ROLE OF THE MICROBIOME
IN HEALTH AND DISEASE

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ABSTRACT

Understanding the role of the microbiota in health and disease may offer new insights into the factors that start and drive the progression of various diseases, like autism, auto-immune disease, obesity, diabetes, and cancer. In turn, this will offer a platform to stratify the risk of patients for complications and also to deliver new personalised therapeutic strategies.

INTRODUCTION

Lederberg and McCray[1] first defined the term microbiota to describe the microorganisms that live in or on the human body. Such microorganisms are found on the skin and in the eyes, gut, mouth, and vagina. About two-thirds of the human microbiota is hosted in the gastrointestinal tract, which is the largest interface to the external environment.

Approximately 1 kg of bacteria is hosted in the human gut! Overall, that equates to about 9.9 million bacterial genes, with the ratio of host DNA to microbiome DNA being 1:10. It is worth mentioning that these microorganisms are also present earlier in life, in the infant gut. Specifically, research has shown that, during delivery, the infant gut is colonised by the microbiome of the maternal anus, skin, and vagina. In addition, the infant gut is inhabited by the bacteria the neonate is exposed to after birth.[2] Other factors structure the neonatal microbiome in both animal models and humans, including antibiotic treatment and diet.[3]

It is posited that microbiota co-evolved in a mutual relationship with humans. In fact, emergent evidence supports the hypothesis that these microorganisms play an important role in maintaining immunologic, metabolic, and nutritional homeostasis in our bodies. However, there are both beneficial and harmful bacteria. Eubiosis occurs if the beneficial bacteria dominate. In contrast, dysbiosis occurs when the harmful bacteria take over. One of the most common diseases caused by dysbiosis is infection.[4] In some specific cases of dysbiosis, consuming live microorganisms in probiotics may improve or restore the gut flora.

In order to understand these host–microbe interactions, researchers use gnotobiotic animal models; animals in which the bacterial strains and other microorganisms present are known. Studies in both these animal models and humans have associated microbiome signatures with disease and health. Indeed, advances in microbial research have provided insight into the role of the human microbiota in diseases such as autism, auto-immune disease, cancer, obesity and diabetes. In turn, all of this knowledge will offer a platform to deliver new personalised therapeutic strategies in the near future.

AUTISM SPECTRUM DISORDERS (ASD)

In recent years, it has become evident that our gut microbiota has far-reaching implications for our brain development and function. Dysbiosis in the gut have been linked with mood disorders (e.g. depression) and autism spectrum disorders (ASD).[5] Even though genetic inheritance has a role in developing ASD, external influences such as gut microbiota may be equally important. While a cause-effect association has not yet been identified, many gastrointestinal problems including abdominal pain, constipation, and diarrhoea are often concomitant with ASD.[6] Indeed, increasing evidence suggests bi-directional communication between the gut microbiota and the central nervous system (known as the "gut-brain axis"), which may play a role in ASD pathogenesis.

The interplay between gut microbiota and ASD may begin even before birth: factors such as diabetes, maternal obesity, and the taking of antibiotics, affect the pre-birth baby gut microbiota, and may be associated with ASD development. Other neonatal factors, such as birth delivery mode (vaginal vs. caesarean section) and breast-feeding affect gut microbiota diversity and the risk of developing ASD. For example, breast-feeding infants for >6 months has been related to a decreased risk of developing ASD,[7] whereas the risk is increased in children born by caesarean section.[8] Indeed, the gut microbiota of children with ASD is typically of a different composition and diversity than that of children without ASD.[9]

Our understanding of the gut microbiota-ASD relationship has greatly improved. As a result, emergent potential therapies for ASD are increasingly focused on gut microbiota modulation. These have included the use of

prebiotics, probiotics, or diet changes in animal models and ASD individuals. Other possible therapies include faecal microbiota transplantation, which involves delivering faecal microbiota from healthy individuals to those with dysbiotic gut microbiota. Overall, changing the gut microbiota might one day provide effective and risk-free therapies for ASD individuals.

OBESITY AND DIABETES

In both developed and developing nations, obesity is associated with a higher risk for chronic diseases. In particular, it is postulated that obesity is linked with chronic, low-grade inflammation which originates from the adipose tissue and the gut and then spreads to other areas of the body. In the gut, the dysregulation of microbiota can increase endotoxin exposure. In addition, the intestine - a barrier against harmful substances from the external environment - can be compromised by factors such as diet, exercise, gastrointestinal peptides, inflammatory cytokines, and pathogens.

In this regard, Pei et al.[10] have shown that lipid profiles, intestinal barrier function, and innate and adaptive immune responses can be improved by consuming yoghurt. Yoghurt, which is dense in nutrients, can decrease inflammation and enhance gut health. Therefore, while yoghurt benefits individuals with constipation and diarrheal diseases, and those with cardiovascular diseases, hypertension, and lactose intolerance, it also improves the health of obese and diabetic people.

