

腸内フローラと小児のアレルギー：コホート研究からの知見

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主な研究テーマ

小児の免疫アレルギー疾患の発症機序の解明・治療・予防

受賞

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要約

近年多くの慢性炎症性疾患の病態における腸内細菌の関与が注目されているが、アレルギー疾患は腸内フローラとの関連についての研究の先駆けと考えられる。2000年代初頭の研究は dysbiosis とアレルギー疾患の相関解析が主であり、疾患と腸内フローラの因果関係は不明であった。その後、北欧を中心とした観察コホート研究においてアレルギー疾患患者では、発症前から健常者との腸内細菌の違いが示され、dysbiosis が発症に深く関与することが明らかとなった。小児のアレルギー疾患、特にアトピー性皮膚炎や食物アレ

アレルギーは、高い発症率・早期発症の観点から、疾患発症における菌叢の関与の機序を調べるのに良いモデルと考えられ、現在まで海外を中心に多くの観察・介入研究が行われており、システマティックレビューやメタ解析が定期的に報告されている。近年、アジアでもいくつかの出生コホート研究が行われるようになってきている。腸内フローラは食事・栄養素を含めた複数の因子により規定される。特に食を含む生活習慣は地域などにより大きく異なることから、日本でも独自のコホート研究からの情報が求められていた。

私たちは、アレルギー発症ハイリスク児や一般集団乳児を対象とした複数の出生コホート研究を通じ、腸内フローラとアレルギー疾患の関連性を縦断的に解析してきた。初期のコホート研究からは、生後1か月時点での黄色ブドウ球菌や成人型ビフィズス菌の定着がその後のアトピー性皮膚炎発症のリスク因子であることを見出した¹。その後、長期フォローが可能であった2つのコホート研究(CHIBA study と Katsushika study)^{2,3}での16S rRNA 解析からも生後1か月時点での菌叢がその後のアレルゲン感作に強く関連していることが明らかになった。生後1か月の腸内細菌叢のエンテロタイプは3つに分類され、中でもビフィズス菌が優位で、プロピオン酸が高値を示す「エンテロタイプ3」の群において、乳幼児期の食物感作リスクが最も低かった⁴。欧州での出生コホート研究では1歳時点での糞便中の酪酸・プロピオン酸高値が同時点での低感作率と関連していた⁵。上記の我々の解析結果は、アレルギー疾患発症前である新生児期におけるプロピオン酸の抗アレルギー作用を示唆している。CHIBA study においては、生後1か月の糞便中プロピオン酸濃度の低下が5歳時における気管支喘息の発症リスクとなることも明らかになっている。マウスモデルにおいて授乳期の母マウスへのプロピオン酸投与が、仔マウスのGPR41受容体を介する機序により喘息発症を予防することも示されている⁶。

このように新生児期にビフィズス菌（特に乳児型ビフィズス菌）が定着することは、アレルギー予防において極めて重要であると考えられる。最近我々が行った出生コホート研究(Fukushima study)⁷ではビフィズス菌種まで調べているが、生後1か月の人工栄養児での*B. breve*の少なさが生後6か月、1歳での卵白に対する高感作率と関連することが明らかになっている（論文投稿中）。乳児型ビフィズス菌の一部が産生するトリプトファン代謝物はアシルヒドロカーボンリセプター（AhR）刺激作用により腸管バリア機能を高めることも知られており⁸、アレルギー予防の機序の一つである可能性がある。母乳には乳児型ビフィズスの菌増殖因子である Human milk oligosaccharides (HMO) が多く含まれており、一般的には母乳栄養児の方が人工栄養児に比してビフィズス菌が多いと考えられている。しかしながら、近年の日本での研究では、母乳栄養児の方が混合栄養児よりもビフィズス菌が少ないとの報告もあり⁹、最近の母乳と以前の母乳とで、あるいはアレルギー児に与えられた母乳と非アレルギー児に与えられた母乳間で異なっている可能性がある。実際、採取時期が24年異なる初乳中のサイトカインの比較解析を行ったところ、腸管バリア機能の向上やビフィズス菌優位な腸内環境に形成に関わるとされるオステオポンチン濃度が近年の母乳で有意に低値であった¹⁰。

乳児期の腸内細菌叢形成には、栄養法に加えて、抗生剤投与など様々な環境因子が影響を及ぼす。我々の乳幼児健診コホートでも、早期の抗生剤使用はアトピー性皮膚炎の早期発症・持続や遷延化と関連し、その後のアレルギーマーチへと進展する結果となっていた¹¹。

