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Mini Review

Co-resilience: A Novel Therapeutic Approach to Resilience-Building of the Host and Gut Microbiota

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ABSTRACT

The resilience of the gut microbiota is a feature of healthy gut microbiota. Since associations between inflammatory-related diseases, such as type 2 diabetes or early-life allergic diseases, and the gut microbiota have been increasingly recognized in humans, besides lifestyle interventions, microbial interventions to increase the resilience of the gut microbiota, including probiotics, prebiotics, and fecal microbial transplantations, have been utilized clinically. However, inconsistent results and limitations are present in practice partially due to the intricate role of the gut microbiota in the disease. Thus, we explore the idea of "co-resilience," which emphasizes the importance of the resilience of the gut microbiota and that of the hosts to fitness with outlining the current evidence showing that gut microbial interventions influence host fitness for resilience-building management of the gut microbiota. We also propose a co-resilience-building approach that integrates gut microbial interventions with conventional therapy. The combined effects can render host-gut microbiota interactions beneficial, and such a novel co-resilience approach is expected to have a potent impact on host fitness.

Keywords: Gut microbiota; Resilience; Fitness; Dysbiosis; Gut microbial interventions; Co-Resilience

INTRODUCTION

Accumulating studies have indicated links between the gut microbiota and health and diseases. The emerging interest in intestinal microbes involves altered microbial communities that are associated with a specific disease, particularly in inflammatory-related diseases (e.g., allergies and metabolic syndrome). This microbial alteration is often described as dysbiosis caused by extrinsic insults such as a disruptive diet and antibiotic medications. Experimental animal models have provided evidence for the role of the gut microbiota in the diseases [1,2], and restoration of the microbiota from an altered state by colonization with beneficial microbes mitigates physiological symptoms [3].

In this review, we consider evidence for resilience-building management of the gut microbiota that involves returning the microbiota to the pre-dysbiotic state with gut microbial interventions. Then, we argue that the idea of "co-resilience," which combines the resilience of the host with gut microbiota, is essential for a deeper understanding of our fitness. Finally, we propose that a co-resilience-building approach may lead to efficacious therapy for diseases.

RESILIENCE-BUILDING MANAGEMENT OF THE GUT MICROBIOTA

The resilience of the gut microbiota

The resilience of the gut microbiota is an expansionary concept derived from ecology, and is defined as "the amount of stress or perturbation that a system can tolerate before its trajectory changes towards a different equilibrium state" [4,5]. In this concept, although an acute disruptive force temporarily affects the gut microbial compositions, the gut microbiota can revert to the initial state due to resilience. For example, although a high-fat diet impacts the microbial communities in humans, a high-fat diet is less disruptive to the communities in the short term interventions than a regular long-term diet consumed over a year [6]. In other words, although what constitutes a "healthy human gut microbiota" is controversial [7] and remains to be defined as a single idealized set of microbial community organisms [8], resilience to disturbance is a feature of the healthy gut microbiota [7].

On the other hand, loss of resilience means that the gut microbiota loses its capacity to tolerate perturbation and thus become susceptible to damage to the gut microbial community. Namely, dysbiosis,

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described in the context of diseases, occurs due to external forces, such as a chronic disruptive diet or antibiotic use that overcome the internal resilience of the gut microbiota. For example, the gut microbiota of patients with Type 2 Diabetes (T2D) is relatively enriched with Bacteroidetes, Proteobacteria [9], and the imidazole propionate-producers, *Eggerthella lenta*, and *Streptococcus mutans* [10]. An increase in Escherichia is associated with Nonalcoholic Steatohepatitis (NASH) [11]. Also, recent studies have shown that neurodegenerative diseases such as Parkinson's Disease (PD) and Alzheimer's Disease (AD) may be linked to dysbiosis triggered by the accumulation of extrinsic insults such as aging, diets, and stress [12,13]. For example, the abundance of Prevotellaceae is reduced in feces of Parkinson's disease (PD) patients. Alzheimer's disease (AD) patients have an increased abundance of Bacteroidetes and a decreased abundance of Firmicutes [13]. Although "dysbiotic patterns" may differ between individuals due to multifactorial causes such as the long-term impact of lifestyle factors, these studies show clinically relevant changes in the gut microbial compositions in association with the loss of resilience of the gut microbiota.

