REVIEW ARTICLE

Periodontitis: An Inevitable Destruction

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ABSTRACT

All over the world, periodontal diseases are still prevalent and negatively affect the quality of life of young and adult population. Chronic periodontitis is an inflammatory polymicrobial disease characterized by episodic progressive destruction of gingivae, periodontal ligament, and bone. The inflamed cells of the periodontal structure undergo senescence (irreversible cell cycle arrest), chromatin condensation, and telomere shortening followed by apoptosis of the cells of periodontium (alveolar bone periodontal ligament and overlying gingiva). The consequences of apoptosis are manifested by gingival recession, bone loss, and exposure of tooth root. In severe case, tooth loss is inevitable. In this mini-review, we discuss briefly the role of apoptosis in the destruction of tooth periodontal structure.

Key words: Apoptosis, fibroblast, periodontitis, senescence, telomere

INTRODUCTION

The pathogenesis of periodontal disease involves the serial activation of components of the host immune response, primarily not only acting to protect periodontal tissues against bacterial aggression but also functioning as mediators of tissue destruction.[1] Elimination of tissue cells is achieved through apoptosis which is a process of programmed cell death that occurs in multicellular organisms. It is considered a vital component of various processes including normal cell turnover, proper development and functioning of the immune system, hormone-dependent atrophy, and embryonic development.[2] Apoptosis also occurs as a defense mechanism such as in immune reactions or when cells are damaged by disease or noxious agents.[3] Although there are a wide variety of stimuli and conditions, both physiological and pathological, that can induce apoptosis, not all cells will necessarily undergo apoptosis in response to the same stimulus.

Gamonal *et al*. studied the apoptotic events in gingival tissue biopsies from periodontitis and healthy individuals and concluded that apoptotic mechanisms could be implicated in the inflammatory process associated with gingival tissue destruction observed in adult periodontitis patients.[4] In another study, gingival crevicular fluid was used to investigate apoptotic biomarkers; it was found that these markers were significantly increased in patients diagnosed with localized aggressive periodontitis.[5] Previous study reported that apoptosis or DNA fragmentation was positively correlated with periodontal pocket depth and clinical attachment level regardless of patient disease status.[6] It was reported that factors such as caspase-3, soluble Fas (sFas), and sFas ligand associated with apoptosis were detected in gingival crevicular fluid in patients with chronic periodontitis; in addition, apoptotic protein expression exhibited increasing trends with increasing pocket depths at baseline and 3 months.[7] Zeidán-Chuliá *et al*. performed a landscape analysis of apoptosis-related genes/proteins and also studied the differential gene expression by analyzing array data from periodontitis patients. The findings of the study revealed that caspase-3 can be a target protein to inhibit periodontitis-associated apoptosis of epithelial cells.[8]

Interestingly, there are several stages at which apoptosis may be inhibited temporarily in periodontitis.[9] Inhibition of apoptosis may result in a prolonged survival of inflamed

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periodontal cells which could be due to the inhibition of apoptosis by tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) decoy receptors and inhibition of the terminal stages of apoptosis signaling by an inhibitor of apoptosis family members.[9]

APOPTOSIS OF FIBROBLASTS

Cheng *et al*. reported that gingival fibroblasts initially adapted to resist LPS-induced oxidative stress and cell apoptosis in periodontal diseases.[10] The mechanism might be related to increased mRNA expression of DNA repair enzymes and balanced anti-apoptotic and pro-apoptotic proteins.[11] The chronic inflammatory response in periodontal disease is thought not only to contribute to the loss of bone and connective tissue but also contribute to the loss of critical matrix-producing cells through the induction of TNF.[12,13] Loss of fibroblasts is one of the most distinguishing cellular changes that occur in progressing periodontal disease.[14] In patients with periodontitis, fibroblasts have the highest rate of apoptosis among the various cells in the gingiva and are observed predominantly in areas where inflammatory cells have been recruited.[15,16] The previous study revealed that *Porphyromonas* gingivalis stimulates fibroblast apoptosis (together with osteoclasts formation) *in vivo* through induction of TNF activity of the innate immune response rather than the direct effect of bacterial products.[17] The clinical significance of fibroblast apoptosis has been manifested, together with the apical migration of junctional epithelium, by the recession of gingival margin attachment, an early feature of periodontitis that precedes the loss of alveolar bone.[18]