小児のアレルギー疾患（おそらく長期的には成人のアレルギー疾患も）の予防においては、適切な抗生剤使用も含めて、早期からの健全な腸内細菌叢の構築が鍵となる。新生児の菌叢形成には母体菌叢の影響も大きいことが知られており、今後、妊娠期から授乳中までの母体、胎児期から乳児期までの児を対象とする包括的な解析とそれに基づくアレルギー発症予防法の確立が期待される。

文献

1. Suzuki S, et al. Differences in the composition of intestinal *Bifidobacterium* species and the development of allergic diseases in infants in rural Japan. Clin Exp Allergy. 2007;37:506-11.
2. Nakano T, et al. Breastfeeding promotes egg white sensitization in early infancy. Pediatr Allergy Immunol. 2020;31:315-318.
3. Dissanayake E, et al. Skin Care and Synbiotics for Prevention of Atopic Dermatitis or Food Allergy in Newborn Infants: A 2 × 2 Factorial, Randomized, Non-Treatment Controlled Trial. Int Arch Allergy Immunol. 2019;180:202-211.
4. Shibata R, et al. Neonatal gut microbiota and risk of developing food sensitization and allergy. J Allergy Clin Immunol. 2025;155(3):932-946
5. Roduit C, et al. High levels of butyrate and propionate in early life are associated with protection against atopy. Allergy 2019;74:799-809.
6. Ito T, et al. The propionate-GPR41 axis in infancy protects from subsequent bronchial asthma onset. Gut Microbes. 2023;15(1):2206507.
7. Aoyama R, et al. Neonatal skin dysbiosis to infantile atopic dermatitis: Mitigating effects of skin care. Allergy. 2024;79:1618-1622.
8. Shao H, et al. *Bifidobacterium breve* M-16V Alleviates Cow's Milk Allergy in a Mouse Model via Gut Microbiota-Derived Indole-3-Propionic Acid-Aryl Hydrocarbon Receptor Signaling Axis. Allergy. 2026;81:1735-1748.
9. Nagpal R, et al. Evolution of gut *Bifidobacterium population* in healthy Japanese infants over the first three years of life: a quantitative assessment. Sci Rep. 2017;7:10097.
10. Takahashi T, et al. Comparison of 30 Cytokines in Human Breast Milk between 1989 and 2013 in Japan. Nutrients. 2023;15:1735.
11. Arima T, et al. Phenotypes of atopic dermatitis up to 36 months of age by latent class analysis and associated factors in Japan. Asia Pac Allergy 2022;12:e2.

Gut microbiota and allergic diseases in children: insights from cohort studies

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Awards:

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Abstract

In recent years, attention has focused on the role of the gut microbiota in the pathogenesis of many chronic inflammatory diseases; however, research on the association between allergic diseases and the gut microbiota is considered pioneering in this field. Research in the early 2000s primarily focused on association analyses between dysbiosis and allergic diseases, and the causal relationship between these diseases and the gut microbiota remained unclear. Subsequently, observational cohort studies, primarily conducted in Northern Europe, demonstrated that patients with allergic diseases exhibited differences in their gut microbiota compared with healthy individuals, even before symptom onset, revealing that dysbiosis is deeply involved in disease initiation. Allergic diseases in children—particularly atopic dermatitis and food allergy—are considered good models for investigating the mechanisms by which the gut microbiota contributes to disease onset, given their high incidence rates and early onset. To date, numerous observational and interventional studies have been conducted, primarily overseas, and systematic reviews and meta-analyses are regularly published. In recent years, several birth cohort studies have also begun to be conducted in Asia. The gut microbiota is determined by multiple factors, including diet and nutrients. Since lifestyle habits—particularly dietary habits—vary significantly by region, there has been a need for information derived from unique cohort studies in Japan as well.

Through several birth cohort studies involving infants at high risk for allergic disease and infants from the general population, we have conducted longitudinal analyses of the association between the gut microbiota and allergic diseases. Early cohort studies revealed that the colonization of *Staphylococcus aureus* and adult-type *Bifidobacteria* at one month of age is a risk factor for the subsequent development of atopic dermatitis.¹ Subsequently, 16S rRNA analysis in two cohort studies (the CHIBA study and the Katsushika study) that allowed for long-term follow-up also demonstrated that the gut microbiota at one month of age is strongly associated with subsequent allergen sensitization.^{2,3} The enterotypes of the gut microbiota at one month of age were classified into three categories; among these, the group classified as “Enterotype 3”—characterized by a predominance of *bifidobacteria* and high levels of propionic acid—exhibited the lowest risk of food sensitization during infancy.⁴ In a European birth cohort study, high levels of butyric acid and propionic acid in stool at age 1 were associated with a low sensitization rate at that time.⁵ Our analysis results described above suggest an anti-allergic effect of propionic acid during the neonatal period, prior to the onset of allergic diseases. The CHIBA study also revealed that low propionic acid concentrations in stool at one month of age are associated with an increased risk of developing bronchial asthma at age 5. In a mouse model, it has been shown that administering propionic acid to nursing mothers prevents asthma

