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Review

Fucosylated human milk oligosaccharide-utilizing bifidobacteria regulate the gut organic acid profile of infants

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Bifidobacteria are the predominant bacteria in the infant gut and have beneficial effects on host physiology. Infant cohort studies have demonstrated that a higher abundance of bifidobacteria in the gut is associated with a reduced risk of disease. Recently, bifidobacteria-derived metabolites, such as organic acid, have been suggested to play crucial roles in host physiology. This review focuses on an investigation of longitudinal changes in the gut microbiota and organic acid concentrations over 2 years of life in 12 Japanese infants and aims to identify bifidobacteria that contribute to the production of organic acid in healthy infants. Acetate, lactate, and formate, which are rarely observed in adults, are characteristically observed during breast-fed infancy. *Bifidobacterium longum* subspecies *infantis* and the symbiosis of *Bifidobacterium bifidum* and *Bifidobacterium breve* efficiently produce these organic acids through metabolization of human milk oligosaccharide (HMO) with different strategies. These findings confirmed that HMO-utilizing bifidobacteria play an important role in regulating the gut organic acid profiles of infants.

Key words: bifidobacteria, infant, gut microbiota, human milk oligosaccharide, organic acid

INTRODUCTION

Gut microbiota development begins immediately after birth, and its dynamics are influenced by various factors, including dietary patterns [1]. The infant gut microbiota has a characteristically higher abundance of bifidobacteria than that of adults [2, 3]. However, the abundance of bifidobacteria during infancy varies among individuals and is influenced by factors, such as gestational age, mode of delivery, type of milk feeding, and host genetic variables [1, 4–6]. Birth cohort studies conducted in various countries have explored relationships with the infant gut microbiota, specifically focusing on the abundance of bifidobacteria and the risk of various diseases, such as pediatric asthma [7, 8], atopic dermatitis [9], and obesity [10]. Recent findings have highlighted the crucial role of bifidobacteria-derived metabolites, particularly organic acids and indole lactate, in these relationships between the infant gut microbiota and human health, prompting further investigation into their physiological functions [11–13].

Through their intricate metabolic pathways, bifidobacteria efficiently utilize complex dietary carbohydrates, such as human milk oligosaccharides (HMOs) [14, 15], starch [16], and arabinoxylan [17, 18], resulting in the production of organic acids. Acetate, one of the predominant organic acids produced by bifidobacteria, is known for its diverse physiological effects. Acetate not only serves as a primary energy source for intestinal epithelial cells but also plays a role in the regulation of metabolic processes [19], immune modulation [20], and prevention of infectious diseases [11]. In addition to acetate, bifidobacteria produce lactate. Lactate is a product of carbohydrate fermentation and is converted to other organic acids, such as butyrate and propionate, in the adult gut [21, 22]. Therefore, lactate is rarely detected in adults, and its physiological effects remain poorly understood. A few reports indicate that bifidobacteria also produce formate [23]. However, the substrates and metabolic pathways involved in formate production are not well understood.

This review focuses on the genetic factors that affect the gut organic acid profile during infancy and aims to elucidate the relationship between bifidobacterial colonization and gut metabolites. Understanding these factors is important to control the risk of diseases associated with the infant gut microbiota.

EARLY GUT MICROBIOTA DEVELOPMENT AND CHANGES IN ORGANIC ACID PROFILE

Individual variation in the timing of colonization by bifidobacteria

The gut microbiota has been shown to change dynamically during the first 2 years of life [24]. Initially, the microbiota was dominated by Enterobacteriales, Lactobacillales, and Bacillales

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(Fig. 1A). Enterobacteriales showed the highest abundance immediately after birth, and their abundance decreased until approximately 6 months of age, after which it remained relatively low (Fig. 1B). Subsequently, the microbiota was dominated by Bifidobacteriales. The timing of Bifidobacteriales-dominated microbiota establishment varied greatly among individuals, ranging from shortly after birth to beyond 6 months of age. The abundance of Bifidobacteriales peaked at approximately 8

