



## **Periodontitis: A Hastened and Destructive Inflammatory Induced Senescence**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Author LTY designed the study and wrote the review components. Authors LTY and FIB searched the literature and wrote the first draft the manuscript. Authors ANAAR and MIAH adjusted the manuscript. All authors read and approved the final manuscript.*

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### **ABSTRACT**

Periodontitis is a chronic inflammation of tooth supporting tissues (periodontal ligament, alveolar bone and gingiva). Due to the chronic and intensive inflammation, these tissues undergo accelerated cellular senescence (premature cells cycle arrest). This accelerated cellular senescence ends up with their degeneration and dramatic changes in the normal aesthetic and architecture of the bone and gingiva of the affected individual. This review will provide insights into the detrimental and inevitable effect of inflammatory cellular senescence during periodontal disease progression.

*Keywords: Periodontitis; inflammatory senescence; cell cycle arrest.*

### **1. INTRODUCTION**

Periodontal disease is an inflammatory disease that involves the supporting tissues of teeth and affects almost 90% of the population [1,2]. The

main aetiology for causing this disease is bacterial infection in the periodontal region and in mostly associated with a progressively destructive changes of the affected structures surrounding the tooth. In severe cases, extreme

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loss of bone and periodontal ligament supporting the teeth may eventually lead to the loss of these teeth [3,4].

Usually, cells undergone senescence due to aging, or in reaction cellular damage, toxic environments, or due to cell inability to replicate as it reaches the end of its life span [5]. Some of the senescent cells are eliminated by the immune system, but in certain circumstances, especially by late life, huge number of these cells would remain and linger that results in the accumulation a sizable proportion of senescent cells in the tissue [6]. In general, senescent cells would affect the tissue negatively by releasing molecules that interfere with the normal cellular activities, provoke chronic inflammation, and destroy the extracellular matrix that is essential to tissue properties such as elasticity or load-bearing strength [7]. Hence, comprehensive clearance and elimination of senescent cells should produce greater benefits to health as compared to partial or uneven removal of these cells [8].

Senescent cells must be cleared first and then be replaced by other cells that perform healing and regeneration [9]. Without new cells migrating into the inflamed or damaged scene, probably the healing process will not take place as usual [10]. Protecting or saving the cells from reaching senescence stage (before /during periodontal inflammation) would be a better solution because once these cells reach the senescence stage, they will not be, any more, part of the healed inflamed tissues. Furthermore, naturally establishing a new batch of cells with almost similar architecture to replace the senescent cells is a hard task especially for the exposed or inflamed periodontium with the unique environment of the oral cavity [11,12].

Rejuvenating or saving periodontal cells from senescence and preserving the normal steps of cells cycle; are crucial factors to prevent the destruction of the tooth supporting tissues. Hence, clinically, senescence can be used as a target to suppress or at least minimize the almost inevitable loss of supporting tissues.

## **2. INFLAMMATORY INDUCED SENESENCE**

It has been reported that gingival fibroblasts were incubated and treated with LPS *in vitro* for 24 and 48 h, to simulate inflammation and induce cellular senescence [13]. LPS result in the induction of ROS [14] which damage the

gingival fibroblast DNA. Furthermore, DNA damage potentiates the release of pro-inflammatory cytokines, apoptosis and senescence as a factor of p53 status [15]. The inflammatory cytokines are main factors in the initiation and maintenance of cellular senescence, and they are also responsible for initiating an innate immune response that eliminates the senescent cells *in vivo* [16].

It has been reported that fading senescent cells have the ability to produce and secrete various inflammatory cytokines, mediating chemokines and matrix remodelling molecules [7,17] that detrimentally affect tissue matrix homeostasis and elicit a chronic inflammation. Therefore, individuals especially elderly people are more prone to a number of autoimmune diseases and inflammatory diseases, including periodontitis [18,19].

In periodontitis, the cells of the periodontium are obviously degraded and cleared by phagocytes, subsequently this process results in the loss of attachment and alveolar bone. Recent studies have shown that senescent myofibroblasts were limiting the extent of fibrogenesis associated with wound healing during tissue repair [20].

