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What is the microbiome?

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INTRODUCTION

There has been an explosion in our understanding of the human microbiome (the genome of all our microbes) in the recent years. Advances in genome sequencing technologies and metagenomic analysis (genetic study of genomes taken directly from environmental samples) have enabled scientists to study these microbes and their function and to research microbiome–host interactions both in health and disease. The human microbiome has an estimated 100 trillion microbes, the bulk of which live in our gut. This summary gives an overview about what is known about the microbiota (microbial community) in paediatric practice. This short article is written for the practising paediatrician. For a scientific overview, the reader is referred to reviews.^{1 2} An understanding of this complex ecological community is important as it affects our patients, and manipulation of the gut microbiome has the potential to be used in the treatment of childhood diseases in the future.

THE HUMAN MICROBIOME: AN ORGAN IN ITS OWN RIGHT

The human microbiome is composed of communities of bacteria (and viruses and fungi) that have a greater complexity than the human genome itself. Large-scale metagenomic projects (community and environmental genomics), such as the European Metagenomics of the Human Intestinal Tract and the Human Microbiome Project, have reported 3.3 million unique protein-encoding genes as compared with the entire human genome, which has around 23 000 genes. These studies have described the beneficial functions of the normal gut microbiota on health down to the genetic level.³ The human microbiome has extensive functions such as development of immunity, defence against pathogens, host nutrition including production of short-chain fatty acids important in host energy metabolism, synthesis of vitamins and fat storage as

well as an influence on human behaviour, making it an essential organ of the body without which we would not function correctly (figure 1).

MICROBIOME COMPOSITION

Unlike the host genome, which is relatively constant, the microbiome is dynamic and changes with early development, environmental factors such as diet and use of antibiotics and especially in response to disease.⁴ The most dramatic changes in composition occur in infancy and early childhood.⁵ The intestinal microbiome of an infant is affected by gestational age (full term or premature), mode of delivery (vaginal birth or caesarean section), type of feed (breast milk or formula feeds), maternal nutritional status (overweight or undernourished) and use of antibiotics.⁶ The complexity and plasticity of the infant microbiota during this early-life development is believed to be important in maintaining homeostasis with the host's immune system and has an impact on health later in life.⁷

A healthy human gut can house at least 1000 different species of bacteria, comprising of two major phyla, namely Bacteroidetes and Firmicutes. Elucidating the microbiome composition in healthy individuals is important to understanding what consequences changes in microbiome composition may have to human health and disease susceptibilities.

Other microbes also live in the gut including viruses, fungi and archaea. However, research on them has been small compared with that on bacteria.

THE HUMAN MICROBIOME AND DISEASE

The relationship between changes in microbiome composition and disease pathogenesis is uncertain. The challenge is to identify whether microbial imbalance is related to disease, sometimes termed 'dysbiosis', and to be able to distinguish between cause and effect. The following section highlights some



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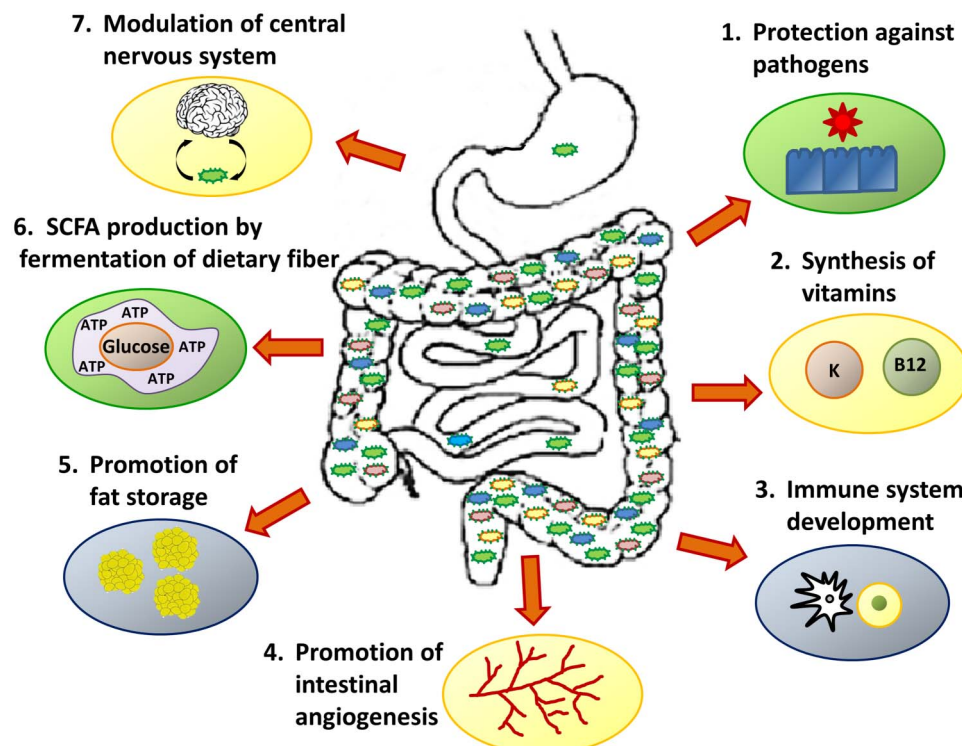


