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Intestinal microbiota and its host: harmony or discord?

Acquisition and alteration of intestinal microbiota from birth to adulthood: consequences for metabolic and neurologic health

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Notes are linked to the references page.

INTRODUCTION

The human intestinal microbiota is known to play a key role in a number of important biologic functions, including extracting nutrients from food, synthesizing essential vitamins, the development of immunity, protection against invading pathogens, and shaping brain development.[1] The microbiome composition can be altered by a number of factors, including antibiotic use, lifestyle factors (such as exercise or time spent sedentary), diet (e.g., carbohydrates and fats can have a profound influence on gut microbiota), and hygiene, which can limit the types of organisms that are able to colonize the gastrointestinal tract.[1] When the microbiota is disrupted, all of these factors can contribute to chronic inflammatory and metabolic diseases.

Most of the human microbiota is established after birth, with the microbial composition gradually increasing in diversity and stability until adulthood, after which it remains relatively stable during most of a healthy adult's life.[2] With advanced age, immunosenescence can destabilize and change the microbiome, and may contribute to neurologic disease.

Early-in-life factors that can shape an infant's microbiome include breastfeeding, vaginal delivery, and skin and oral contact. Factors that can disrupt the microbiome and affect microbiota maturation include administration of antibiotics to the infant or mother (prenatally or during nursing), and Caesarean section delivery.[3] Studies in mice and epidemiologic studies both indicate that disruption of microbiota early in life can have effects on immunologic development, behavior, as well as growth and metabolism.[3]

ROLE OF MICROBIOTA IN THE DEVELOPMENT OF OBESITY

A potential role of gut microbiota in the development of obesity was first proposed over 10 years ago by Turnbaugh and colleagues, following a series of elegant experiments in which microbiota from genetically obese mice were transferred into germ-free, non-obese recipients.[4] Within 2 weeks, the recipients had significantly increased levels of body fat, providing the first evidence that gut microbes can drive obesity.

Based on the finding that microbiota can influence obesity, it is also plausible that agents which modulate the microbiota, such as antibiotics, could affect body weight. Subtherapeutic doses of antibiotics have been widely used to promote weight gain and feed efficiency in the agricultural industry since the 1950s in a variety of farm animals using many different types of antibiotics.[5] Cho and colleagues studied whether administration of subtherapeutic doses of four different antibiotics to young mice would alter the structure of the gut microbiome as well as its metabolic capabilities.[6] They observed elevated fat mass at 10 weeks of age with several classes of antibiotic, with the greatest increase observed with penicillin. Further studies have investigated when, in the developmental window, microbiota disruptions had the greatest effects. After administration of low-dose penicillin in mice at either birth or weaning, male mice receiving the antibiotic at birth had significantly greater fat mass at 20 weeks than mice receiving the antibiotic at weaning,[7] indicating that the window of vulnerability for later obesity development is greatest if the microbiota is disrupted between birth and weaning.

In a separate experiment, in which mice received low-dose penicillin or control in combination with a high-fat or normal diet, the greatest fat mass increase was observed in mice with antibiotic-induced microbiota disruption who were fed the high-fat diet.[7] These findings suggest a synergistic effect between microbiota disruption and diet. To determine whether this would also be observed with limited antibiotic exposure, the

experiment was repeated with penicillin administration for 4 weeks, 8 weeks, or lifelong. Significant increases in lean mass were observed up to around week 20 in female mice, after which there were significant elevations in fat mass. These findings were independent of the length of antibiotic exposure, suggesting that 4 weeks of antibiotic exposure is sufficient to cause sustained effects on body composition.[7] Although the microbiota recovered over a period of 4 weeks after the antibiotic exposure was stopped by 8 weeks of age, the changes in phenotype remained, providing one of the first lines of evidence that the early-life disruption of the microbiota can influence life-long metabolism.[7]

The mouse gut microbiota was sequenced at 10 different time points to examine which microbes were affected by high-fat diet.[7] This showed that levels of *Allobaculum* in control animals were present at around 5% early in life and increased to nearly 50% when a high-fat diet was introduced. In contrast, *Allobaculum* levels were significantly reduced in mice treated with antibiotics. Other microbial species affected by low-dose penicillin included *Lactobacillus*, *Rikenellaceae* and *Candidatus Arthromitus*, suggesting that these bacteria may have a protective role in shaping adult metabolism and promoting intestinal defense.

Studies suggest that a weakened intestinal defense can lead to low-grade inflammation and obesity.[8] The intestinal microbiota play a key role in the development of intestinal immune responses. For example, the gut microbiota provide antigens that can trigger differentiation of T-helper cells. These then act on downstream effectors which secrete antimicrobial peptides, thus completing the loop with the immune system modulating the gut microbiota.[9] Treatment of mice in early life with low-dose penicillin resulted in downregulation of several immune genes expressed in the ileum that are involved in antigen presentation, generation of a type 17 T helper (Th17) cell response, and antimicrobial peptides.[7]

To determine whether the altered microbiota played a causal role in obesity, not the antibiotics alone, microbiota from penicillin-treated mice were transferred to germ-free mice by oral gavage.[7] After only 5 weeks, these animals had significant increases in total mass and fat mass, indicating that the antibiotic-altered microbiota caused the observed metabolic changes. In both the donor and recipient mice, the expression of ileal-defense genes, including Th17 and antimicrobial peptides, was down-regulated, demonstrating that both the immunologic and metabolic phenotype had been transferred. Recipient mice also demonstrated reduced levels of *Lactobacillus*, *Allobaculum*, and *Rikenellaceae*.[7]

HOW DO THESE FINDINGS TRANSLATE TO HUMANS?

