Japanese Journal of Gastroenterology Research

www.jjgastro.com

Review Article

Open Access, Volume 2

Role of gut microbiome in health & disease

***Corresponding Author: Rakesh Kumar**
Indraprastha Apollo Hospital, Delhi, India
Email: drkumarrakesh@gmail.com

Received: Sep 09, 2022
Accepted: Oct 07, 2022
Published: Oct 14, 2022
Archived: www.jjgastro.com

Keywords: Gut microbiome; Immunomodulation; Gut health; Microbial diversity; Gastrointestinal disease.

Abstract

There has been a great deal of research going on in the subject of gut microbiome. The human gut microbiome harbors more than 100 trillion of different kinds of microbes which are essential for the normal functioning of the day-to-day metabolism and physiological functions. The disruption in the population and balance of gut microbiome can lead to various types of gastrointestinal conditions. The major pathological conditions caused are irritable bowel syndrome, obesity, metabolic syndrome, non-alcoholic fatty liver disease, and non-alcoholic steatohepatitis. The gut microbiome community also plays an important role in maintaining the immunological stability of the human body. Several circumstantial reviews have continued to evidence the association of composition of human intestinal microbiota with the ever-increasing range of diseases, syndromes, and aberrations. This review summarizes the associations that have garnered the focused attention: the opportunity of a hyperlink between the intestinal microbiota and continual gastrointestinal illnesses such as IBS and IBD, and systemic metabolic diseases, such as type-II diabetes and obesity.

Introduction

The intestinal microbiota is the community of microorganisms including bacteria, archaea and eukaryote majorly comprised of strict anaerobes that outnumber facultative anaerobes and aerobes by a factor of up to 100 [1]. Till date although more than 50 bacterial phyla have been detected in the human intestine [2], the microbiota are dominated by means of solely two phyla: the Bacteroidetes and the Firmicutes. As expected, owing to the complex interplay of genetic, environmental, social factors, estimates of the number of bacterial species present in a human intestine reported by several studies is largely divergent. However, it is typically usual that people harbor more than a thousand microbial, species-level phylotypes [3-5].

Development and composition

One of the postulates is that the evolution of microbial colonization of the human intestine begins at birth [1]. Although there is conflicting hypothesis with few studies detecting the presence of microbes in the womb and placental tissues [2,3], the prevailing view is that Gastrointestinal Tract (GIT) is rapidly colonized immediately after birth [4]. As a neonate passes via the start canal, he or she is exposed to the microbial populace of the mother's vagina. This influences the microbial colonization of an infant's intestine with similarities to the vaginal microbiota composition of the mother.

The mode of delivery at childbirth is an influential factor determining the microbial population of intestine during the first month following birth [5,6]. However, the difference becomes undiscernible by sixth month. In general, the inter-individual variation in the composition of the intestinal microbiota is easy to note during the first year of life [7-9] specifically, the intestines of infants delivered by vaginal mode are dominated by *Bifidobacterium* sp [10,11]. In the case of babies delivered by C-section, there is relatively lower colonization of *Bacteroides* and *Bifidobacterium* and there is increased prevalence of hospital acquired opportunistic pathogens of *Enterococcus*, *Enterobacter*, and *Klebsiella* species [12].

Preliminary intestinee colonization is instrumental in shaping the composition of the adult's intestine microbiota. Despite the relative similarities of the intestine microbiota in moms and their offspring, microbial succession in the GIT is additionally influenced via complex interplay of several environmental and internal, host-related factors. In addition to the maternal microbiota, external elements such as the type of meals, feeding habits, environmental factors including exposure to other individuals or siblings or furry pets influence the variations [11]. The infant's intestine microbiota endure a succession of adjustments that are correlated with a shift in feeding mode from breast- or formula-feeding to weaning and the introduction of stable food [10]. Brest feeding mode was the significant influ-

encing factor in the microbiome composition during the developmental phase [11]. Additionally, type of diet, temperature and other stress factors can impact the succession of microbes. Some of the iinternal factors include intestinal pH; microbial interactions; physiological factors, like peristalsis; bile acids; host secretions and immune responses; drug therapy; and bacterial mucosal receptors [10].