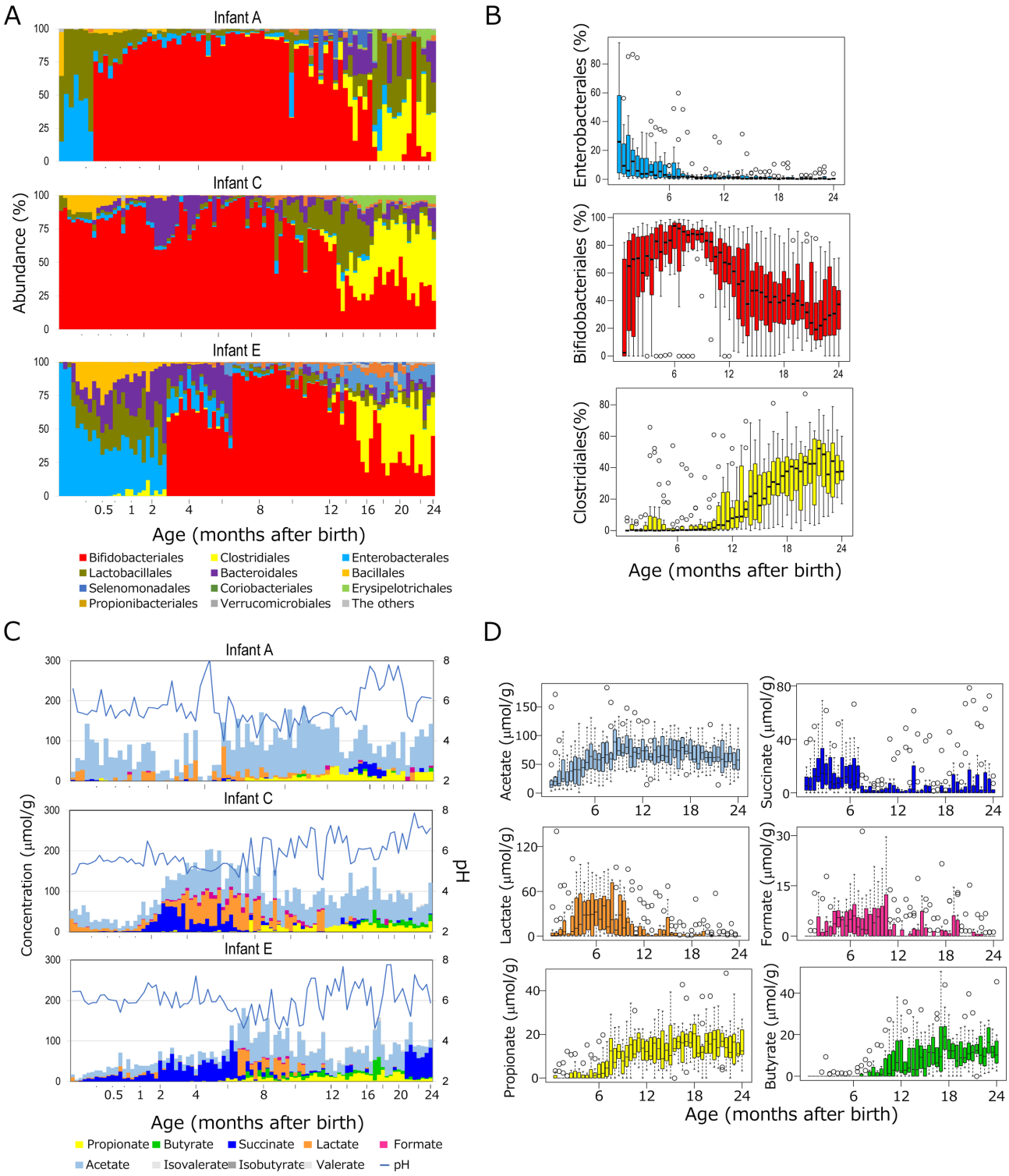

Fig. 1. Infant gut microbiota development and the changes in gut organic acid profiles during the first 2 years of life. (A) Order-level dynamics in the gut microbiota of three infants. Vertical bars along the x-axis indicate intervals of 2 months; dots along the x-axis indicate intervals of 1 week for the duration of 1 month. (B) Temporal shift of bacterial abundance in 12 infants at the order level. (C) Fecal organic acid and pH dynamics of 3 infants. (D) Temporal shift of organic acid concentrations and pH in fecal matter. The original publication is available at https://doi.org/10.1038/s41396-021-00937-7 [24].

months, after which it decreased (Fig. 1B). Subsequently, the microbiota transitioned to a Clostridiales-dominated state. In many of the infants, this transition coincided with the cessation of breastfeeding. The transition between different dominating bacterial orders in the infant gut microbiota has been reported previously [25, 26].