The microbiota in infants is relatively unsettled over the first 3 years of life compared to adults [14]. In early-life development, an infant's microbial community is mostly shaped by maternal microbiota via prenatal and neonatal events such as birth mode and feeding [15]. In this context, the resilience of the gut microbiota of an infant is established during a critical period, and indeed, dysbiosis of the gut microbiota of both mothers and infants is considered to be co-dependently associated with health risk of infants. For example, in humans, *Bifidobacterium* breve (*B. breve*) and *Bifidobacterium* infantis in the mother's feces are associated with bifidobacteria counts and their diversity in the neonate's feces [16]. Moreover, decreased colonization with *Lactobacillus*, *Bifidobacterium*, and the butyrate-producer *Anaerostipes caccae* has been linked to food allergy and atopic diseases [3,17,18], whereas increased abundance of *Clostridium* and *Ruminococcus gnavus* is linked to allergy-related diseases [17-19]. These studies suggest that infants need to form a resilient microbial community during this critical time.

The resilience-building management of the gut microbiota

Gut microbial interventions (probiotics, prebiotics, and fecal microbiota transplantation) constitute resilience-building management of the gut microbiota. The association between dysbiosis and disease is still unclear regarding whether dysbiosis is a cause or consequence of diseases [20]; however, given that the gut microbiota largely contributes to host fitness, rectifying altered microbiota through gut microbial interventions is reasonable. For example, when a mixture of *Bifidobacterium* and *Lactobacillus* strains was ingested by healthy obese subjects for 6 months, a reduction in body weight and improved quality of life were observed [21]. Also, in patients with the chronic liver disease nonalcoholic fatty liver disease, the alanine aminotransferase concentration was reduced following administration of a mixture of *Bifidobacterium* and *Lactobacillus* strains combined with Fructooligosaccharides (FOS) [22]. Psychometric tests were improved following treatment with *Bifidobacterium* and Fructooligosaccharides (FOS) in patients with hepatic encephalopathy associated with liver disease [23]. Administration of *Lactobacillus rhamnosus* (*Lactobacillus* GG) or *B. breve* and *Bifidobacterium longum* to prenatal mothers and their neonates, respectively, more effectively prevented atopic dermatitis relative to the placebo group [24,25].

Dietary interventions using prebiotics are also feasible for resilience-building management because they provide fermentable resources for the selected microbiota. Prebiotic intervention in children with genetic and diet-induced obesity changes the gut microbiota compositions and improves health outcomes [26]. Similarly, substantial evidence suggests that prebiotics improve allergic diseases early in life. Therapeutic use of prebiotic 1-kestose, a component of Fructooligosaccharides (FOS), improves the clinical symptoms of atopic dermatitis in infants [27]. Table 1 summarizes the clinical evidence for gut microbial interventions. Thus, resilience-building management of the gut microbiota successfully increases the beneficial health outcomes in clinical trials [28-33].

Table 1: Clinical studies of gut microbial interventions.

Gut microbial interventions	Participants	Main results	Refs
Obesity			
Bifidobacterium adolescentis IVS-1, *Bifidobacterium lactis BB-12* with or without galactooligosaccharide for 3 weeks.	151 obese adults (BMI ≥30 kg/m^2)	Colonization with B. adolescentis IVS-1	[28]
Oligofructose for 12 weeks.	48 overweight or obese adults and older adults (BMI ≥25 kg/m^2)	Reduced body weight Suppressed ghrelin and enhanced peptide YY	[29]
Lactobacillus salivarius Ls-33 for 12 weeks.	51 obese adolescents (BMI ≥30 kg/m^2)	Altered fecal microbiota	[30]
Bifidobacterium animalis with or without polydextrose for 6 months.	225 obese adults (BMI 28-34.9 kg/m^2)	Altered fecal microbiota Reduced body fat mass by administration of synbiotics	[31] [32]
Whole grain pasta containing barley β-glucans and Bacillus coagulans for 12 weeks.	41 overweight and obese adults (BMI ≥25 kg/m^2)	No effect	[33]
Oligofructose-enriched inulin for 16 weeks.	42 overweight and obese children (BMI >85th percentile)	Reduction in body fatIncrease in *Bifidobacterium* spp.	[34]
Inulin-type fructans (ITF) or whey protein with or without ITF for 12 weeks.	125 overweight and obese adults (BMI ≥25 kg/m^2)	Reduction in appetiteIncrease in fecal *Bifidobacterium*	[35]
Inulin plus resistant maltodextrin with energy-restricted diet for 12 weeks.	116 overweight and obese adults (BMI ≥28 kg/m^2)	No effect on weight loss. Increase in fecal Parabacteroides and *Bifidobacterium*.	[36]

