotal role in the pathogenesis of intervertebral disc degeneration, cellular senescence has emerged as a promising intervention point for delaying or potentially reversing degenerative changes. This article provides a comprehensive overview of recent scientific developments in this area, aiming to inform future investigations and guide the design of targeted therapeutic approaches.

2. Molecular Characteristics of Nucleus Pulposus Cell Senescence

As the central and most prominent component of the intervertebral disc, the nucleus pulposus accounts for over half of the disc's cross-sectional area and typically exhibits a rounded or semi-elliptical morphology. It consists predominantly of water and a collagen-proteoglycan matrix, forming a soft, gel-like core. This structure, in coordination with the annulus fibrosus and cartilaginous endplates, forms an integrated biomechanical unit that effectively dissipates axial loads and cushions mechanical forces exerted on the spine. Beyond its mechanical function, the nucleus pulposus also serves as a metabolic hub, maintaining high hydration levels and facilitating nutrient uptake via diffusion through the adjacent cartilage endplate—its principal source of nourishment [5,6].

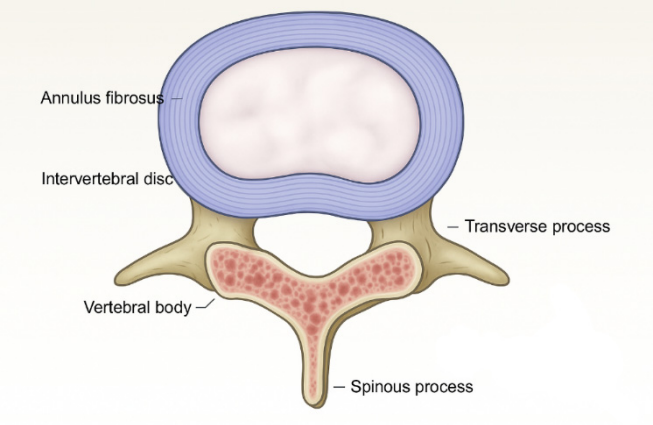

Figure 1. Diagram of the Lumbar Intervertebral Disc Structure

The aging process of nucleus pulposus cells encompasses a multifaceted cascade of cellular and molecular alterations. As senescence progresses, cells exhibit a marked decline in proliferative potential and a reduction in extracellular matrix production, likely due to impaired biosynthetic activity. Concurrently, structural disruptions in the plasma membrane and morphological abnormalities in intracellular organelles become evident, often accompanied by hallmarks of cellular aging and increased apoptotic signaling [7]. Research by Di Wang and colleagues revealed that the progression of intervertebral disc degeneration is marked by substantial dehydration of the nucleus pulposus, a pronounced decline in proteoglycan content, and a significant reduction in the viability of nucleus pulposus cells (NPCs). These pathological changes collectively accelerate the structural and functional deterioration of the disc as a whole [8]. In addition to functional decline, aging nucleus pulposus cells are characterized by suppressed expression of key growth factors

and disruption of the local disc microenvironment. Emerging evidence suggests that periostin, a protein secreted by senescent NPCs, may accelerate cellular aging by activating the NF-κB signaling cascade, thereby enhancing catabolic processes and further impairing disc homeostasis [9]. Such metabolic disturbances perpetuate the senescence of nucleus pulposus cells by enhancing periostin production and maintaining persistent NF-κB pathway activation, thereby establishing a self-reinforcing feed-forward loop. This pathological cycle may contribute to the irreversibility and acceleration of the aging process. Mechanistically, these alterations are thought to stem from underlying factors such as genomic instability, elevated oxidative stress, and disrupted cellular metabolism within the disc microenvironment [10]. A variety of molecular pathways have been implicated in driving the senescence of nucleus pulposus cells. Key contributors include telomere attrition, dysregulation of the p16^INK4a^–pRB axis, and altered signaling through metabolic regulators such as mTOR and AMPK. These pathways collectively modulate cellular aging by affecting cell cycle progression, metabolic balance, and stress responses [11]. In summary, nucleus pulposus cell senescence represents a multifaceted biological process, characterized by dynamic molecular and cellular alterations within the intervertebral disc microenvironment