Metabolism

With increasing realization of several unique roles of microbial metabolites in processes, there is a profound interest and gathering of evidence towards their mechanistic role in human metabolism, immune system and ageing. As the intestine microbiota encode a substantively large range of genes than its human host, it follows that they are independently able to undertake a wide range of metabolic features those human beings are unable to process or are solely capable of executing metabolic processes in a restrained capacity. Although gold standard of human gut microbiota could not be established, the general consensus is their role in the metabolic disorders [13].

The intestine microbiota plays a significant role in the bioavailability of micronutrients [14,15]. They can produce a range of vitamins, synthesize all vital and nonessential amino acids, facilitate increased absorption of minerals and elevate out biotransformation of bile [14-17]. Additionally, the microbiome can regulate and execute the fundamental biochemical pathways for the metabolism of non-digestible carbohydrates including giant polysaccharides, such as resistant starches, cellulose, hemicellulose, pectin, and gums; some oligosaccharides that get away with digestion; unabsorbed sugars and alcohols from the diet [13]; and host-derived mucins [14]. As a consequence, there is a recuperation of electricity and availability of absorbable substrates for the host. This also serves as a self- provider of power and vitamins required for bacterial boom and proliferation [15]. Metabolism of carbohydrates remains the fundamental player in the supply of strength in the colon.

Gut microbiota in disease

Several anecdotal reviews and massive cohort studies have continued to evidence the association of composition of human intestinal microbiota with the ever-increasing range of diseases, syndromes, and aberrations. The subsequent section summarizes the associations that have garnered the focused attention: the opportunity of a hyperlink between the intestinal microbiota and [1] continual gastrointestinal illnesses such as IBS and IBD, and [2] systemic metabolic diseases, such as type-II diabetes and obesity.

Irritable Bowel Syndrome (IBS)

IBS is described as a crew of functional bowel problems resulting in belly soreness or pain due to disordered defecation or changes to bowel habits. In addition to the classification according to the Rome three standards, medical practitioners [18], have proposed further classification based on the groundwork of a patient's stool traits (Table 1).

Table 1: Etiological classification of symptoms of IBS.

IBS Subtype	Abbreviation	Characteristics
IBS with diarrhea	IBS-D	• Loose stools >25% of the time and hard stools <25% of the time • Up to one-third of cases • More common in men
IBS with constipation	IBS-C	• Hard stools >25% of the time and loose stools <25% of the time • Up to one-third of cases • More common in women
Mixed or cycling	IBS –M	• Both hard and soft stools >25% of the time One-third to one-half of cases
Unsubtyped IBS		• Insufficient abnormality of stool consistency to meet criteria

IBS is prevalent in about 10% to 20% of adults and youngsters worldwide [18,19]. IBS includes Crohn's Ailment (CD) and Ulcerative Colitis (UC). CD is characterized via a cobblestone-like sample of irritation (i.e., affected areas interrupted through wholesome tissue), that could be alongside the size of the GIT. Typically, ulcerations spanning the entire intestinal wall could result in fissures. The ensuing perforations of the intestinal wall may also have an impact on different organs such as the kidney or uterus [24]. UC generally manifests as contiguous irritation involving solely the floor layers of the intestinal wall. It is especially localized in the colon and normally originates at the rectum [25].

IBS is a multifactorial disease, and its progression is influenced by genetic factors, motor dysfunction of the GIT, visceral hypersensitivity, infection, and immunity, psychopathological elements [19]. Alterations in the microbiome composition of the intestine and low-grade intestinal infections are also associated with IBS [19]. Disturbed colonic fermentation in IBS sufferers might also play a necessary function in worsening of IBS symptoms [20]. There has been a significant, 2-fold extend in the ratio of Firmicutes to Bacteroidetes observed in the IBS patients [23]. There is an increased risk of IBS following acute gastroenteritis [20]. In a healthy gut, the intestinal microbiota may impart beneficial effects directly via bbactericidal action or can inhibit the adherence of pathogenic microorganism to the wall of the GIT (21) On the other hand, the prevailing hypothesis is that dysbiosis, especially fungal [21] due to microbial imbalance in the gut may lead to the adhesion of enteric pathogens that may also be associated with IBS symptoms [22,23].

