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Chapter 15

Role of the Hypoxia-Inducible Factor in Periodontal Inflammation

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http://dx.doi.org/10.5772/66037

Abstract

Human periodontitis is a chronic inflammatory disease induced by opportunistic Gram-negative anaerobic bacteria at the tooth-supporting apparatus. Within the gingivitis-affected sulcus or periodontal pocket, the resident anaerobic bacteria interact with the host inflammatory reactions leading to a lower oxygen or hypoxic environment. A cellular/tissue oxygen-sensing mechanism and its appropriate regulation are needed to assist tissue adaptation to natural/pathology-induced variations in oxygen availability. In this chapter, we reviewed the biological relevance of hypoxia in periodontal/oral cellular development, epithelial barrier function, periodontal inflammation, and immunity. The role of hypoxia-inducible factor-1α in pathogen-host cross talk and alveolar bone homeostasis was also discussed. The naturally occurring pathophysiological process of hypoxia appeared to entail fundamental relevance for periodontal defense and regeneration.

Keywords: cell hypoxia, chronic periodontitis, hypoxia-inducible factor-1, alpha subunit

1. Introduction

Regardless of the oxygen sources, when an animal acquires oxygen through its breathing apparatus, the oxygen will have to pass under a reducing partial oxygen pressure (pO_2) gradient from the source via circulation to different organs and then tissues and cells. In mammals, such as rats, inspired pO_2 is around 21.3 kPa at sea level. When blood flows through the alveolar capillaries, it drops to approximately 14 kPa and is then progressively reduced to 2.1, 1.3, and 0.27–3.3 kPa in the spleen, thymus, and retina, respectively [1, 2], while in the brain, it may be as low as 0.05–1.07 kPa, depending on the cranial location [3].

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Due to the colonization by subgingival biofilm, oxygen is persistently consumed to various extents by the facultative anaerobic microbes within the periodontal sulcus (2.33–8.40 kPa). In the gingivitis-affected sulcus or periodontal pocket, the inflammation induced by the residential anaerobic bacteria with or without microulcerations or wounding leads to an even lower oxygen tension [4]. At the tissue level, the availability of oxygen is dependent on the distance from the oxygen-supplying blood vessels. Although the diffusion distance of oxygen *in vivo* is estimated to be 100–200 μm, a pO_2 of almost zero has been recorded in tissues 100 μm away from the nourishing blood vessels [5]. Therefore, a cellular/tissue oxygen-sensing mechanism is needed to assist tissue adaptation to nature/pathology-induced variations in oxygen availability.

In humans, a drop in oxygen concentration in the atmosphere is sensed by the carotid body at the bifurcation of the carotid arteries, which then increases the rate and depth of breathing. At the levels of tissues and cells, including the human periodontium, such adaptive responses to low oxygen tension or hypoxia are mainly mediated through a key cellular transcription factor named the hypoxia-inducible factor (HIF) [6].

2. Hypoxia in the oral/periodontal environment

Oxygen is an essential molecule for survival. Mammals—including humans—depend on oxygen for electron transport, oxidative phosphorylation, and energy generation. Variations in tissue oxygen needs are attributed to a number of physiological or pathological states, meaning that the tissues concerned have to be able to adapt to various O_2 environments including hypoxia. To survive, mammalian cells evolved in such a way that cellular O_2 availability or homeostasis could be monitored and tightly regulated [7]. This is made possible by a cellular HIF system. Cellular hypoxia, or a lower than "normal" concentration of O_2 in cells, occurs commonly and could induce significant changes, immediate or delayed, on cellular processes, including cell growth and apoptosis, cell proliferation and survival, pH regulation and energy metabolism, cell migration, matrix and barrier function, angiogenesis, and vasomotor regulation [8–13]. These biological processes involve active responses by the body to secure an additional oxygen supply via circulation. Such dynamic processes of cellular/tissue oxygen monitoring, O_2 consumption, and delivery, corresponding to the respective cellular/tissue functional state, are tightly controlled to ensure proper survival of the multicellular organism concerned [14].