3. Molecular Characteristics of Nucleus Pulposus Cell Senescence

Cellular senescence is a permanent and non-reversible state characterized by the progressive decline in proliferative capacity, differentiation potential, and functional activity of cells, ultimately culminating in cell death. Key features of senescent cells include telomere attrition, genomic damage, and elevated oxidative stress, all of which can be initiated by intrinsic aging, pathological insults, or environmental stressors such as radiation. These factors collectively induce cell cycle arrest and promote cellular dysfunction. Moreover, inflammatory signaling, extracellular matrix degradation, and metabolic dysregulation are also implicated in driving and sustaining the senescence phenotype [12].

Senescence in intervertebral disc cells can be triggered by a range of intrinsic and extrinsic stressors, including telomere erosion, oxidative damage, nutrient insufficiency, inflammatory cytokine dysregulation, and aberrant mechanical forces. Numerous signaling molecules have been implicated in orchestrating this process, such as p16^INK4a^, p53, mTOR, and NF-κB. These factors exert regulatory control over cellular metabolism and function, thereby modulating cell fate decisions. Notably, NF-κB, a central mediator of inflammation, can drive catabolic gene expression and amplify inflammatory cascades under stress conditions, contributing to the disruption of normal cellular homeostasis [13].

3.1. The Senescence-Associated Secretory Phenotype

The senescence-associated secretory phenotype (SASP) represents a distinctive feature of aged cells, typified by the excessive release of pro-inflammatory cytokines and matrix-modifying molecules, including IL-1α, IL-1β, IL-6, and IL-8 [14]. In the context of intervertebral disc degeneration, disc cells subjected to chronic stress and damage can undergo senescence and adopt the SASP profile, leading to the secretion of a broad array of inflammatory mediators and apoptosis-associated factors. These secretions promote immune cell infiltration and paracrine signaling, thereby accelerating the degenerative cascade. Once the SASP is established, senescent cells continuously release inflammatory cytokines, matrix metalloproteinases, and reactive oxygen species, which not only trigger senescence and cell death in adjacent nucleus pulposus cells but also disrupt the composition and mechanical integrity of the extracellular matrix [15]. Progressive loss of nucleus pulposus cells, coupled with alterations in extracellular matrix components, results in decreased hydration and shrinkage of the nucleus pulposus. These changes compromise the disc's biomechanical properties, particularly its elasticity and capacity to absorb mechanical loads, ultimately contributing to disc height reduction and the advancement of degenerative pathology.

Li and colleagues reported a marked downregulation of IL-37 expression during the progression of intervertebral disc degeneration [16]. In vitro studies demonstrated that IL-37 effectively mitigated the expression of SASP-associated factors and senescence characteristics in IL-1β-stimulated neural progenitor cells. Complementary in vivo experiments revealed that IL-37 administration alleviated disc degeneration in a rat model subjected to pro-degenerative stimuli. Mechanistic analyses further indicated that IL-37 exerts its protective effects by engaging IL-1R8 and inhibiting activation of the NF-κB signaling pathway in neural progenitor cells.

3.2. Autophagy

Autophagy and cellular senescence represent two critical stress-adaptive mechanisms that contribute to the preservation of cellular and tissue homeostasis. Notably, these processes are intricately linked, with a dynamic and context-dependent interaction influencing their respective roles in cellular aging and survival [17]. Autophagy and senescence may exert both cooperative and opposing influences, depending on the cellular context. Notably, dysregulation of autophagy—whether through excessive activation or impaired function—can contribute to the initiation or progression of cellular senescence [18]. Conversely, autophagy also plays a protective role by facilitating the removal of damaged organelles and senescence-associated cellular components, thereby attenuating stress accumulation and delaying the onset of cellular aging [19]. The impact of autophagy on cellular senescence is highly context-dependent and may differ across tissue types, physiological states, and environmental exposures, reflecting the complexity of its regulatory role in aging processes.