onset in their offspring via a mechanism mediated by the GPR41 receptor.⁶ Thus, the colonization of bifidobacteria (particularly infant-type bifidobacteria) during the neonatal period is considered to be extremely important for allergy prevention. In a recent birth cohort study we conducted (the Fukushima study⁷), which examined bifidobacteria down to the species level, we found that low levels of *B. breve* in formula-fed infants at 1 month of age were associated with high rates of sensitization to egg white at 6 months and 1 year of age (paper in submission). It is also known that tryptophan metabolites produced by some infant-type bifidobacteria enhance intestinal barrier function by stimulating the aryl hydrocarbon receptor (AhR), which may be one of the mechanisms underlying allergy prevention.⁸

Breast milk contains high levels of human milk oligosaccharides (HMOs), which act as growth factors for infant-type bifidobacteria; it is generally believed that breastfed infants have higher levels of bifidobacteria than formula-fed infants.⁹ However, recent studies in Japan have reported that breastfed infants have fewer bifidobacteria than mixed-fed infants, suggesting that there may be differences between recent breast milk and breast milk from earlier periods, or between breast milk given to children with allergies and that given to children without allergies. In fact, a comparative analysis of cytokines in colostrum collected 24 years apart revealed that osteopontin concentrations—which are thought to be involved in improving intestinal barrier function and establishing a *Bifidobacterium*-dominant gut environment—were significantly lower in recent breast milk.¹⁰

In addition to feeding practices, various environmental factors—such as antibiotic administration—influence the development of the gut microbiota during infancy. In our infant and toddler health checkup cohort as well, early antibiotic use was associated with the early onset, persistence, and chronicity of atopic dermatitis, leading to progression along the “allergy march.”¹¹ In the prevention of allergic diseases in children (and likely, in the long term, in adults as well), the establishment of a healthy gut microbiota from an early age—including appropriate antibiotic use—is key. It is known that the maternal microbiota has a significant influence on the formation of the neonatal microbiota; therefore, it is hoped that comprehensive analyses will be conducted on pregnant women, breastfeeding mothers, and children from the fetal stage through infancy, and that allergy prevention methods based on these findings will be established.

References

1. Suzuki S, et al. Differences in the composition of intestinal *Bifidobacterium* species and the development of allergic diseases in infants in rural Japan. *Clin Exp Allergy*. 2007;37:506-11.
2. Nakano T, et al. Breastfeeding promotes egg white sensitization in early infancy. *Pediatr Allergy Immunol*. 2020;31:315-318.

3. Dissanayake E, et al. Skin Care and Synbiotics for Prevention of Atopic Dermatitis or Food Allergy in Newborn Infants: A 2×2 Factorial, Randomized, Non-Treatment Controlled Trial. *Int Arch Allergy Immunol*. 2019;180:202-211.
4. Shibata R, et al. Neonatal gut microbiota and risk of developing food sensitization and allergy. *J Allergy Clin Immunol*. 2025;155(3):932-946
5. Roduit C, et al. High levels of butyrate and propionate in early life are associated with protection against atopy. *Allergy* 2019;74:799-809.
6. Ito T, et al. The propionate-GPR41 axis in infancy protects from subsequent bronchial asthma onset. *Gut Microbes*. 2023;15(1):2206507.
7. Aoyama R, et al. Neonatal skin dysbiosis to infantile atopic dermatitis: Mitigating effects of skin care. *Allergy*. 2024;79:1618-1622.
8. Shao H, et al. *Bifidobacterium breve* M-16V Alleviates Cow's Milk Allergy in a Mouse Model via Gut Microbiota-Derived Indole-3-Propionic Acid-Aryl Hydrocarbon Receptor Signaling Axis. *Allergy*. 2026;81:1735-1748.
9. Nagpal R, et al. Evolution of gut *Bifidobacterium* population in healthy Japanese infants over the first three years of life: a quantitative assessment. *Sci Rep*. 2017;7:10097.
10. Takahashi T, et al. Comparison of 30 Cytokines in Human Breast Milk between 1989 and 2013 in Japan. *Nutrients*. 2023;15:1735.
11. Arima T, et al. Phenotypes of atopic dermatitis up to 36 months of age by latent class analysis and associated factors in Japan. *Asia Pac Allergy* 2022;12:e2.