As described earlier, the normal tissue/cellular pO_2 levels in mammals are dependent on their location and physiology and, hence, vary among different human body compartments and cell/tissue conditions [15]. Hypoxia in oral cells/tissues is, in fact, a common occurrence [6]. The local hypoxic microenvironment is considered a consequence of growth/development, wound healing, smoking habits, or concurrent oral inflammation/infection/diseases.

Taking oral cellular development/regeneration as an example, the blood vessel network is promoted by vascular endothelial growth factors (VEGF) secreted by stem cells from apical papilla under hypoxia, suggesting a role of hypoxia in pulp revascularization and bioengineered pulp

http://dx.doi.org/10.5772/66037

replacements [16]. On the other hand, it is reported that extreme hypoxia-like response induced by the chemical cobalt chloride ($CoCl_2$) could stimulate periodontal ligament (PDL) stem cell cytotoxicity through mitochondria-apoptotic and autophagic pathways involving HIF-1α [17]. During pathological processes, it is reported that a low oxygen level may regulate cell migration of oral cancer cells, thus influencing the invasion and metastasis in malignant oral lesions [18].

With reference to growth, increasing evidence shows that certain hormonal regulation could be interfered with hypoxia or HIF [19]. For instance, it is reported that growth hormone expression in lymphocytes and parathyroid hormone-related protein in articular chondrocytes can be induced by hypoxia [20, 21]. We postulate that if similar biology could be expressed in the head and neck region, HIF or hypoxia may bring profound effects on the growth and development of orofacial structures.

3. Hypoxia and chronic periodontal inflammation

Metabolic shifts under hypoxia are common occurrences in the periodontal inflammatory process as a result of the imbalance between the tissue oxygen supply and consumption [22]. The accumulation of intracellular HIF-1 promotes the transcription of a spectrum of genes to maintain cellular homeostasis. Hypoxia induces the expression of a number of angiogenic factors to improve the blood supply in needed areas including inflamed periodontium [6]. These include VEGF, platelet-derived growth factor (PDGF), and angioprotein-1 and -2. Related genes produce controlling perfusion, such as the PDGF-β receptor, cyclooxygenase-2, and nitric oxide synthase (NOS), of which NOS modulates vascular smooth muscle cells' functions and reacts to changes in the cellular HIF-1 level [23]. Moreover, HIF activation promotes a metabolic switch to reduce oxygen consumption by shifting energy metabolism from aerobic respiration to glycolysis. Activation of HIF also upregulates the expression of pyruvate dehydrogenase kinase, which reduces the incorporation of pyruvate into the citric acid cycle [24]. This metabolic switch is essential for the hosts' defense because such HIF-1α–regulated glycolytic metabolism is required in B cell development [25] and T cell metabolism [26].

Under a chronic inflammatory state, hypoxia induces protective cellular responses or a local defense. However, if the cause of inflammation cannot be eradicated, such hypoxic cell/tissue reactions contribute to the pathophysiology of inflammation and, hence, disease pathogenesis [27]. A similar scenario can be observed within the human periodontium in periodontitis. Periodontitis is characterized by chronic inflammation of the tooth-supporting tissues, initiated by a multitude of Gram-negative anaerobic pathogens including *Aggregatibacter actinomycetemcomitan*s, *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, and so on [28]. At sites where a chronic inflammatory reaction could be found, oxygen consumption is elevated and blood perfusion is stimulated, but the actual local microcirculation could be compromised [29]. This local tissue pO_2 change is partly due to increased oxygen consumption, including oxygen usage by both resident cells and infiltrated defense cells, and partly because of diminished oxygen availability due to endothelial damage and vasoconstricted microcirculation.

