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# The Mechanism of Nrf2/ARE Signaling Pathway in Periodontitis with Atherosclerosis

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**Abstract:** Background Periodontitis is a high prevalence disease, affecting up to 80% of the world's population. Recently studies have shown a connection between periodontal disease and cardiovascular disease, as oxidative stress plays an important role in chronic inflammatory diseases such as periodontal disease and cardiovascular disease. Nuclear factor erythroid 2 - related factor 2 (Nrf2) is the core transcriptional regulator of endogenous antioxidant system and plays a cellular defense role in antioxidant, anti-inflammatory and immune response. Objective To explore Nrf2/antioxidant responsive element (ARE) signaling pathway in periodontitis or periodontitis complicated with atherosclerosis. Method With "Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2), Periodontitis, Atherosclerosis, Oxidative Stress" as the search terms, the authors searched related articles published during 2016-2021 in PubMed, CNKI, Science Direct and other databases by computer, and made the following review through screening, induction and summary. Result & Conclusion Nrf2/ARE signaling pathway is one of the important mechanisms connecting chronic periodontitis and atherosclerosis. Nrf2 can slow down the occurrence and development of periodontitis by promoting osteoblast differentiation, inhibiting osteoclast activation, regulating mesenchymal stem cell proliferation, differentiation and apoptosis. However, inhibition of Nrf2/ARE signaling pathway may increase the risk of periodontitis with atherosclerosis by destroying the integrity of vascular endothelium, increasing lipid accumulation and promoting inflammation.

**Keywords:** Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2), Periodontitis, Atherosclerosis, Oxidative Stress

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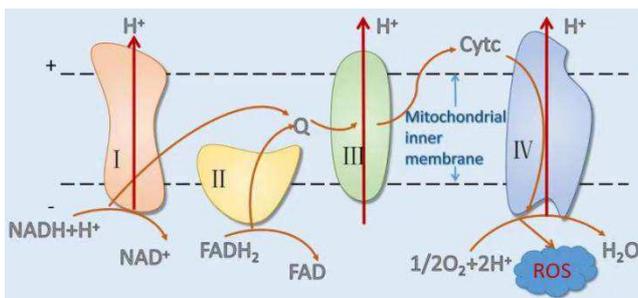
## 1. Introduction

Periodontitis is caused by plaque biofilm, which is a chronic, destructive, and inflammatory disease affecting a large portion of the adult population. And it is a major cause of tooth loss in adults. Periodontitis usually causes bacteremia, and two or more periodontal disease bacteria are detected in cases of heart valves and aortic aneurysms. Therefore, it has been recognized that periodontal infection may also affect the progression of cardiovascular disease (CVD). In the pathogenesis of periodontitis, oxidative stress is an

inseparable part, which is a consequence of aggravated inflammation caused by excessive production of reactive oxygen species (ROS) [1, 2]. Nuclear factor erythroid 2 - related factor 2 (Nrf2), as an important endogenous antioxidant transcription factor, can prevent ROS from damaging cells by interacting with antioxidant responsive element (ARE). This paper reviews the role of Nrf2/ARE signaling pathway in periodontitis or periodontitis complicated with atherosclerosis.

## 2. Effect of Oxidative Stress on Periodontitis

Under normal circumstances, redox homeostasis, which is mainly based on the balance of ROS generation and scavenging, is very important to human health. Oxidative stress (OS) tends to oxidative state, resulting in excessive ROS in the body, directly or indirectly causing cell damage (Figure 1). ROS plays a critical role on the physiological processes of eukaryotic cells, such as cell signal, signal transduction, cell differentiation, apoptosis and autophagy. Excessive ROS will inhibit antioxidant enzymes and lead to antioxidant imbalance. Periodontitis is closely related to redox imbalance [3]. The normal neutrophil-mediated response to bacteria involves the production of ROS. ROS can directly damage periodontal tissue by producing toxic effects or directly degrading extracellular matrix (ECM). The toxic effects of ROS include destroying the stability of tissue cells by oxidizing proteins and stimulating ECM decomposition by decomposing glycosaminoglycans and mechanism proteases. ROS can also cause protein damage in gingival tissue by indirectly enhancing the activity of matrix metalloproteinases (MMP) [4]. Hyperresponsiveness and excess ROS production likely contribute to relapse after chronic periodontitis (CP) treatment. Excessive ROS plays a central role in triggering inflammatory and activating of NF- $\kappa$ B signal pathway, and can activate protein kinase C (PKC), mitogen activated protein kinase (MAPK) and other pathways. Downstream inflammatory cytokines are produced, such as interleukin 6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and Intercellular adhesion factor-1 (ICAM-1). And these inflammatory factors can attract more neutrophils to the site of inflammatory destruction, resulting in further destruction of periodontal tissue [5].