Fructooligosaccharides (FOS) with or without multistrain probiotics (*Lactobacillus* paracasei, *Lactobacillus rhamnosus*, *Lactobacillus* acidophilus, and B. lactis) for 15 days.	9 obese adults scheduled for Roux-en-Y gastric bypass (BMI >40 kg/m^2 or >35 kg/m^2 with at least one comorbidity)	Reduced body weight with FOS	[37]
Arabinoxylans for 6 weeks.	47 overweight and obese adults (BMI 28-35 kg/m^2)	Increased fecal SCFAs	[38]
L. paracasei or flaxseed mucilage for 6 weeks.	58 obese postmenopausal women (BMI 30-45 kg/m^2)	Improved insulin sensitivity with flaxseed mucilageAltered fecal microbiota with flaxseed mucilage	[39]
L. rhamnosus for 24 weeks.	125 obese adults (BMI 29-41 kg/m^2)	Reduced body weight in women	[40]
Multistrain probiotic (L. acidophilus, *L. plantarum*, *Bifidobacterium* bifidum, and B. animalis subsp. lactis) for 6 months.	220 overweight and obese adults (BMI 25-34.9 kg/m^2)	Reduced body weight Improved quality of life	[21]
Nonalcoholic Fatty Liver Disease (NAFLD)			
Multistrain probiotics (*L. plantarum*, L. deslbrueckii, L. acidophilus, *L. rhamnosus*, and B. bifidum) for 6 months.	20 adult and older adult patients with histology-proven NASH	Reduced intrahepatic triglyceride content Decreased serum aspartate aminotransferase	[41]
Synbiotics (L. casei, *L. rhamnosus*, S. thermophilus, *B. breve*, L. acidophilus, B. longum, and L. bulgaricus plus FOS) for 28 weeks.	52 adult and older adult patients with NAFLD (presence of steatosis, ALT >60 U/L)	Decreased in serum alanine aminotransferase (ALT)	[22]
Multistrain probiotics (S. thermophilus, *B. breve*, B. infantis, B. longum, L. acidophilus, *L. plantarum*, *L. paracasei*, and L. delbrueckii subsp. bulgaricus) for 4 months.	48 obese children with NAFLD (BMI >85th percentile)	Improvement in fatty liver Decrease in BMI	[42]
Lactobacillus rhamnosus GG for 8 weeks.	20 obese children (BMI >95th percentile)	Decrease in serum ALT	[43]
Type 2 Diabetes (T2D)			
Xylooligosaccharides (XOS) for 8 weeks.	13 prediabetic adults and older adults (BMI 27-35 kg/m^2, fasting glucose level >100 mg/dL)	Altered fecal microbiota	[44]
Multistrain probiotics (*B.bifidum, B. lactis, L. acidophilus, L. brevis, Lactobacillus casei, L. salivarius, and Lactococcus lactis*) for 6 months.	96 adult and older adult patients with T2D	Decrease in HOMA-IR	[45]
Multistrain probiotics (*Lactobacillus, Lactococcus, Bifidobacterium, Propionibacterium, and Acetobacter*) for 8 weeks.	53 adult and older adult patients with T2D	Improved insulin resistance	[46]
Metabolic Syndrome (MetS)			
Intestinal microbial transfer from lean donor	18 male obese patients with MetS (BMI >30kg/m^2, fasting plasma glucose level >5.6 mmol/L)	Improved insulin sensitivity 6 weeks after infusion. Increased butyrate-producing intestinal microbiota.	[47]
L. casei Shirota for 12 weeks.	30 adult patients with MetS	Increase in fecal Parabacteroides	[48]
Hypercholesterolemia			
L. plantarum for 12 weeks.	49 adults (total cholesterol 5.16-7.64 mmol/L)	Reduction in total cholesterol in high-cholesterol group	[49]
L. reuteri for 9 weeks.	127 hypercholesterolemic adults and older adults (LDL-cholesterol >3.4 mmol/L)	Reduction in LDL-Cholesterol	[50]
Cystic Fibrosis (CF)			
L. reuteri for 6 months.	61 pediatric and adult patients with CF	Decreased risk of pulmonary exacerbations. Reduced upper respiratory tract infections.	[51]
Chronic Kidney Disease (CKD)			
Synbiotics (*L. plantarum, L. rhamnosus, L. gasseri, B. infantis, B. longum, L. acidophilus, L. salivarius, Lactobacillus sporogenes, and S. thermophilus* plus inulin) for 4 weeks.	30 adult and older adult participants with CKD (stage 3-4 CKD)	Lowered plasma total p-cresol concentrations	[52]
Psychosis			
Galactooligosaccharides for 12 weeks.	39 adult patients with psychotic disorder	Improved cognitive assessment	[53]