While the interplay between cellular senescence and autophagy has been explored in numerous studies, a unified theoretical framework or definitive conclusion has yet to emerge. Despite both processes being stress-induced adaptive responses essential for cellular homeostasis, their mechanistic relationship remains ambiguous and incompletely understood [20]. Initial investigations into the connection between autophagy and cellular senescence posited that autophagy functions as an anti-aging mechanism by degrading damaged intracellular components and mitigating cellular stress. However, as research has progressed, this once-linear view has been replaced by a more sophisticated understanding of autophagy as a context-dependent process with potentially dual roles. Rather than viewing autophagy solely as protective,

emerging perspectives recognize its ability to exert both beneficial and detrimental effects depending on the cellular environment. A recurring theme in recent studies is that autophagy can suppress senescence by preserving protein homeostasis and clearing senescence-inducing agents such as oxidized DNA, misfolded proteins, and defective organelles. This regulatory role has been substantiated by experiments demonstrating that inhibition of autophagy promotes the accumulation of reactive oxygen species (ROS), thereby accelerating cellular aging [21]. Conversely, emerging evidence has highlighted a paradoxical aspect of autophagy—its potential role in promoting cellular senescence. This pro-senescent function stands in contrast to the well-documented cytoprotective effects of autophagy. Notably, during the senescence process, autophagy has been shown to mediate the degradation of SIRT1, a key longevity-associated protein. Nuclear SIRT1 can be selectively targeted as autophagic cargo and eliminated through the autophagosome–lysosome pathway, thereby diminishing its protective influence on cellular homeostasis and contributing to the advancement of the senescent phenotype [22]. These findings shed light on the regulatory mechanisms governing SIRT1 protein homeostasis and offer a conceptual framework for developing strategies aimed at stabilizing SIRT1, thereby harnessing its protective functions to promote healthy or delayed cellular aging.

3.3. DNA Damage and Telomere Shortening

DNA damage denotes alterations in the structure or function of the genetic material that compromise essential cellular processes such as metabolism and mitotic division. These abnormalities contribute to genomic instability, increasing the likelihood of gene mutations and chromosomal abnormalities that impair cellular homeostasis. In response, cells activate the DNA damage response (DDR), a sophisticated signaling cascade designed to detect, signal, and repair DNA lesions. In addition to facilitating repair, DDR can enforce cell cycle arrest, initiate apoptosis, or drive cells into senescence, thus safeguarding genomic integrity. Importantly, sustained activation of DDR signaling has been implicated in establishing irreversible cell cycle arrest, serving as a critical trigger for the onset of cellular senescence[21,22].

In eukaryotic cells, telomeres serve as essential protective elements at chromosomal ends, safeguarding genome stability by preventing degradation, end-to-end chromosomal fusion, and aberrant recombination. With each round of cell division, telomeres progressively shorten, and once they reach a critical threshold, DDR is initiated, triggering a cascade that culminates in cellular senescence. Emerging evidence suggests that during the course of intervertebral disc degeneration, telomere attrition in disc cells is accompanied by a decline in telomerase activity. Concurrently, key senescence-associated pathways—most notably the p53–p21–Rb and p16–pRb signaling axes—become activated, supporting the notion that telomere shortening plays a pivotal role in initiating replicative senescence and driving the degenerative process in disc tissues[23].

DNA damage is recognized as a major driver of cellular senescence, exerting wide-ranging effects on molecular signaling, metabolic pathways, and cellular fate. Accumulating evidence indicates that such genomic insults can accelerate spinal aging. One of the primary pathways mediating the cellular response to DNA lesions is the ataxia telangiectasia mutated (ATM) signaling cascade. In a study by Han , the role of ATM in human intervertebral discs was explored, revealing that persistent genotoxic stress leads to sustained ATM activation, which in turn exacerbates disc cell senescence and disrupts extracellular matrix homeostasis [24]. These findings suggest that modulation of the ATM pathway may offer a viable therapeutic approach for attenuating age-associated spinal degeneration.