Lactate and formate are specifically observed during breastfeeding

The composition of organic acids in the infant gut has also been shown to change dynamically over the first 2 years of life (Fig. 1C). Initially, the concentrations of organic acids were low, but they increased from approximately 1–3 months of age. During this time, an increase in the acetate, lactate, and formate concentrations was observed (Fig. 1D). Acetate was the predominant organic acid during the first 2 years. In many individuals, lactate and formate were no longer detected at approximately 1 year of age. Lactate and formate are detected at a significantly low concentrations in adult feces [27]; therefore, their detection at relatively high concentrations for a certain period can be considered a characteristic of the organic acid composition of the gut during breast-fed infancy. An increase in propionate concentration was observed at around 8–12 months of age, followed by an increase in the butyrate concentration. Several studies have suggested that the low expression of organic acid synthesis genes and low acetate concentrations in the feces of infants are negatively correlated with their risk of developing type 1 diabetes [28] and pediatric asthma [7, 8]. This highlights the potential contribution of organic acids in the gut of infants to their health.

ASSOCIATION BETWEEN BIFIDOBACTERIA AND ORGANIC ACID

Correlation analyses have been conducted between organic acid concentrations and bacterial abundance to identify bacteria that contribute to organic acid production in infant guts [24]. Strong positive correlations were found between the abundance of bifidobacteria and concentrations of lactate, formate, and acetate (Fig. 2A). Therefore, the timings of bifidobacteria colonization and increases in organic acid concentrations were compared. The timing of bifidobacteria colonization coincided with an increase in organic acid concentrations in some infants, unlike the majority of the infants (Fig. 2B). Therefore, the presence of bifidobacteria did not always influence the concentrations of organic acids in the gut. Based on these findings, it was hypothesized that the utilization of specific carbohydrates, such as HMO, present in the infant gut may vary among individuals owing to different strains of bifidobacteria colonizing the gut.

UTILIZATION OF HMOS BY BIFIDOBACTERIA

Fucosyllactose utilization ability differs among bifidobacterial strains

HMOs include fucosylated lactoses, long-chain fucosylated oligosaccharides, and acidic oligosaccharides [29]. Multiple strains of bifidobacteria have been isolated from infants and cultured in a medium containing HMOs as the sole carbon source, and certain strains were able to grow well, unlike others (Fig. 3A) [14]. Examination of the residual oligosaccharide composition in the medium confirmed that strains capable of growing in HMO-supplemented medium exhibited lower concentrations of residual HMOs, with fucosyllactose levels in particular being significantly reduced (Fig. 3B). Furthermore, a comparative genomic analysis revealed the presence of an ABC transporter responsible for the uptake of fucosylated lactose in strains that grew well in HMO-containing medium (Fig. 3C). The utilization of fucosylated lactose varied depending on the species or strain of bifidobacteria in both this study and a study performed by Sakanaka *et al.* [14, 15]. All strains of *Bifidobacterium longum* subsp. *infantis* (*B. infantis*) and *Bifidobacterium bifidum*, but only a few strains of *Bifidobacterium breve* and *Bifidobacterium pseudocatenulatum*, utilized fucosylated lactose [14]. The majority of *Bifidobacterium longum* and *Bifidobacterium adolescentis* strains were unable to utilize fucosyllactose. The fucosyllactose transporter was present in all strains capable of utilizing fucosyllactose, with the exception of *B. bifidum*.

HMO utilization strategies vary among bifidobacterial species

Long-chain fucosylated oligosaccharides have various structures, including lacto-*N*-fucopentaose and lacto-*N*-difucohexaose [29]. Previous studies reported that the representative species capable of utilizing long-chain oligosaccharides were *B. infantis* [15, 30], *B. bifidum* [15], and *Bifidobacterium kashiwanohense* [31]. *B. infantis* possesses diverse ABC transporters that are involved in HMO utilization and are responsible for the uptake and utilization of long-chain fucosylated oligosaccharides [32, 33]. However, *B. bifidum* possesses extracellular fucosidases that cleave fucose outside the bacterial cell, allowing the cellular uptake of lacto-*N*-tetraose [33, 34]. This indicates that *B. infantis* and *B. bifidum* can utilize various structures of HMOs through different strategies. The two species are expected to proliferate well in the infant gut, leading to increased production of organic acids. As noted earlier, correlation analyses of the abundance of each species of bifidobacteria and the concentrations of organic acids in the gut of each infant have been reported [24]. As expected, positive correlation was observed between the presence of *B. infantis* and *B. bifidum* and the concentrations of lactate and formate.

ORGANIC ACID PRODUCTION BY *B. INFANTIS* AND *B. BIFIDUM*

Organic acid production by B. infantis

When the colonization of *B. infantis* was examined in 12 Japanese infants, it was found to have coincided with an increase in lactate, acetate, and formate concentrations in 4 of the 12 infants [24]. Furthermore, *B. infantis* produced lactate, acetate, and formate when utilizing HMO as a substrate (Fig. 4A and 4C). However, when it was cultured with lactose as a substrate, only lactate and acetate were produced. RNA-seq analysis was conducted to compare the gene expression profiles of *B. infantis* cultured with fucosyllactose and those cultured with lactose as substrates. The expression of genes encoding fucosyllactose and fucose transporters, as well as that of genes involved in the metabolism of fucose to formate, were found to be upregulated in *B. infantis* cultured with fucosyllactose compared with that in *B. infantis* cultured with lactose. These results suggested that *B. infantis* was responsible for converting fucose into formate in the infant guts.