Phagocytic cells activity has an important role in subsiding the inflammation through engulfing and eliminating the apoptotic cells, which subsequently reduce the exposure of tissues to the harmful effect of the inflammatory and immunogenic contents of fading cells [21].

Clearance of the senescent cells is a crucial step to maintain the function and restore the normal un-damaged condition of the tissue. Therefore, tissue dysfunction can be expected in chronic pathological conditions as the senescent cells are not effectively eliminated, leading to their accumulation in the tissue [22], a condition which would further aggravate the inflammation and debilitate the normal surrounding cells [23]. It has been concluded that the double-edged sword of senescence is similar to that of inflammation; hence, senescence is beneficial when it is temporary and effectively cleared but pathological if it is chronically lasting and un-cleared [24]. These expressions and complexities of senescence would require further investigations to determine the therapeutic pathway, either by increasing or blocking senescence, depending on the context [9,25]. In periodontitis, chronic inflammation causes un-replaceable loss of the damaged periodontium.

Hence, blocking of senescence would be one of the important targets in the periodontal therapy [26].

### **3. INFLAMMATORY SENESCENCE AND DNA DAMAGE RESPONSE RELATIONSHIP**

More than half a century ago, Hayflick and Moorhead concluded that cultured primary human cells have a restricted replication capacity [27]. It has been demonstrated that after repeated cell divisions, these cells moved into a permanent cell cycle arrest condition, which is termed replicative or cellular senescence where normal diploid cells are unable to divide [28]. Cellular replication induces telomere shortening that ultimately triggers a DNA damage response associated with permanent cell cycle arrest, a condition called replicative senescence [28,29]. It has been stated that senescence is a model-in-miniature of events leading to aging or degenerating and fading of organism [27].

Senescence is driven by intracellular signals which remained unclear until the discovery of telomere erosion and telomerase. Telomeres are made of repetitive nucleotide sequences at each end of a chromosome and protect them from degradation or fusion with neighbouring chromosomes. Telomeres undergo erosion during the division of cell, therefore, telomeres have been used as a “molecular clock” that determines how many times a cell can divide before attaining replicative senescence [30]. Telomerase, also called telomere terminal transferase, is an enzyme made of protein and RNA subunits and it adds a specific-dependent to end of telomere [31,32]. Activated telomerase promotes division potential of several types of cultured primary cells, such as fibroblasts [33]. Reduced activity of telomerase leads to shortening of telomeres which subsequently lose their protective function [34], this is followed by a DNA damage response (DDR) which stimulates suppressing factors that interrupt the progression of cells cycle, a process which ends up with cellular senescence [35].

Telomere erosion is not the only cause for cellular senescence [6,36]. Other causes that provoke DDR, such as various types of oxidants, gamma-irradiation, ultraviolet light, and certain chemotherapies, can also induce senescence [37-39].

Cellular stress eliciting a DDR can also trigger a programmed cell death which is called apoptosis.

Apoptosis is a step ahead to remove the damaged, degraded or pre-neoplastic cells. This will be followed by phagocytosis to clear the apoptotic senescent cells. Senescent cells actively express and secret several types of extracellular modulators such as chemokines, cytokines, and matrix-remodelling enzymes known as senescence-associated secretory phenotype (SASP) [40-42]; are also responsible for promoting the clearance of senescent cells by the host immune system or provoke autocrine signalling to sustain the cell senescent state [40, 42,43].

DDR also leads to the induction of nuclear factor kappa B (NF- $\kappa$ B). NF- $\kappa$ B orchestrates the cell survival pathway, and, together with the coordination of cell-cycle check points and DNA repair, it enables the cell with limited damage to restore and continue a normal life cycle, unharmed [44]. It has been reported that during inflammation or induction by reactive oxygen species, the cells produce a signalling pathways that link DNA damage in the nucleus with activation of NF- $\kappa$ B in the cytoplasm [45]. Other studies found that DNA damage-dependent NF- $\kappa$ B stimulation may play an undesirable role in induction of cellular senescence, especially with persistence of DNA damage [46].