Microbiota in early life

If disruption of gut microbiota in early life can contribute to obesity in animal models, could the same be true in humans, where there is currently an epidemic of obesity worldwide? A number of epidemiologic studies have investigated whether antibiotic use in the first year of life can increase the risk of obesity in childhood and adolescence. International data from more than 180,000 children indicate that antibiotic treatment in infancy is associated with higher weight later in childhood.[10-14]

In addition to the importance of the gut in human metabolism, a bidirectional communication system, known as the gut–brain axis, allows the gut and central nervous system to communicate via the nerves, endocrine system and immune system.[15,16] It now appears that the intestinal microbiota can communicate with the brain via this circuit, to influence brain development and behavior, and may also influence a broad spectrum of diseases, including irritable bowel syndrome, psychiatric disorders, and demyelinating conditions such as multiple sclerosis (MS). The effectors of this communication include microbial products, such as short chain fatty acids, that can alter entero-endocrine cell secretion, and thereby influence mood and behavior.[15] Microbes themselves can also produce neurotransmitters, although there is debate about whether these can actually enter the circulation and influence the brain.

Several lines of evidence indicate that early-life disruption to the developing gut microbiota can impact neurodevelopment and potentially lead to adverse mental health outcomes later in life.[17, 18] This was first demonstrated by Sandler and colleagues, who found that short-term vancomycin treatment could temporarily reverse symptoms of some forms of autism.[17] Research in animal models of autism has suggested that disruption of gut microbiota in early life results in reduced integrity of the gut epithelial barrier, with subsequent leakage of gastrointestinal metabolites into the bloodstream.[18] These lines of research have led to treatments such as microbiota transfer therapy, which involves transfer of gut microbiota from healthy individuals into autistic patients.[19] In 2017, a promising study of children with autism spectrum disorders showed improvements in gastrointestinal symptoms after microbiota transfer.[19]

Microbiota in mid-life and adulthood

Emerging evidence suggests that microbiota disruption may play a role in the pathogenesis of MS. This immune-mediated demyelination disease is driven by T and B cells that infiltrate the central nervous system and attack myelin. As gut microbiota are known to regulate immunity by influencing production of both pro-inflammatory and anti-inflammatory cells, studies have investigated whether there are alterations in the microbiota of patients with MS. Using ribosomal RNA sequencing, the microbiome of 60 patients with MS was compared with that of 43 healthy controls.[20] Increases in *Methanobrevibacter* and *Akkermansia* and decreases in *Butyricimonas* were observed in patients with MS, which correlated with variation in the expression of genes involved in dendritic cell maturation, interferon signaling, and NF-κB signaling pathways in circulating T cells and monocytes.[20] *Methanobrevibacter* is also elevated in inflammatory bowel disease and obesity, while *Akkermansia* has been shown to reverse high-fat diet induced obesity,[21] and *Butyricimonas* is a prominent butyrate producer, thus may induce regulatory T cells in the gut.[22] The microbiota changes were greater in untreated MS patients and appeared to normalize in patients on disease-modifying therapy.[20]

In another study, microbiota from monozygotic human twins, one of whom had MS, were transplanted into a transgenic mouse model of spontaneous brain autoimmunity.[23] Microbiota from the twin with MS induced a significantly higher incidence of autoimmunity than that from the healthy twin, suggesting that altered microbiota may play a causal role in MS.[23]

Microbiota in late life

With advanced age, disruptions to the microbiota occur in combination with increased levels of systemic inflammation. However, an animal study showed that mice do not display an age-related increase in circulating pro-inflammatory cytokines when maintained under germ-free conditions.[24] Macrophages obtained from these aged germ-free mice maintained anti-microbial activity, whereas when germ-free mice were housed with aged conventionally raised mice, they developed macrophage dysfunction as well as elevated tumor necrosis factor (TNF-α) and interleukin-6 (IL-6) levels, suggesting that the aged microbiota of conventionally raised mice had a pathologic effect.[24] Colonizing aged germ-free mice with microbiota from young mice restored macrophage phagocytic function and resulted in lower levels of TNFα and IL-6.

Advanced age is one of the greatest known risk factors for Alzheimer's disease (AD), raising the question of whether aged microbiota could also play a role in the development of this neurodegenerative disease. Gut microbiota from a transgenic mouse model of AD differ significantly from those of non-transgenic wild-type mice.[25] Germ-free amyloid beta precursor protein (APP) transgenic mice demonstrated lower deposition of beta amyloid compared with control mice. Furthermore, colonization of germ-free mice with microbiota from conventionally raised APP mice also increased beta amyloid pathology.[25] In another study, amyloid plaque deposition in a murine model of AD was significantly reduced when antibiotics were administered from 2 weeks to 6 months of age.[26]

Many studies have shown that the microbiota can affect metabolic and neurologic health throughout a lifespan. Infancy and advanced age are periods when disrupted microbiota can lead to an increased likelihood of metabolic disturbances and disease. Ongoing research is investigating how to control microbiota during these vulnerable time periods.

SUMMARY AND CONCLUSION

The gut microbiota is established during the first few years of human life, and is essential for metabolic and neurologic health. Animal studies have begun to define a critical period during early development and in advanced age in which disruption of the microbiota can have a critical impact on health and disease. The central nervous system and the gastrointestinal tract are in constant, bidirectional communication, and as a result, perturbations of the microbiota during these periods can lead to modifications in brain chemistry and behavior and an increased risk of disease. Early life disruptions in microbiota have been implicated in childhood obesity and autism, while later in life they have been associated with multiple sclerosis and Alzheimer's disease. Ongoing research is investigating the role of diet or antibiotic therapy to stabilize disrupted microbiota in these metabolic and neurologic diseases.

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