In obese and type 2 diabetic mice, Everard et al. (2014) showed that the probiotic yeast *Saccharomyces boulardii* alters gut microbiota and decreases metabolic features, such as fat mass development, hepatic steatosis, and low-grade inflammation.[11] Similarly, Balakumar et al. (2018)[12] investigated the effect of probiotics of Indian gut origin (*Lactobacillus* spp.) in mice and found that in high-fat diet mice, the probiotic intervention resisted insulin-resistance and diabetes. In general, this could lead to different probiotic treatments in the future.
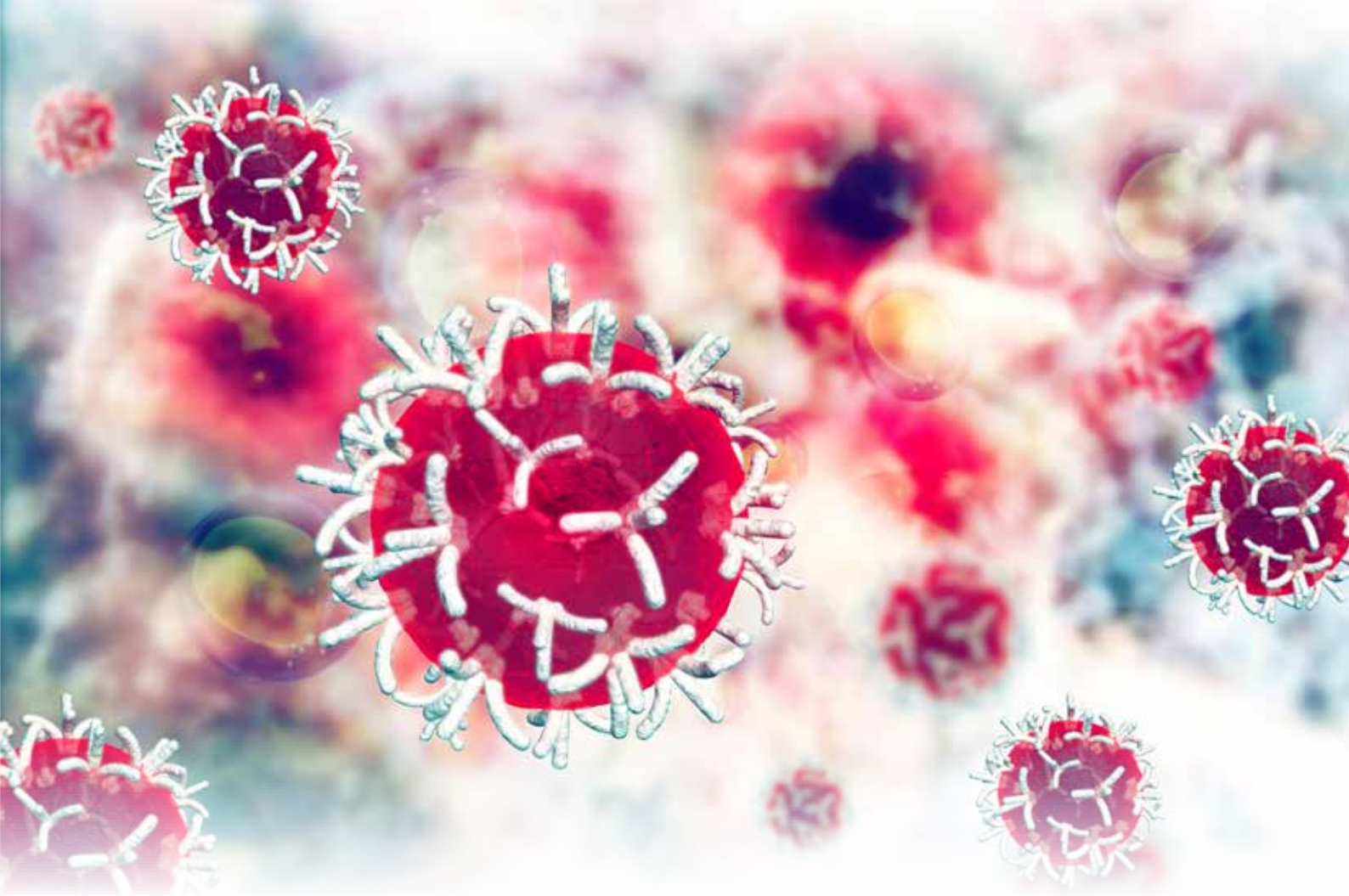
AUTO-IMMUNE DISEASES

It is known that the gut microbiota plays a role in the development of the lymphoid system.[13] In fact, dysbiosis of gut microbiota also occurs in patients with autoimmune diseases such as Hashimoto's thyroiditis, systemic lupus erythematosus, systemic sclerosis, as well as type 1 diabetes mellitus.