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The pathway of fucose to formate metabolism in bifidobacteria

Based on the results of the RNA-seq analysis, the metabolic pathway responsible for the conversion of fucose to formate was estimated [24]. Fucose was initially transported to the cell via a transporter, where it was converted to fuconolactone by fucose dehydrogenase (Fig. 4D). Following this, L-fuconolactonase and L-fuconate dehydratase acted sequentially on fuconolactone to produce 2-dehydro-3-deoxy-L-fuconate. Formate C-acetyltransferase then converted 2-dehydro-3-deoxy-L-fuconate to formate. Additionally, 2-dehydro-3-deoxy-L-fuconate was cleaved by aldolase into pyruvate and lactaldehyde. Pyruvate was converted to formate by formate C-acetyltransferase, while lactaldehyde was converted to 1,2-propanediol by lactaldehyde reductase. The fucose-to-formate pathway was associated with NADH/NAD^+ redox homeostasis. Upon investigating the presence of this pathway in bifidobacteria, all strains of *B. infantis* and *B. breve* were found to possess a gene cluster encoding the enzymes that convert fucose to formate.

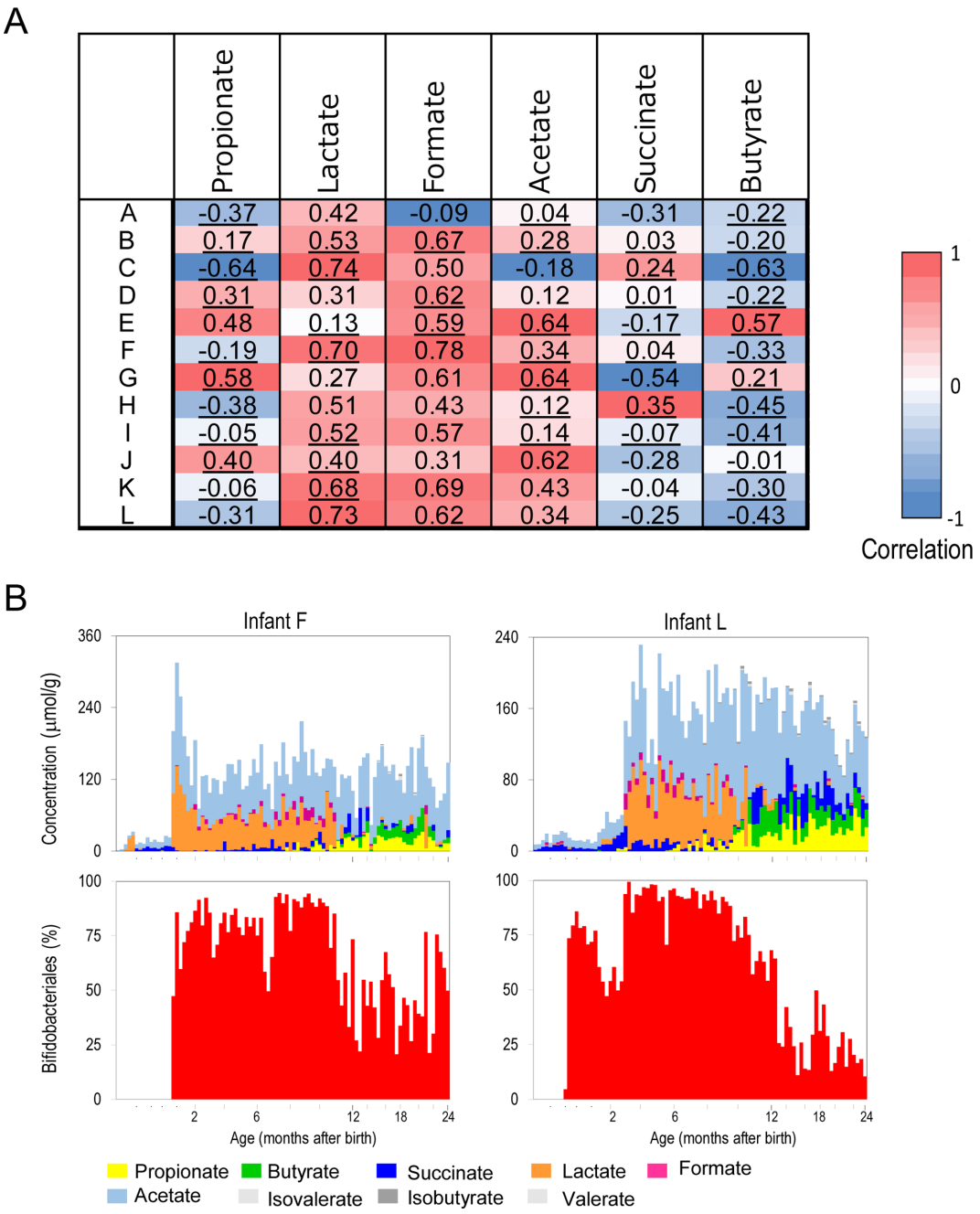