Figure 1 The human microbiome plays an important role in control of vital homeostatic mechanisms in the body. These include enhanced metabolism, resistance to infection and inflammation, prevention against autoimmunity as well as an effect on the gut–brain axis. SCFA, short-chain fatty acid.

conditions seen in paediatrics that have been associated with changes in the gut microbiota (table 1).^{8–16}

Inflammatory bowel disease (IBD)—This is one of the most extensively studied human conditions associated with the gut microbiota. The composition of the gut microbiota differs between healthy individuals and patients with IBD both in terms of species richness (ie, numbers of bacterial species) and species abundances (ie, number of individuals per species). As bacteria are identified by sequencing, rather than by functional characteristics in the culture laboratory, the individual bacterial species or genus (depending on the classification of sequence data) are commonly referred to as operational taxonomic units in microbiota research.

Studies have reported patients with IBD to have decreased bacterial diversity, and reduced abundances of Firmicutes and Bacteroidetes and an increased abundance of Proteobacteria compared with healthy individuals.¹⁷ Latest research suggests that IBD pathogenesis is due to the interaction of environmental factors (eg, smoking, diet and stress) and the host's genetic susceptibility, which is influenced by commensal microbiota, which activates either pathogenic or protective immune responses.¹⁸ Evidence from mouse models provides further support for the role of gut microbiota in pathogenesis of IBD.¹⁹

Necrotising enterocolitis (NEC)—The pathogenesis of NEC is multifactorial although the gut microbiota

is thought to play a crucial role. Studies in both humans and animal models have described changes in the gut microbiota including a reduction in bacterial diversity and increased abundances of Proteobacteria in preterm infants with NEC compared with healthy preterm infants.²⁰ However, the results have been inconsistent across studies, and to date, no single causative set of microorganisms has been identified.

Atopic diseases—Conditions such as eczema, asthma and food allergies are increasing in incidence. This is often linked to the hygiene hypothesis. It is thought that the lack of early-life exposure to microbial antigens in hygienic developed countries alters the microbiota composition of the infant gut, which disrupts immune development causing allergic disease.²¹ For example, species like *Bacteroides fragilis* reportedly induces immunological tolerance through immune receptor signalling pathways.²² Also the infant gut microbiota is affected by environmental factors including pets, residing in rural homes and siblings shown to have protective effects against asthma and allergies.²³ The concept that altered microbiome composition influences childhood allergic disease susceptibility is further supported by data from epidemiological studies that report higher prevalence of atopic diseases in infants delivered by caesarean sections, formula fed infants and those exposed to antibiotics.²⁴

Type 1 diabetes—The gut microbiota is involved in regulation of the metabolic–immune axis.⁸ Research

Table 1 Alterations in gut microbiota exert an influence on organ systems in the body leading to disease

Organ	Examples of diseases linked with altered microbiota	Microbiota-mediated changes	References
Brain	Autism spectrum disorder	Abundance of bacterial toxins Disrupted fermentation	9, 25
Lung	Asthma Cystic fibrosis	Reduced immunological tolerance Altered gene expression	11, 12, 21, 23, 24
Heart	Cardiovascular disease	Production of proinflammatory metabolites	13
Pancreas	Type 1 and type 2 diabetes	Reduced insulin sensitivity	8
Liver	Non-alcoholic fatty liver disease	Altered bile acid metabolism	10
Adipose tissue	Metabolic syndrome Obesity	Reduced intestinal gluconeogenesis Insulin resistance	8, 14, 15
Gastrointestinal tract	Inflammatory bowel syndrome Irritable bowel syndrome Gut infections	Dysregulated immune response Altered mucosal barrier	17–20, 22
Skin	Acne Eczema Allergic diseases	Increased pathogenic strains Dysregulated immune response	16

studies speculating the specific causative microbial composition and function have not been consistent. However, Bifidobacteria is believed to be protective, while Proteobacteria is a reported risk factor. Similarly, changes in gut microbiota caused by lifestyle (eg, mode of delivery and diet) are known risk factors for the development of type 1 diabetes, like birth by caesarean section reportedly increases the risk of developing type 1 diabetes by 20%.⁷

Autistic spectrum disorder (ASD)—The gut microbiota can influence human behaviour by modulating the gut–brain axis via endocrine (cortisol), immune (cytokines) and neural (vagus and enteric nervous system) signalling pathways. Several studies have described an altered gut microbiota in children with ASD compared with developmentally normal children.²⁵ However, more work is needed to establish if this is important in the pathogenesis of the condition.

FUTURE POTENTIAL OF MICROBIOTA MANIPULATION FOR THE TREATMENT OF DISEASE

Manipulation of the microbiota as a therapeutic tool is a rapidly advancing field in microbiome research. There is an abundance of data suggesting treatments capable of reversing dysbiosis are effective in managing certain human diseases. Targeted antibiotic use to eliminate select microbiota, probiotics and prebiotics to encourage the expansion of beneficial bacteria and faecal microbiota transplantation to restore bacterial communities are some of the approaches that are currently under investigation or in use. These studies will provide a greater understanding of the host–microbiome interactions that impact on disease.

As paediatricians, we need to keep abreast of the research as within the next decade, it is highly likely that we may be using such treatments in our practice.

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