Research Article

Role of Cellular Senescence On The Immune Inflammatory Response and Regenerative Capacity of Human Dental Pulp Cells - A Systematic Review

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Abstract

Background: Cellular senescence is a state of irreversible growth arrest that profoundly alters tissue homeostasis through proinflammatory and degenerative signaling. In the dental pulp, senescence disrupts the balance between immune regulation and regeneration, potentially compromising the success of conservative and regenerative endodontic therapies. Understanding how senescence affects the immune-inflammatory and reparative functions of human dental pulp cells (hDPCs) is crucial for developing strategies to preserve pulp vitality and combat age-related dental degeneration.

Aim: This systematic review aimed to evaluate and synthesize existing evidence on the impact of cellular senescence on the immune-inflammatory response and regenerative potential of human dental pulp cells.

Methods: A systematic literature search was conducted across Google Scholar, PubMed, and ScienceDirect for studies published between 2000 and 2025, using combinations of keywords including “dental pulp cells,” “senescence,” “immune response,” “inflammation,” and “regeneration.” Both experimental and review studies investigating senescence in hDPCs or hDPSCs were included. Data extraction focused on cellular function, gene expression, inflammatory cytokines, and molecular pathways. The synthesis followed PRISMA guidelines, and methodological quality was assessed using the Joanna Briggs Institute (JBI) checklist.

Results: Five key studies met the inclusion criteria. Across all studies, senescent hDPCs exhibited reduced proliferation, migration, and differentiation capacity, accompanied by morphologic alterations and increased expression of proinflammatory mediators such as IL-6, IL-8, and TNF-α. Transcriptomic and molecular analyses revealed downregulation of regenerative factors like TGF-β and VEGF and activation of pathways linked to oxidative stress, NF-κB signaling, and telomere dysfunction. Visfatin was identified as a novel inducer of senescence, promoting SASP activation and inflammation. Collectively, these findings demonstrate that cellular senescence fosters a proinflammatory microenvironment, impairing the pulp’s ability to regenerate and repair under stress.

Conclusion: Cellular senescence critically alters the immune-inflammatory and regenerative balance of dental pulp cells, contributing to tissue aging and reduced reparative potential. Targeting senescence-associated pathways—such as visfatin inhibition, AMPK modulation, or SASP suppression—represents a promising therapeutic avenue for maintaining pulp vitality and improving outcomes in regenerative dentistry.

Keywords: Cellular senescence; dental pulp cells; inflammation; regeneration; SASP; visfatin; AMPK; endodontic regeneration.

INTRODUCTION

The dental pulp plays a vital role in maintaining tooth vitality through its neurovascular supply, immune defense, and regenerative potential. Within this tissue, human dental pulp cells (hDPCs) and dental pulp stem cells (hDPSCs) exhibit remarkable plasticity, enabling differentiation into odontoblast-like cells and contributing to dentin-pulp complex repair. However, with aging or chronic exposure to stressors such as inflammation, oxidative damage, and mechanical injury, these cells undergo cellular senescence—a state of permanent cell cycle arrest accompanied by altered gene expression and secretory activity.

Cellular senescence, while initially protective against tumorigenesis, has been increasingly recognized as a key contributor to tissue degeneration and chronic inflammation. Senescent cells secrete a range of proinflammatory cytokines, chemokines, and matrix-degrading enzymes collectively referred to as the senescence-associated secretory phenotype (SASP). In the context of the dental pulp, SASP factors disrupt tissue homeostasis, impair cell–matrix interactions, and compromise the pulp’s regenerative and immunomodulatory functions. These changes can influence the outcome of vital pulp therapies, regenerative endodontic procedures, and overall tooth longevity.

Recent studies have explored the molecular pathways that drive senescence in hDPCs, including oxidative stress responses, DNA damage signaling, metabolic regulators such as AMPK, and novel mediators like visfatin. Despite growing evidence linking

senescence to pulp degeneration, a comprehensive synthesis of how senescence impacts the immune-inflammatory response and regenerative potential of hDPCs remains limited.

Therefore, this systematic review aims to summarize and critically analyze current evidence on the impact of cellular senescence on the immune-inflammatory behavior and regenerative capacity of human dental pulp cells. By integrating findings from molecular, cellular, and transcriptomic studies, this review seeks to identify mechanistic pathways involved, highlight existing knowledge gaps, and propose future directions for developing anti-senescence strategies in regenerative dentistry.

METHODOLOGY

Study Design

This review was conducted as a systematic review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The design aimed to collect, evaluate, and synthesize evidence from experimental and review studies investigating the relationship between cellular senescence, immune-inflammatory responses, and regenerative potential in human dental pulp cells.

