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Modulating the Affinity of KEAP1-Nrf2 Complex as a New Target for Periodontitis

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Perspective

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ABOUT THE STUDY

In the development of periodontitis, Damage-Associated Molecular Patterns (DAMPs) activate innate immune response by affecting the metabolic adaptation, while Pathogen-Associated Molecular Patterns (PAMPs) bind to Pattern Recognition Receptors (PRRs) and activate the adaptive immune response, directly or indirectly driving a permanent pro-inflammatory state and leading to oxidative damage. Recently, there has been increasing interest in the role of oxidative stress activated by DAMPs and PAMPs in establishing the microenvironment that underlies the progression of periodontitis and increased attachment loss. Effector cells (e.g., macrophages) in periodontal tissue have specialized defense systems to minimize oxidative damage. A key step in preventing oxidative damage involves the activation of antioxidants, which is mainly regulated by the Antioxidant Response Elements (AREs) downstream of the Nuclear factor E2-related factor 2 (Nrf2). Under physiological conditions, cytoplasmic Nrf2 binds to Kelch-like ECH-Associated Protein 1 (KEAP1), a cytoskeletal binding protein that mediates the degradation of Nrf2 protein through the CUL3 ubiquitin-proteasome system, thereby avoiding the unneeded transcription of AREs and maintaining cellular redox homeostasis. During periods of periodontitis, Nrf2 is released from KEAP1, allowing its translocation to the nucleus and initiating the antioxidant response cascade. As an adaptor protein of Nrf2, KEAP1 serves as the primary Nrf2 regulatory mechanism.

Therefore, modulating the interaction between Keap1 and Nrf2 could provide new therapeutic options for alleviating oxidative stress and improving periodontal treatments. Metabolites emerged as immune effector molecules that play specific roles in the regulation of the immune system.

They act as second messengers associated with transcription factors, modifying the structure and function of proteins and altering cellular signaling pathways. Immuno metabolism treatment is the latest proposed therapeutic

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concept, in which an endogenous metabolite itaconate has been proven to possess a prominent immunomodulatory function. Itaconate is diverted from the Tricarboxylic Acid (TCA) cycle and is synthesized from aconitate *via* IRG1/Aconitate Decarboxylase 1 (ACOD1). Four-octyl itaconate (4-OI), a cell-permeable itaconate derivative, has been used as a substitute for itaconate for immunomodulation. 4-OI induces alkylation of cysteine residues on KEAP1, including cysteine 151 (C151). Alkylation of C151 inactivates KEAP1 and subsequently initiates Nrf2-dependent antioxidant cascade. As expected, our previous study innovatively proposed that 4-OI can be a novel option for periodontitis treatment. *In vitro*, we have shown that 4-OI exerted protective effects on inflammation control and oxidative damage. Molecular docking simulation and co-immunoprecipitation assay revealed the binding sites and potential mechanism of 4-OI for periodontitis management. This was confirmed as silencing Nrf2 to down regulate the expression of AREs blocked the therapeutic effect of 4-OI. Meanwhile, we applied Nrf2-/- mice for the first time to verify *in vivo* that 4-OI has no salvage effect on alveolar bone loss, underlining the importance of modulating the affinity of KEAP1-Nrf2 complex in 4-OI-mediated periodontitis treatment. Taken together, as a novel Nrf2 agonist, 4-OI shows promising immunometabolic modulation in periodontitis treatment.

The KEAP1-Nrf2 complex is a key player in the cellular defense against oxidative stress. The KEAP1 protein acts as a sensor for oxidative stress, while the Nrf2 protein functions as a transcription factor that regulates the expression of a variety of antioxidant and detoxification genes. The KEAP1-Nrf2 complex is essential for maintaining the proper balance between oxidative stress and cellular defense mechanisms. Recent studies have focused on the modulation of the affinity between KEAP1 and Nrf2 as a means of enhancing the cellular defense against oxidative stress. One approach involves the use of small molecules that bind to KEAP1 and disrupt its interaction with Nrf2. These small molecules, known as KEAP1-Nrf2 disruptors, have been shown to activate the Nrf2 pathway and increase the expression of antioxidant and detoxification genes. Another approach to modulating the affinity of the KEAP1-Nrf2 complex involves the use of Nrf2 activators. These activators stimulate the transcriptional activity of Nrf2, leading to the upregulation of antioxidant and detoxification genes. Some Nrf2 activators have been shown to directly bind with Nrf2, while others act indirectly by activating upstream kinases that phosphorylate Nrf2 and promote its nuclear translocation.

The modulation of the affinity of the KEAP1-Nrf2 complex has potential implications for the treatment of a variety of diseases. Oxidative stress has been implicated in the pathogenesis of numerous diseases, including cancer, neurodegenerative disorders, and cardiovascular diseases. Modulators of the KEAP1-Nrf2 complex have shown promise in preclinical studies for the treatment of these diseases. Modulating the affinity of the KEAP1-Nrf2 complex is a promising approach for enhancing the cellular defense against oxidative stress. Both KEAP1-Nrf2 disruptors and Nrf2 activators have been shown to upregulate the expression of antioxidant and detoxification genes. This approach has potential implications for the treatment of a variety of diseases, and further research in this area is warranted.