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GASTROINTESTINAL BACTERIA IN OBESITY AND TYPE 2 DIABETES – A REVIEW OF CURRENT KNOWLEDGE

The gastrointestinal tract is home to over 10^{14} bacteria that collectively form the intestinal microbiome, and their joint genetic repertoire is larger than the human genome.[1] These symbiotic bacteria establish and maintain the gut immune system, and contribute to the breakdown of complex non-digestible plant-derived polysaccharides.[2,3] The relatively recent technological advances in genomics have revolutionized the study of the intestinal microbiome. It is now possible to sequence mixed microbial genetic material directly extracted from environmental samples without prior laboratory culture of individual species. This emerging field, known as metagenomics, enables a survey of the different microorganisms present in a specific environment.[4] Several large-scale projects such as the Human Microbiome Initiative have characterized microbial genomes from hundreds of isolated human symbionts and have shed light on the complex interplay between the human host and its microbial populace, and how this changes in health and disease.

This article aims to discuss the emerging body of knowledge that links the gut microbiome to the development of obesity and metabolic disease. The growing prevalence of overweight and obesity are easily linked to the sedentary lifestyles and calorie-dense diets typical of 'Westernized' countries. There is, however, growing evidence that there are powerful physiological processes that restrict any cognitive mechanisms to reduce excessive weight by drastic changes in lifestyle. The reason is that those same physiological processes maintain body weight within a narrow range.[5] In this respect, obesity is increasingly recognized as a disease rather than as a willful choice.

THE OBESITY MICROBIOME

The involvement of the gut microbiome in obesity came to light from studies that compared the microbiota between lean and obese mice and human subjects. Using obese, leptin-deficient *ob/ob* mice, Ley *et al* showed a difference in the ratio of the two dominant intestinal phyla – *Bacteroides* and *Firmicutes*, between obese mice and their lean counterparts.[6] The reason for using leptin-deficient mice is that they exhibit relatively mild hyperglycemia and obesity. This seminal paper showed that in mice, kinship is a strong determinant of caecal microbial composition. Furthermore, Ley *et al* showed that regardless of family membership, obesity is associated with a 50% reduction of *Bacteroides* species and a greater proportion of *Firmicutes* relative to lean mice. These findings were reproduced by Ley *et al* in humans[7] and subsequently by other investigators.[8-10] Other investigators have however failed to fully reproduce these findings,[11] possibly due to methodological differences in determining the composition of the microbiome.

Further insight into the role of the microbiome in obesity comes from germ-free (GF) mice. GF mice are born and bred under special conditions to control their exposure to microbes, and can be inoculated by specific bacterial strains for research purposes (gnotobiotics). Studies have shown that GF mice are leaner and resistant to obesity when consuming a high fat, high carbohydrate diet.[12] Subsequently, Backhead *et al* showed that the transfer of caecal bacteria harvested from normal mice to their GF counterparts is accompanied by a 60% increase in body fat content and insulin resistance, despite a reduced fat intake.[13] Turnbaugh *et al* proposed that the gut microbiota of obese individuals are more efficient at extracting calories from the diet when compared to microbes from lean individuals. In a series of elegant experiments, they transferred caecal microbes from obese and lean mice to GF mice, the investigators showed that wild-type GF mice exhibit a greater increase in body fat when colonized by bacteria from obese donors than GF mice colonized by caecal bacteria from lean donors.[14] Similar findings have been reported in human studies, where a randomized controlled trial reported significantly improved insulin sensitivity in male patients with metabolic syndrome who

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received allogenic fecal bacteria from a lean donor compared to those who received an autologous gut microbiota infusion.[15] This study also identified a significant increase in intestinal butyrate-producing bacteria in recipients of microbiota from a lean donor. Comparable results have been reported in two large metagenome-wide association studies.[16-17] Karlson *et al* showed that T2DM is accompanied by a decrease in butyrate-producing *Roseburia* and *Faecalibacterium prauznitzii* when compared to healthy subjects.[16]