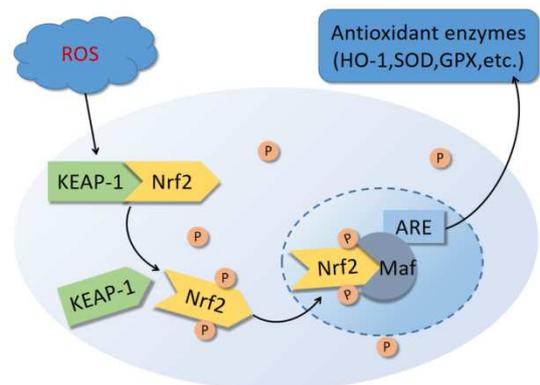
**Figure 1.** Generation of ROS (Mitochondrial electron transport chain).

Notes: (1) I, II, III, IV: Protein complex I, II, III, IV (2) NADH: Nicotinamide adenine dinucleotide (reduced state) (3) NAD<sup>+</sup>: Nicotinamide adenine dinucleotide (oxidized state) (4) FADH<sub>2</sub>: Flavine adenine dinucleotide (reduced state) (5) FAD: Flavine adenine dinucleotide (oxidized state) (6) Cyt c: Cytochrome C (7) Q: ubiquinone.

## 3. Effect of Nrf2/ARE Signal Pathway in Periodontitis

Clinical studies showed that the levels of superoxide dismutase (SOD) and glutathione peroxidases (GPX) in saliva of patients with chronic periodontitis decreased and

the level of lipid peroxidation product malonaldehyde (MDA) increased, suggesting that the antioxidant capacity was inhibited and the level of oxidative stress increased [6]. Kelch-like ECH-associated protein-1 (KEAP-1)-Nrf2/ARE is the key signal pathway of antioxidant capacity [7]. When ROS is excessive *in vivo*, KEAP-1 conformation is changed and Nrf2 phosphorylation can cause uncoupling. Nrf2 is transferred to the nucleus to form a dimer with Maf protein and then binds to ARE, so as to activate the expression of a series of downstream antioxidant enzyme genes (Figure 2). Nrf2 is an antioxidant transcription factor widely expressed in cells and an important regulator of cell redox homeostasis. It has been found that the expression of Nrf2 and its downstream SOD and catalase (CAT) is down regulated in polymorphonuclear leukocytes (PMNs) in the oral cavity of patients with chronic periodontitis. PMNs play a key role in initiating periodontitis in the gin-gival lamina propria and in the pocket epithelium, where they are the predominant inflammatory cell in early periodontal lesions. Excessive ROS produced by PMNs under long-term oxidative stress may inhibit Nrf2 activity in patients with periodontitis [8]. It is also pointed out that Nrf2 down-regulation in blood and oral PMNs (oPMNs) of CP patients may predispose to severe periodontal tissue breakdown, likely through increased local oxidative damage [9]. The main symptoms of periodontitis include periodontal pocket formation, progressive alveolar bone absorption and tooth loosening. The serious loss of supporting structure eventually leads to teeth loss. It has been proved that Nrf2 can inhibit LPS-induced inflammation of gingival fibroblasts by activating MAPK signaling pathway. Some scholars also proposed that Nrf2 signaling pathway could induce the antioxidant activity of gingival fibroblasts [10].



**Figure 2.** Schematic diagram of activation of Nrf2/ARE signal pathway.

Notes: (1) KEAP-1: Kelch-like ECH-associated protein-1 (2) Nrf2: nuclear factor erythroid 2-related factor 2 (3) ARE: antioxidant responsive element (4) Maf: Maf protein (5) ROS: reactive oxygen species.

Osteogenic differentiation of periodontal ligament stem cells (PDLSC) plays an important role in the regeneration of bone in periodontitis. In addition, damaged PDLSCs in periodontitis may destroy the microenvironment by increasing host immune response, promoting abnormal angiogenesis and

boosting osteoclast activity, and strengthen periodontal homeostasis disorder [11]. The differentiation and mineralization of PDLSCs were weakened, and the inflammatory response and apoptosis were strengthened by inhibiting the expression of Nrf2 [12].

