

# Cellular Senescence in Orthodontic Tooth Movement: Biological Mechanisms, Clinical Implications and Future Perspectives

*Running Title: Cellular Senescence in Orthodontic Tooth Movement*

**Dr. Shivaprasad Gaonkar<sup>1</sup>, Dr. Anadha N. Gujar<sup>1\*</sup>, Dr. Hemanth M<sup>1</sup>, Dr. Kavya B R<sup>1</sup>, Dr. Manju Prasad M<sup>2</sup>, Dr. Naveen Kumar Krishna<sup>2</sup>**

<sup>1</sup>Department of Orthodontics, Dayananda Sagar College of Dental Sciences, Shavige Malleshwara Hills, Kumaraswamy Layout, Bangalore - 560111, Karnataka, India

<sup>2</sup>Department of Orthodontics, KGF College of Dental Sciences, Bangalore, Karnataka, India

<sup>1</sup>Reader (Dr. Shivaprasad Gaonkar) | ORCID: <https://orcid.org/0000-0001-5712-1928>

<sup>1\*</sup>Professor (Dr. Anadha N. Gujar) | ORCID: <https://orcid.org/0000-0003-0592-0941>

<sup>1</sup>Principal and Head (Dr. Hemanth M) | ORCID: <https://orcid.org/0000-0001-9447-487X>

<sup>1</sup>Senior Lecturer (Dr. Kavya B R) | ORCID: <https://orcid.org/0009-0008-4819-6335>

<sup>2</sup>Reader (Dr. Manju Prasad M)

<sup>2</sup>Principal and HOD (Dr. Naveen Kumar Krishna)

**\*Corresponding Author:** Dr. Anadha N. Gujar, Professor, Department of Orthodontics, Dayananda Sagar College of Dental Sciences, Shavige Malleshwara Hills, Kumaraswamy Layout, Bangalore - 560111, Karnataka, India | ORCID: <https://orcid.org/0000-0003-0592-0941> |

## Abstract

Aging, inflammation, and tissue remodeling are all impacted by cellular senescence, a biological process marked by irreversible cell-cycle halt and the emergence of a senescence-associated secretory phenotype (SASP). Senescence may have an impact on the results of orthodontic tooth movement (OTM) and plays a major role in oral health, according to mounting research. With a focus on periodontal ligament remodeling, alveolar bone metabolism, and tissue responses to mechanical pressures, this review investigates the molecular mechanisms connecting cellular senescence to orthodontic treatment. Pro-inflammatory cytokines, chemokines, matrix-degrading enzymes, and extracellular vesicles are released by senescent cells, which together change the local microenvironment and upset the equilibrium between bone formation and resorption.

Slower tooth movement, longer treatment times, poor tissue regeneration, and heightened vulnerability to negative consequences including root resorption and periodontal problems can all be caused by the age-related buildup of senescent cells in periodontal tissues. Additionally, recent research shows how aging affects osteoblast, osteoclast, and osteocyte function, which in turn affects orthodontic biomechanics and treatment prediction. Promising prospects for enhancing treatment results and creating individualized orthodontic treatments are presented by new research on senescence biomarkers and senotherapeutic techniques, such as senolytic and senomorphic drugs. Clinical orthodontics may be better equipped to incorporate biologically informed treatment planning if the molecular mechanisms behind cellular senescence are well understood. To elucidate the direct connection between senescence and OTM and to convert these discoveries into successful treatment therapies, more research is required.

**Keywords:** Cellular Senescence; Molecular mechanisms; Orthodontic tooth movement; Senescence-associated secretory phenotype.

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## Introduction

Understanding the molecular processes behind age-related pathology and developing successful treatment approaches has grown more crucial as the number of elderly people increased. Among these mechanisms, cellular senescence has been identified as a major factor in both oral health and disease as well as systemic aging and chronic illness.<sup>1</sup> Cellular senescence's clinical significance in oral health is becoming more apparent, highlighting the

need for a greater comprehension of its causes, mechanisms, and treatment implications.<sup>1,2</sup>

Cells are subjected to a variety of physiological and environmental stresses that compromise their integrity as the body matures. Cells use a number of defense mechanisms to stop carcinogenesis and maintain tissue function in response to such damage. Cellular senescence, which derives from the Latin senex, which means "old," is one such mechanism. It is characterized by a