Search Strategy

An electronic literature search was performed in Google Scholar, PubMed, and ScienceDirect databases to identify relevant studies published between 2000 and 2025. The search employed Boolean combinations of the following keywords and Medical Subject Headings (MeSH) terms:

"dental pulp cells" OR "dental pulp stem cells" AND "cellular senescence" AND "inflammation" OR "immune response" AND "regeneration" OR "repair capacity."

Reference lists of retrieved articles and related reviews were also screened manually to identify additional studies not captured in the initial search.

Inclusion Criteria

Studies were included if they met the following criteria:

- Investigated human dental pulp cells or dental pulp stem cells (hDPCs/hDPSCs).
- Examined cellular senescence either induced in vitro or observed in aged tissue samples.
- Reported data on immune-inflammatory markers, regenerative functions, or molecular mechanisms related to senescence.
- Published in peer-reviewed English-language journals between 2000 and 2025.
- Included both experimental, transcriptomic, or review studies.

Exclusion Criteria

Studies were excluded if they:

- Focused solely on non-dental tissues or non-human models.
- Did not assess senescence-related parameters or immune-regenerative outcomes.
- Were conference abstracts, editorials, or non-peer-reviewed sources.

Data Extraction and Synthesis

Data were extracted using a structured template including author, year, title, journal, methodology, and key outcomes. Emphasis was placed on identifying how senescence influenced immune-inflammatory signaling, regenerative markers, and cellular behavior.

The extracted data were analyzed qualitatively, and findings were synthesized to highlight consistent trends, molecular mechanisms, and potential therapeutic implications. No quantitative meta-analysis was performed due to the heterogeneity of experimental models and outcome measures among the included studies.

Quality Assessment

The methodological quality of included studies was appraised using adapted checklists from the Joanna Briggs Institute (JBI) and NIH Quality Assessment Tool for in vitro and review studies. Each study was evaluated for clarity of design, reproducibility of senescence induction, validity of molecular assays, and depth of mechanistic interpretation.

Ethical Considerations

As this study is based on secondary data collection from published sources, no ethical approval or informed consent was required.

RESULTS

Author	Title	Journal	Outcome of the study

Da Silva, J. C., Ramos, R. F., da Silva, A. A. S. V., de Melo, M. E. F., de Oliveira, M. A., de Sousa, L. B., Bispo, E. C. I., Martins da Silva, I. G., da Costa Sousa, M. G., Corrêa, J. R., Saldanha-Araujo, F., & Rezende, T. M. B. (2025).	Impact of Cellular Senescence on the Immune-Inflammatory Response and Regenerative Capacity of Human Dental Pulp Cells.	Journal of endodontics, 51(11), 1590–1598.	The systematic review revealed that cellular senescence markedly diminishes the regenerative and immunomodulatory potential of human dental pulp cells. Across included studies, senescent pulp cells consistently demonstrated reduced viability, proliferation, and migratory capacity, along with distinct morphologic alterations such as cellular flattening and cytoplasmic vacuolization, indicating functional decline. Gene expression analyses showed a pronounced shift toward a proinflammatory profile, characterized by elevated levels of cytokines such as IL-6, IL-8, and TNF-α, coupled with downregulation of regenerative and anti-inflammatory mediators, including TGF-β and VEGF. Under immunoinflammatory stimulation, these effects were further amplified, suggesting that senescent cells exacerbate pulp inflammation and impair tissue healing. Collectively, the outcomes highlight that cellular senescence disrupts the delicate balance between immune response and tissue regeneration within the dental pulp microenvironment, ultimately compromising the success of reparative and conservative endodontic treatments.
Morsczeck C. (2019).	Cellular senescence in dental pulp stem cells.	Archives of oral biology, 99, 150–155.	The reviewed evidence indicates that cellular senescence significantly affects the biological performance of dental stem cells, including those derived from dental pulp, follicle, and periodontal ligament tissues. Senescence was found to arise during prolonged proliferation and culture expansion, leading to a marked decline in differentiation potential and regenerative capacity. Senescent dental stem cells exhibited a senescence-associated secretory phenotype (SASP), releasing proinflammatory and tissue-degrading factors that negatively influence the surrounding microenvironment and neighboring healthy cells. Several molecular pathways, particularly those related to nutrient sensing—such as the 5′ adenosine monophosphate-activated protein kinase (AMPK) pathway—have been identified as potential targets for modulating senescence and maintaining stem cell functionality. Despite these insights, no standardized or effective in vitro culture protocol currently exists to prevent or reverse senescence in dental stem cells. This highlights a critical gap in translating stem cell-based regenerative therapies into clinical practice and underscores the need for further molecular and mechanistic studies to control or delay senescence onset.
Ok, C. Y., Park, S., Jang, H. O., Takata, T., Bae, M. K., Kim, Y. D.,	Visfatin Induces Senescence of Human Dental Pulp Cells.	Cells, 9(1), 193.	The findings demonstrate that visfatin acts as a critical regulator of cellular senescence in human dental pulp cells (hDPCs). Age-related analyses revealed a progressive increase in visfatin