It suggests that Nrf2 signaling pathway can promote periodontitis from stationary phase to active phase by inhibiting the differentiation of PDLSCs [13]. Other studies have found that Diaformin Metformin promotes osteoblast differentiation by activating Nrf2 signaling pathway of PDLSC, and protects PDLSCs against oxidative stress injury [14].

There is evidence that persistent inflammation, oxidative stress and Nrf2 signaling dysfunction in periodontal tissues may be the cause of alveolar bone resorption, and eventually lead to periodontitis and inhibition of osteoblasts. The excessive activation of osteoclasts is the main pathological response of periodontitis. Different scholars have found that the intracellular ROS level can be reduced and Nrf2/NF- $\kappa$ B/NFATc1 signaling pathway can be regulated to inhibit osteoclast formation and alveolar bone resorption by inducing the transcription of antioxidant genes mediated by Nrf2 [15, 16]. Nrf2 is known to regulate osteoclast differentiation and function by decreasing ROS via induction of anti-oxidant enzymes, such as sulfiredoxin (Srx) and peroxiredoxin (Prx). Some experiments also pointed out that the activation of Nrf2 inhibited RANKL induced NFATc1 expression and osteoclast differentiation [17]. In addition, studies have shown that miR-455-3p inhibits KEAP-1 by negatively regulating HDAC2 protein levels, thereby activating Nrf2/ARE signaling pathway, inhibiting oxidative stress, promoting osteoblast growth and maintaining bone homeostasis [18]. Some scholars have found that compound antler bone capsule can significantly reduce the oxidative damage of osteoblasts induced by hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) through Nrf2 signaling pathway [19].

#### 4. Role of Antioxidants in Periodontitis

Based on the effect of oxidative stress on the occurrence and development of periodontitis, it is a new idea to treat periodontitis by increasing antioxidants to rebalance the production and removal of ROS and eliminate the decompensation state of oxidative stress [20].

Nrf2 pathway is an important antioxidant pathway, and its activator has great potential for targeted therapy of periodontitis. Trimer Motif16 (TRIM16) has been identified as a new regulatory protein to cope with oxidative and protein toxicity stress. Overexpression of TRIM16 can enhance cell antioxidant capacity, reduce intracellular ROS, alleviate H<sub>2</sub>O<sub>2</sub>-induced oxidative stress, improve cell viability, inhibit apoptosis and depolarization of mitochondrial membrane potential [21]. TRIM16 can alleviate the oxidative damage of human periodontal ligament stem cells by activating Nrf2 pathway, suggesting that TRIM16 is expected to be a target for effective treatment of periodontitis. Hesperetin can inhibit osteoclastogenesis by inhibiting the activation of NF- $\kappa$ B and MAPK signaling pathways, clearing ROS, activating

Nrf2/heme-oxygenase 1 (Nrf2/HO-1) signaling pathway. It is suggested that hesperidin may be a candidate drug for the treatment of destructive bone diseases such as periodontal disease [22].

In addition to Nrf2 inducers that alleviate periodontal tissue damage and inflammation, some antioxidants can also directly inhibit periodontal tissue cell senescence and apoptosis. 1.5 × 10<sup>-3</sup>% hydrogen peroxide solution can decrease the survival rate of gingival fibroblasts and promote the secretion of TNF- $\alpha$  by gingival fibroblasts, which can be inhibited by non-enzymatic antioxidant  $\alpha$ -tocopherol (vitamin E) [23]. The combination of resveratrol and insulin can reduce the level of pro-inflammatory factors and increase the level of SOD, thereby inhibiting the progress of experimental periodontitis, and reducing the loss of alveolar bone, which has a beneficial effect on the repair of bone tissue [24]. Some scholars collected serum and gingival specimens by local injection of vitamin C into the subgingival periosteum of male SD rats [25]. Then they detected serum IL-1 $\beta$ , oxidative stress index (OSI), CTX and MDA levels, and performed gingival MMP-8 immunostaining. According to the histological section measurement of rat mandible, alveolar bone loss and attachment loss were determined. The results showed that vitamin C prevented inflammation-induced alveolar bone resorption by reducing oxidative stress and inflammation-induced tissue decomposition, suggesting that vitamin C may be a therapeutic drug for periodontitis [25].