APOPTOSIS OF OSTEOBLASTS

Bone remodeling is regulated by the correct balance between osteoclast and osteoblast formation and activity.[19,20] Alveolar bone loss could be due to an increased bone resorption by osteoclasts or a decreased bone formation by osteoblasts or both.[21,22] Periodontal disease is characterized by an increased osteoclast resorption activity and a decreased osteoblast activity in bone formation. Mori *et al*. investigated the level of TRAIL in relation to the alveolar bone loss by utilizing osteoblasts obtained from alveolar bone of periodontitis patients. Mori's study suggested that alveolar bone loss could be due to the increased TRAIL-mediated apoptosis of osteoblasts.[23,24] The study also demonstrated that DNA fragmentation and activation of caspase-8 and caspase-3 in periodontitis patients' osteoblasts occurred in shorter time; moreover, these osteoblasts were more prone to apoptosis when compared to the control group.[23,24]

Apoptosis can occur throughout the lifespan of osteoblasts, beginning from the early stages of differentiation and continuing throughout all stages of their working life. It was found that the undifferentiated osteoblasts had increased sensitivity to the cytotoxic/apoptotic effects of tumor necrosis factor (TNF) which is involved in the inflammatory process during periodontitis.[25] These findings inferred that, during periodontitis, osteoblasts differentiation is limited, and consequently, osteoblasts number is remarkably reduced.

Periodontal infection stimulates the production of TNF and ligand for receptor activator of nuclear factor Kappa B (NF-κB) that induces osteoclastogenesis.[26-28] Although NF-κB is typically antiapoptotic, in case of long-term inflammation, it has been shown to have an indirect proapoptotic effects through induction of apoptotic factors such as TNFα and Bcl-2-associated protein X.[29]

In an animal study, the mice were injected with the periodontal pathogen *P.* gingivalis adjacent to calvarial bone with or without prior immunization against the bacterium.[30] The findings of the study indicated that activation of the acquired immunity by a periodontal pathogen increases bone lining cell apoptosis and reduces the coupling of bone formation and resorption. The study also inferred that during periodontal disease, the formation of osteolytic lesions occurs in conjunction with deficient bone formation and activation of an acquired immune response. Other previous investigations showed that immunization resulted in increasing the intensity of inflammation and tissue destruction in response to *P. gingivalis*.[17,31] These investigations established that activation of the acquired immunity by periodontal pathogens increases the inflammatory and destructive responses which occur in part through provoking the innate immune response and escalating osteoclastogenesis accompanied with apoptosis of fibroblast and bone lining cells.[32]

Graves proposed a general model, whereby inflammation is induced by bacteria, leading to osteoclast formation and subsequent bone resorption as well as an increased rate of osteoblast apoptosis. The increased apoptosis of these cells may be linked to the immune response generated by periodontal pathogens in connective tissue. This, in turn, may cause impaired bone formation and, together, leads to uncoupling and greater periodontal bone loss.[33]

It is important to note that acute gingivitis can be relieved and cured when the causative microbes (dental biofilm) are brushed and removed timely. Contrary to early and acute gingivitis, chronic gingival inflammation results in extensive telomere shortening, DNA damage, and cells apoptosis.[10]

TELOMERE SHORTENING AND APOPTOSIS

Telomeres, which consist of tandem repeats of the TTAGGG sequence, serve as essential protective caps of the linear chromosomal ends in mammalian cells.[34] Telomerase is an enzyme, also called telomere terminal transferase. It is made of protein and RNA subunits that elongate chromosomes by adding TTAGGG sequences to the end of existing chromosomes. Activated telomerase is capable of triggering division potential of several types of primary cells in culture, such as fibroblasts.[35] Reduced activity of telomerase leads to shortening of telomeres which subsequently lose their protective function,[36] and this is followed by a DNA damage response (DDR) that stimulates inhibitors of cell cycle progression, a process which ends up with senescence growth arrest.[37]

