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Press Release

研究成果

February 14,2024

Research field: Life science and medicine
Keywords: halitosis, Fusobacterium, metabolism, odor-care

Discovery of a "Halitosis Enhancement Mechanism" Where Symbiosis of Specific Oral Bacteria Increases Oral Odor-causing Substances

-Expected Applications to Halitosis Preventive Methods and Various Odor-Care Products-

【Key Research Findings】

- Methyl mercaptan,*1 the major malodorous compound causing halitosis, also commonly known as bad breath, is most abundantly produced by periodontitis-related Fn bacteria.*2
- An oral odor enhancement mechanism has been identified in which Fn bacteria enhance methyl mercaptan production merely by coculturing with the common oral bacteria Sg.*3
- Ornithine excreted by Sg bacteria accelerates the synthesis of polyamines in Fn bacteria, thereby increasing the demand for methionine. As a result, the methionine metabolic pathway is activated, resulting in increased methyl mercaptan production.
- Focusing on this new mechanism may facilitate the development of more effective prevention and treatment strategies for halitosis. In addition, the research findings are expected to be applied to developing various odor control products, including oral and body deodorants.

- Overview

Our research group led by Associate Professor Masae Kuboniwa and Professor Atsuo Amano of Osaka University Graduate School of Dentistry, and Mandom Corporation has discovered a odor-enhancing mechanism by which the production of methyl mercaptan, a compound responsible for halitosis, is increased when certain oral bacteria coexist (Fig.1).

In this study, the research group focused on methyl mercaptan, a contributor to halitosis,

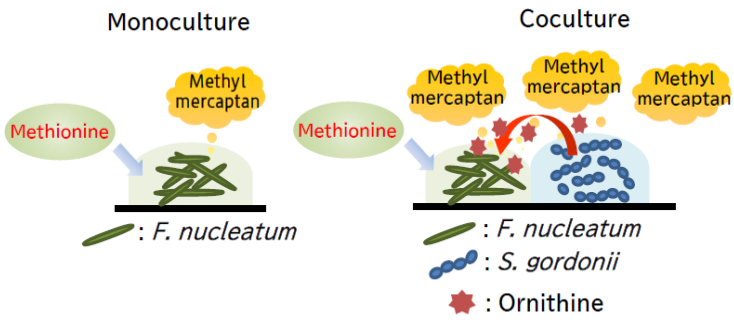

Fig.1. Halitosis enhancement mechanism
Left : *F. nucleatum* alone
Right : *F. nucleatum* cocultured with *S. gordonii*

that emits a strong characteristic odor in minute amounts. They showed that the oral bacterium *Fusobacterium nucleatum* (Fn) plays a significant role in methyl mercaptan production. They also found that cocultures of Fn bacteria with *Streptococcus gordonii* (Sg) produced about three times more methyl mercaptan than did Fn bacteria monocultures (Fig. 2). Furthermore, they identified the mechanism of this enhanced production, in which ornithine excreted by Sg bacteria activates the methionine metabolic pathway in Fn bacteria, thereby increasing methyl mercaptan production (Fig. 3).

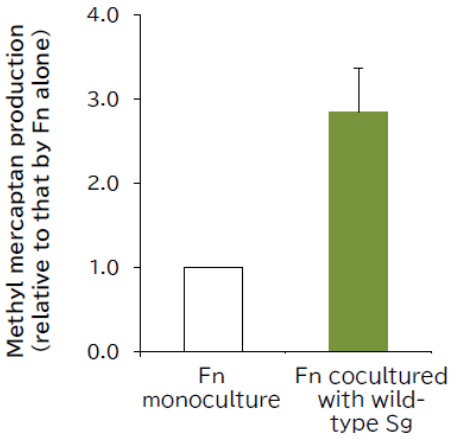

Fig. 2 Comparison of methyl mercaptan production between monoculture and coculture of *F. nucleatum* with *S. gordonii*

These findings highlight the importance of selectively and intensively targeting the relationships between oral bacteria and bacterial contributors to halitosis, which have been previously overlooked. This approach is expected to facilitate the development of more effective prevention and treatment strategies for halitosis. In addition, a deeper understanding of the interspecies interactions and coexistence of common human bacteria is expected to be applied to the development of various odor control products, including body deodorants.

This work was published in mSystems on January 30, 2024.

- Background of the research

Although halitosis is too sensitive a topic to discuss openly, it ranks as one of the odors that people are most concerned about in surveys. Since halitosis is difficult to self-recognize, many people are unaware of their own bad breath, yet it can negatively affect interpersonal communication. At the same time, some people suffer from psychosomatic halitosis (also known as halitophobia). Methyl mercaptan is the main halitosis-causing compound with an extremely low olfactory threshold value, which means that a noticeable odor is generated in minute amounts. This substance is strongly associated with halitosis and periodontitis. Recent studies have reported that interspecies interactions between different oral bacteria play a role in oral diseases such as periodontal disease. However, their possible involvement in the development of halitosis remains undetermined.

