Hidden pathway of periodontal disease and alveolar bone resorption

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Abstract:

Periodontal disease is an inflammatory disease, involving plaque production through several bacteria, that affects our global population health. Individuals with extreme periodontal disease face a gradual increase in tooth loss. Recent research has displayed the possible molecular pathway for how the inflammatory disease causes the acceleration of alveolar bone loss through the NLRP3 (NLR family pyrin domain containing 3) inflammasome. Here I review recent studies that illuminate the NLRP3 pathway and its contribution to periodontal disease. Researchers have found the activation of the NLRP3 pathway is influenced through the presence of functioning mitochondria and K+ efflux, but not dependent upon their roles. Once the inflammasome is produced, it proceeds to activate caspase-1, caspase-4, and caspase-5. These caspases lead to production of IL-1β, which causes the differentiation of osteoclasts and the breakdown of bone. Over time, the breakdown of bone from osteoclasts can lead to the loss in teeth. Tranilast, MCC950, and Urolithin A are inhibitors of NLRP3 and can be potentially used in periodontal patients to slow down the effects of alveolar bone resorption. From the information gathered, the in vitro evidence found in the articles in this review paper leads to strong molecular evidence that the NLRP3 inflammasome and its subsequent bone loss is one of the many causes of periodontal disease.

Apical Periodontitis Immunology

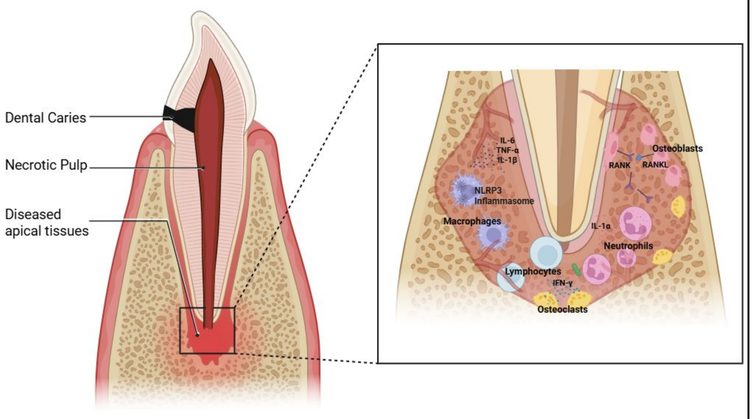

Figure 1. Breakdown of bone in the root of a canine tooth. Displays the relative location of the NLRP3 pathway in relation to the breakdown of the tooth's root. (Adapted from Petean et. al 2022).

Methods:

Peer-reviewed primary scientific articles were analyzed to further understand:

- The pathway of NLRP3 inflammasome activation
- Connection between gram-negative oral bacteria to expression of NLRP3 assembly
- NLRP3 inflammasome relationship to IL-1β release
- Alveolar bone resorption caused by periodontal disease and upregulation of IL-1β