Hashimoto's thyroiditis, or HT, is an organ-specific disorder in which both environmental factors and genetic predisposition are disease triggers. Zhao et al. (2018)[14] performed a systematic comparative analysis of the gut microbiota in HT patients and healthy controls and revealed that HT patients have altered gut microbiota. They also showed that gut microbiota is associated with clinical parameters, therefore suggesting that the composition of the microbiome could be used in disease stratification.

Systemic lupus erythematosus is another autoimmune disease. It is a complex disorder with no known cure, characterised by persistent inflammation. Mu et al. (2017)[15] recently reported that in lupus, the gut microbiota is involved in the pathogenesis of renal dysfunction. Mu et al. used a model of lupus nephritis and found a significant depletion of *Lactobacillales* in the gut microbiota. Intriguingly, increasing the *Lactobacillales* in the gut enhanced renal function and extended survival in mice. Although promising, future studies will determine whether this can be replicated in humans.

CANCER

Over a quarter of a million people each year develop colorectal cancer (CRC). CRC is fundamentally a genetic disease. Specifically, there is an accumulation of mutations in oncogenic genes that foster autonomous colonic epithelial cell proliferation, which over 10 to 40 years, results in colon adenomas. A small number of these adenomas, in some individuals, progress to cancer. Although, it is still unknown what events precipitate the initial mutation(s) or the later progression from adenomas to cancer, the gut microbiome is a main suspect. Indeed, one finds several attempts to associate individual bacterial microbes with CRC in humans.[16,17] Some, based on the 'keystone species' concept, argue that a microbial leader recruits other microbes and these start the fostering events of CRC.[18-20] Thus, it is proposed that over the years, several microbes may be involved and their metabolic activities interact with the host diet, ingested pharmaceuticals, or physiology.

An example of such interplay between the host and gut microbes is observed in bile acid metabolism. The liver secretes the conjugated bile acids, cholic acid and chenodeoxycholic acid. Bacteria can deconjugate these conjugated bile acids producing lithocholic acid and deoxycholic acid. These secondary bile acids are the two principal faecal bile acids and it has been proposed that they may contribute to carcinogenesis. Indeed, back in 2002, Reddy[21] already showed that these faecal bile acids are increased in diets rich in saturated fats and are associated with higher incidence of CRC. Gill and Rowland[22] studied the correlation of dietary fat intake and CRC risk and found that CRC patients, when compared to healthy controls, had elevated faecal lithocholic and deoxycholic acid. Lithocholic and deoxycholic acid were thus proposed that they may be pro-carcinogenic bacterial metabolites. This proposition still stands today and recent studies have shown that they can be pro-inflammatory through the production of reactive oxygen and nitrogen species and NF-κB activation in the cells of intestinal epithelia.[23] In 2018 Le Gall et al.[24] showed that CRC patients had increased faecal concentrations of branched chain fatty acids, besides other potential metabolites that may be responsible for carcinogenesis.

The exact mechanism by which the unconjugated bile acids are responsible for carcinogenesis is still being researched. Barrasa et al.[25] showed *in vitro* that chronic

exposure to deoxycholic acid causes DNA adduct, decreases apoptosis, and augments epithelial cell proliferation. In 2016 Farhana et al.[26] proposed that the unconjugated secondary bile acids modulate muscarinic 3 receptor and Wnt/β-catenin signals and cause cancer stem cells in the epithelial cells of the colon.

However, gut microbiota can also have positive effects on the host physiology. One mechanism is in promoting anti-tumour immunity. Sivan et al.[27] studied melanoma growth in mice and found that the commensal *Bifidobacterium* promotes anti-tumour immunity. Indeed, *Bifidobacterium* alone, given orally, controlled tumour growth to the same extent as antibody therapy with programmed cell death ligand 1 (PD-L1) (a check point blockade type of immunotherapy). Similarly, Spranger et al.[28] clinically found that some cancer patients fail to respond to immunotherapy. This could be due to lack of activated T-cell infiltration inside the tumour microenvironment. They propose that intersubject heterogeneity might be responsible and includes variations in the mutations of specific oncogene pathways. But it may also be due to environmental factors like the commensal microbial composition. This has clinical utility in that, by manipulating the gut microbiota, one might modulate cancer immunotherapy and increase the number of patients that respond.

CONCLUSION

Overall, recent research has demonstrated that keeping your gut flora healthy has extensive implications. Though still an emerging field, the gut microbiota may be playing important roles in autism, auto-immune disease, cancer, obesity and diabetes. As a result, research efforts are being focused on developing gut microbiota modulation therapies and using the microbiome for diagnosis and treatment stratification. Hippocrates might have been right when he said that 'All disease begins in the gut' and 'Let food be thy medicine'.

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