In periodontal disease, chronic inflammatory process could represent the driver of telomere shortening.[38] A strong correlation was found between the telomere length and senescence marker secretory-associated β-galactosidase (SA-βgal) in gingival fibroblasts.[39] However, telomere erosion is not the only cause for cellular senescence.[40,41] Other causes that provoke the DDR, such as exposure to oxidants, γ-irradiation, UVB light, DNA damaging chemotherapies, and TNF-α, can also induce senescence and eventually apoptosis.[42-46]

Sahin *et al*. reported that telomere dysfunction upregulates p53 expression which may promote cell-growth arrest, apoptosis, or PGC-1 downregulation. PGC-1 is a family of master regulators of mitochondrial function, and its decreased activity may result in mitochondrial-derived accumulated reactive oxygen species (ROS), which consequently damages mitochondrial DNA.[47,48] Inhibiting or neutralizing the excessive ROS through increasing genes and encoding mitochondrial antioxidant component expression may rejuvenate the senescent fibroblast telomeres and protects human gingival fibroblasts from the loss of proliferative capacity.[49] It was reported that protecting telomere length would be beneficial in reducing the number of senescent cells and protect the telomere from dysfunction and instability, subsequently preserving cells' viability and minimizing tissue destruction.[50-53]

CONCLUSION

Chronic inflammation of periodontitis elicits a host defense mechanism which aggravates the loss of the host tissues supporting the tooth. Irreversible cell cycle arrest, suppression of cell DNA proliferation, cell apoptosis, and lack of timely replacement mechanism of the degraded tissue cells result in an inevitable destruction of the periodontal tissue and change normal architecture around the teeth.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Bascones A, Noronha S, Gómez M, Mota P, Gónzalez Moles MA, Villarroel Dorrego M, *et al.* Tissue destruction in periodontitis: Bacteria or cytokines fault? Quintessence Int 2005;36:299-306.
2. Elmore S. Apoptosis: A review of programmed cell death. Toxicol Pathol 2007;35:495-516.
3. Norbury CJ, Hickson ID. Cellular responses to DNA damage. Annu Rev Pharmacol Toxicol 2001;41:367-401.
4. Gamonal J, Bascones A, Acevedo A, Blanco E, Silva A. Apoptosis in chronic adult periodontitis analyzed by *in situ* DNA breaks, electron microscopy, and immunohistochemistry. J Periodontol 2001;72:517-25.
5. Makhoul H, Bashutski J, Halubai S, Dabiri D, Benavides E, Kapila YL, *et al.* Apoptotic activity of gingival crevicular fluid from localized aggressive periodontitis. J Int Acad Periodontol 2013;15:2-7.
6. Abuhussein H, Bashutski JD, Dabiri D, Halubai S, Layher M, Klausner C, *et al.* The role of factors associated with apoptosis in assessing periodontal disease status. J Periodontol 2014;85:1086-95.
7. Dabiri D, Halubai S, Layher M, Klausner C, Makhoul H, Lin GH, *et al.* The role of apoptotic factors in assessing progression of periodontal disease. Int J Dent Oral Sci 2016;3:318-25.
8. Zeidán-Chuliá F, Gursoy M, de Oliveira BH, Gelain DP, Könönen E, Gursoy UK, *et al.* Focussed microarray analysis of apoptosis in periodontitis and its potential pharmacological targeting by carvacrol. Arch Oral Biol 2014;59:461-9.
9. Lucas H, Bartold PM, Dharmapatni AA, Holding CA, Haynes DR. Inhibition of apoptosis in periodontitis. J Dent Res 2010;89:29-33.
10. Cheng R, Choudhury D, Liu C, Billet S, Hu T, Bhowmick NA, *et al.* Gingival fibroblasts resist apoptosis in response to oxidative stress in a model of periodontal diseases. Cell Death Discov 2015;1:15046.
11. Cheng R, Hu T, Bhowmick NA. Be resistant to apoptosis: A host factor from gingival fibroblasts. Cell Death Dis 2015;6:e2009.
12. Graves DT, Cochran D. The contribution of interleukin-1 and tumor necrosis factor to periodontal tissue destruction. J Periodontol 2003;74:391-401.
13. Williams RC. Periodontal disease. N Engl J Med 1990;8:373-82.
14. Zappa U, Reinking-Zappa M, Graf H, Case D. Cell populations associated with active probing attachment loss. J Periodontol 1992;63:748-52.
15. Koulouri O, Lappin DF, Radvar M, Kinane DF. Cell division, synthetic capacity and apoptosis in periodontal lesions analysed by *in situ* hybridisation and immunohistochemistry. J Clin Periodontol 1999;26:552-9.
16. Tonetti MS, Cortellini D, Lang NP. *In situ* detection of apoptosis at sites of chronic bacterially induced inflammation in human gingiva. Infect Immun 1998;66:5190-5.
17. Graves DT, Oskoui M, Volejnikova S, Naguib G, Cai S, Desta T, *et al.* Tumor necrosis factor modulates fibroblast apoptosis, PMN recruitment, and osteoclast formation in response to *P. gingivalis* infection. J Dent Res 2001;80:1875-9.
18. Ekuni D, Tomofuji T, Yamanaka R, Tachibana K, Yamamoto T, Watanabe T, *et al.* Initial apical migration of junctional epithelium in rats following application of lipopolysaccharide and proteases. J Periodontol 2005;76:43-8.
19. Tanaka Y, Nakayamada S, Okada Y. Osteoblasts and osteoclasts in bone remodeling and inflammation. Curr Drug Targets Inflamm Allergy 2005;4:325-8.