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permanent stoppage of the cell cycle in which cell division stops.<sup>2</sup>

The permanent loss of a cell's capacity to divide and proliferate, together with specific morphological and functional changes, is known as cellular senescence. The slow buildup of damage to cellular components like DNA, proteins, and organelles characterizes this state, which develops naturally as a result of aging. Replicative senescence is the process by which aging cells undergo a series of changes that eventually prevent them from proliferating.<sup>3</sup>

The senescence-associated secretory phenotype (SASP) is a unique phenotype that frequently coexists with cellular senescence.<sup>4</sup> Additionally, there is growing recognition of the impact of cellular senescence on the results of orthodontic treatment. Cellular senescence, which causes periodontal tissue cells to age, can have an impact on the durability and efficacy of orthodontic treatments.<sup>5</sup>

To address the particular difficulties posed by cellular senescence, it is essential to understand these mechanisms to develop more effective and individualized orthodontic treatment options.<sup>3</sup> Senescent cell buildup in periodontal tissues might hinder remodeling and jeopardize therapy results. A study looks at how periodontal tissue cells are affected by aging, where one turnover and reactivity to orthodontic stresses are impacted by senescent cells' decreased proliferative capability and changed secretory patterns.<sup>6</sup>

Recent research examined how human-derived periodontal ligament cells age both before and after orthodontic force application.<sup>7,8</sup> The direct connection between cellular senescence and orthodontic tooth movement has not yet been the subject of any research.<sup>3</sup>

With regard to orthodontics, this review seeks to provide insight on the idea of cellular senescence. It explores the function of senescent cells in bone remodeling, tissue response to orthodontic stresses, and age-related differences in treatment outcomes by analyzing the existing data. Additionally, the article describes possible future uses of senescence research in customized orthodontic treatment.

## ***SASP- Mediated Cellular Responses to Orthodontic Forces***

SASP is the most well-known indicator of senescence and a significant cause of numerous age-related illnesses. A complex mixture of pro-inflammatory cytokines (e.g., IL-1 $\alpha$ , IL-6, TNF- $\alpha$ ), chemokines (CXCLs and CCLs), matrix-modifying enzymes (e.g., MMPs), ROS, and extracellular vesicles, including exosomes, are released when cells enter a hypersecretory state during senescence.<sup>9-11</sup> The

production of exosomes, a crucial mechanism for intercellular communication, is noticeably elevated in senescent cells. The effects of the SASP are amplified by these exosomes because they contain proteins, nucleic acids, and microRNAs that can spread senescence signals, alter the tissue microenvironment, and affect immunological responses.<sup>12-14</sup>

Mechanical forces can influence senescence in orthodontics in a context-dependent way. For example, human periodontal ligament [PDL] cells exposed to orthodontic treatment exhibit decreased SA- $\beta$ -Gal activity and increased  $\alpha$ -klotho expression, while excessive mechanical stress causes senescence in PDL cells and cementoblasts, which contributes to root resorption.<sup>15,16</sup> These results show how difficult it can be to manage senescence in patients who need a lot of orthodontic movement or in older people who have greater baseline levels of senescent cell accumulation.<sup>1</sup>

Senescence among the osteoblast, osteoclast, and osteocyte lineages in the alveolar bone causes dysregulated bone remodeling, which is a characteristic of both aging and periodontitis. By inhibiting osteogenesis and increasing osteoclast activity, senescent osteocytes and osteoblasts worsen bone homeostasis and hasten age-related bone loss. Cumulative stresses decrease osteogenic potential and increase bone resorption susceptibility as people age.<sup>17-19</sup>

The buildup of senescent osteocytes and prolonged exposure to bacterial products like lipopolysaccharide (LPS) cause a pro-inflammatory SASP characterized by IL-6, IL-8, IL-1 $\beta$ , TNF- $\alpha$ , and other proteases, which exacerbates the severity of periodontal disease.<sup>19</sup>

Chronic periodontal inflammation is caused by SASP factors and matrix-degrading enzymes from senescent cells that disturb the surrounding milieu, encourage dysbiosis, and spread senescence to nearby cells. As a result, osteoblastic and osteoclastic activities become more unbalanced with age, and mesenchymal progenitor cells' immunomodulatory, migratory, and differentiation capacities decrease, all of which contribute to increased alveolar bone loss.<sup>20,21</sup>

## ***Hallmarks of Cellular Senescence***

Recent research, however, has broadened this perspective by detecting a wider range of morphological alterations across several cellular compartments, which are generally referred to as senescence-associated morphological phenotypes (SAMPs).<sup>22</sup> Senescent osteoblasts and osteoclasts may be less able to sustain the dynamic equilibrium between bone creation and resorption, increasing the likelihood of unfavorable side effects.