Local hypoxia in periodontitis in turn enhances the anaerobic Gram-negative pathogens' survival and further lowers the oxygen tension at the vicinity. The tissue hypoxia in periodontal disease has been characterized by increased HIF-1α protein that is detectable in periodontitis-affected tissue biopsies using Western blot and anti–HIF-1α immunostaining [6, 30]. Myeloid cell lineage of HIF-1$\alpha^{-/-}$ (deprived) mice had impaired immune effector molecules, such as nitric oxide (NO) and tumor necrosis factor-alpha (TNF-α) production, thus reducing their bactericidal capability [31]. Therefore, the ability to adapt to a reduced oxygen supply, which maintains immune cell surveillance capability in all tissue environments, is important and necessary in the successful elimination of pathogens [32].

Proinflammatory cytokines and matrix metalloproteinases (MMPs) act as mediators for the inflammation process or play a role in extracellular matrix degradation, respectively. Researchers often investigate the levels of such biological markers in the periodontium in attempts to gauge the severity of periodontal disease and monitor periodontal treatment outcomes [33]. Recent studies reported that a hypoxic environment may upregulate proinflammatory cytokines and MMPs' expression from host cells during periodontal disease [34]. The idea was that hypoxia further encourages lipopolysaccharide (LPS)-induced TNF-α, interleukin-1β, and interleukin 6 (IL-6) expressions via LPS toll-like receptor (TLR) interaction that, in turn, activates the nuclear factor kappa B (NF-κB) pathway in human PDL cells upon exposure to the aforementioned Gram-negative bacterial surface component [35–37].

At the collagen destruction front, periodontal epithelial cells could produce MMPs in response to bacteria-induced activation of pathogen-associated molecular patterns (PAMP) including TLRs. These host enzymes contribute to the extracellular matrix degradation that accommodates local inflammatory reactions, as well as the later tissue remodeling that ensues once inflammation stops [38, 39]. Inhibition of HIF-1α activity by chetomin, a *Chaetomium* metabolite that can incapacitate tumor cells' hypoxic adaptation or knockdown HIF-1α gene expression by small, interfering RNA, could markedly attenuate the production of LPS- and nicotine-stimulated MMPs and prostaglandin E_2 from PDL cells. Such observations suggest the possibility of HIF-1α being a potential target in periodontal tissue destruction associated with smoking and dental plaque [40]. Further supporting the idea that hypoxia may be one of the key biological responses in periodontal inflammation.

Certain periodontopathogens, other than acting as effective mediators of periodontal inflammation, are capable of doing more harm to a host under a low pO_2 environment. For instance, *P. gingivalis* LPS under hypoxia increases PDL fibroblasts' oxidative stress and induces a reduction of catalase, indicating a collapse of the protective machinery favoring the increase in reactive oxygen species (ROS) and the progression of inflammatory oral diseases [41].

Considering the healing of oral wounds, several studies reported that the biological process in general could be enhanced or accelerated under hypoxia via HIF-1 [42, 43]. For example, the wound healing of rat palatal mucosa was enhanced by the hydroxylase inhibitor dimethyloxalylglycine, a HIF-1α stabilizer, under a hypoxic environment, and this enzyme was reported to induce hypoxia-mimetic angiogenesis [44]. With reference to hard tissue

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healing, $CoCl_2$ triggered the expression of angiogenic mediators and bone turnover-related genes, which promoted fracture healing and repair *in vivo* [45]. The research report also indicated that, during distraction osteogenesis, an angiogenic effect and bone healing could be promoted by conditioned media collected from dental pulp cells under hypoxia [46]. These findings implied the possibility that a low tissue oxygen level may act as a biological signal, promoting soft and hard tissue healing, including that of the orofacial regions, mediated through inflammation.