#### 5. Potential Relationship of Nrf2/ARE Signaling Pathway in Periodontitis and Atherosclerosis

Antioxidant dysfunction associated with periodontitis may promote the pathological development of distal parts of the body. Chronic periodontitis and atherosclerosis are inflammatory diseases with high incidence in the world. A large number of studies have proved the correlation between them in microbiology, animal experiments and clinical practice. Studies have shown that oxidative stress plays an important role in chronic periodontitis and atherosclerosis, and the degree of oxidation is closely related to the severity of the disease.

Nrf2/ARE, as an important anti-oxidative stress pathway in the body, plays an anti-AS role by protecting vascular endothelial integrity, reducing lipid accumulation and inhibiting inflammation.

When chronic periodontitis and AS occur simultaneously, the levels of serum total cholesterol (TC) and low-density lipoprotein (LDL) are increased. The presence of periodontal pathogens may increase the atherosclerosis ability of LDL, thereby increasing the atherosclerosis risk of periodontal patients [26]. LDL is the main factor causing atherosclerosis. LDL can promote the formation of atherosclerotic plaque after oxidative modification. Clinical studies have revealed that periodontal treatment can significantly reduce oxidized low

density lipoprotein (ox-LDL) and very low density lipoprotein cholesterol [27]. The increase in oxidative stress caused by periodontitis produces a large amount of ROS that gradually consumes antioxidants in the body, which breaks the double bond of LDL polyunsaturated fatty acids and finally generates a large amount of lipid peroxide.

Endothelial injury will lead to vascular wall thickening, affecting vascular relaxation, and conducive to plasma cholesterol and cholesterol ester infiltration into the arterial intima. Studies have displayed that inhibiting or blocking Nrf2/ARE signaling pathway induces endothelial injury factor elevation, resulting in endothelial dysfunction [28]. A large number of inflammatory cells will be recruited to the vascular endothelium after lipid deposition in the arterial intima, resulting in local production of more cytokines and ROS. ROS can make the subcutaneous gap of LDL oxidized into ox-LDL, and promote the formation of foam cells. Loss of Nrf2 in macrophages accelerates the uptake of ox-LDL receptors and the formation of foam cells [29]. It is suggested that Nrf2 is involved in the regulation of scavenger receptor transcription in macrophages and thus affects lipid uptake. In addition, studies have shown that Nrf2/ARE pathway inhibits IL-1 $\beta$  and IL-6 release, suggesting that activation of Nrf2/ARE pathway can effectively alleviate inflammation and avoid further aggravation of AS.

Compared with healthy people, a hyperreactive phagocyte phenotype characterized by higher ROS production was found in peripheral blood PMN of patients with chronic periodontitis. A large number of monocytes in the endothelium form a monocyte derived foam cell by binding to the infiltrated lipid through scavenger receptor. The migration and proliferation of smooth muscle cells in arterial media is an important link in the progression of atherosclerosis. During vascular surgical intervention, selective delivery of Nrf2 activator to injured blood vessels can reduce oxidative stress, reduce excessive proliferation of vascular smooth muscle cells (VSMC) and migration to the inner wall of blood vessels [30]. The proliferation and migration of smooth muscle cells undergo phenotypic transfer and become a synthetic type, which is conducive to lipid absorption and myogenic foam cells formation. In the rat abdominal aortic coarctation model, choline attenuates VSMC phenotypic transformation and vascular remodeling by activating Nrf2 antioxidant signal pathway, suggesting that Nrf2 plays a new role in VSMC phenotypic regulation [31].

## 6. Summary

In conclusion, Nrf2 plays a protective role in periodontitis, mainly through antioxidant stress, inhibiting osteoclast activation, regulating mesenchymal stem cell proliferation, differentiation and apoptosis. Antioxidant dysfunction is one of the links between periodontitis and atherosclerosis. Nrf2/ARE antioxidant signaling pathway reduces the possibility of atherosclerosis in patients with chronic periodontitis by protecting vascular endothelial integrity, reducing lipid accumulation and inhibiting inflammation. It is

suggested that antioxidants acting on Nrf2/ARE antioxidant signaling pathway have great potential in the treatment of periodontitis with atherosclerosis.

## Conflicts of Interest

The authors declare no conflict of interest.

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