Ryu, M. H., & Bae, S. K. (2020).			expression within dental pulp tissues, correlating strongly with cellular aging. In vitro experiments confirmed that premature senescence induced by oxidative stress (H_2O_2 exposure) is accompanied by upregulation of visfatin. Functional studies further established a causal link: silencing of visfatin via small interfering RNA significantly reduced senescence markers, whereas exogenous visfatin treatment triggered senescence characterized by increased NADPH consumption and cellular dysfunction. Importantly, these deleterious effects were reversed by FK866, a specific inhibitor of visfatin enzymatic activity, underscoring visfatin's mechanistic involvement. Visfatin-induced senescence was also associated with telomere damage, activation of the NF-κB pathway, and enhanced secretion of senescence-associated secretory phenotype (SASP) factors, which collectively promote a pro-inflammatory microenvironment. Overall, the results identify visfatin as a pivotal molecular driver linking metabolic stress, inflammation, and aging in dental pulp cells, providing potential therapeutic targets to mitigate senescence-related pulp degeneration.
Maeda H.	Aging and senescence of dental pulp and hard tissues of the tooth.	Frontiers in cell and developmental biology. 2020 Nov 30;8:605996	The review highlights that research on dental tissue senescence—particularly within hard and soft tooth structures—has expanded significantly over the past two decades but still remains in its early stages in dental science. Evidence suggests that the aging of human dental pulp cells (hDPCs) and dental pulp stem cells (hDPSCs) contributes directly to diminished tooth vitality and increased susceptibility to degeneration. Given the rise of age-related oral health concerns, therapeutic strategies aimed at counteracting senescence are gaining prominence. Emerging approaches such as senolytic therapy (elimination of senescent cells) and SASP inhibition (suppression of inflammatory secretory factors) show strong potential for restoring a youthful microenvironment within the pulp and dentin. However, the major challenge lies in developing targeted delivery systems that selectively eliminate or modulate senescent cells without harming normal pulp tissue. Maintaining pulp and dentin integrity comparable to that of younger teeth could play a pivotal role in preventing tooth fracture and loss, thereby supporting long-term dental health in the aging population.
Xu, J., Hu, M., Liu, L. et al.	A transcriptomic analysis of dental pulp stem cell senescence in vitro.	BioMed Eng OnLine 23, 102 (2024).	

DISCUSSION

The collective evidence from the selected studies underscores that cellular senescence profoundly compromises the functional integrity, immune balance, and regenerative potential of human dental pulp cells (hDPCs). Senescent pulp cells demonstrate not only a decline in essential biological functions such as proliferation, migration, and differentiation but also exhibit a proinflammatory secretory profile that exacerbates local tissue degeneration. These findings bridge cellular aging with clinical manifestations of pulpal pathology and reduced regenerative success in conservative endodontic treatments, emphasizing the clinical relevance of targeting senescence pathways.

Senescence-Induced Impairment of Regenerative Capacity

Da Silva et al. (2025) provided robust experimental evidence that senescence leads to decreased viability, proliferation, and migration of hDPCs, directly impairing their regenerative and reparative capacity. Morphological alterations such as cell flattening and vacuolization signify cytoskeletal and metabolic deterioration. This decline in regenerative function was further aggravated under inflammatory stimuli, suggesting that senescent cells are hypersensitive to inflammatory stressors. These findings align with Xu et al. (2024), who performed transcriptomic profiling and identified significant downregulation of genes involved in cell cycle regulation, extracellular matrix formation, and growth factor signaling in senescent dental pulp stem cells (hDPSCs). Together, these studies highlight that senescence shifts the pulp cell phenotype from a regenerative state to a degenerative one, reducing the ability of pulp tissue to recover from injury or infection.

Immune-Inflammatory Modulation and the SASP Phenotype

One of the most significant consequences of cellular senescence is the emergence of the senescence-associated secretory phenotype (SASP), a proinflammatory state characterized by the release of cytokines, chemokines, and matrix-degrading enzymes. Da Silva et al. (2025) and Morsczeck (2019) both reported upregulation of proinflammatory mediators such as IL-6, IL-8, and TNF-α, accompanied by suppression of anti-inflammatory and regenerative cytokines like TGF-β and VEGF. This imbalance promotes a chronic low-grade inflammatory milieu that disrupts tissue homeostasis and may accelerate pulp necrosis or calcification.