4. Hypoxia and periodontal immunity

Hypoxic responses or HIF is reported to be strongly related to innate human responses, with low oxygen modulating energy metabolism and various genes' expression within defense cells that, in turn, dictate the immune performance and the host protection outcomes [47]. The biological impact of low pO_2 on T cells' functions was reflected by the HIF-1– and adenosine receptor–modulated effects [48]. Indeed, both lymphocytes and myeloid cells were affected and the hypoxia-induced adaptive immune response changes would interfere or affect the innate immunity. The relevance of hypoxia in pathological processes was well established upon the appreciation that wounds, infectious loci, and tumor growth each involved extremely low oxygen tension [1].

It has been well appreciated that low oxygen tension is common at inflamed periodontitis sites [4]; thus, the corresponding local immune responses must adapt to the hypoxic challenges. As mentioned above, hypoxia plays an important role in modulating the cellular activities of innate and adaptive immunity, so the impact of low pO_2 in periodontal immune responses is quite significant.

Oral innate immunity is the first line of defense against periodontopathogens, which functions to recognize, attenuate, and eliminate the nonself invaders and to trigger downstream immune responses. Granulocytes and monocytes/macrophages are the main cell types for innate periodontal immunity [49, 50]. When extensive inflammation takes place, these cells have to travel into the tissue compartment with low pO_2 (i.e., the infected area) to provide defense and wall-off the invasion. To prevent the invasion, intense energy metabolism has to occur within the involved innate defense cells. An appropriate hypoxic cellular reaction and adaptation is, therefore, very important in the periodontal innate immune cells, which develop functional and survival responses regulated by the oxygen sensor HIF [51].

Defense cells rely heavily on glycolysis for the production of ATP to compensate for the limited oxidative metabolism in hypoxia. Immune cell energy metabolism appeared to significantly influence its corresponding response. As a critical modulator for the expression of glycolytic enzymes, the absence of HIF-1α leads to a significant reduction of ATP availability in myeloid cells [52]. It was reported that a knockdown of HIF-1α protein led to a nullified IL-6 production when exposed to LPS, suggesting that HIF-1α supported the LPS-dependent expression

of IL-6 that, in turn, prevented the depletion of ATP and, therefore, protected myeloid cells against LPS/TLR4-induced apoptosis [53]. In human monocytes, LPS and hypoxia synergistically activated HIF-1 through p44/42 mitogen-activated protein kinases (MAPK) and NF-κB; however, repetitive exposure to LPS could induce tolerance to bacterial endotoxins and, hence, impair corresponding HIF-1α induction, which reduces the ability of monocytic cells to survive and function under low oxygen [54, 55].

To combat invading pathogens, HIF also promotes polymorphonuclear neutrophil (PMN) recruitment via the restoration of blood flow at inflamed tissues and enhances neovascularization. With hypoxia, the HIF restored perfusion also facilitates PMNs' diapedesis [56, 57]. Furthermore, PMN apoptosis was attenuated under hypoxia, with HIF-1α reported to be a protective factor in the regulation of its functional longevity [58]. Such longevity regulation involved NF-κB signaling that was found to be essential in constitutive HIF-1 protein translation [58, 59].

The cellular stress-related transcription factor NF-κB is closely related to hypoxia despite the fact that the relationship is not yet completely understood. It was reported that classical or canonical NF-κB activation under the stress of hypoxia often involves the activation of transforming growth factor-B-activating kinase and the inhibitor of κB kinase (IKK) complex [60]. In addition to classical NF-κB signaling, the noncanonical NF-κB pathway could be activated by hypoxia independent of HIF-1α via NF-κB-inducing kinase and IKK homodimer activation [61]. ROS, a key inflammatory regulator in chronic periodontal inflammation, is confirmed to mediate HIF-1α induction dependent on NF-κB [62].