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Senescent cells exhibit a variety of molecular characteristics associated with gene expression and genomic integrity in addition to their distinctive morphological alterations. A crucial decision point that establishes whether a cell will experience apoptosis, enter senescence, or repair the damage and restore normal function is the activation of the DNA damage response.<sup>24,25</sup>

A variety of biological characteristics, such as distinctive morphological changes, set senescent cells apart from proliferative cells. Senescent cells have historically been described as being flattened and swollen.<sup>26,27</sup>

DNA damage, shortened telomeres, high mitogenic signals, irreversible proliferation arrest, and elevated ROS both in vitro and in vivo specifically, stress-induced premature senescence caused by a variety of stressors, including mechanical, oxidative, radiation, and genotoxic agents, is mostly dependent on DNA damage.<sup>28-31</sup>

Because these cells are unable to recycle their DNA, the accumulation of senescent cells contributes to the reduction of the self-renewal and regeneration process of the lost tissues. Additionally, they can't make the typical kinds of proteins needed to rebuild the tissues.<sup>32</sup> DNA damage increases the release of senescence, apoptosis, and pro-inflammatory cytokines.<sup>33,34</sup>

Adverse orthodontic root resorption and overexpression of caspase 3 and caspase 8, which were brought on by strong or ideal orthodontic force, are linked to high levels of cementocyte/ cementoblast apoptosis.<sup>35,36</sup> Telomere degradation may result from persistently high amounts of reactive oxygen species.<sup>37,38</sup> Telomere shortening may trigger a DNA damage response (DDR) that triggers cell cycle progression inhibitors, ultimately leading to senescence growth arrest.<sup>38</sup>

## ***Age- Related Cellular Senescence and Orthodontic Tooth Movement (OTM)***

This process, which is essentially a localized aseptic inflammatory response in the alveolar bone and periodontal ligament (PDL), is mediated by mechanical stresses and causes the bone modeling and remodeling to take place. These age-related alterations of OTM may be caused by changes in the tooth, surrounding periodontium, and alveolar bone.<sup>39</sup>

Reduced rate of OTM is correlated with the PDL's declining physiological response and rebuilding capacity with age. From 6 Additionally, adult human PDLs (hPDLs) showed reduced  $\alpha$ -Klotho expression and accelerated senescence with enhanced beta-galactosidase activity.<sup>40</sup> Senescence-associated beta-galactosidase (SA- $\beta$ -GAL), whose activity dramatically increases in senescent cells, is a widely

used biomarker to identify and measure the aging status of cells.<sup>39</sup>

Age-related changes in PDL remodeling and bone turnover capacities slow down the rate of OTM and have an impact on orthodontic side effects such as root resorption and orthodontic pain. Age-related changes during the orthodontic process are influenced by cellular state, cytokine expression, and tissue structural alterations. The current body of research on age-related changes in orthodontics is extremely diverse and primarily focuses on phenotypic changes; the underlying mechanisms are still poorly understood.

An essential regulator of tissue homeostasis, aging, and bone remodeling is cellular senescence, a state of irreversible cell-cycle arrest accompanied by prolonged metabolic activity and the release of pro-inflammatory mediators. When mechanical pressures are applied in orthodontics, the periodontal ligament and alveolar bone undergo a series of cellular and molecular reactions that create a microenvironment where senescent cells may have an impact on both physiological and pathological remodeling processes. These cells influence inflammatory signaling, osteoclast and osteoblast activity, and extracellular matrix turnover through the SASP. This may have an impact on the rate of orthodontic tooth movement, treatment duration, periodontal health, and susceptibility to unfavorable outcomes like root resorption.