### **4. EFFECT OF INFLAMMATORY INDUCED SENESCENCE ON PERIODONTAL TISSUES HEALING AND CELLS MIGRATION**

#### **4.1 Biology of Oral Periodontal Wound Healing and Cell Migration**

Hammerle & Giannobile [47] had carried out a thorough search the literature related to the healing of oral tissues and concluded a “*Consensus Report of Group 1 of the 10th European Workshop on Periodontology*” which stated that “oral soft tissue healing at teeth, implants and the edentulous ridge follows the same phases as skin wound healing” [47]. However, the same study recommended that there is a necessity to appropriately outline valid and reproducible pre-clinical models for the assessment of procedures of soft tissue regeneration around teeth and implants. In another study, Hakkinen et al. [48] concluded that the basic wound healing events of gingival tissues are similar to the healing principles at the

tooth-gingiva interphase, especially above the crest of alveolar bone [48].

During evolution, wound healing has become physiologically well preserved due to its crucial importance for survival [48,49]. Many factors and molecules involved in wound healing appear to work and intersect the functions of each other. It has been reported that during wound healing, certain factors responsible for embryonic development are also existed in the granulation tissue (10). Epithelial cells involved in wound healing are found to contain extracellular matrix receptors that are not usually exist in other epithelial cells [50]. In addition, special phenotype of fibroblasts are also found in the granulation tissue during healing [51-53].

Wound repair requires the participation of several types of cells, such as macrophages, fibroblasts, and contractile myofibroblasts, during the proliferative phase [54]. Myofibroblasts, a specific phenotype of mesenchymal cells, is derived from fibroblasts in the connective tissue and epithelium at the edges of wound, bone marrow fibrocytes, and other nearby transdifferentiating cells circulating in the blood vessels [55,56]. Myofibroblasts play a significant role during wound closure by forming new matrix constituents which remodel the healing tissues [55]. Cellular senescence can deleteriously affect the differentiation of myofibroblasts, hence, it halts fibrosis during wound repair [57]. A massive suppression of differentiation of myofibroblasts has been detected in senescent cardiac tissue [58] and in old skin fibroblasts [59]. It is sensible to assume that protecting the cells from inflammatory senescence would be beneficial to sustain or promote the healing process at the periodontal wounds.

#### **4.2 Importance of Cell Migration in Periodontal Wound Healing**

Migration of epithelial cells and fibroblasts from the edges of the wound to fill the wound gap is crucial step for re-epithelialization [54,60-63]. Clot formation is the initial response to traumatic injury or surgical procedure. The forming clot protects the opened wound temporarily; and it acts as a scaffold matrix for the epithelial and fibroblasts migration [64]. The scaffold matrix is later replaced by a newly formed collagen matrix made by the migrating fibroblasts into the wound gap. Formation of specific ECM molecules by migrating fibroblasts in the wound gap is controlled by vascular endothelial growth factor

(VEGF), transforming growth factors- $\beta$ 1 (TGF- $\beta$ 1) and other proteins such as IL-1 $\alpha$ , IL-1 $\beta$ , and IL-4 [54]. In order to shape and remodel the healing wound area, cells migrating into the wound area are also controlling the proteolysis into the leading edge of epithelium by proteolytic enzymes activated at specific sites of the cell membrane [53,65,66].

#### **4.3 Cellular Senescence and Periodontal Wound Healing**

Differentiation, proliferation, and migration of mesenchymal or stem-like cells to the wound site are vital part of several events to achieve an optimal wound healing [67]. Senescence or accelerated cell cycle arrest elicits a damaging effect on the wound healing of oral tissues, including the periodontium and the masticatory mucosa [12,68]. Senescence detrimentally disrupts the three phases of tissue repair, including the transient inflammatory phase, new tissue matrix formation, and tissue remodelling phase. Steps of wound healing result in tissues restoration and prevention of infection and chronic inflammation. Therefore, senescent tissues are very susceptible for bacterial colonization and subsequently inflammatory reactions [11].

Cáceres et al. (2014) found that senescent gingival fibroblasts were not participating in tissue remodeling during wound healing as they had no ability to synthesize actin fibers when compared to the healthy fibroblasts [12]. These results suggest that senescence adversely affects normal collagen production and reorganization during wound healing, and halting proper tissue homeostasis and function [11,12].