Microbial species have a full-size role in immunomodulation. Factors including infestations by pathogens, environmental factors, inflammation, may breach the epithelial confinement of the intestinal microbiota causing aberrations of the intestine microbiome. The function of the intestine microbiota in IBD pathogenesis has been tested via research displaying that antibiotic use can minimize or forestall inflammation, each in murine fashions of disorder and in patients [24,26]. A recent study demonstrates that a specific diet that acts as a prebiotic favoring growth of intestinal microbes or transplantation of fecal microbiota could restore the levels of gut endocrine cells comparable to those of normal healthy population [25]. In UC sufferers inoculated with stool accumulated from wholesome donors, there was an indication of disorder remission within

one week of receiving their fecal transfer, with a complete healing reported after four months [27].

Obesity, metabolic syndrome, non-alcoholic fatty liver disease, and non-alcoholic steatohepatitis

Several mechanisms involving the microbiota in the pathogenesis of Nonalcoholic Fatty Liver Disorder (NAFLD) and Nonalcoholic Steatohepatitis (NASH) have been identified. In particular, there is increasing interest pertaining to the function of microbiota in the pathogenesis of weight related problems [28,29]. Pertinent findings include the ability of gram-negative anaerobes, such as Bacteriodes thetaiotamicron, to break most of the glycosidic linkages and help metabolize plant polysaccharides. This provides the host with 10% to 15% of its calorific requirement [28-31]. The microbiota of overweight individuals, as properly as the fecal microbiota of ob/ob mice, is greater environment friendly at the extraction of strength from the eating regimen and in the manufacturing of SCFAs [30,32]. Furthermore, the microbiota suppresses the Lipoprotein Lipase (LPL) inhibitor fasting-induced adipose element (also regarded as angiopoietin-like 4) activity has been proven to stimulate the production of hepatic triglyceride manufacturing, This facilitates the persisted expression of LPL, a key regulator of fatty acid launch from triglycerides in the liver [33]. The intestine microbiota can modulate systemic lipid metabolism through change of bile acid metabolic patterns, impacting at once emulsification and absorption of bile acids and, while, not directly acting on the storage of fatty acids in the liver [33]. Abnormality in metabolic syndrome that affects electricity balance, glucose metabolism, and causes low-grade inflammatory response has been related to weight changes and metabolic disorders. Its position in choline metabolism [34,36], inactivation of pro-inflammatory cytokines (such as TNF-α), seems applicable to the improvement of NAFLD and development to NASH. Any leak of metabolites of the gut microbiota into systemic circulation can cause heightened immune response in the liver to the circulating microbial antigens [26]. In response to this, the toll-like receptors of the liver activate an inflammatory immune cascade of responses that may trigger the development of NAFLD/NASH [27,28,37]. Small Intestinal Bacterial Overgrowth (SIBO) leading to enhanced release of proinflammatory cytokines and fatal steatohepatitis has been implicated in several liver disorders including NAFLD [38,39].

Systemic metabolic diseases

Systemic metabolic ailments encompass weight problems and type-II diabetes. In extra current human studies, the researchers observed that the composition of the intestine microbiota modified in response to host's physical weight and remains significantly altered in overweight individuals compared to normal healthy weight balanced individuals [40]. Subsequent research has failed, however, to reveal a regular relationship between weight problems and the ratio of Firmicutes to Bacteroidetes. A comprehensive literature of the pertinent studies has been reviewed by Tagliabue and Elli [41].

Type-II diabetes is a complicated multifactorial disorder influenced by genetic and environmental elements. This has been the frequently discussed public fitness subject [42]. Several genome-wide studies have tried to evaluate the genetic association of type -II diabetes Research investigating the underlying genetic contributors or genetic elements to type-II diabetes [43]. Such studies have identified changes in the composition of microbial biota as a significant risk factor that impedes the improvement of metabolic outcomes of type-II diabetes. There has been an associated decline in butyrate-producing micro-organism [44]. This commentary suggests that the notion of purposeful dysbiosis, as an alternative to any particular microbial species, may have a direct implication on the pathophysiology of type-II diabetes. Increasing presence of opportunistic pathogenic microorganisms is detected, albeit with inter-individual variability in the classes of organisms present [44].