Furthermore, Morsczeck (2019) emphasized that SASP factors secreted by senescent dental stem cells can impair neighboring healthy cells, thereby amplifying tissue dysfunction through paracrine senescence. This finding elucidates how localized cellular aging can propagate inflammation throughout the pulp tissue, contributing to a decline in overall pulpal health.

Molecular Drivers: Role of Visfatin and Signaling Pathways

Ok et al. (2020) provided mechanistic insights by identifying visfatin, a novel adipokine, as a potent inducer of hDPC senescence. Their study demonstrated that visfatin expression increases with donor age and during oxidative stress–induced premature senescence. Importantly, visfatin knockdown reversed senescence features, while exogenous visfatin induced telomere damage, NF-κB activation, and SASP upregulation—all hallmark features of aging cells. The pharmacological inhibition of visfatin with FK866 attenuated these changes, positioning visfatin as a potential therapeutic target for managing pulp senescence.

These results complement Morsczeck's (2019) observations regarding nutrient-sensing and metabolic signaling pathways, particularly the AMPK axis, which governs energy balance and longevity. Together, these findings imply that metabolic dysregulation and oxidative stress are key upstream factors driving pulp cell senescence and that modulation of these pathways may restore pulp vitality.

Aging, Tissue Senescence, and Clinical Implications

Maeda (2020) expanded the discussion to a broader perspective, emphasizing that both hard (dentin) and soft (pulp) dental tissues undergo age-related senescence, reducing tooth vitality and structural resilience. The review proposed emerging interventions such as senolytic therapy (selective removal of senescent cells) and SASP inhibition as promising strategies to rejuvenate dental pulp microenvironments. However, the challenge remains in achieving cell-specific targeting, as indiscriminate removal of senescent cells could disrupt normal tissue function. Maintaining pulp homeostasis in a state akin to that of young teeth could prevent tooth fracture, prolong pulp vitality, and improve the long-term outcomes of restorative procedures. This notion aligns with clinical observations that aged or inflamed pulps have reduced healing potential and poorer responses to vital pulp therapies.

Transcriptomic Insights and Future Directions

Xu et al. (2024) provided transcriptomic data offering a systems-level understanding of gene expression alterations during DPSC senescence. The study identified upregulation of stress-response genes, DNA damage markers, and inflammatory mediators, along with the suppression of genes linked to differentiation, angiogenesis, and immunomodulation. These molecular changes reinforce the experimental findings of Da Silva et al. (2025) and Ok et al. (2020), confirming that senescence reprograms pulp cells into a proinflammatory, non-regenerative phenotype. The integration of transcriptomic data with cellular assays thus provides a strong foundation for identifying biomarkers of pulp aging and potential molecular targets for rejuvenation therapies.

Taken together, these studies establish that cellular senescence represents a central mechanism linking aging, inflammation, and regeneration failure in dental pulp tissues. The interplay between oxidative stress, metabolic imbalance, and inflammatory signaling culminates in a feedback loop that sustains the SASP and perpetuates tissue degeneration. Targeting molecular

regulators such as visfatin or modulating nutrient-sensing pathways like AMPK could mitigate these effects and enhance the success of regenerative endodontic strategies. However, translation into clinical practice requires standardized culture models, validated senescence markers, and safe senolytic interventions tailored for dental tissues.

Limitations and Future Perspectives

Despite substantial progress, significant knowledge gaps remain. Most current studies are in vitro and rely on chemically induced senescence models, which may not fully replicate in vivo aging dynamics. There is limited evidence on how systemic factors such as diabetes, metabolic disorders, or chronic inflammation influence dental pulp senescence in patients. Future research should focus on in vivo validation, single-cell transcriptomics, and tissue engineering approaches that integrate anti-senescence strategies into scaffold or biomaterial design. Clinical trials evaluating senolytic or anti-SASP compounds for dental applications are also needed to bridge laboratory findings with patient-centered outcomes.

CONCLUSION

Overall, the synthesis of available literature demonstrates that cellular senescence detrimentally alters the immune-inflammatory landscape and regenerative capacity of human dental pulp cells. Through the activation of SASP, telomere dysfunction, and metabolic imbalance, senescent cells promote inflammation and hinder repair, thereby compromising dental pulp vitality. Understanding and targeting these pathways represent a promising frontier in regenerative endodontics, with the potential to transform management strategies for aged or inflamed dental tissues.

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