It has been reported that expression of collagen 1A1 gene is reduced in the senescent periodontal ligament as the gene promoter has undergone hypermethylation in the senescent cells [69]. TGF- $\beta$ 1 expression is crucially affecting the production of collagen [70]. Previous experiments have shown that massive loss of collagen in the aged skin is probably due to reduced TGF- $\beta$  expression together with declined levels of connective tissue growth factor (CTGF) [71]. Though the mechanism of TGF- $\beta$  expression may differ in oral tissues compared to skin [72], it is probable that gingival tissue cells would undergo changes due to the reduced level of TGF- $\beta$  in the senescent cells. Other molecules involved in the modification and reorganisation of extracellular matrix components are matrix

metalloproteinases (MMPs) which regulate the formation of new tissue constituents in gingival wounds [73]. Senescent periodontal ligament cells were found to have high levels of MMPs and tissue inhibitors of MMPs (TIMPs) compared with young periodontal cells donors [74]. Increased levels of proteolytic enzymes would lead to disruption of tissue repair in senescent tissues as degradation process surpasses reconstruction of new tissue [75,76].

Previous investigation found that the levels of interleukin-1 $\alpha$  (IL-1 $\alpha$ ) that stimulates plasminogen activator inhibitor-2 (PAI-2) were increased during inflammatory senescence of human dermal fibroblasts [77]. Other studies investigated senescent human periodontal ligament fibroblasts have revealed persistent formation of interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) which subsequently caused a prolonged inflammation [78]. These results showed that chronic inflammatory phase in senescent tissues is a significant factor that delay periodontal wound healing [11].

One of the most important known tissue change resulted from cellular senescence is the reduction of cells capability to migrate [79-83]. The limited migration ability is attributed to the structural changes which occur to the cell cytoskeleton in senescent tissues [84,85]. The dynamic actin framework is an important part of the cytoskeleton as it regulates protrusion, adhesions, contraction, and retraction from the cell front to the rear during cell migration [85,86]. Previous studies have shown that vimentin production surpasses action formation in senescent fibroblasts [84,86,87]. As such, migration deficit is one of the critical properties of senescent cells and has negative impact during wound healing. Since senescent cells tend to secrete cytokines and mediators which provoke the inflammation and degrade the matrix, normal process of wound repair would be further impaired. Another reason for the reduced migration ability of senescent cells is the loss or deficiency of the migratory response to tissue forming factors such as growth factors [88,89].

## 5. CONCLUSION

During periodontitis, cellular senescence affects the implicated periodontal tissues adversely, shortens the cell telomere and induces unrepairable DNA damage. It also affects fibroblasts migration, which detrimentally affects

the healing of tooth supporting tissue. In severe untreated cases, the inevitable destruction may lead to the loss of affected teeth.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. Kayal RA. The role of osteoimmunology in periodontal disease. *Biomed Res Int*. 2013; 2013:639368.
2. Pihlstrom BL, Tabak L. The National Institute of Dental and Craniofacial Research: Research for the practicing dentist. *J Am Dent Assoc*. 2005;136(6): 728-37.
3. Listgarten MA. Pathogenesis of periodontitis. *J Clin Periodontol*. 1986; 13(5):418-30.
4. Socransky SS, Haffajee AD. Dental biofilms: Difficult therapeutic targets. *Periodontology*. 2002;28:12-55.
5. Naylor RM, Baker DJ, van Deursen JM. Senescent cells: A novel therapeutic target for aging and age-related diseases. *Clin Pharmacol Ther*. 2013;93(1):105-16.
6. van Deursen JM. The role of senescent cells in ageing. *Nature*. 2014;509(7501): 439-46.
7. Davalos AR, Coppe JP, Campisi J, Desprez PY. Senescent cells as a source of inflammatory factors for tumor progression. *Cancer Metastasis Rev*. 2010;29(2):273-83.
8. Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, et al. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. *Nature*. 2016;530(7589): 184-9.
9. Lujambio A. To clear, or not to clear (senescent cells)? That is the question. *Bioessays*. 2016;38(Suppl 1):S56-64.
10. Eming SA, Martin P, Tomic-Canic M. Wound repair and regeneration: Mechanisms, signaling, and translation. *Sci Transl Med*. 2014;6(265):265sr6.

