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The Microbiome and Obesity


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In 2016, the World Health Organization (WHO) estimated that, globally, over 1.9 billion adults and 340 million children and adolescents (between the ages of 5 and 19 years), were overweight or obese. Since 1975, the worldwide prevalence of obesity has tripled, and, currently, the majority of the world's population lives in countries where being overweight or obese kills more than being underweight.[21] An increased body mass index (BMI) is a risk factor for cardiovascular disease, musculoskeletal disorders, diabetes, and a number of malignancies, including endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and colon cancers.[21] Traditional weight loss therapies have proven largely ineffective, and given the dire consequences of obesity on general health, the development of better treatment modalities has become a scientific imperative. There is a growing body of research suggesting that obesity, metabolic syndrome, and insulin resistance are associated with predictable phyla and gene level compositional changes in the intestinal microbiome of humans and mice; [8,9] with a better understanding of these changes, we can develop new, robust therapeutic strategies. In this article, we will briefly discuss some of the definitive research related to the microbiome and its impact on obesity and other metabolic derangements.

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Contemporary, culture-independent techniques for microbial DNA sequencing have identified four dominant bacterial phyla which reside in the mammalian gut.[17] They are the Gram-negative *Bacteroidetes* and *Proteobacteria* and the Gram-positive *Actinobacteria* and *Firmicutes*.[17] In two foundational studies, one by Ley et al. and another by Turnbaugh et al., researchers used 16S rRNA gene sequencing to demonstrate that the microbial composition of the distal gut of leptin-deficient *ob/ob* mice was reduced in *Bacteroidetes* and enriched in *Firmicutes* when compared to their lean *ob*/+ and wild-type siblings, despite being fed the same diet.[15,17,19] In subsequent research, Ley et al. corroborated the findings in the murine studies, observing a similar increase in the *Firmicute/Bacteroidetes* ratio in obese humans.[13,14,18] However, other researchers have not noted the same pattern of colonization and more recent literature stresses biomarker composition and host-microbe genetics over phyla level profiles.[10,16]

One way by which the microbiome affects body weight is through its link to fat storage and energy extraction. For example, Flint et al. showed that the gut microbiota enables energy extraction from otherwise indigestible polysaccharides.[12] Backhed et al. demonstrated that germ-free mice, once conventionalized, exhibited increased triglyceride content in their livers and adipose tissue, as well as increased luminal monosaccharide uptake.[4] They hypothesized that this change was due to the microbial modulation of Fiaf, also known as angiopoietin-like protein 4, and its inhibitory effect on lipoprotein lipase (LPL). LPL is an enzyme that increases cellular uptake of fatty acids. During feeding, Fiaf is induced in germ-free mice; however, in conventionalized mice, it is functionally suppressed.[1,4] Years later, Backhed et al. shed light on another possible mechanism of microbe-mediated energy capture. They identified Ampk as a "fuel gauge" enzyme and found that the phosphorylated form was increased in the skeletal muscle of lean, germ-free mice.[3,17] Yet another pathway of the microbiome's influence on host metabolism is through its production of hydrolases, which digest carbohydrates to short-chain fatty acids (SCFA). SCFAs like acetate and propionate are not only energy sources, but also interact with G protein-coupled receptors in the gut, altering motility and affecting inflammatory pathways.[15,17]

In addition to the direct effects on host metabolism, it has been proposed that the microbiota composition may cause low-grade, systemic inflammation and play a role in the development of insulin resistance.[1,7] Researchers have determined that lipopolysaccharide (LPS), a proinflammatory molecule, derived from Gram-negative bacteria in the mammalian microbiome is increased in the plasma of mice on a high-fat diet; this has also been observed in human studies.[1,7] Furthermore, it has been noted that the gut permeability of obese mice is increased secondary to expressional changes in tight-junction proteins. This, coupled with increased LPS production, elucidates a possible pathway to the generalized inflammation associated with metabolic diseases.[1,5,6,7] From a microbial ecology perspective, there has been an association of diabetic patients with a core microbiota rich in Proteobacteria.[1] Vrieze et al. found that the introduction of intestinal microbes from lean donors resulted in temporary improvements in insulin sensitivity in patients with metabolic syndrome.[1,20] This would lead one to think that fecal microbiota transplantation (FMT) is not a modality restricted to the treatment of *C. difficile* infection, but could possibly be used to treat obese and/or diabetic patients as well. As we discuss various biomarker-disease associations, it is appropriate to point to a microbiome classification paradigm associated with microbiota composition and biomarker levels. Arumugam et al. found that three energy-modulating molecules correlate with a host's BMI, which may mean that there are common microbiome compositions associated with various disease states; this would potentially enable intervention through diet, pre- and probiotics, and medication.[1,2] Lastly, more recent literature has highlighted the interaction between host genes and the microbiome, noting the relationship between leptin ("the satiety hormone") and commensal bacterial populations, the declines and rises in various bacteria associated with the apolipoprotein A1 gene, and the phospholipase D1 gene, which may offer insight into host genotypic effects on microbiome.[11]

Obviously, there is a strong body of science linking obesity and other metabolic disease states to changes in the gut microbiome; however, our

understanding of the relationship between microbe and host must continue to be refined. Expanding research and interest in the human microbiome could lead to improved treatment strategies for obesity and its long list of comorbidities. With the increasing complexity of the microbe-host relationship, new ground must be broken with new ideas. ■

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Answers to this month's crossword puzzle:

1 F	I	2 B	R	3 O	S	4 I	5 S	■	6 S	7 C	R	8 E	E	9 N
E	■	U	■	H	■	10 N	I	11 H	■	U	■	X	■	O
12 C	Y	T	O	M	E	T	R	Y	■	13 B	L	O	O	D
A	■	T	■	■	■	E	■	B	■	I	■	M	■	E
14 L	I	E	■	15 G	A	S	T	R	I	C	■	16 E	17 S	S
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19 O	F	F	■	20 B	L	I	N	D	■	21 O	U	22 N	C	E
B	■	L	■	■	■	N	■	■	■	S	■	A	■	■
23 S	A	Y	■	24 S	T	E	R	25 E	O	M	E	T	R	Y
T	■	■	■	W	■	■	■	H	■	I	■	A	■	■
R	■	26 M	Y	E	N	27 T	E	R	I	C	■	28 L	Y	29 E
U	■	A	■	L	■	U	■	L	■	■	■	■	■	C
30 C	A	J	A	L	■	31 B	R	I	E	32 F	■	33 B	I	O
T	■	O	■	34 E	35 D	U	■	C	■	R	■	R	■	L
36 S	T	R	I	D	E	S	■	37 H	P	Y	L	O	R	I