Dendritic cells (DCs), a group of professional antigen-presenting cells, are key members that enable cross talk between the innate and adaptive immune systems. They present an antigen to activate naive lymphocytes and assist in the development of specific adaptive immune responses to pathogens. Hypoxia has been found to play an important role in the maturation and cytokines release of DCs, but the mechanism of the related divergent effects still remains controversial [63]. Studies found that the knockdown of HIF-1α in DCs inhibited their maturation and significantly impaired their capability to stimulate allogeneic T cells, probably because of the reliance on the HIF-controlled glycolysis [64, 65]. In contrast, it is reported that low oxygen tension inhibited the DCs' defense against LPS, but strongly upregulated the production of proinflammatory cytokines in the cells involved [66]. Similar results can be observed in the human antifungal response: hypoxia at the site of *Aspergillus fumigatus* infection inhibited the full activation and function of DCs [67]. These findings suggest that hypoxia may function as a regulator against DCs' mediated immune overreaction.

Lymphocytes are known to be involved in periodontal tissues' health homeostasis, and their functional upset was believed to be associated with periodontal pathogenesis. An HIF-1α deficiency was associated with abnormal B cell development, which led to autoimmunity in a mouse model [68]. A recent study also indicated that T cells' HIF-1α regulation played a critical role in avoiding cardiac damage in diabetic mice [69]. We postulated that a similar protection mechanism may be called to function in diabetic periodontium. Therefore, hypoxia or HIF-1α regulation in DCs and lymphocytes may confer a marked impact on the innate and adaptive cellular immunity in periodontal tissues, with the exact mechanism yet to be elucidated.

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5. HIF and epithelial barrier function

The human periodontium is a unique environment for microorganisms. One special characteristic is the nonshedding tooth's hard tissue surface, allowing microorganisms to remain *in situ*. To counter the invasion of possible pathogens, the corresponding epithelial tissues build up an effective barrier against the colonizing microbes [70]. With appropriate daily oral hygiene, the continued host-bacteria interaction maintains the periodontium in health or low grade/subclinical inflammation. Those who have inadequate oral hygiene tip the balance toward a proinflammatory state, resulting in inflammatory responses that present clinically as gingivitis. Due to poor oral hygiene and inherited or acquired risks, approximately 20% of the human population, develop chronic periodontal inflammation with tissue destruction resulting in what is known as periodontitis [71]. Regardless of the host-parasitic interaction outcomes, humans and their complex residential microflora have coevolved over time [72].

TLRs on the periodontal/gingival epithelial cells recognize the conserved molecular patterns on pathogenic bacteria that are also known as PAMP, limiting invasion of the microbes, and help to maintain oral health [73]. Other than providing a physical barrier to the outside world, the skin and mucosal membrane produce a number of antimicrobial peptides (AMPs). The AMPs have a broad activity spectrum against both Gram-negative and Gram-positive bacteria colonization, enveloped viruses, fungi, and even transformed or cancerous cells.

It has become clear that AMPs, such as defensins and the cathelicidins family of peptides—especially LL-37, play important roles independently or together in maintaining oral health, including antimicrobial effects and mediating chemotaxis of the immune cells [74, 75]. Researchers reported that a deficit of cathelicidin allowed infection by *A. actinomycetemcomitans* and the development of severe periodontitis [76].

The epithelial cells in both oral mucosa and the gut are relatively hypoxic [4, 77]. The corresponding oxygen gradient between the epithelium and subepithelial perfusion in turn provides a matching cellular HIF-1α gradient in the tissues involved and perhaps the respective physiological function in cellular homeostasis. In human intestine, when the oxygen supply was impaired due to stasis of the local perfusion, the affected site would be left with increased susceptibility to infection [78]. As such, appropriate adaptive response to hypoxia at the epithelial barriers is vital. HIF-1α functions as an intracellular pO_2 sensor, enabling appropriate adaptive responses for cell survival. Using prolyl hydroxylase inhibitor or AKB-4924, a HIF-1α stabilizing agent, production of cathelicidin and β-defensin in uroepithelial cells was significantly enhanced, and *Escherichia coli* infection was deterred [79]. On the other hand, a deletion of HIF-1α in skin keratinocytes decreased the production of cathelicidin and led to increased susceptibility of infection by a group of *A. Streptococcus* [80]. Naturally occurring low-grade hypoxic reaction and hence HIF-1 accumulation in gut/urogenital/skin epithelia followed by corresponding HIF-1 downstream genes expression were recently postulated to be a key concept that underpin biological barrier function of intestinal epithelium [77, 81]. If in case the same biological process is also in action at the dentogingival junction, HIF-1 would contribute in the periodontal epithelial barrier function that maintains periodontal health and prevents oral pathogenic microorganism invasion.