11. Smith PC, Caceres M, Martinez C, Oyarzun A, Martinez J. Gingival wound healing: An essential response disturbed by aging? *Journal of Dental Research*. 2015;94(3):395-402.
12. Caceres M, Oyarzun A, Smith PC. Defective Wound-healing in Aging Gingival Tissue. *Journal of Dental Research*. 2014; 93(7):691-7.
13. Cheng R, Choudhury D, Liu C, Billet S, Hu T, Bhowmick NA. Gingival fibroblasts resist apoptosis in response to oxidative stress in a model of periodontal diseases. *Cell Death Discovery*. 2015;1:15046.
14. Sanikidze TV, Tkhillava NG, Papava MB, Datunashvili IV, Gongadze MT, Gamrekelashvili DD, et al. Role of free nitrogen and oxygen radicals in the pathogenesis of lipopolysaccharide-induced endotoxemia. *Bulletin of Experimental Biology and Medicine*. 2006; 141(2):211-5.
15. Bishayee K, Paul A, Ghosh S, Sikdar S, Mukherjee A, Biswas R, et al. Condurango-glycoside-A fraction of *Gonolobus condurango* induces DNA damage associated senescence and apoptosis via ROS-dependent p53 signalling pathway in HeLa cells. *Mol Cell Biochem*. 2013;382(1-2):173-83.
16. Ren JL, Pan JS, Lu YP, Sun P, Han J. Inflammatory signaling and cellular senescence. *Cell Signal*. 2009;21(3):378-83.
17. Ohtani N, Hara E. Roles and mechanisms of cellular senescence in regulation of tissue homeostasis. *Cancer Sci*. 2013; 104(5):525-30.
18. Gomez CR, Nomellini V, Faunce DE, Kovacs EJ. Innate immunity and aging. *Exp Gerontol*. 2008;43(8):718-28.
19. Domon H, Tabeta K, Nakajima T, Yamazaki K. Age-related alterations in gene expression of gingival fibroblasts stimulated with *Porphyromonas gingivalis*. *Journal of Periodontal Research*. 2014; 49(4):536-43.
20. Jun Ji, Lau LF. The matricellular protein CCN1 induces fibroblast senescence and restricts fibrosis in cutaneous wound healing. *Nat Cell Biol*. 2010;12(7):676-85.
21. Maderna P, Godson C. Phagocytosis of apoptotic cells and the resolution of inflammation. *Biochim Biophys Acta*. 2003; 1639(3):141-51.
22. McCulloch K, Litherland GJ, Rai TS. Cellular senescence in osteoarthritis pathology. *Aging Cell*. 2017;16(2):210-8.
23. Loaiza N, Demaria M. Cellular senescence and tumor promotion: Is aging the key? *Biochim Biophys Acta*. 2016;1865(2):155-67.
24. Campisi J. Cellular Senescence and Lung Function during Aging. Yin and Yang. *Ann Am Thorac Soc*. 2016;13(Suppl 5):S402-s6.
25. Serrano M. Senescence helps regeneration. *Dev Cell*. 2014;31(6):671-2.
26. Younis LT, Abu Hassan MI, Taiyeb Ali TB, Effindi TJB. 3D TECA hydrogel reduces cellular senescence and enhances fibroblasts migration in wound healing. *Asian Journal of Pharmaceutical Sciences*. 2018;13(4):317-25.
27. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. *Exp Cell Res*. 1961;25:585-621.
28. Tominaga K. The emerging role of senescent cells in tissue homeostasis and pathophysiology. *Pathobiol Aging Age Relat Dis*. 2015;5:27743.
29. Victorelli S, Passos JF. Telomeres and Cell Senescence - Size Matters Not. *EBioMedicine*. 2017;21:14-20.
30. Bodnar AG, Ouellette M, Frolkis M, Holt SE, Chiu CP, Morin GB, et al. Extension of life-span by introduction of telomerase into normal human cells. *Science (New York, NY)*. 1998;279(5349):349-52.
31. Greider CW, Blackburn EH. Identification of a specific telomere terminal transferase activity in *Tetrahymena* extracts. *Cell*. 1985;43(2 Pt 1):405-13.
32. Aksenova AY, Mirkin SM. At the Beginning of the End and in the Middle of the Beginning: Structure and Maintenance of Telomeric DNA Repeats and Interstitial Telomeric Sequences. *Genes (Basel)*. 2019;10(2).
33. Ouellette MM, McDaniel LD, Wright WE, Shay JW, Schultz RA. The establishment of telomerase-immortalized cell lines representing human chromosome instability syndromes. *Hum Mol Genet*. 2000;9(3):403-11.
34. Lendvay TS, Morris DK, Sah J, Balasubramanian B, Lundblad V. Senescence mutants of *Saccharomyces cerevisiae* with a defect in telomere replication identify three additional EST genes. *Genetics*. 1996;144(4):1399-412.