3.4. Oxidative Stress

Oxidative stress represents a critical pathogenic factor in the development of intervertebral disc degeneration. It arises when the production of reactive oxygen species (ROS) overwhelms the cell's intrinsic antioxidant defenses, resulting in molecular dysfunction and structural deterioration. This imbalance contributes to disc pathology by promoting cellular senescence, apoptosis, and tissue degradation. Mechanistically, oxidative stress induces a cascade of damaging events, including genomic instability, protein oxidation, lipid peroxidation, and mitochondrial impairment, all of that compromise cellular integrity and alter tissue architecture. A growing body of evidence supports the pivotal role of oxidative stress in both the initiation and progression of disc degeneration.

Oxidative stress-induced intervertebral disc degeneration involves several molecular cascades, among which the p38 mitogen-activated protein kinase (p38/MAPK) signaling axis plays a critical regulatory role in both cellular senescence and inflammation. Activation of the p38/MAPK pathway has been shown to upregulate TNF-α, which subsequently reinforces the same pathway via a positive feed-forward mechanism, amplifying inflammatory signaling. Notably, pharmacological inhibition of this pathway suppresses the expression of key pro-inflammatory mediators, including TNF-α, COX-2, MMP-1, and MMP-13, thereby enhancing chondrocyte viability and preserving extracellular matrix integrity[25]. The nuclear factor erythroid 2–related factor 2 (Nrf2) signaling pathway plays a central role in orchestrating the cellular antioxidant defense system, safeguarding cells from oxidative stress–induced damage and degeneration, including within intervertebral disc tissues. As a redox-sensitive transcription factor, Nrf2 is activated upon exposure to oxidative stimuli and translocates to the nucleus, where it binds to antioxidant response elements (AREs) in the promoter regions of target genes. This activation drives the expression of a wide array of cytoprotective genes, including those encoding detoxifying enzymes, free radical scavengers, and DNA repair proteins. Through this mechanism, Nrf2 enhances the cellular capacity to neutralize ROS and maintain redox balance, thereby attenuating oxidative injury and delaying the progression of disc degeneration. Given its broad protective functions, Nrf2 has emerged as a promising therapeutic target in the prevention and treatment of oxidative stress–related diseases such as IDD, malignancies, and neurodegenerative conditions.

3.5. Inflammation

Inflammation has emerged as a key pathological driver in the initiation and progression of intervertebral disc degeneration. Throughout the degenerative cascade, disc cells and their microenvironment are subjected to diverse physicochemical stressors—including oxidative insults and abnormal mechanical loading—that activate inflammatory signaling pathways. This leads to the recruitment of immune cells and the elevated secretion of pro-inflammatory cytokines such as IL-1β, TNF-α, IL-6, and IL-8. These

mediators not only induce apoptosis and cellular senescence but also contribute to structural deterioration of disc tissue. Additionally, inflammation enhances extracellular matrix breakdown and upregulates catabolic enzymes, further accelerating the degenerative process. Collectively, these findings underscore the pivotal role of inflammation in driving the structural and functional decline of intervertebral discs.

A complex and mutually reinforcing interplay exists between inflammation and cellular senescence. Inflammatory stimuli can actively promote senescence through the release of pro-inflammatory cytokines and reactive oxygen species (ROS), which induce genomic instability and cellular damage. These stressors not only impair cellular homeostasis but also initiate signaling cascades—most notably the NF-κB pathway—that further amplify senescence-associated phenotypes. Thus, inflammation not only arises as a consequence of tissue damage but also serves as a potent driver of the senescence process itself [26].