Besides AMPs, there are also many factors regulated by HIF at the periodontal epithelial barrier. For instance, trefoil factors (TFF), secreted molecules from mucous epithelia, were involved in oral protection against tissue damage and immune response [82, 83]. Their expression was influenced by cellular pO_2 levels. It was reported that HIF-1 mediated the induction of TFF gene expression and provided an adaptive link for the maintenance of the barrier function during hypoxia of gastric/intestinal lining cells [84, 85]. Salivary mucins form a protective layer on the oral surfaces including that of oral sulcular and junctional epithelia, which serve as a physical barrier against bacterial invasion and function as essential antimicrobial macromolecules [86, 87]. Similar to TFF, mucins' production was upregulated in hypoxia [88]. This evidence indicated that the epithelial barrier cells' HIF regulation may constitute an important defense mechanism. Such oral protective machinery could contribute an additional local defense mechanism against periodontal diseases.

6. HIF in the periodontopathogen-host cross talk

Hypoxia is common in the inflammatory microenvironment, and appropriate cellular responses to hypoxia contribute to mucosal defense through the oxygen-sensitive transcription regulator HIF-1α. Hypoxia increases the expression of certain TLRs on human gingival keratinocytes [89], the interaction of low oxygen with appropriate bacteria ligands *in vivo* could potentially enhance the production of cytokines and antimicrobial peptides and thus, in theory, could help to eliminate or reduce the pathogen-related concerns.

The human periodontium is persistently exposed to risks of infection; the source is the commensal and pathogenic oral microorganisms constituting the dental plaque adhering onto teeth. Bacterial components, such as LPS and peptidoglycans, released by bacteria recognized by TLRs on the surface of host cells could instigate the inflammatory reaction cascade [38]. Under steady-state conditions, activation of TLRs by commensal bacteria is critical for the maintenance of oral health [73]. Thus, TLRs provide the first line of defense in periodontal health maintenance. When stimulated, such as via TLRs recognition, PMNs exhibit increased chemotaxis and proinflammatory cytokine production [90].

Our group previously reported that bacterial components may induce HIF-1α accumulation during periodontal disease pathogenesis independent of hypoxia [91]. An immunoprecipitation experiment showed that human gingival fibroblasts' HIF-1α accumulation was induced by LPS in the dose- and time-dependent manner. The accumulation of HIF-1α may be modulated by TLRs and pattern recognition in certain ways, since a TLR4 neutralizing antibody could attenuate such an effect from *E. coli* LPS. Moreover, the expression of TLR4, CD14, and MD-2 in both human gingival keratinocytes and fibroblasts is confirmed, and the TLR4 protein expression in periodontal epithelial compartments appeared different *in vivo*, indicating that LPS sensing in the dentogingival front in health could be heterogeneous in nature [92].

A recent study on oral squamous cell carcinoma provided a novel mechanism of HIF-1 and TLRs' interplay. It was reported that the activation of TLR3 and TLR4 stimulated the expression of HIF-1 through NF-κB, while HIF-1 accumulation increased the expression of TLR3

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and TLR4 through direct promoter binding [93]. This observation provided evidence that the TLR3/4-NF-κB pathway may form a positive feedback loop with HIF-1, which theoretically could also happen in the periodontal tissue. Further investigations are needed to confirm such a postulation.

7. HIF and bone homeostasis

HIF appears to play important functional roles in bone homeostasis. The regulatory system seemed complex because HIF is known to stimulate both bone resorption and regeneration, the two essential biological processes in bone homeostasis/repair.