Fig. 2. Association between the abundance of bifidobacteria and levels of organic acid in the guts of the infants. (A) Heatmap of the within-participant correlation between levels of organic acids and the abundance of Bifidobacteriales in the gut. Numbers represent the r values for each infant (calculated using Spearman's correlation). False discovery rate-corrected p values < 0.01 are underlined. (B) Comparison of the timing of the increase in organic acid concentrations (top panel) and bifidobacterial colonization (bottom panel) in two infants. The original publication is available at https://doi.org/10.1038/s41396-021-00937-7 [24].

***Organic acid production by symbiosis of* B. bifidum *and* B. breve**

When the colonization of *B. bifidum* was examined in the 12 Japanese infants, it was found to have coincided with an increase in lactate, acetate, and formate concentrations in 5 of the 12 infants [24]. In vitro experiments demonstrated that *B. bifidum* utilized HMO as a substrate, producing only lactate and acetate (Fig. 4B and 4C). As previously stated, the HMO-utilization mechanism of *B. bifidum* involves the extracellular breakdown of HMO by fucosidases [15, 34, 35], after which the resulting products are taken up into bacterial cells. During this process, accumulation of the monosaccharide fucose was observed in the culture medium. The observed increase in formate concentration upon colonization by *B. bifidum* led to the hypothesis that other gut bacteria might convert the fucose cleaved by *B. bifidum* into