Autism			
Galactooligosaccharide for 6 weeks.	26 autistic children	Improved antisocial behavior by exclusion diet and prebiotics	[54]
L. acidophilus for 2 months.	22 autistic children	Decreased D-Arabinitol (DA) and the ratio of D-/L-arabinitol (DA/LA) in the urine	[55]
Atopic Dermatitis (AD)			
Synbiotics (*B. breve plus galacto-*/fructooligosaccharide mixture) for 12 weeks.	90 infants with AD	No effect on AD severity Altered fecal microbiota	[56]
Cyanotic Congenital Heart Disease (CCHD)			
B. lactis plus inulin for 8 weeks.	100 infants with CCHD	Reduced incidence of nosocomial sepsis, necrotizing enterocolitis, and death	[57]

Abbreviations: BMI: Body Mass Index; ITF: Inulin-Type Fructans; FOS: Fructooligosaccharides; SCFA: Short-Chain Fatty Acid; NAFLD: Nonalcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; ALT: Alanine aminotransferase; T2D: Type 2 Diabetes; XOS: Xylooligosaccharides; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; MetS: Metabolic Syndrome; LDL: Low-Density Lipoproteins; CF: Cystic Fibrosis; CKD: Chronic Kidney Disease; AD: Atopic Dermatitis; DA: D-Arabinitol; LA: L-arabinitol; CCHD: Cyanotic Congenital Heart Disease.

Co-resilience

The studies mentioned above emphasize the implications of being a human-microbe hybrid, i.e., a superorganism (Figure 1), and suggest the idea of "co-resilience" of the superorganism [34-39]. Conventional therapies target host tissues/organs that are susceptible to damage. Although tissues/organs can recover from damage, which is defined as resilience of the host, the damage results in severe diseases when the resilience of the host is lost [40-45]. When resilience is lost, drugs, exercise, and other interventions support the recovery of tissues/organs to the pre-disease state by repairing damage [46-51]. For this reason, treatment for Type 2 Diabetes (T2D) and atopic dermatitis often include metformin and topical corticosteroids [52-57], which target glucose metabolism in the liver and skin inflammation, respectively [58,59]. However, because altered gut microbiota is linked to diseases both in adults and infants, guiding the establishment of health-promoting microbiota is essential for regaining host fitness. Such "co-resilience" may be promising for improving physiological outcomes.

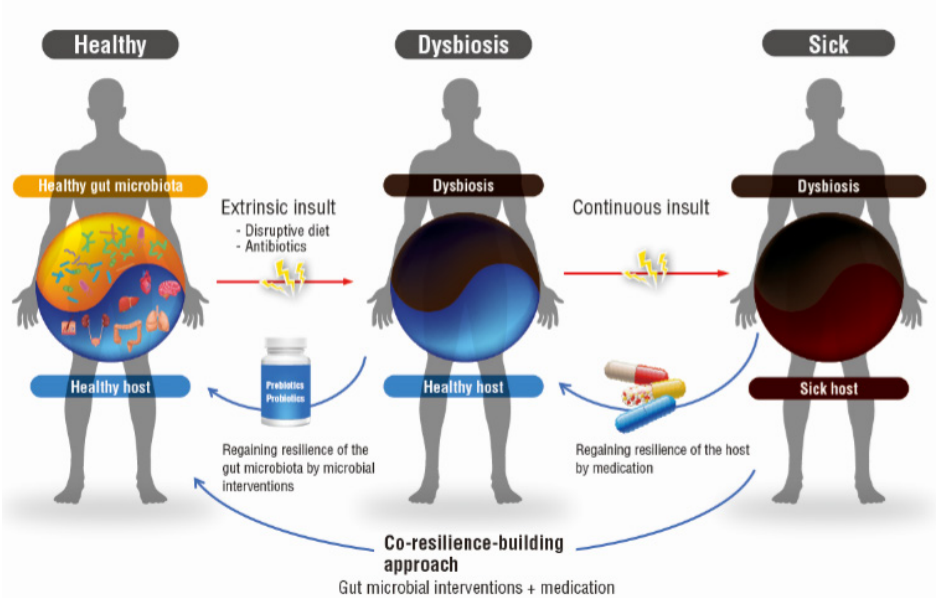

Figure 1: Co-resilience-building approach. Humans are human-microbe hybrids, also called superorganisms (Left). In a healthy host, human tissues/organs and gut microbiota maintain fitness and a co-resilient state. External insults such as disruptive diet cause dysbiosis of the gut microbiota. The pre-dysbiotic state can be restored by gut microbial interventions (Middle). In a sick host, both human tissues/organs and the gut microbiota are damaged (Right). Conventional therapy such as medications is used as intervention in a sick host. However, treatments targeting the host and the gut microbiota, known as a "co-resilience-building approach", will lead to the restoration of the superorganism fitness.