Conversely, inflammation may also arise as a secondary effect accompanying cellular senescence. In response to exogenous insults—such as viral or bacterial infections—the body mounts an inflammatory response characterized by immune cell activation and the release of pro-inflammatory mediators to eliminate the threat and maintain tissue integrity. However, this heightened immune activity can inadvertently accelerate the transition of nearby or affected cells into a senescent state, linking immune defense mechanisms with the progression of cellular aging.

Therefore, the interplay between inflammation and cellular senescence is bidirectional and dynamic, rather than a unidirectional cause-effect relationship. Although inflammation can accelerate the onset of senescence through various molecular pathways, it may also arise as a downstream response to senescent cell activity, functioning as part of the organism's intrinsic defense strategy. This reciprocal relationship underscores the complexity of their roles in maintaining tissue homeostasis and contributing to age-related degeneration.

4. Therapeutic Strategies

4.1. Immunotherapy

Immunotherapy represents a promising strategy that leverages the host immune system to recognize and eliminate diseased or aberrant cells, thus exerting therapeutic effects. This approach can be achieved through diverse modalities, including immune checkpoint inhibitors, interleukins, cytokines, and tumor-associated antigens that potentiate immune activation. Importantly, senescent cells are particularly susceptible to immune surveillance, that positions immunotherapy as a viable avenue for selectively targeting cellular senescence. A novel example is senolytic vaccination—a hybrid strategy that combines senescence-targeting agents with immunological precision to promote the clearance of senescent cells. In a recent study, Suda et al. identified glycoprotein non-metastatic melanoma protein B (GPNMB) as a senescence-enriched transmembrane marker. Utilizing this molecule as an immunogenic target, they demonstrated that vaccination against GPNMB significantly reduced the burden of GPNMB-positive senescent cells in aged mouse models, highlighting a potential immunotherapeutic route for senescence intervention [27,28]. Additionally, senolytic vaccination has been shown to markedly ameliorate both physiological and pathological aging phenotypes, and notably, to extend the lifespan in models of accelerated aging, further supporting its therapeutic potential in age-related disorders.

The sustained expression of pro-apoptotic and pro-inflammatory components of the senescence-associated secretory phenotype (SASP) can have deleterious consequences. Under normal physiological conditions, senescent cells are efficiently cleared by innate immune cells such as macrophages and natural killer (NK) cells within a short time frame. However, when the burden of senescent cells surpasses the immune system's clearance capacity, these cells begin to accumulate. This is thought to result from the paracrine and endocrine actions of SASP factors, which propagate senescence to neighboring or even distant cells, thereby accelerating the accumulation of new senescent populations beyond the threshold of immune surveillance. Once this tipping point is reached, the ongoing presence of SASP-expressing cells can inflict tissue damage and drive the onset or exacerbation of aging-related pathologies. Furthermore, age-associated immune dysfunction may amplify this feed-forward loop, contributing to the chronic retention of senescent cells in tissues [29].

Immune cells constitute a fundamental component of senescence-targeted immunotherapeutic strategies. A dynamic interaction exists between cellular senescence and the immune system, wherein senescence-associated signaling pathways actively recruit and modulate immune responses. Importantly, p53 and p21—two key cell cycle regulators—contribute to immune surveillance by enhancing immune cell infiltration, promoting the recognition of senescent cells, and stimulating M1 polarization of macrophages, that facilitates their effective clearance. In addition, a broad spectrum of immune cells—including natural killer (NK) cells, dendritic cells, monocytes/macrophages, neutrophils, B cells, and T lymphocytes—are capable of detecting and eliminating senescent cells via tissue-specific receptors, chemokine gradients, and microenvironmental modulation. This cellular coordination underscores the immune system's critical role in maintaining tissue homeostasis and preventing the pathological accumulation of senescent cells.