35. d'Adda di Fagagna F, Reaper PM, Clay-Farrace L, Fiegler H, Carr P, Von Zglinicki T, et al. A DNA damage checkpoint response in telomere-initiated senescence. *Nature*. 2003;426(6963):194-8.
36. Campisi J, d'Adda di Fagagna F. Cellular senescence: when bad things happen to good cells. *Nat Rev Mol Cell Biol*. 2007; 8(9):729-40.
37. von Zglinicki T. Role of oxidative stress in telomere length regulation and replicative senescence.
38. von Zglinicki T. Oxidative stress shortens telomeres. *Trends Biochem Sci*. 2002; 27(7):339-44.
39. Kepinska M, Szyller J, Milnerowicz H. The influence of oxidative stress induced by iron on telomere length. *Environ Toxicol Pharmacol*. 2015;40(3):931-5.
40. Coppe JP, Patil CK, Rodier F, Sun Y, Munoz DP, Goldstein J, et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS Biol*. 2008;6(12):2853-68.
41. Coppe JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. *Annu Rev Pathol*. 2010;5:99-118.
42. Lopes-Paciencia S, Saint-Germain E, Rowell MC, Ruiz AF, Kalegari P, Ferbeyre G. The senescence-associated secretory phenotype and its regulation. *Cytokine*. 2019;117:15-22.
43. Ritschka B, Storer M, Mas A, Heinzmann F, Ortells MC, Morton JP, et al. The senescence-associated secretory phenotype induces cellular plasticity and tissue regeneration. *Genes Dev*. 2017; 31(2):172-83.
44. Janssens S, Tschopp J. Signals from within: The DNA-damage-induced NF-kappaB response. *Cell Death Differ*. 2006; 13(5):773-84.
45. McCool KW, Miyamoto S. DNA damage-dependent NF-kappaB activation: NEMO turns nuclear signaling inside out. *Immunol Rev*. 2012;246(1):311-26.
46. Rodier F, Coppe JP, Patil CK, Hoeijmakers WA, Munoz DP, Raza SR, et al. Persistent DNA damage signalling triggers senescence-associated inflammatory cytokine secretion. *Nat Cell Biol*. 2009; 11(8):973-9.
47. Hammerle CH, Giannobile WV. Biology of soft tissue wound healing and regeneration-- consensus report of Group 1 of the 10th European Workshop on Periodontology. *J Clin Periodontol*. 2014; 41(Suppl 15):S1-5.
48. Hakkinen L, Uitto VJ, Larjava H. Cell biology of gingival wound healing. *Periodontology*. 2000;24:127-52.
49. Han G, Ceilley R. Chronic Wound Healing: A Review of Current Management and Treatments. *Adv Ther*. 2017;34(3):599-610.
50. Volk SW, Iqbal SA, Bayat A. Interactions of the Extracellular Matrix and Progenitor Cells in Cutaneous Wound Healing. *Adv Wound Care (New Rochelle)*. 2013; 2(6):261-72.
51. Hakkinen L, Larjava H. Characterization of fibroblast clones from periodontal granulation tissue in vitro. *Journal of dental research*. 1992;71(12):1901-7.
52. Koivisto L, Heino J, Hakkinen L, Larjava H. Integrins in Wound Healing. *Adv Wound Care (New Rochelle)*. 2014;3(12):762-83.
53. Xue M, Jackson CJ. Extracellular Matrix Reorganization During Wound Healing and Its Impact on Abnormal Scarring. *Adv Wound Care (New Rochelle)*. 2015;4(3): 119-36.
54. Leoni G, Neumann PA, Sumagin R, Denning TL, Nusrat A. Wound repair: role of immune-epithelial interactions. *Mucosal Immunol*. 2015;8(5):959-68.
55. Hinz B, Phan SH, Thannickal VJ, Prunotto M, Desmouliere A, Varga J, et al. Recent developments in myofibroblast biology: paradigms for connective tissue remodeling. *Am J Pathol*. 2012;180(4): 1340-55.
56. Peng H, Herzog EL. Fibrocytes: emerging effector cells in chronic inflammation. *Curr Opin Pharmacol*. 2012;12(4):491-6.
57. Jun JI, Lau LF. Cellular senescence controls fibrosis in wound healing. *Aging (Albany NY)*. 2010;2(9):627-31.
58. Cieslik KA, Trial J, Entman ML. Defective myofibroblast formation from mesenchymal stem cells in the aging murine heart rescue by activation of the AMPK pathway. *Am J Pathol*. 2011;179(4):1792-806.
59. Simpson RM, Wells A, Thomas D, Stephens P, Steadman R, Phillips A. Aging fibroblasts resist phenotypic maturation because of impaired hyaluronan-dependent CD44/epidermal growth factor