Cardiovascular disease

There exists a hyperlink between gut dysbiosis and cardiovascular disease [29,30]. Recently, surmounting evidence from direct experimental observations is suggesting a causal link of gut microbiota in CVD [30]. Impaired gut barrier function and bowel oedema has been observed in heart failure patients [31,32]. Primarily the association is based on the facts displaying the role of microbial metabolism of dietary phosphatidylcholine on the pro-atherosclerotic metabolite Trimethylamine-N-Oxide (TMAO) [45]. TMAO titers have been related with a higher risk of cardiovascular problems in prone individuals [46] Studies indicate that administration of antibiotics could suppress the dietary phosphatidyl choline induced plasma titres of TAMO. Additionally vegan diet devoid of L-carnithine that is majorly present in meat components did no longer exhibit elevated plasma TMAO ranges after dietary phosphatidylcholine challenge. This trait used to be attributed to status of fecal microbiota composition [47]. Hence, this microbiota-dependent pathway might provide a diagnostic tool and have therapeutic value for cardiovascular disease management.

Host-microbe interactions on the immune system

From an evolutionary and ecological perspective, there is a complex interplay of mutual interactions between the microbiota and the host immune gadget. There is a strict balance between immune tolerance towards commensals and immune reactions against potential pathogens. The experience with commensal microbiota is therefore vital to teaching and training the immune machine to adapt, recognize and develop immune tolerance. A sequence of experiments confirmed that collections of nonpathogenic species of Clostridia from clusters IV, XIVa and XVIII, could induce colonic Treg response. One of the mechanisms could be the manufacturing of butyrate that influences epigenetic manage of the Foxp3 promoter that controls Treg improvement [49,50,51-54]. Antibiotic usage induced disturbances to microbiota could lead to overstimulation of immune cells including macrophages, mast cells, expansion of pro-inflammatory T helper cells [33].

Atopic eczema and other allergic disease

Atopic eczema a complex chronic inflammatory skin condition is triggered by several environmental factors. Genetically, a loss of function mutation in the gene encoding filaggrin, involved in epidermal barrier, predisposes the infants to this condition. Additionally, the mode of delivery of baby (i.e., vaginal vs. cesarean) and a mutation in a unique human gene is concerned with skin-barrier feature [55]. Characterization of the intestine microbiota of victims of atopic eczema confirmed that infants in the age of about one month with atopic eczema had a drastically decreased bacterial diversity, especially with regard to the Bacteroidetes phylum [56]. Also, at 12-month of age, there was a lowered variety of Bacteroidetes in the atopic-eczema group, suggesting that victims might also keep a decreased stage of bacterial variety when in contrast with healthy population. In

addition, a decrease variety of Proteobacteria, with unique lipopolysaccharide molecules, was once determined in toddlers imparting with atopic eczema. Lipopolysaccharides have the capability to elicit a host's immune response, and low exposure to lipopolysaccharides in infancy is linked with a greater danger of atopic eczema [57].

As a clarification for the marked extend in allergic disease, the notion of decreased quantitative and qualitative publicity to the microbial world at some point of the neonatal duration has been termed the hygiene speculation and is primarily based on the commentary of improved atopy in smaller, and specifically urbanized, households [58]. This underexposure to microbial antigens results in an aberrant effect to allergen processing of immunological response than an immunological tolerance [59].

Conclusions and perspective

The evolution of intestine microbiota in people all through existence seems to play a pivotal role in fitness and disease. In a healthy state, the intestine microbiota has myriad fine functions, such as power recuperation from metabolism of non-digestible elements of foods, defensive action against pathogenic invasion, and modulation of the immune system. Dysbiosis or disrupted state of the intestine microbiota has several negative implications on health. Identified as an environmental element the intestinal microbiota interacts with host's metabolism and has a function in pathological conditions. There seems to be an association with each systemic disorder including obesity, diabetes, and atopy-and gut-related IBS and IBD, although the precise interplay of the intestine microbiota to the prevailing host conditions in these illnesses remains unclear. The heterogeneous etiology of metabolic and gastrointestinal ailments has been related with one-of-a-kind microbes, even though little facts exist about the causal course of the association.

