Importance of bacterial hydrogen sulfide in the pathogenesis of periodontal diseases

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V. Basic A, Serino G, Leonhardt Å, Dahlén G. Induction of interleukin (IL)-1β and IL-18 secretion by hydrogen sulfide in periodontitis patients and healthy controls: a clinical cross-sectional study. In manuscript
Importance of bacterial hydrogen sulfide in the pathogenesis of periodontal diseases

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Abstract
Hydrogen sulfide (H$_2$S) is one of many end-products of the proteolytic activities in the subgingival microbiota in patients with periodontal diseases, such as gingivitis and periodontitis. Although H$_2$S is generally regarded as toxic, the mechanisms that underlie its production and its effects on human cells and tissues are poorly understood. Therefore, the role of H$_2$S in the pathogenesis of periodontal diseases was investigated. Two colorimetric methods, the bismuth test (BT) and the methylene blue (MB) method, were used to estimate the amounts of H$_2$S produced by the bacteria in vitro and ex vivo (Papers I, II and V). Oral bacteria, e.g., *Fusobacterium* spp., *Porphyromonas gingivalis* and *Treponema denticola*, were found to have strong capacities to degrade cysteine and produce H$_2$S in vitro (Paper I). The *Fusobacterium* spp. were found to express several enzymes that are involved in the production of H$_2$S. The expression patterns of the different enzymes varied among *Fusobacterium* subspecies and strains (Paper III). In an ex vivo experiment using BT, we showed that the subgingival plaques of subjects (N=43) with poor oral hygiene had the capacity to produce H$_2$S (Paper II). High levels of periodontitis-associated bacteria were detected, and the BT values reflected the proteolytic activities of the bacteria and gingival inflammation rather than disease progression and periodontitis. A correlation between a positive BT and gingival inflammation was confirmed in Paper V, where H$_2$S-producing bacteria were significantly more prevalent in the subgingival pockets of periodontitis patients (N=32) than of healthy controls (N=32), which indicates potent bacterial proteolytic activities in the untreated deep periodontal pockets. Paper IV described how the peripheral blood mononuclear cells (PBMCs) of blood donors and a monocytic cell line increased their secretion of the pro-inflammatory cytokines IL-1$\beta$ and IL-18 in vitro when exposed to the H$_2$S-donor sodium hydrosulfide (NaHS). This secretion was shown to be mediated by the NLRP3 inflammasome. These results were verified in Paper V, where the PBMCs of periodontitis patients and healthy controls secreted significantly higher levels of IL-1$\beta$ and IL-18 when exposed to NaHS. In addition, both unexposed and exposed PBMCs of the periodontitis patients secreted higher levels of the two cytokines than the corresponding cells of healthy controls. These results suggest that the susceptibility of the host to develop disease can be attributed in part to enhanced secretion of pro-inflammatory cytokines following exposure to bacterial metabolites, such as H$_2$S. In summary, toxic bacterial metabolites, such as H$_2$S, may play an important role by affecting the cells of the host immune system, thereby inducing and sustaining gingival inflammation.

Keywords: Hydrogen sulfide, Periodontitis, Gingivitis, IL-1$\beta$, IL-18, NLRP3 inflammasome, Oral microbiota, *Fusobacterium* spp., Bismuth test, L-cysteine

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