Pathway of NLRP3 inflammasome

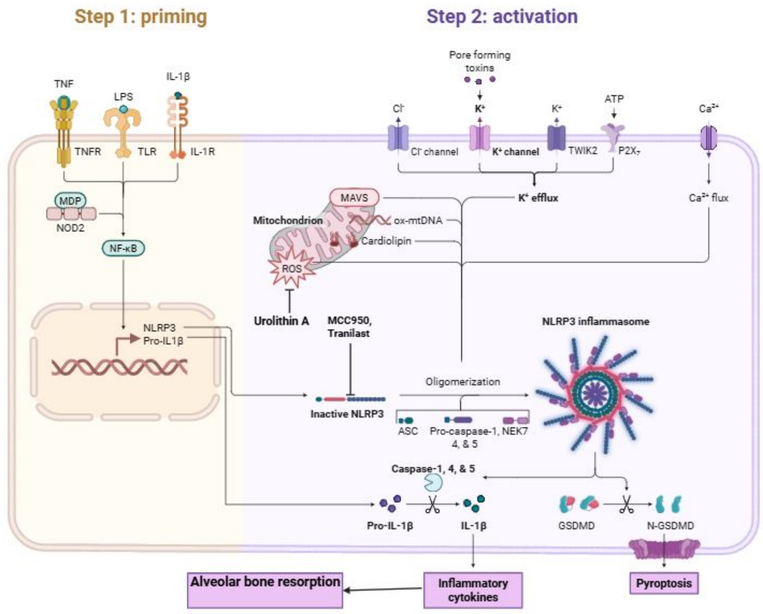

Figure 2. Displays the pathway of NLRP3 inflammasome. The orange side represents the priming and expression of NLRP3 and Pro-IL1β. The purple region shows the activation and assembly of the NLRP3 pathway, leading into alveolar bone resorption. (adapted from Swanson et. al 2019).

Expression of NLRP3:
Various researchers found that stimulation of various receptors (TLR, IL-1R, and TNFR) induce the assembly of NF-κB within macrophages. Periodontal disease had an overall census amongst researchers to use LPS for Toll-like receptors when compared to the other receptors. Once the assembled NF-κB enters the nucleus, gene expression enables the production of Pro-IL1β and NLRP3.

Assembly & Activation of NLRP3 Inflammasome:
Mitocondria: The mitochondria has important functions in activating and assembling the inflammasome.
- The electron transport chain, alongside the four mitochondrial complexes, were found to be crucial in the activation of the pathway. When one of these components were removed or inhibited, production of the pathway was slightly lowered, but not significantly (Billingham et. al, 2022).
- In the absence of ROS and components of the mitochondria, amounts of IL-1β levels were found to be lowered (Billingham et. al, 2022).

K+-Efflux:
- The efflux of potassium was found to promote the assembly of NLRP3. As the extracellular concentration of potassium increases (5-45 M), so does the amount IL-1β production. However, when concentrations exceed 45 M, amounts of IL-1β were found to be lowered, indicating inhibitory effects (Muñoz-Planillo et. al, 2013).
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Cleaving of Pro-IL-1β
Caspases become activated through the NLRP3 inflammasome, which then proceed to cleave Pro-IL-1β to become activated and proceed through to exit the cell.
- Caspase-1 was observed to have the most effect in IL-1β levels from the three caspases in the pathway (Yamaguchi et. al, 2017).
- Caspase-4 had the lowest effect in production of IL-1β when compared to the other caspases (Ding et. al, 2020).
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Breakdown of Tooth
Once the NLRP3 inflammasome has been produced and released from the macrophages, IL-1β increases osteoclastogenesis around the tooth within the gums. The increase of osteoclasts leds to the breakdown of the tooth's surface in a day, eventually leading towards tooth movement and loss (Zhang et. al, 2020).

Potential Inhibitors

- **Tranilast** has been previously utilized to treat other inflammatory diseases. Studies have found that it prevents ASC oligomerization, which is crucial for caspase-1 activation and IL-1β produced (Huang et. al, 2018). Most readily used for inhibition of periodontal disease.
- **MCC950**, a small compound, has been most recently investigated to explicitly reduce the amount of NLRP3, caspase-1, and IL-1β levels in periodontal disease mice (Zang et. al, 2020). It has also been shown to reduce bone resorption in first molars (Chen et. al, 2021).
- **Urolithin A**, natural metabolites produced by our gut cells, has yet to be utilized in periodontal disease models, but has shown potential in reducing inflammatory cytokines and IL-1β through reducing ROS in the mitochondria (Qiu et. al, 2022).

Future Directions:

***In Vivo* Research:** Most of the current research conducted was done *In vitro*. Future research may begin to look at more *in vivo* levels to investigate how levels in the NLRP3 pathway may differ.

Oral Bacteria: A lack of research has been conducted on other oral bacteria and how they contribute to the NLRP3 inflammasome. Further research in these microbes may identify other potential targets and hidden intermediates in the pathway.

Assess Inhibitors: In addition to lack of *in vivo* research, investigating discussed inhibitors, such as Urolithin A and tranilast, in the context of periodontal patients could potentially display promising results to allow options for patients to reduce alveolar bone resorption.

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REFERENCES