References

1. Maier E, Anderson RC, Roy NC. Understanding how commensal obligate anaerobic bacteria regulate immune functions in the large intestine. Nutrients. 2014; 7: 45-73.
2. Sittipo P, Shim JW, Lee YK. Microbial metabolites determine host health and the status of some diseases. International journal of molecular sciences. 2019; 20: 5296.
3. Claesson MJ, O'Sullivan O, Wang Q, Nikkilä J, Marchesi JR, et al. Comparative analysis of pyrosequencing and a phylogenetic microarray for exploring microbial community structures in the human distal intestine. PLoS One. 2009; 4: e6669.
4. Rakoff-Nahoum S, Coyne M, Comstock L. An ecological network of polysaccharide utilization among human intestinal symbionts. Current Biology. 2014; 24: 40-49.
5. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature. 2012; 489: 220-230.
6. Lederberg and mocray, The Scientist, 2001.
7. Sartor RB. Gastroenterol. 134: 577: 2008.
8. Jiménez E, Marín ML, Martín R, Odriozola JM, Olivares M, et al. Is meconium from healthy newborns actually sterile? Res Microbiol. 2008; 159: 187-193.
9. Huurre A, Kalliomäki M, Rautava S, Rinne M, Salminen S, et al. Mode of delivery-effects on gut microbiota and humoral immunity. Neonatology. 2008; 93: 236-240.
10. Collado MC, Cernada M, Neu J, Pérez-Martínez G, Gormaz M, et al. Factors influencing gastrointestinal tract and microbiota immune interaction in preterm infants. Pediatric research. 2015; 77: 726-731.
11. Walters WA, Xu Z, Knight R. Meta-analyses of human gut microbes associated with obesity and IBD. FEBS letters. 2014; 588: 4223-4233.
12. Vyas U, Ranganathan N. Probiotics, prebiotics, and synbiotics: gut and beyond. Gastroenterol Res Pract. 2012; 2012: 872716.
13. Silva YP, Bernardi A, Frozza RL. The role of short-chain fatty acids from gut microbiota in gut-brain communication. Frontiers in endocrinology. 2020; 11: 25.
14. Koropatkin NM, Cameron EA, Martens EC. How glycan metabolism shapes the human gut microbiota. Nat Rev Microbiol. 2012;10: 323-335.
15. Guarner F, Malagelada JR. Gut flora in health and disease. Lancet. 2003; 361: 512-519.
16. Gill. Science, 2006. Tremaroli & Bäckhed, Nature. 2012.
17. Quigley EMM. Gut microbiome as a clinical tool in gastrointestinal disease management: are we there yet? Nat Rev Gastroenterol Hepatol. 2017: 14.
18. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, et al. Functional bowel disorders. Gastroenterology. 2006; 130: 1480-1491.
19. Ghoshal UC, Shukla R, Ghoshal U, Gwee KA, Ng SC, et al. The gut microbiota and irritable bowel syndrome: friend or foe? Int J Inflam. 2012; 2012: 151085.
20. Guinane CM, Cotter PD. Role of the gut microbiota in health and chronic gastrointestinal disease: understanding a hidden metabolic organ. Therap Adv Gastroenterol. 2013; 6: 295-308.
21. Kellow JE, Azpiroz F, Delvaux M, Gebhart GF, Mertz HR, et al. Applied principles of neurogastroenterology: physiology/motility sensation. Gastroenterology. 2006; 130: 1412-1420.
22. Rinttilä T, Lyra A, Krogius-Kurikka L, Palva A. Real-time PCR analysis of enteric pathogens from fecal samples of irritable bowel syndrome subjects. Gut Pathog. 2011; 3: 6.
23. Ponnusamy K, Choi JN, Kim J, Lee SY, Lee CH. Microbial community and metabolomic comparison of irritable bowel syndrome faeces. J Med Microbiol. 2011; 60: 817-827.
24. Nagalingam NA, Lynch SV. Role of the microbiota in inflammatory bowel diseases. Inflamm Bowel Dis. 2012; 18: 968-984.
25. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet. 2007; 369: 1641-1657.
26. Swidsinski A, Weber J, Loening-Baucke V, Hale LP, Lochs H. Spatial organization and composition of the mucosal flora in patients with inflammatory bowel disease. J Clin Microbiol. 2005; 43: 3380-3389.
27. Soleimanpour S, Hasanian SM, Avan A, Yaghoubi A, Khazaei M. Bacteriotherapy in gastrointestinal cancer. Life sciences. 2020; 254: 117754.
28. Bäckhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine. Science. 2005; 307: 1915-1920.
29. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, et al. Obesity alters gut microbial ecology. Proc Natl Acad Sci USA. 2005; 102: 11070-11075.

30. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, et al. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006; 444: 1027-1031.

31. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature. 2006; 444: 1022-1023.