4.2. Senolytics

Recent research has revealed that beyond conventional interventions targeting senescence-associated signaling cascades or employing genetic manipulation of p16^Ink4a^, an innovative anti-aging paradigm is gaining traction: the selective elimination of senescent cells. This senolytic strategy offers a promising avenue to mitigate age-related decline and extend lifespan by directly reducing the burden of deleterious, senescence-associated cells [30,31]. Senolytics refer to a class of pharmacological agents specifically designed to target and eliminate senescent cells by inducing programmed cell death. This therapeutic strategy has garnered significant attention for its potential to alleviate age-related dysfunctions by reducing the burden of senescent cells within tissues. Senolytic compounds primarily exert their effects through two key mechanisms: first, by activating apoptotic pathways to trigger cell death in senescent populations, and second, by compromising the survival mechanisms that allow these cells to resist apoptosis. One such compound, quercetin, has been shown to inhibit key pro-survival signaling molecules such as PI3K and PKB in senescent cells, thereby facilitating their clearance through

apoptosis[30]. Administration of dasatinib in combination with quercetin (D+Q) has demonstrated functional benefits in preclinical models of senescence. In mice subjected to hindlimb irradiation, this senolytic regimen led to sustained improvements in locomotor performance throughout the treatment window, indicating that pharmacological clearance of senescent cells can transiently alleviate aging-associated functional decline [32]. Another promising senolytic agent, ABT-263 (navitoclax), has been shown to induce apoptosis in WI-38 lung fibroblasts undergoing senescence due to ionizing radiation, replicative exhaustion, or oncogenic Ras activation. In addition to its pro-apoptotic effects, ABT-263 effectively downregulates several SASP-associated cytokines and chemokines, including IL-1α, TNF-α, CCL5, and CXCL10, further supporting its potential as a dual-action senescence-targeting therapeutic [33].

Integrative analyses of proteomic and transcriptomic datasets have identified the upregulation of one or more senescent cell anti-apoptotic pathways (SCAPs) in senescent cells. These pathways are believed to confer resistance to apoptosis, enabling the survival of senescent cells despite their secretion of tissue-damaging, pro-apoptotic SASP factors. Interestingly, similar SCAP mechanisms have also been observed in certain malignancies—such as B-cell lymphomas and chronic lymphocytic leukemia—where tumor cells evade apoptosis while contributing to tissue dysfunction. Importantly, transient disruption of SCAP activity has been shown to induce selective apoptosis in senescent cells with a deleterious SASP signature, while sparing non-senescent cells and senescent cells expressing non-destructive, pro-growth SASP profiles. This evidence suggest that SCAPs represent promising therapeutic targets for senolytic interventions aimed at minimizing collateral tissue damage [34,35].

Beyond their role in targeting senescent cells, senolytic agents have demonstrated broader systemic benefits. In aged mouse models, senolytic treatment has been associated with improved skeletal muscle performance, alleviation of anxiety-like behaviors, and a notable extension of lifespan. These findings highlight the therapeutic potential of senolytics not only in mitigating age-related tissue degeneration but also in enhancing overall physiological function and healthspan [29]. Moreover, early clinical investigations have indicated that senolytic therapy may offer therapeutic benefits in age-associated human diseases. Preliminary evidence suggests improvements in conditions such as osteoarthritis and Down syndrome, highlighting the translational promise of senolytics beyond preclinical models and underscoring their potential in managing diverse aging-related pathologies [36–38].

4.3. Senomorphics

In parallel with senolytics, senomorphics have emerged as a novel class of anti-aging agents that offer an alternative therapeutic approach. Unlike senolytics, that function by selectively eliminating senescent cells, senomorphics act by modulating the senescence-associated secretory phenotype (SASP), suppressing the production and secretion of pro-inflammatory and tissue-damaging factors while preserving cell viability. Rather than inducing apoptosis, senomorphics aim to attenuate the deleterious effects of senescent cells and stabilize their phenotype, thus slowing or potentially reversing aspects of cellular aging without triggering cell death [39,40].