20. Rucci N. Molecular biology of bone remodelling. Clin Cases Miner Bone Metab 2008;5:49-56.
21. Kim JH, Lee DE, Cha JH, Bak EJ, Yoo YJ. Receptor activator of nuclear factor-κB ligand and sclerostin expression in osteocytes of alveolar bone in rats with ligature-induced periodontitis. J Periodontol 2014;85:e370-8.
22. Hienz SA, Paliwal S, Ivanovski S. Mechanisms of bone resorption in periodontitis. J Immunol Res 2015;2015:615486.
23. Mori G, Brunetti G, Colucci S, Ciccolella F, Coricciati M, Pignataro P, *et al.* Alteration of activity and survival of osteoblasts obtained from human periodontitis patients: Role of TRAIL. J Biol Regul Homeost Agents 2007;21:105-14.
24. Mori G, Brunetti G, Colucci S, Oranger A, Ciccolella F, Sardone F, *et al.* Osteoblast apoptosis in periodontal disease: Role of TNF-related apoptosis-inducing ligand. Int J Immunopathol Pharmacol 2009;22:95-103.
25. Brunetti G, Oranger A, Carbone C, Mori G, Sardone FR, Mori C, *et al.* Osteoblasts display different responsiveness to TRAIL-induced apoptosis during their differentiation process. Cell Biochem Biophys 2013;67:1127-36.
26. Graves DT, Li J, Cochran DL. Inflammation and uncoupling as mechanisms of periodontal bone loss. J Dent Res 2011;90:143-53.
27. Darveau RP. Periodontitis: A polymicrobial disruption of host homeostasis. Nat Rev Microbiol 2010;8:481-90.
28. Valerio MS, Herbert BA, Griffin AC 3rd, Wan Z, Hill EG, Kirkwood KL, *et al.* MKP-1 signaling events are required for early osteoclastogenesis in lineage defined progenitor populations by disrupting RANKL-induced NFATc1 nuclear translocation. Bone 2014;60:16-25.
29. Rai A, Kapoor S, Singh S, Chatterji BP, Panda D. Transcription factor NF-κB associates with microtubules and stimulates apoptosis in response to suppression of microtubule dynamics in MCF-7 cells. Biochem Pharmacol 2015;93:277-89.
30. Behl Y, Siqueira M, Ortiz J, Li J, Desta T, Faibish D, *et al.* Activation of the acquired immune response reduces coupled bone formation in response to a periodontal pathogen. J Immunol 2008;181:8711-8.
31. Leone CW, Bokhadhoor H, Kuo D, Desta T, Yang J, Siqueira MF, *et al*. Immunization enhances inflammation and tissue destruction in response to *Porphyromonas gingivalis*. Infect Immun 2006;74:2286-92.
32. Li CH, Amar S. Inhibition of SFRP1 reduces severity of periodontitis. J Dent Res 2007;86:873-7.
33. Graves D. Cytokines that promote periodontal tissue destruction. J Periodontol 2008;79 8 Suppl:1585-91.
34. Shay JW, Wright WE. Role of telomeres and telomerase in cancer. Semin Cancer Biol 2011;21:349-53.
35. 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;9:403-11.
36. 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;144:1399-412.
37. 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;426:194-8.