- receptor signaling. *Am J Pathol.* 2010; 176(3):1215-28.
60. Juhasz I, Murphy GF, Yan HC, Herlyn M, Albelda SM. Regulation of extracellular matrix proteins and integrin cell substratum adhesion receptors on epithelium during cutaneous human wound healing in vivo. *Am J Pathol.* 1993;143(5):1458-69.
  61. Pastar I, Stojadinovic O, Yin NC, Ramirez H, Nusbaum AG, Sawaya A, et al. Epithelialization in Wound Healing: A Comprehensive Review. *Adv Wound Care (New Rochelle).* 2014;3(7):445-64.
  62. Landen NX, Li D, Stahle M. Transition from inflammation to proliferation: a critical step during wound healing. *Cell Mol Life Sci.* 2016;73(20):3861-85.
  63. Begnaud S, Chen T, Delacour D, Mege RM, Ladoux B. Mechanics of epithelial tissues during gap closure. *Curr Opin Cell Biol.* 2016;42:52-62.
  64. Polimeni G, Xiropaidis AV, Wikesjo UM. Biology and principles of periodontal wound healing/regeneration. *Periodontology.* 2006;41:30-47.
  65. Shapiro SD. Matrix metalloproteinase degradation of extracellular matrix: biological consequences. *Curr Opin Cell Biol.* 1998;10(5):602-8.
  66. Caley MP, Martins VL, O'Toole EA. Metalloproteinases and Wound Healing. *Adv Wound Care (New Rochelle).* 2015; 4(4):225-34.
  67. Guo S, Dipietro LA. Factors affecting wound healing. *Journal of Dental Research.* 2010;89(3):219-29.
  68. Benatti BB, Neto JB, Casati MZ, Sallum EA, Sallum AW, Nociti FH, Jr. Periodontal healing may be affected by aging: A histologic study in rats. *Journal of Periodontal Research.* 2006;41(4):329-33.
  69. Ohi T, Uehara Y, Takatsu M, Watanabe M, Ono T. Hypermethylation of CpGs in the promoter of the COL1A1 gene in the aged periodontal ligament. *Journal of Dental Research.* 2006;85(3):245-50.
  70. Brown RL, Ormsby I, Doetschman TC, Greenhalgh DG. Wound healing in the transforming growth factor-beta-deficient mouse. *Wound Repair Regen.* 1995; 3(1):25-36.
  71. Quan T, Shao Y, He T, Voorhees JJ, Fisher GJ. Reduced expression of connective tissue growth factor (CTGF/CCN2) mediates collagen loss in chronologically aged human skin. *J Invest Dermatol.* 2010;130(2):415-24.
  72. Mah W, Jiang G, Olver D, Cheung G, Kim B, Larjava H, et al. Human gingival fibroblasts display a non-fibrotic phenotype distinct from skin fibroblasts in three-dimensional cultures. *PLoS One.* 2014; 9(3):e90715.
  73. Ravanti L, Hakkinen L, Larjava H, Saarialho-Kere U, Foschi M, Han J, et al. Transforming growth factor-beta induces collagenase-3 expression by human gingival fibroblasts via p38 mitogen-activated protein kinase. *J Biol Chem.* 1999;274(52):37292-300.
  74. Benatti BB, Silverio KG, Casati MZ, Sallum EA, Nociti FH, Jr. Influence of aging on biological properties of periodontal ligament cells. *Connect Tissue Res.* 2008; 49(6):401-8.
  75. Ben-Porath I, Weinberg RA. The signals and pathways activating cellular senescence. *Int J Biochem Cell Biol.* 2005; 37(5):961-76.
  76. Demidova-Rice TN, Hamblin MR, Herman IM. Acute and impaired wound healing: Pathophysiology and current methods for drug delivery, part 1: Normal and chronic wounds: biology, causes, and approaches to care. *Adv Skin Wound Care.* 2012; 25(7):304-14.
  77. Kumar S, Millis AJ, Baglioni C. Expression of interleukin 1-inducible genes and production of interleukin 1 by aging human fibroblasts. *Proc Natl Acad Sci U S A.* 1992;89(10):4683-7.
  78. Benatti BB, Silverio KG, Casati MZ, Sallum EA, Nociti FH, Jr. Inflammatory and bone-related genes modulated by aging in human periodontal ligament cells. *Cytokine.* 2009;46(2):176-81.
  79. Schneider EL, Mitsui Y. The relationship between in vitro cellular aging and *in vivo* human age. *Proc Natl Acad Sci USA.* 1976;73(10):3584-8.
  80. Sandeman SR, Allen MC, Liu C, Faragher RG, Lloyd AW. Human keratocyte migration into collagen gels declines with *in vitro* ageing. *Mech Ageing Dev.* 2000; 119(3):149-57.
  81. Reed MJ, Corsa AC, Kudravi SA, McCormick RS, Arthur WT. A deficit in collagenase activity contributes to impaired migration of aged microvascular endothelial cells. *J Cell Biochem.* 2000; 77(1):116-26.
  82. Reed MJ, Ferrara NS, Vernon RB. Impaired migration, integrin function, and actin



