Paneth 細胞αディフェンシンによる腸内細菌叢の制御

中村 公則
北海道大学大学院先端生命科学研究院

略歴

a）出生年・地：1968年、北海道

b）最終学歴：北海道医療大学大学院歯学研究科、歯学博士

c）主な職歴：

2004年-2009年　札幌医科大学 医学部　分子医学研究部門 助教
2009年-2013年　北海道大学大学院先端生命科学研究院 助教
2013年-2025年　北海道大学大学院先端生命科学研究院 准教授
2025年－現在　　北海道大学大学院先端生命科学研究院 教授

d）主な研究テーマ：腸管自然免疫と腸内微生物の共生制御、疾患発症機序について研究

要約

我々は、皮膚、口腔、消化管などにおいて膨大な数の細菌と共生している。とくに腸には40兆もの共生菌が形成する腸内細菌叢が存在し、腸内環境を保つことで生体恒常性維持に関与している。近年、腸内細菌叢の組成異常（dysbiosis）と肥満症などの生活習慣病、精神疾患など様々な疾病との関係が報告され、予防医療における腸内細菌叢制御の重要性が高まってきている。腸内細菌叢の組成に影響を及ぼす因子として食事などの生活習慣や加齢をはじめとする様々な因子が知られてきており、その予防的介入としてプロバイオティクスなどの共生する細菌側を対象とした研究が進んでいるが、宿主側からの共生制御のメカニズムは未だ多くが不明である。

小腸上皮細胞の一系統であるPaneth細胞は、細菌刺激などに応答して抗菌ペプチド・αディフェンシンを分泌し、病原体を直接的に死滅させることで、腸管自然免疫の主要な役割を担っている。私たちはこれまでに、αディフェンシンは、病原菌および日和見的に病原性を持つ一部の常在菌に対し強い殺菌活性を示す一方、常在菌であるビフィズス菌や乳酸菌などには殺菌活性を示さず、宿主に有益な選択的殺菌活性により腸内細菌叢を制御する重要な因子であることを明らかにした[1)]。また、クローン病モデルマウスの発症早期から、Paneth細胞の小胞体ストレスによる構造異常を伴うαディフェンシンの分泌がdysbiosisを誘導し、病態進行に関与することを示した[2)]。さらに、ヒト横断研究において加齢および睡眠時間低下におけるαディフェンシン分泌量低下を介した腸内細菌叢破綻の関与を明らかにするとともに[3,4)]、移植片対宿主病およびうつ病モデルにおいて、αディフェンシン分泌異常を起点とするdysbiosisに伴う菌代謝物の異常を介した疾患発症という軸をはじめて実証し、αディフェンシン正常化による新たな疾患予防・治療戦略を示した[5,6)]。 以上より、抗菌ペプチド・αディフェンシンは腸内細菌叢の形成に大きく関

与し、その破綻が疾患リスクを形成する要因となる可能性が考えられる。本発表では、αディフェンシンによる腸内細菌叢と宿主との共生機構の解明と、それを標的とした食成分による、疾患の予防に直結する新規先制医療シーズ創出への取り組みについて紹介する。

参考文献

1. Masuda, K. et al. Bactericidal Activity of Mouse α-Defensin Cryptdin-4 Predominantly Affects Noncommensal Bacteria. J Innate Immun 3, 315-26 (2011).
2. Shimizu, Y. et al. Paneth cell α-defensin misfolding correlates with dysbiosis and ileitis in Crohn's disease model mice. Life Sci Alliance 3, e201900592 (2020).
3. Shimizu, Y. et al. Lower human defensin 5 in elderly people compared to middle-aged is associated with differences in the intestinal microbiota composition: the DOSANCO Health Study. Geroscience 1-13 (2021).
4. Shimizu, Y. et al. Shorter sleep time relates to lower human defensin 5 secretion and compositional disturbance of the intestinal microbiota accompanied by decreased short-chain fatty acid production. Gut Microbes 15, (2023).
5. Hayase, E. et al. R-Spondin1 expands Paneth cells and prevents dysbiosis induced by graft-versus-host diseaseR-Spondin1 restores gut microbial ecosystem. J Exp Medicine 214, 3507-3518 (2017).
6. Suzuki, K. et al. Decrease of α-defensin impairs intestinal metabolite homeostasis via dysbiosis in mouse chronic social defeat stress model. Sci Rep 11, 9915 (2021).

