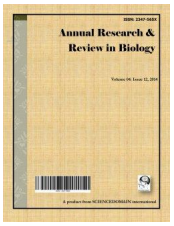

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Periodontitis: A Cellular Tactic to Escape Cancer

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Authors' contributions

This work was carried out in collaboration between all authors. Author LTY designed and wrote the review. Authors MIAH and TBTA managed and edited the versions of the review. All authors read and approved the final manuscript.

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ABSTRACT

During acute inflammation of gingiva (gingivitis), the cells can resist apoptosis and, at the same time, serve as a barrier to tumour formation. However, during chronic inflammation (periodontitis), the cells will undergo degradation which also helps in tumour restraining. Unlike the cellular senescence during cancer, periodontal cells undergo a unique senescence activity due to the microbial infection from the dental biofilm. The distinctive senescence activity of the inflamed periodontal cells results in the cell cycle arrest which leads to an inevitable degradation of periodontal tissues superpose the regeneration of them. If this activity is not resolved, continuous destruction of the supporting periodontal tissues may eventually result in the loss of teeth. In this mini-review, we discussed briefly the cellular senescence and its sequelae in periodontitis and cancer.

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1. LITERATURE REVIEW PERIODONTAL DISEASE

Periodontal disease is an inflammatory disease that affects almost 90% of the population [1] and involves the supporting structure of teeth [2]. It is caused by bacterial infection in the gingival region and usually accompanied by a progressively destructive change of the surrounding structures leading to loss of bone and periodontal ligament supporting the teeth which may eventually lead to their loss. The infection affects in the gingival tissues leading to gingivitis, and under certain conditions it will progress into the underlying connective tissues leading to periodontitis [3,4].

Although they may appear similar, the inflammatory process and immune reaction in periodontal tissue are rather different from those seen in other parts of the body [1,5]. For the most part, this is due to the unique anatomy of the periodontium and the unique character of the infection. At the gingival crevice, the connective tissue of the periodontal structure is separated from the oral cavity by a thin permeable junctional epithelium. This epithelium has remarkable cell and fluid dynamics that permits the flow of bacterial toxins and by-products in, and inflammatory cytokines and mediators out. Microbiome studies indicate that the defensive process in the periodontium occurs in response to a consortium of microbes that resides on the tooth surface and are planktonic in a biofilm community in the gingival sulcus [6,7]. This contrasts with most other infections where the host contends with one organism [8,9]. Anatomical anomalies of tooth and root morphology may adversely become retentive areas for dental plaque and calculus [10]. These morphological abnormalities may facilitate the development of periodontal disease [11,12].

2. CELLULAR SENESCENCE

Cells can respond to exogenous and endogenous stimuli by suspending their cycle, a condition called cellular senescence [13]. Other than aging, senescence is also caused by radiation [14], H_2O_2 [15,16], and bacterial lipopolysaccharide [17] which provoke immune response and induce inflammation. The inflammatory cytokines play an essential role in the initiation and maintenance of cellular senescence (irreversible cells cycle arrest) [18], and are responsible for triggering an innate immune response that clears the senescent cells in vivo [19]. In periodontitis, inflammatory cytokines create a sequence of events where the periodontal cells are eventually destroyed and cleared if the healthy feedback mechanism is destroyed, this will subsequently result in loss of periodontal attachment and alveolar bone [1,20,21].

The hallmark of cellular senescence is an inability to progress through the cell cycle. Senescence arrests cells growth although they remain metabolically active [22-25]. During senescence, accumulation of membrane-impermeant proteins in cells increases the osmotic pressure within the cell [26]. Senescent cells are unable to release their proteins to be part of the connective stroma. Protein accumulation in a cell creates inflows of water and/or ions across the water-permeable plasma membrane, and results in cell distention and swelling [27-30].

Senescent cells may promote tissues remodelling [31], or adversely affect the neighbouring healthy cells [32-38]. In case of periodontitis, senescent periodontal cells provoke the inflammatory process by releasing cytokines which cause further destruction of the tooth supporting tissues [39,40], however, no tissue replacement is taking place after clearance of the senescent cells.

Healing of the lost periodontal structure requires restoring their architecture and function by regeneration [41,42] . During regeneration, the lost specialized tissue is replaced by the proliferation of the nearby undamaged specialized cells [43]. If the inflammatory senescence ensues, periodontal cells proliferation will be halted which result in a massive suppression of regeneration and inevitable loss of tooth supporting structure.

It is suggested that p53 expression associated with DNA damage is a prevalent phenomenon in chronically inflamed human gingiva, and that apoptosis may be a relevant process for the maintenance of local immune homeostasis at sites of chronic bacterial challenge in vivo [44].

Cheng et al. (2015) found that gingival fibroblast may resist apoptosis in the initial stages of inflammation; however, cell apoptosis in gingival tissues might take place if the DNA damage is un-repairable [45]. In Cheng's study, gingival fibroblasts were provoked by LPS *in vitro* to simulate acute inflammation (gingivitis). This stimulation resulted in building up reactive oxygen species (ROS), which represents oxidative stress in gingival fibroblasts. DNA damage was expected as a result of ROS accumulation. A time-dependent accumulation of DNA double- stranded breaks was evident after 48 h of LPS-induced oxidative stress. DNA damage may potentiate apoptosis or senescence as a factor of p53 status [46]. As expected, p53 had increased as a response to acute LPS exposure. However, apoptosis was detected after recurrent and chronic LPS exposure.

3. CONCLUSION

Cellular senescence is a tumour suppressor mechanism to stop incipient cancer cells from proliferating [13,47,48,49]. Senescent cells secrete proinflammatory cytokines which trigger a variety of cellular responses. The proliferative rate, migration, and invasion of premalignant cells are enhanced when they are co-cultured with senescent fibroblasts [34,37,38]. However, unlike cancer cells, senescent periodontal cells ultimately undergo hastened apoptosis in an evolutionary attempt to escape mutagenic changes. Periodontal cells apoptosis is subsequently manifested by the gum recession and alveolar bone loss.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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