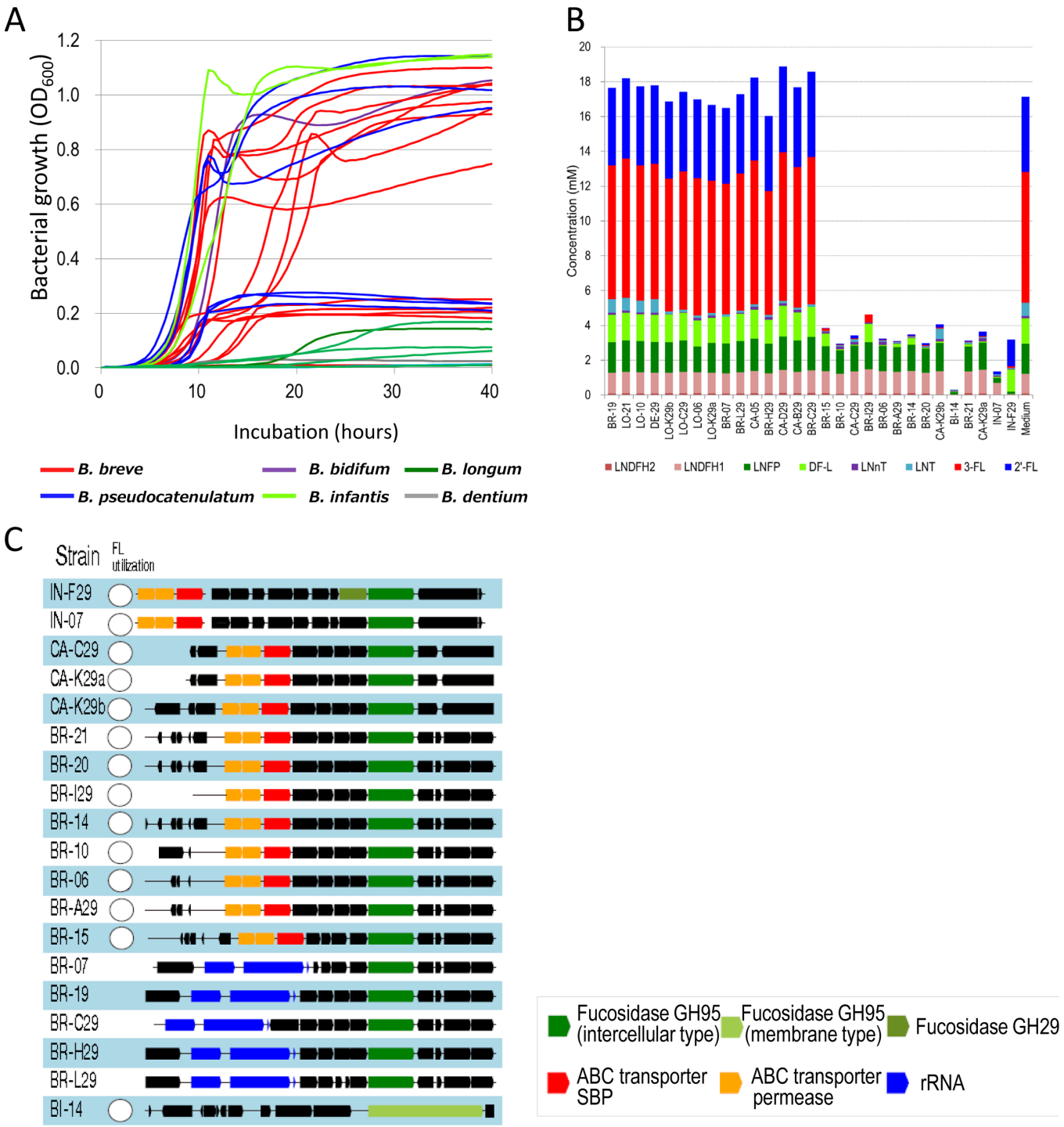

Fig. 3. Utilization of human milk oligosaccharides (HMOs) by bifidobacterial strains. (A) Growth curves of 29 bifidobacterial strains in medium containing HMOs. (B) Oligosaccharide profiles of bacterial supernatants after 40 hr of cultivation. Samples are ordered based on their OD600 values after 40 hr of cultivation. (C) Visual summary of the draft genomes of the 29 bifidobacterial strains sequenced in this study. The original publication is available at https://doi.org/10.1038/ncomms11939 [14].

formate (Fig. 4B). As all the *B. breve* strains detected in this study possessed fucose transporters and their corresponding metabolic genes, the symbiosis between *B. breve* and *B. bifidum* was investigated. When both strains were co-cultured *in vitro* with fucosyllactose as a substrate, formate production was observed in the medium (Fig. 4C). These results strongly suggest that *B. bifidum* and *B. breve* collaborate in the gut to produce organic acids, including formate, from HMO. The symbiotic relationship between *B. bifidum* and *B. breve* has been demonstrated in several other studies [34, 36], and the results of the study discussed here [24] further strongly support a symbiotic relationship between both species in the infant gut.

CONCLUSION

This review discussed the colonization of HMO-utilizing bifidobacteria in the infant gut and described their associations with increased concentrations of organic acids, including lactate, formate, and acetate (Figs. 5 and 6). Through a detailed analysis of bifidobacteria isolated from infant guts, the gene clusters, metabolic pathways, and interspecies interactions involved in organic acid production were partially clarified. High abundances of bifidobacteria and high concentrations of organic acids in the gut during infancy were found to be negatively correlated with the risk of various diseases. The administration of HMO-utilizing