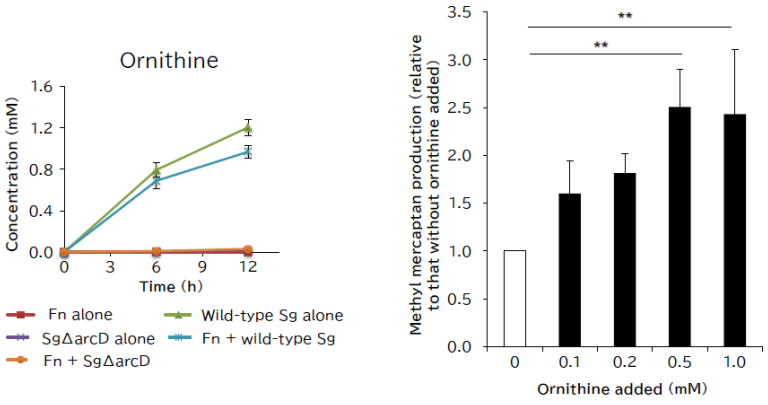

Fig.3. Ornithine metabolism of *F. nucleatum* and *S. gordonii*
Left : Ornithine excretion by *S. gordonii* and uptake by *F. nucleatum*
Right : Methyl mercaptan production by *F. nucleatum* when ornithine is added to the culture

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- Research content

The research group developed a noncontact coculture system to culture two bacterial species together under anaerobic conditions without physical contact. They investigated methyl mercaptan production by major oral bacteria and the effects of interspecies interactions between the oral bacteria. The results showed that Fn bacteria produced large amounts of methyl mercaptan by metabolizing methionine and that this production increased approximately three fold when cocultured with Sg bacteria, early colonizers*4 (Fig.1). Analysis using an Sg mutant lacking the arginine-ornithine antiporter (ArcD)—a transmembrane protein regulating arginine uptake and ornithine excretion—revealed that ornithine secreted by Sg bacteria plays a significant role in boosting methyl mercaptan production by Fn bacteria. Furthermore, to demonstrate how Fn bacteria utilize the methionine they take up, the researchers conducted stable-isotope labeling analysis*5 using stable isotope-labeled methionine and gene expression analysis. The results showed that Fn bacteria took up ornithine secreted by Sg bacteria and used it to synthesize polyamines,*6 bioactive substances in bacterial cells, increasing the demand for methionine. As a result, the methionine metabolic pathway was activated in Fn bacteria, resulting in increased methyl mercaptan production. These findings suggest that the coexistence of Fn and Sg bacteria may exacerbate halitosis.

- Impact of this research achievement on society

Understanding the interspecies interactions between oral bacteria involved in methyl mercaptan production, including the new halitosis enhancement mechanism found in this study, will facilitate the development of effective preventive and therapeutic strategies for halitosis and periodontal disease. In addition, a deeper understanding of the interspecies interactions between human commensal bacteria could be applied to developing odor-care products for various odors generated by humans.

- Special notes

This work was published in the U.S. scientific journal mSystems (with an impact factor of 6.4 in 2023) on January 30, 2024.
Title: Interspecies metabolic transfer fuels methionine metabolism of Fusobacterium nucleatum to stimulate volatile methyl mercaptan production
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DOI: https://doi.org/10.1128/msystems.00764-23

This research was partly supported by Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science and conducted by a joint research team from the Graduate School of Dentistry, Osaka University; the Graduate School of Pharmaceutical Sciences, Osaka University; Mandom Corporation; and the University of Louisville (USA).

- Glossary

*1 Methyl mercaptan
A sulfur-containing gas that emits a very strong characteristic odor even in minute quantities. It has gained attention not only as the major contributor to halitosis but also as an aggravating factor in periodontal disease.

*2 Fn bacteria
Fn stands for *Fusobacterium nucleatum* (*F. nucleatum*), a gram-negative bacterium that resides in the human oral cavity and is known as a causative agent of periodontal disease.

*3 Sg bacteria
Sg stands for *Streptococcus gordonii* (*S. gordonii*), a gram-positive coccus.

*4 Early colonizers
Bacteria that colonize in tooth surfaces and other oral cavity surfaces, creating conditions favorable for the colonization of different microorganisms

*5 Stable-isotope labeling analysis
This analysis involves the uptake of a stable isotope-labeled substrate by bacteria to determine the pathway and transformations that the substrate undergoes.

*6 Polyamines
Bioactive compounds involved in cell proliferation, biofilm formation, and protection against oxidative stress