A novel dihydroxy derivative of ligustrazine, tetramethylpyrazine (TMP), has recently been identified as a promising anti-aging compound. Preclinical studies have shown that TMP inhibits NF-κB signaling, enhances the viability of bone marrow–derived mesenchymal stem cells (BM-MSCs), and significantly delays age-associated decline in rodent models [41]. Supporting the therapeutic relevance of senescence-targeted approaches, Farr et al. emphasized that targeting cellular senescence offers a robust means of extending healthspan—defined as the disease-free period of life. Complementing this perspective, Lim et al. identified avenanthramide C (Avn C), a bioactive compound derived from oats, as a novel senomorphic agent. Avn C was shown to suppress NF-κB activity, reduce the secretion of inflammatory cytokines, and restore mitogen signaling pathways impaired by SASP-mediated autocrine feedback, further validating its role as a SASP modulator with anti-senescent potential [42–44]. Although research on the application of senomorphics in specific age-related diseases remains limited, several naturally derived compounds have shown promising senomorphic activity. For example, apigenin and kaempferol—two well-characterized flavonoids—have been demonstrated to attenuate SASP expression in senescent cells. Additionally, other phytochemicals such as luteolin, nobiletin, tangeretin, genistein, and wogonin have exhibited comparable capabilities in modulating senescence-associated inflammatory signaling, highlighting their potential as senomorphic candidates for future therapeutic development [45,46]. To date, research has largely concentrated on either eliminating senescent cells or harnessing their biological features as therapeutic targets for age-associated diseases. Nevertheless, the molecular underpinnings and signaling networks that govern these processes remain incompletely understood. Further investigation is needed to validate the roles of many candidate molecules and to elucidate the precise mechanisms by which they contribute to senescence-related pathophysiology.

4.4. Stem Cell–Based Therapy

Stem cells possess remarkable plasticity, enabling their differentiation into a wide variety of specialized cell types, which positions them as a promising therapeutic avenue for mitigating age-associated degeneration. Accumulating evidence suggests that stem cells can facilitate tissue repair, attenuate chronic inflammation, and enhance cellular functionality—key processes that may help counteract the manifestations of aging. In addition to their regenerative properties, stem cells exhibit robust immunomodulatory capabilities that may contribute to improved systemic health and resilience in aged individuals. Among them, mesenchymal stem cells (MSCs) have garnered particular attention for their dual roles in promoting tissue regeneration and suppressing pro-inflammatory signaling. By restoring immune homeostasis and limiting inflammaging, MSC-based therapies hold considerable promise as an anti-aging strategy. Notably, MSC treatments have already undergone phase I and II clinical trials in human subjects, where they have demonstrated both safety and therapeutic efficacy, further supporting their translational potential in age-related interventions [47].

5. Future Perspectives

Cellular senescence can occur throughout the lifespan and,

when persistent, may lead to tissue dysfunction due to the secretion of numerous abnormal proteins. In preclinical models, targeting long-lived senescent cells that contribute to tissue damage has been shown to delay, prevent, or alleviate a range of chronic diseases. Nevertheless, the underlying mechanisms of senescence remain highly complex, and many aspects are yet to be fully elucidated. In recent years, increasing attention has been paid to the role of nucleus pulposus cell senescence in intervertebral disc degeneration, given its strong association with degenerative spinal disorders such as degenerative disc disease and lumbar disc herniation. As population aging accelerates, the prevalence of these conditions is rising, underscoring the urgency of exploring both the mechanistic basis and therapeutic strategies targeting NP cell senescence.

Current studies suggest that NP cell senescence is closely linked to oxidative stress, impaired autophagy, and chronic inflammation. Strategies aimed at mitigating oxidative damage, enhancing autophagic activity, and controlling inflammatory responses have shown potential for slowing the senescence of disc cells and offer novel avenues for treating IVDD. In addition, emerging therapeutic approaches such as stem cell transplantation, gene editing, and the development of novel small-molecule agents represent promising directions for combating disc cell senescence, potentially leading to more effective and safer treatment options for patients suffering from degenerative disc disorders.

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