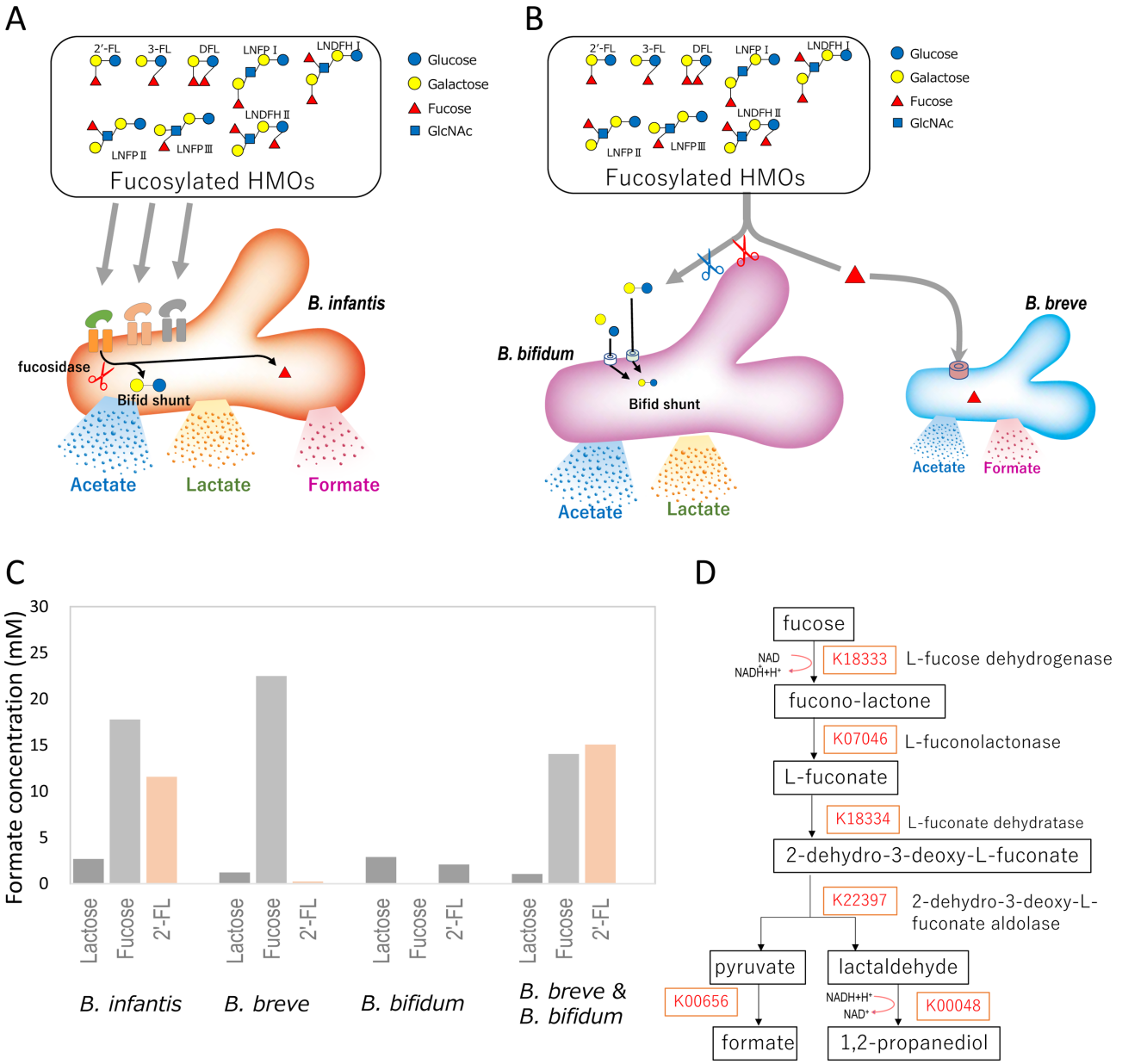

Fig. 4. Organic acid production by *Bifidobacterium infantis* and *Bifidobacterium bifidum*. (A) Utilization of fucosylated human milk oligosaccharides (HMOs) by *B. infantis*. (B) Utilization of HMOs by *B. bifidum* and *Bifidobacterium breve*, which do not possess a fucosyllactose transporter. (C) Formate production by different bifidobacterial strains using lactose, fucose, and 2'-FL (2'-fucosyllactose) as substrates. (D) The metabolic pathway responsible for the conversion of fucose to formate is annotated with KO (Kyoto Encyclopedia of Genes and Genomes) numbers. The original publication is available at https://doi.org/10.1038/s41396-021-00937-7 [24].

bifidobacteria as probiotics to infants is expected to increase gut organic acid concentrations. This review provides valuable information for developing strategies to address diseases related to the gut microbiota in infants.

CONFERENCE PRESENTATION

The contents of this article received the 2022 Research Encouragement Award of Intestinal Microbiology Society (IMS) and were presented at the Annual Meeting of IMS, held on June 27, 2023.