It is reported that a lack of oxygen in periodontal tissues may contribute to alveolar bone resorption and, in theory, accelerated periodontitis [94]. Chromatin immunoprecipitation showed that HIF-1α binds to the receptor activator of the NF-κB ligand (RANKL) promoter region, and mutations of the putative HIF-1α binding site prevented hypoxia-induced RANKL transcriptional promotion, thus suggesting that HIF-1α mediates hypoxia-induced upregulation of RANKL expression and enhanced osteoclastogenesis [95]. Furthermore, it was reported that hypoxia triggered the differentiation of peripheral mononuclear blood cells into functional osteoclasts in a HIF-dependent manner [96].

Conversely, in recent studies, HIF-1α was considered to be a critical mediator of neoangiogenesis required for bone regeneration. Exposure of PDL stem cells to hypoxia improved their osteogenic potential, mineralization and paracrine release, and the mitogen-activated protein kinase kinase/extracellular signal-regulated kinase, and p38 MAPK signaling pathways were involved [97–99]. It was suggested that HIF, HIF mimicking agents, or HIF stabilizing agents were considered triggers for the initiation and promotion of angiogenic-osteogenic coupling [100, 101]. A recent animal study reported new bone and vessels formation induced by the overexpression of HIF-1α via adenovirus, leading to enhanced alveolar bone defect regeneration [102]. A similar result was reported from a study investigating bone loss arrest in ovariectomized C57BL/6 J mice via activated HIF-1α and Wnt/β-catenin signaling pathways [103]. Cementoblastic differentiation of human dental stem cells, a key cellular mechanism concerning periodontal regeneration, was reported to be stimulated by hypoxia in an HIF-1-dependent manner [104].

Taken together, these reports suggested that HIF-1α plays a part in alveolar bone homeostasis, resorption, or periodontal regeneration, while the exact nature of HIF-1α's roles in these processes and the way in which the related pathophysiological processes were regulated warrants further investigations.

8. Conclusions

It seems that tissue/cellular hypoxia, or more specifically, expression of HIF-1α, is involved in periodontal inflammation. HIF-1 not only mediates the host's immune response, providing

defense against microbial invaders and maintaining periodontal health, but also could facilitate periodontal-supporting tissue breakdown and, hence, the progression of periodontitis.

Putting all currently available information together, it appears that hypoxia could bring either beneficial or detrimental effects on periodontal health. At the present juncture, we hypothesize that similar to the intestines, a low-grade hypoxia or low level of HIF-1 is expressed in the human periodontium for baseline defense or to act as a surveillance "alarm" against significant invasion or periodontitis. A successful immune response that associates with appropriate HIF-1 mediated biological reactions would result in periodontal health maintenance. Over- or underactivation of the immune system with or without the corresponding dysregulation of HIF-1 biology in tissues as well as alveolar bone, however, could give rise to periodontal tissue damages. We also postulate that other risk indicators related to progression of periodontitis, such as smoking and diabetes mellitus, under the influence of periodontal plaque biofilm, may exert their harmful effects via inappropriate activation of the HIF pathway. Effects of these risks indicators are particular relevant as they often undermine proper periodontal healing/regeneration after therapy [105].

The mechanisms underlying the role of HIF-1 and periodontal defense/pathogenesis, however, remain elusive. Further investigations are, therefore, required in these directions to decipher what leads to the unfavorable immune reactions in periodontal inflammation and the reasons why that came about. Such new knowledge not only fosters the further understanding of human periodontal disease pathogenesis, but may provide novel therapeutic strategies that take advantage of the new understandings of periodontal HIF biology, an important element relevant for periodontal defense and regeneration.

Acknowledgments

The work described in this paper was substantially supported by grants from the Research Grants Council of the Hong Kong Special Administrative Region, China (HKU 17113114), the University of Hong Kong Small Project Funding (201007176307, 201109176129), and Seed Funding (200911159126).

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