THE EFFECTS OF MICROBIOME-DERIVED PRODUCTS

Butyrate, along with propionate and acetate, are short-chain fatty acids (SCFAs) derived from the bacterial degradation of complex polysaccharides in the gut.[18] They have important metabolic roles, with butyrate acting as a metabolic substrate for colonic epithelial cells. Studies have implicated these SCFAs in the pathogenesis of inflammatory bowel disease (IBD). Vernia *et al* identified low fecal concentrations of butyrate in ulcerative colitis,[19] and butyrate enemas suppress inflammation in distal ulcerative colitis[20] Other studies have investigated the systemic anti-inflammatory effect of butyrate in IBD,[21-22] while Gao *et al* report that oral butyrate administration improves insulin sensitivity and energy expenditure in obese mice.[23]

Butyrate is a histone deacetylase (HDAC) inhibitor. Lysine residues in histone proteins undergo post-translational modification as part of the epigenetic regulation of gene expression. The acetylation of lysine residues in histone proteins leads to nucleosome unfolding and transcriptional activation. Conversely, histone deacetylase removes acetyl groups on lysine in histone proteins, leading to transcriptional repression.[24] Gao *et al* showed that butyrate administration is associated with increased expression of PGC-1α, which leads to increased fatty acid oxidation, mitochondrial activity and energy expenditure.[23] This directly links microbiome-derived SCFA to changes in host gene expression pathways that promote insulin sensitivity.

SCFA also act on host signaling pathways by binding to G-protein coupled receptors in enteroendocrine cells. Butyrate has been shown to trigger production and release of the peptide hormone PYY from intestinal enterocytes.[25] Butyrate is also postulated to play a role in the maintenance of intestinal epithelial integrity, thereby preventing the translocation of endotoxins produced by intestinal Gram-negative bacteria. Obesity and insulin resistance are associated with a chronic subclinical inflammatory response,[26] and studies have shown that high fat diets in mice increase the proportion of endotoxin-producing gut microbes and lead to insulin resistance.[27]

The gut microbiome is intimately linked to the regulation of carbohydrate and lipid metabolism in the host. Specifically, research has shown that butyrate-producing bacteria improve insulin sensitivity in both animal and human subjects,[23,28] T2DM and obesity are also linked to changes in the composition of the microbiome, although evidence regarding the causality of these changes is not clear, for the observed changes in the microbiome might be secondary to the altered intestinal motility and bacterial overgrowth seen in T2DM. Critically, clinical trials involving SCFA supplementation and microbial transfer are needed in order to evaluate any therapeutic application from this emerging field of research.

THE EFFECT OF HOST FACTORS ON THE GUT MICROBIOME

The widespread availability of antibiotics has resulted in a number of public health benefits and a reduced infectious disease burden. However, a growing body of evidence links antibiotic use to the obesity pandemic.[29] Thuny *et al* link long term (6 week) vancomycin use in infective endocarditis to weight gain in adult males.[30] Short term administration of oral ciprofloxacin has been linked to rapid and permanent changes in the composition and diversity of the gut microbiome.[31] In a cohort of over 28,000 Danish subjects, born from normal weight women, an early exposure to antibiotics before the sixth month of age has been linked to an increased risk of being obese later on in life.[32] These findings reinforce the need for more judicious use of antibiotics, and further emphasize the functional interaction between the gut microbiome and host metabolism.

Host diet is also an important determinant of microbiome composition. Changes in fecal enterotypes, as determined by *Prevotella* and *Bacteroides*, have been shown to occur in response to long term protein-rich vs carbohydrate-rich diets in man.[33]

CONCLUSION

The gut microbiome has an intimate relationship with the host organism that is vital for energy homeostasis. Studies suggest that changes in microbial composition can lead to obesity through various mechanisms. Although this area of research is still in its infancy, it opens up a number of potential therapeutic approaches to facilitate weight loss or treat obesity and its complications.

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