32. Schwiertz A, Taras D, Schafer K, Beijer S, Bos NA, et al. Microbiota and SCFA in lean and overweight healthy subjects. Obesity (Silver Spring). 2010; 18: 190-195.

33. Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci USA. 2004; 101: 15718-15723.

34. Dumas ME, Barton RH, Toye A, Cloarec O, Blancher C, et al. Metabolic profiling reveals a contribution of gut microbiota to fatty liver phenotype in insulin-resistant mice. Proc Natl Acad Sci U S A. 2006; 103: 12511-12516.

35. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, et al. Gut flora metabolism of phosphatidyl-choline promotes cardiovascular disease. Nature. 2011; 472: 57-63.

36. Rak K, Rader DJ. Cardiovascular disease: the diet-microbe morbid union. Nature. 2011; 472: 40-41.

37. Henao-Mejia J, Elinav E, Jin C, Hao L, Mehal WZ, et al. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. Nature. 2012; 482: 179-185.

38. Abu-Shanab A, Quigley EM. The role of the gut microbiota in nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol. 2010; 7: 691701.

39. Abu-Shanab A, Scully P, Crosbie O, Buckley M, Mahony LO, et al. Small intestinal bacterial overgrowth in nonalcoholic steatohepatitis: association with toll-like receptor 4 expression and plasma levels of interleukin 8. Dig Dis Sci. 2011; 56: 1524-1534.

40. Tremaroli V, Bäckhed F. Functional interactions between the gut microbiota and host metabolism. Nature. 2012; 489: 242-249.

41. Tagliabue A, Elli M. The role of gut microbiota in human obesity: recent findings and future perspectives. Nutr Metab Cardiovasc Dis. 2013; 23: 160-168.

42. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest. 2005; 115: 1111-1119.

43. Scott LJ, Mohlke KL, Bonnycastle LL, Willer CJ, Li Y, et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science. 2007; 316: 1341-1345.

44. Qin J, Li Y, Cai Z, Li S, Zhu J, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012; 490: 55-60.

45. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011; 7: 472: 57-63.

46. Tang WH, Wang Z, Levison BS, Koeth RA, Britt EB, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. The New England journal of medicine. 2013; 368: 1575-1584.

47. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nature medicine. 2013; 19: 576-585.

48. Tang WH, Hazen SL. The contributory role of gut microbiota in cardiovascular disease. J Clin Invest. 2014; 124: 4204-4211.

49. Arpaia N, Campbell C, Fan X, Dikiy S, van der Veeken J, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature. 2013; 504: 451-455.

50. Atarashi K, Tanoue T, Oshima K, Suda W, Nagano Y, et al. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. Nature. 2013; 500: 232-236.

51. Atarashi K, Tanoue T, Shima T, Imaoka A, Kuwahara T, et al. Induction of colonic regulatory T cells by indigenous Clostridium species. Science. 2011 21; 331: 337-341.

52. Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature. 2013; 504: 446-450.

53. Narushima S, Sugiura Y, Oshima K, Atarashi K, Hattori M, et al. Characterization of the 17 strains of regulatory T cell-inducing human-derived Clostridia. Gut microbes. 2014: 18; 5.

54. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science. 2013; 341: 569-73.

55. Williams HC, Grindlay DJ. What's new in atopic eczema? An analysis of systematic reviews published in 2007 and 2008, I: definitions, causes and consequences of eczema. Clin Exp Dermatol. 2010; 35: 12-15.

56. Abrahamsson TR, Jakobsson HE, Andersson AF, Björkstén B, Engstrand L, et al. Low diversity of the gut microbiota in infants with atopic eczema. J Allergy Clin Immunol. 2012; 129: 434-440.

57. Olin A, Acevedo N, Lakshmikanth T, Chen Y, Johansson C, et al. Longitudinal analyses of development of the immune system during the first five years of life in relation to lifestyle. Allergy. 2022; 77: 1583-1595.

58. Scudellari M. Cleaning up the hygiene hypothesis. Proceedings of the National Academy of Sciences. 2017; 114: 1433-1436.

59. Shen CY, Lin MC, Lin HK, Lin CH, Fu LS, et al. The natural course of eczema from birth to age 7 years and the association with asthma and allergic rhinitis: a population-based birth cohort study. Allergy Asthma Proc. 2013; 34: 78-83.