## ***Clinical Implications of Cellular Senescence in Orthodontic Tooth Movement***

The advent of surgically assisted orthodontic treatments, such as corticotomy-facilitated orthodontics, which aims to speed up tooth movement and shorten treatment times, has contributed to advancements in orthodontic treatment.<sup>41</sup> However, further research is still needed to determine how cellular senescence affects the effectiveness and durability of these methods.

Reduced proliferative ability and changed secretory profiles are characteristics of senescent cells that affect bone remodeling and tissue regeneration, which are essential for orthodontic tooth movement.<sup>5,40</sup> Older individuals may experience slower and less consistent tooth movements as a result.<sup>5,40</sup>

Reduced reactivity to orthodontic forces and poor bone turnover are caused by senescent cells.<sup>42</sup> By interfering with the delicate balance of bone formation and resorption required for optimal tooth movement, the buildup of senescent cells in periodontal tissues can jeopardize treatment results.<sup>43</sup>

The risk of problems such as root resorption, dental caries, and gingival recession increases with longer treatment durations, which are frequently

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required due to slower remodeling in the presence of senescent cells. Senescent cells' reduced ability to regenerate could make these problems worse.<sup>43,44</sup>

According to studies, cellular senescence can affect the degree of periodontal disease, the rate at which tissue remodeling occurs, and how responsive periodontal cells are to orthodontic forces. All of these factors are crucial in determining the effectiveness and stability of orthodontic interventions.<sup>6,45</sup>

Clinically, orthodontic therapy in adults is frequently associated with longer treatment durations and increased periodontal risks compared to adolescents, which may impede the use of orthodontic treatment in adults.<sup>46</sup> This has to do with the process of maturity and aging. The cumulative effect of several molecular and cellular impairments at the microscopic level results in a time-dependent loss in function as the human body ages.<sup>40,43</sup>

The effects of cellular senescence highlight the necessity of individualized treatment plans, particularly for elderly individuals. When planning and carrying out orthodontic therapy, factors such as the patient's age, general health, and the degree of cellular senescence in periodontal tissues should be taken into account.<sup>43,47</sup>

Understanding the relationship between cellular senescence and orthodontic biomechanics has grown more important as the need for orthodontic treatment among adult and elderly populations continues to rise. In addition to highlighting new therapeutic approaches and potential avenues for incorporating senescence-related research into precision orthodontics, this review offers a thorough summary of the biological underpinnings of cellular senescence, its function in orthodontic tooth movement, and its clinical implications.

Research on cellular senescence's role in orthodontic tooth movement is still in its early stages and has a lot of promise for therapeutic use in the future. To fully understand how senescent cells affect alveolar bone metabolism, periodontal ligament remodeling, and orthodontic treatment outcomes, more research is needed. Finding trustworthy biomarkers linked to senescence may help predict treatment response, root resorption susceptibility, and age-related changes in tooth movement.

Furthermore, new methods to control senescent cell activity and promote tissue regeneration during orthodontic therapy may be made possible by developments in senotherapeutics, such as senolytic and senomorphic drugs. Personalized orthodontic treatments based on an individual's biological age and ability for regeneration may be made possible by the integration of cellular senescence research with genomics, biomarker-based diagnostics, and artificial intelligence-driven treatment planning. The field of

orthodontics could become more accurate, patient-specific, and biologically informed as our understanding of senescence develops.

## Conclusion

A crucial biological process that affects tissue remodeling, inflammation, and bone metabolism all of which are essential to orthodontic tooth movement is cellular senescence. Alveolar bone remodeling, periodontal ligament dynamics, and the general response to orthodontic stresses can all be greatly impacted by the buildup of senescent cells and the release of senescence-associated secretory phenotype proteins. Senescence may be a factor in age-related variations in periodontal health, treatment effectiveness, and vulnerability to negative consequences including root resorption, according to mounting data.

Even while experimental and translational research has contributed much to our present understanding of cellular senescence in orthodontics, its applicability to clinical practice is becoming more and more clear. The development of focused therapeutic tactics and individualized treatment approaches may be aided by a better knowledge of the molecular processes underlying senescence and how they interact with orthodontic biomechanics. Cellular senescence is expected to play a significant role in optimizing orthodontic outcomes and enhancing patient-centered care as research in this area progresses.

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