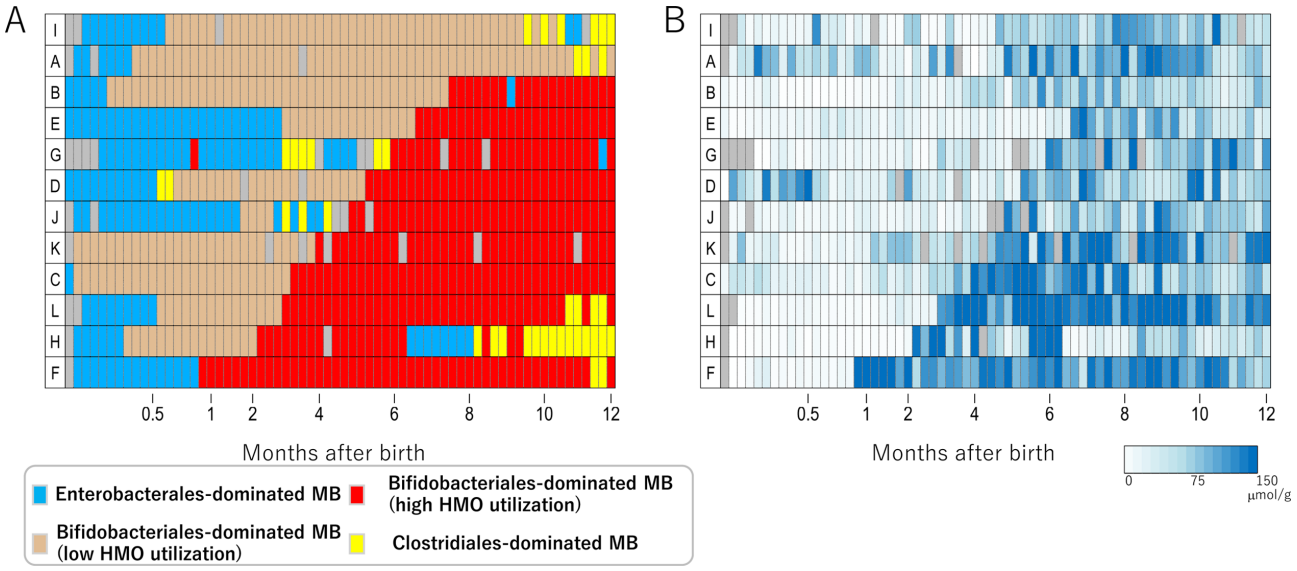

Fig. 5. Comparison between the changes of the dominating order in microbiota and the concentrations of organic acids in the gut. (A) Changes in the dominating order of bacteria in the microbiota over time. (B) Organic acid concentration (sum of the acetate, lactate, and formate concentrations) in the gut.

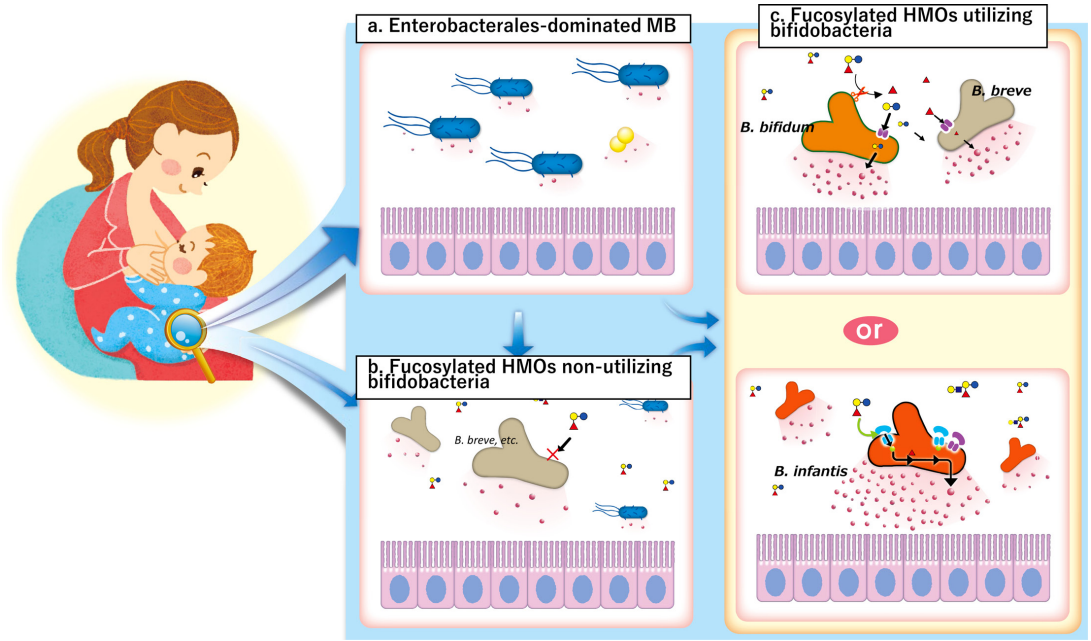

Fig. 6. Graphic abstract of the development of the infant gut microbiota during the breastfeeding period. Initially, an Enterobacteriales-dominated microbiota is established, after which the gut is predominantly populated by low-human milk oligosaccharide (HMO)-utilizing bifidobacteria. Then, HMO-utilizing bifidobacteria with higher HMO-utilization capacity become the most abundant. Among the HMO-utilizing bifidobacteria, *Bifidobacterium infantis* utilizes HMOs to produce organic acids, including formate, while *B. bifidum* produces formate-containing organic acids through a symbiotic relationship with *B. breve.*

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CONFLICT OF INTEREST

The author declares no competing interests.

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