

Recent advances in epigenetic mechanisms, diagnosis, and treatment of pediatric gastrointestinal allergic disorders

Eell Ryoo, MD, PhD

Department of Pediatrics, Gachon University Gil Medical Center, Incheon, Korea

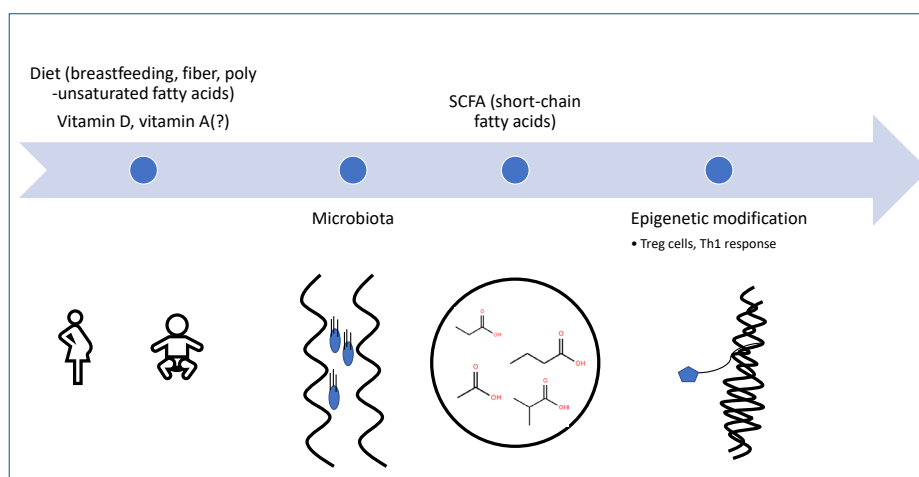
Key message

- Epigenetic mechanisms are involved in rapidly increasing food allergy.
- There is still no definitive way to diagnose food allergy.
- Early introduction of peanuts, eggs, and cow's milk reduces food allergy incidence.
- Administration of probiotics such as *Lactobacillus rhamnosus* GG, *Bifidobacterium bifidum* can partially reduce the occurrence of allergic symptoms.

The rapidly increasing prevalence of food allergy cannot be explained by classical genetics and is therefore explained by gene-environment interactions.¹⁾ Nutritional factors, especially during gestation and lactation, have been described as being by epigenetics mechanisms described as transmissible alterations that modify gene expression without altering the underlying DNA sequence.^{1,2)} Maternal nutrition, diet, and especially breastfeeding or formula feeding affect the gut microbiome, and short-chain fatty acids, one of postbiotics, which is a bacterial metabolite derived from the gut microbiota, is involved in regulatory T (Tregs) cells and Th1 immune responses.^{3,4)} It has also been reported that polyunsaturated fatty acids are involved

in epigenetic mechanisms and T-cell maturation.⁵⁾ The diverse and abundant oligosaccharides contained in breast milk affect intestinal immune function by functioning as prebiotics that enable mitigation of *Bifidobacterium* et al.⁶⁾ And secretory IgA contained in breast milk not only has a direct effect on microbial colonization, but also has a prebiotic effect that promotes the growth of certain bacterial species, affecting intestinal immune function.⁷⁾ These mechanisms suggest that breast milk is highly enriched in miRNAs, thus explaining one of the epigenetic mechanisms.⁸⁾ Vitamin D deficiency is known to affect the Th2 immune response, Treg cells, and epigenetic mechanisms by TSLP (thymic stromal lymphopoietin), an epithelial cell-derived cytokine associated with allergic diseases.^{9,10)} Retinoic acid, a vitamin A metabolite, acts as an important modulator and antagonist for Th9 cells, although its function in food allergy is not yet clear.¹¹⁾

Methods for diagnosing food allergy include skin prick test, Immuo-CAP assay to measure allergen-specific IgE, basophil activation tests, and mast cell activation tests in addition to the gold standard double-blind placebo-controlled food challenge, bead-based epitope assays, etc. are being used, and omics approaches that can predict patients at risk of developing food allergy



Graphical abstract

Corresponding author: Eell Ryoo, MD, PhD. Department of Pediatrics, Gachon University Gil Medical Center, 21, Namdong-daero, 774 beon-gil, Namdong-gu, Incheon 21565, Korea

✉ Email: ryoo518@gilhospital.com, <https://orcid.org/0000-0002-0785-5314>

Received: 22 January, 2023, Revised: 10 April, 2023, Accepted: 20 April, 2023

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyright © 2023 by The Korean Pediatric Society

in the future are also being studied.¹²⁾

Recent studies have demonstrated that early introduction of peanuts, eggs, and cow's milk can lower the risk of food allergy, but further research on early introduction of other foods is needed.¹²⁾

Based on this pathophysiology, desensitization oral immunotherapy, biological agent therapy such as omalizumab, ligelizumab, dupilumab, etokimab, Bruton's tyrosine kinase inhibitor (acalabrutinib), administration of probiotics such as *Lactobacillus rhamnosus* GG, *Bifidobacterium bifidum*, and fecal microbial transplantation have been attempted.¹²⁾

Footnotes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

Funding: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID:

Eell Ryoo  <https://orcid.org/0000-0002-0785-5314>

References

1. Peters RL, Mavoa S, Koplin JJ. An overview of environmental risk factors for food allergy. *Int J Environ Res Public Health* 2022;19:722.
2. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nat Genet* 2003; 33 (Suppl 3):245-54.

3. Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* 2013;504:446-50.
4. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly-Y M, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science* 2013;341:569-73.
5. Harb H, Irvine J, Amarasekera M, Hii CS, Kesper DA, Ma Y, et al. The role of PKC ζ in cord blood T-cell maturation towards Th1 cytokine profile and its epigenetic regulation by fish oil. *Biosci Rep* 2017;37:BSR20160485.
6. van Esch BCAM, Porbahaie M, Abbring S, Garssen J, Potaczek DP, Savelkoul HFJ, et al. The impact of milk and its components on epigenetic programming of immune function in early life and beyond: implications for allergy and asthma. *Front Immunol* 2020;11:2141.
7. Davis EC, Castagna V, Sela DA, Hillard MA, Lindberg S, Mantis NJ, et al. Gut microbiome and breast-feeding: implications for early immune development. *J Allergy Clin Immunol* 2022;150:523-34.
8. Alsaweed M, Hartmann PE, Geddes DT, Kakulas F. MicroRNAs in breastmilk and the lactating breast: potential immunoprotectors and developmental regulators for the infant and the mother. *Int J Environ Res Public Health* 2015;12:13981-4020.
9. Cañas JA, Núñez R, Cruz-Amaya A, Gómez F, Torres MJ, Palomares F, et al. Epigenetics in food allergy and immunomodulation. *Nutrients* 2021; 13:4345.
10. Poole A, Song Y, Brown H, Hart PH, Zhang GB. Cellular and molecular mechanisms of vitamin D in food allergy. *J Cell Mol Med* 2018;22:3270-7.
11. Badolati I, Sverre-remark-Ekström E, van der Heiden M. Th9 cells in allergic diseases: a role for the microbiota? *Scand J Immunol* 2020;91:e12857.
12. Sindher SB, Long A, Chin AR, Hy A, Sampath V, Nadeau KC, et al. Food allergy, mechanisms, diagnosis and treatment: Innovation through a multi-targeted approach. *Allergy* 2022;77:2937-48.

How to cite this article: Ryoo E. Recent advances in epigenetic mechanisms, diagnosis, and treatment of pediatric gastrointestinal allergic disorders. *Clin Exp Pediatr* 2023;66:250-1.