Regulation of Gut Microbiota by Paneth Cell α-Defensin

Kiminori Nakamura
Faculty of Advanced Life Science, Hokkaido University

Brief Curriculum Vitae

a) Date and Place of Birth: 1968, Hokkaido, Japan

b) Final Academic Degree: Ph.D. in Dentistry, Graduate School of Dentistry, Health Sciences University of Hokkaido

c) Work Experience:

2004-2009: Assistant Professor, Department of Molecular Medicine, Sapporo Medical University School of Medicine

2009-2013: Assistant Professor, Graduate School of Advanced Life Science, Hokkaido University

2013-2025: Associate Professor, Graduate School of Advanced Life Science, Hokkaido University

2025-Present: Professor, Graduate School of Advanced Life Science, Hokkaido University

d) Main Research Topics: Studies on the regulation of symbiosis between intestinal innate immunity and gut microbiota, and the mechanisms of disease onset.

Abstract

Humans coexist with a vast number of bacteria on body surfaces such as the skin, oral cavity, and gastrointestinal tract. In particular, the intestine harbors approximately 40 trillion commensal bacteria that form the gut microbiota, contributing to the maintenance of host homeostasis. In recent years, dysbiosis—an imbalance in the composition of the gut microbiota—has been implicated in various diseases, including lifestyle-related conditions such as obesity and mental disorders. As a result, the regulation of the gut microbiota has become increasingly important in preventive medicine.

Factors known to influence the composition of the gut microbiota include dietary habits, aging, and other lifestyle-related elements. Although research on bacterial interventions, such as probiotics, has advanced, host-derived mechanisms that regulate symbiosis remain largely unclear.

Paneth cells, a lineage of small intestinal epithelial cells, play a key role in intestinal innate immunity by secreting the antimicrobial peptide α-defensin in response to bacterial stimuli, thereby directly killing pathogenic microorganisms. We have previously demonstrated that α-defensins exhibit strong bactericidal activity against pathogenic and opportunistic bacteria, but not against beneficial commensals such as Bifidobacterium and Lactobacillus [1]. This selective bactericidal activity suggests that α-defensins are important host factors that shape gut microbiota. Furthermore, in a mouse model of Crohn's disease, we showed that secretion of abnormal

α-defensins due to endoplasmic reticulum stress in Paneth cells occurs at an early stage of disease onset, inducing dysbiosis and contributing to disease progression [2]. In human cross-sectional studies, we also revealed that aging and reduced sleep duration are associated with decreased α-defensin secretion and the consequent disruption of the gut microbiota [3, 4]. Additionally, in models of graft-versus-host disease and depression, we were the first to demonstrate that impaired α-defensin secretion induces dysbiosis, which in turn leads to disease onset via altered microbial metabolites, and that normalization of α-defensin levels can restore gut microbiota and provide a novel strategy for disease prevention and treatment [5, 6].

These findings suggest that α-defensins play a critical role in the formation and maintenance of the gut microbiota, and that their disruption may increase disease risk. In this presentation, we will discuss our efforts to elucidate the symbiotic mechanisms between the gut microbiota and the host mediated by α-defensins and to develop novel preventive strategies based on dietary components targeting this mechanism.

References

1. Masuda, K. *et al.* Bactericidal Activity of Mouse α-Defensin Cryptdin-4 Predominantly Affects Noncommensal Bacteria. *J Innate Immun* 3, 315-26 (2011).
2. Shimizu, Y. *et al.* Paneth cell α-defensin misfolding correlates with dysbiosis and ileitis in Crohn's disease model mice. *Life Sci Alliance* 3, e201900592 (2020).
3. Shimizu, Y. *et al.* Lower human defensin 5 in elderly people compared to middle-aged is associated with differences in the intestinal microbiota composition: the DOSANCO Health Study. *Geroscience* 1-13 (2021).
4. Shimizu, Y. *et al.* Shorter sleep time relates to lower human defensin 5 secretion and compositional disturbance of the intestinal microbiota accompanied by decreased short-chain fatty acid production. *Gut Microbes* 15, (2023).
5. Hayase, E. *et al.* R-Spondin1 expands Paneth cells and prevents dysbiosis induced by graft-versus-host diseaseR-Spondin1 restores gut microbial ecosystem. *J Exp Medicine* 214, 3507-3518 (2017).
6. Suzuki, K. *et al.* Decrease of α-defensin impairs intestinal metabolite homeostasis via dysbiosis in mouse chronic social defeat stress model. Sci Rep 11, 9915 (2021).