Co-resilience-building approach

Combining conventional therapy with gut microbial interventions will require reconsideration of how we manage fitness. As mentioned, "Co-resilience" involving recovery from clinical disorders entails correction of damage to the gut microbial community via gut microbial interventions in addition to conventional therapy. Such a novel approach may provide more efficacious therapy than conventional therapy alone. Thus, we propose a co-resilience-building approach (Figure 1). Evidence supporting the efficacy of this co-resilience-building approach is sparse at present (Table 2). A good example illustrating this approach is treatment for constipation, which is common in patients with Parkinson's Disease (PD) [60,61].

Table 2: Tentative co-resilience-building approach.

Gut microbial interventions	Drugs	Participants	Main results	Ref.
Constipation in Parkinson's Disease (PD)				
Multistrain probiotics (*Streptococcus salivarius subsp thermophilus, Enterococcus faecium, Lactobacillus rhamnosus* GG, *Lactobacillus acidophilus,Lactobacillus plantarum, Lactobacillus paracasei, L. paracasei, delbrueckii subsp bulgaricus, Bifidobacterium breve*, and *animalis subsp lactis* plus FOS) for 4 weeks.	Laxatives, Dopamine agonist	120 patients with PD	Improved constipation	[60]
Small-intestinal ulcers (adverse effect of acetylsalicylic acid)				
After 6-week acetylsalicylic acid intake, *B. breve* for 8 weeks.	Acetylsalicylic acid	75 healthy adults	Lowered Lewis score (validation for ulcers)	[62]
Type 2 Diabetes (T2D) with Non-Alcoholic Fatty Liver Disease (NAFLD)				
Multistrain probiotics (*Lactobacillus, Lactococcus, Bifidobacterium, Propionibacterium*, and *Acetobacter* plus omega-3 fatty acids) for 8 weeks.	Metformin, Sulfonylurea, Insulin	48 adult patients with T2D and NAFLD	Reduced fatty liver index. Improved serum lipids	[63]
Candidemia				
Lactobacillus reuteri or *L. rhamnosus* for 6 weeks.	Liposomal Amphotericin B, Antibiotics	249 pre-term infants	Lowered candida stool colonization	[64]

***Note:** The list includes clinical trials that can be considered to use a co-resilience-building approach.
Abbreviations: PD: Parkinson's Disease; FOS: Fructooligosaccharides; T2D: Type 2 Diabetes; NAFLD: Non-Alcoholic Fatty Liver Disease.

DISCUSSION

In a clinical trial, constipation improved in patients with Parkinson's disease (PD) following administration of multistrain probiotics for 4 weeks. Because medications are unavoidable in Parkinson's disease (PD), patients in the trial were allowed to take dopamine agonists and laxatives. Although how probiotics improve constipation in PD is still to be determined, this trial indicates that targeting tissues/organs and gut microbiota is effective in PD. Likewise, in T2D rats, the bioavailability of the drug, gliclazide, was enhanced by administration of probiotics, suggesting that probiotics have an adjuvant function with gliclazide [62-65]. Thus, rethinking conventional therapy and broadening the potential of the co-resilience-building approach will be worthwhile.

A potent co-resilience-building approach involves two considerations; one is an adjuvant role, and the other is minimizing the adverse effects of drugs. The former was described above regarding PD trials [60]. For the latter, probiotic *Bifidobacterium* intake, for example, reduces the number of ulcers, which is an adverse effect of acetylsalicylic acid [62], implying the potency of a co-resilience-building approach to minimize the adverse effects of drugs. Diseases can be treated with conventional medications and fine-tuned with gut microbial interventions, and thus, such a co-resilience approach may be efficacious (Figure 1) [66].

CONCLUSION

The evidence presented here is not comprehensive, and the adverse effects of drug-microbiota interactions need to be considered. For example, non-antibiotic drugs have anticommensal activity, and 24% of screened drugs demonstrate inhibition of at least one species *in vitro*. Because the gut microbiota is seldom binary and intricate, studying how theses alterations caused by gut microbial interventions affect the host will be essential. Thus, our proposal needs to be tested rigorously in animal models and clinical trials, and the co-resilience-building approach should be implemented with the right combination of drug-microbiota interactions. With a shift in the co-resilience-building approach, treatment of a disease may improve the outcome for patients, and continuous active interventions will help create and sustain a healthy state for both the host and the gut microbiota.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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