- cytoskeletal organization in dermal fibroblasts from a subset of aged human donors. *Mech Ageing Dev.* 2001;122(11): 1203-20.
83. Ruiz-Torres A, Lozano R, Melon J, Carraro R. Age-dependent decline of *in vitro* migration (basal and stimulated by IGF-1 or insulin) of human vascular smooth muscle cells. *J Gerontol A Biol Sci Med Sci.* 2003;58(12):B1074-7.
84. Nishio K, Inoue A. Senescence-associated alterations of cytoskeleton: Extraordinary production of vimentin that anchors cytoplasmic p53 in senescent human fibroblasts. *Histochemistry and Cell Biology.* 2005;123(3):263-73.
85. Pollard TD, Cooper JA. Actin, a central player in cell shape and movement. *Science (New York, NY).* 2009;326(5957): 1208-12.
86. Tang DD, Gerlach BD. The roles and regulation of the actin cytoskeleton, intermediate filaments and microtubules in smooth muscle cell migration. *Respir Res.* 2017;18(1):54.
87. Danielsson F, Peterson MK, Caldeira Araujo H, Lautenschlager F, Gad AKB. Vimentin Diversity in Health and Disease. *Cells.* 2018;7(10).
88. Matsuda T, Okamura K, Sato Y, Morimoto A, Ono M, Kohno K, et al. Decreased response to epidermal growth factor during cellular senescence in cultured human microvascular endothelial cells. *Journal of Cellular Physiology.* 1992;150(3):510-6.
89. Cavallaro U, Castelli V, Del Monte U, Soria MR. Phenotypic alterations in senescent large-vessel and microvascular endothelial cells. *Mol Cell Biol Res Commun.* 2000; 4(2):117-21.

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