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Effect of Hypoxia on the Induction of Premature Cellular Senescence in the Cells of Periodontium during Orthodontic Tooth Loading

Luay Thanoon Younis[1*], Faisal Ismail Elsayed Bahnasi[1], Aida Nur Ashikin Abd Rahman[1] and Mohamed Ibrahim Abu Hassan[1]

[1]Faculty of Dentistry, Universiti Teknologi MARA, Sungai Buloh Campus, 47000 Sungai Buloh, Malaysia.

Authors' contributions

This work was carried out in collaboration among all authors. Authors LTY and FIEB designed the study and wrote the first draft of the manuscript. Author LTY managed the literature searches. Authors MIAH, ANAAR, FIEB and LTY read and approved the final manuscript.

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ABSTRACT

During orthodontic treatment, application of forces to move the teeth within the dento-alveolar complex is associated with structural and biological tissues changes. One of the main changes is hypoxia which is due to the compression of blood vessels resulting in insufficient oxygenation of the tissues. On orthodontic loading, hypoxia causes irreversible cell cycle arrest (or so called cellular senescence) and apoptosis of the tissue cells around the teeth especially on the compression zone. Excessive hypoxia, in turn leads to a massive, an inevitable and detrimental destruction of tissues supporting the tooth such as remarkable root resorption. This mini-review is highlighting the effect of orthodontic force in inducing a local hypoxic environment and its consequences in causing cells death of the periodontal cells.

Keywords: Periodontal ligament; hypoxia; cellular senescence; tooth movement.

**Corresponding author: E-mail: drluay@uitm.edu.my;*

1. INTRODUCTION

Orthodontic treatment requires moving or aligning the teeth into a favorable position aesthetically and functionally [1]. To achieve that, the teeth are subjected to forces to push them to their new position. When the force is placed on the crown of the tooth, initial tipping occurs. The periodontal ligament (PDL) is compressed adjacent to the alveolar bone on the side toward which the force is directed [2]. On the opposite side, away from the force direction, the PDL is widened, experiencing tension. Blood vessels are compressed and blood flow is decreased on the compression side, hence less oxygen supply is received on that side [3].

2. IMPACT OF HYPOXIA ON CELLS

Oxygenation of tissues is one of the most important processes that occur within the human body [4]. Insufficient oxygenation of tissues affects negatively the metabolic processes and cellular functions of the tissues. Hypoxia describes the reduction of oxygen level in tissue due to decreased oxygen partial pressure beyond the physiologic level [5]. Hypoxic cells release cellular mediators, such as the hypoxia-inducible factor 1 (HIF-1), a heterodimer composed of HIF-1α and HIF-1β [6,7].

HIF-1 formation is influenced by the subunit HIF-1α. During hypoxia, HIF-1α is stabilized and aggregate, while in case of normoxia, HIF-1α undergoes proteolysis [8]. HIF-1α degradation takes place through binding to the Von Hippel-Lindau tumor suppressor protein (pVHL) which allow the binding of a polyubiquitin chain to HIF-1α [9]; subsequently, this facilitate the anchorage of HIF-1α to the proteasome which degrades HIF-1α [6,10].

During hypoxia, the aggregating HIF-1α binds to HIF-1β, creating the active form of transcription factor HIF-1 which induce endothelial cell proliferation, promote angiogenesis, and enhance cell survival [11]. Paradoxically, in certain instances, HIF-1 may provoke apoptosis to prevent cells mutations which caused by the reduction of oxygen level in tissue [12,13]. Hypoxia subsequently reduces glycolytic activity and ATP production; hence, it reduces cellular energy. Therefore, the normal cell cycle will be disturbed that would shorten the cell life span [14].

3. DESTROYING EFFECT OF CELLULAR SENESCENCE AND APOPTOSIS

Irreversible cell cycle arrest (cellular senescence) is a permanent state of cell cycle arrest. Senescence deteriorates the life cycle of cells [15], suppresses new DNA or collagen formation and limit cells migration [16]. Senescent cells actively secrete several cytokines, chemokines, and matrix-remodeling enzymes known as the senescence-associated secretory phenotype (SASP) [17], which are thought to be responsible for stimulating the clearance of senescent cells by the host immune system or to provoke autocrine signalling to sustain the senescent state [18].

Accumulation of senescent cells plays a role in reducing the self-renewal / regeneration process of the lost tissues, because these cells are unable to renew their DNA. They are also unable to produce the regular types of proteins used to re-build the tissues [19]. DNA damage potentiates the release of pro-inflammatory cytokines, senescence and apoptosis [20,21]. High level of cementocytes/cementoblasts apoptosis is associated with adverse orthodontic root resorption and upregulation of caspase 3 and caspase 8 which were induced by heavy or optimum orthodontic force [22,23]. Extreme levels of reactive oxygen species were observed on the compression zone that subsequently resulted in cell cycle arrest and apoptosis of the cells involved in the zone [24]. Stretching force may also cause apoptosis. Experiments done by stretching human PDL resulted in the induction of early apoptosis of PDL cells which increased. in a time and force-dependent manner in response to stretching strain within 6 h, and then apoptosis decreased at 12 h [25].

Constant extreme levels of reactive oxygen species may lead to telomere erosion [26-28]. Telomere shortening may elicit a DNA damage response (DDR) that stimulates inhibitors of cell cycle progression, a process which ends up with senescence growth arrest [29]. Continuous loading and stresses eliciting a DDR can also induce a programmed cell death, apoptosis [30]. Apoptosis plays a critical role during normal development and aging and as homeostatic mechanism to maintain cells populations of adult tissues [31]. It is characterized by several distinct changes in cell morphology, such as cell shrinkage, plasma membrane blebbing, and nuclear condensation, in response to the

stimulation of several factors and receptors specific for the apoptotic pathway [32]. Apoptosis is a step ahead to remove the damaged, degraded or pre-neoplastic cells [31,33]. This will be followed by phagocytosis to clear the apoptotic senescent cells [34,35].

4. IMPACT OF ORTHODONTIC FORCES ON PERIODONTAL LIGAMENT BLOOD VESSELS

Heavy orthodontic force leads to the constriction or closure of the microvasculature of the periodontal ligament in the pressure area. Diminished blood supply results in local ischemia, hypoxia, focal areas of necrosis and histological features of hyalinization [36]. Hyalinization is associated with death of the cells under compression. As a result, a limited osteoclast differentiation occurs within the compressed PDL space [37]; together with a delayed recruitment/differentiation of osteoclasts from adjacent bone marrow space. Subsequently, these events result in hampering osteoclastgenesis [38]. Therefore, tooth movement may delay and take place 7–14 days after the application of a heavy orthodontic loading [39]. By contrast, light orthodontic forces would not cause total blood supply impairment; hence recruitment of osteoclasts either locally within the PDL or from bone marrow is likely to occur in the compression zone [40]. Consequently, tooth movement usually takes place within 2 days after light force application [3].

5. CONCLUSION

The level of hypoxia induced during orthodontic loading plays a crucial role in determining the rate of tooth movement and the scale of cells death/proliferation of periodontal tissues supporting the tooth. Hence, hypoxia is a pivotal in shaping the aesthetic outcomes of orthodontic loading and can be used as a target to improve and boost the orthodontic treatment.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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