38. Steffens JP, Masi S, D'Aiuto F, Spolidorio LC. Telomere length and its relationship with chronic diseases - New perspectives for periodontal research. Arch Oral Biol 2013;58:111-7.
39. Takahashi K, Nishida H, Takeda H, Shin K. Telomere length in leukocytes and cultured gingival fibroblasts from patients with aggressive periodontitis. J Periodontol 2004;75:84-90.
40. Campisi J, d'Adda di Fagagna F. Cellular senescence: When bad things happen to good cells. Nat Rev Mol Cell Biol 2007;8:729-40.
41. van Deursen JM. The role of senescent cells in ageing. Nature 2014;509:439-46.
42. von Zglinicki T. Role of oxidative stress in telomere length regulation and replicative senescence. Ann N Y Acad Sci 2000;908:99-110.
43. von Zglinicki T. Oxidative stress shortens telomeres. Trends Biochem Sci 2002;27:339-44.
44. Kepinska M, Szyller J, Milnerowicz H. The influence of oxidative stress induced by iron on telomere length. Environ Toxicol Pharmacol 2015;40:931-5.
45. Arkus N. A mathematical model of cellular apoptosis and senescence through the dynamics of telomere loss. J Theor Biol 2005;7,235:13-32.
46. Younis LT, Hassan MA, Ali TB, Bustami TJ. 3D TECA hydrogel reduces cellular senescence and enhances fibroblasts migration in wound healing. Asian J Pharm Sci 2017. DOI: 10.1016/j.ajps.2017.12.003.
47. Sahin E, Colla S, Liesa M, Moslehi J, Müller FL, Guo M, *et al.* Telomere dysfunction induces metabolic and mitochondrial compromise. Nature 2011;470:359-65.
48. Kelly DP. Cell biology: Ageing theories unified. Nature 2011;470:342-3.
49. Xia Y, Sun M, Xie Y, Shu R. MTOR inhibition rejuvenates the aging gingival fibroblasts through alleviating oxidative stress. Oxid Med Cell Longev 2017;2017:6292630.
50. Coluzzi E, Buonsante R, Leone S, Asmar AJ, Miller KL, Cimini D, *et al.* Transient ALT activation protects human primary cells from chromosome instability induced by low chronic oxidative stress. Sci Rep 2017;7:43309.
51. Babizhayev MA, Yegorov YE. Biomarkers of oxidative stress and cataract. Novel drug delivery therapeutic strategies targeting telomere reduction and the expression of telomerase activity in the lens epithelial cells with N-acetylcarnosine lubricant eye drops: Anti-cataract which helps to prevent and treat cataracts in the eyes of dogs and other animals. Curr Drug Deliv 2014;11:24-61.
52. Babizhayev MA, Yegorov YE. Tissue formation and tissue engineering through host cell recruitment or a potential injectable cell-based biocomposite with replicative potential: Molecular mechanisms controlling cellular senescence and the involvement of controlled transient telomerase activation therapies. J Biomed Mater Res A 2015;103:3993-4023.
53. Coluzzi E, Colamartino M, Cozzi R, Leone S, Meneghini C, O'Callaghan N, *et al.* Oxidative stress induces persistent telomeric DNA damage responsible for nuclear morphology change in mammalian cells. PLoS One 2014;9:e110963.

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