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PERIODONTITIS: AN INEVITABLE DESTRUCTION

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ABSTRACT

All over the world, periodontal diseases are still prevalent and negatively affecting 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, 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.

KEYWORDS: Periodontitis; apoptosis, senescence; fibroblast; telomere.

INTRODUCTION

The pathogenesis of periodontal disease involves the serial activation of components of the host immune response, primarily 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. (2001) 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 (sFasL) 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. (2014) performed a landscape analysis of apoptosis-related genes/proteins and also studied the differential gene expression by analysing 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 periodontal cells which could be due to the inhibition of apoptosis by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) decoy receptors and inhibition of the terminal stages of apoptosis signaling by inhibitor of apoptosis (IAP) family members.[9]

Apoptosis of Fibroblasts

Cheng et al. (2015) 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 to contribute, not only, 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] Previous study revealed that *P. 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 recession of gingival margin attachment, an early feature of periodontitis that precedes the loss of alveolar bone.[18]

Apoptosis of Osteoblasts

Bone remodelling 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. (2007, 2009) investigated the level of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in relation to the alveolar bone loss by utilising 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 life span 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 tumour 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) (RANKL) that induce osteoclastogenesis.[26,27,28] Although NF-κB is typically anti-apoptotic, in case of long term inflammation it has been shown to have an indirect pro-apoptotic effects through induction of apoptotic factors such as TNFα and Bcl-2-associated protein (BAX).[29]

In an animal study, the mice were injected with the periodontal pathogen *Porphyromonas 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 *Porphyromonas 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 (2008) 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] 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] 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. (2011) 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, which consequently damage mitochondrial DNA.[47,48] Inhibiting or neutralising the excessive reactive oxygen species (ROS) through increasing genes encoding mitochondrial antioxidant component expression may rejuvenate the senescent fibroblast telomeres and protects human gingival fibroblasts from 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 minimise tissue destruction.[50-53]

CONCLUSION

Chronic inflammation of periodontitis elicits a host defence 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

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