Objective: to summarize the current evidence of differences in microbiota composition between lean and obese individuals, including the specific microbes *Faecalibacterium prausnitzii*, *Akkermansia muciniphila*, *Christensenella* spp., *Bacteroides thetaiotaomicron*, and *Ruminococcus bromii*.

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Recent analyses have estimated that about 34% of adults in the United States have metabolic syndrome (1), a group of risk factors including obesity that are strongly associated with an increased risk of developing many chronic diseases (2). The primary clinical recommendation for this spectrum of diseases is weight-loss as it is thought that much of the related pathology stems directly from obesity. Central to disease, and to metabolism in general, is the intestinal milieu, consisting of microbes now known to be important for health in many ways. Recent interest in the communities of intestinal microbes has propelled sequencing and computing technology to identify differences in microbial communities between lean (i.e. healthy) and obese individuals. The practical implication of this research is therapeutic manipulation of such profiles. Important characteristics of microbial communities include relative proportions of phyla, species richness and diversity, and genus- and species-level differences in abundance and prevalence.

Early studies in animals demonstrated an interesting phenomenon. Mice that did not harbor any intestinal microbes (germ-free) had a lower percent body fat than conventional mice, and when these germ-free mice were inoculated with bacteria from the conventional mice, body fat was quickly restored (3). This experiment suggested a direct relationship between microbes and regulation of body fat. When microbes from either obese mice (*ob/ob* knockouts) or lean/conventional mice were transferred to germ-free mice, the mice that received "obese" microbes demonstrated an increased capacity to harvest energy from their food, resulting in a significantly higher fat mass compared to mice that received "lean" microbes (4). This suggested that the obese microbes directly affected body weight regulation and must be different from lean microbes.

At the phylum level, Ley *et al.* reported that *ob/ob* mice have a higher abundance of Firmicutes and lower abundance of Bacteroidetes compared to wild-type mice, even when the mice of different genotypes are siblings (same mother) and are co-housed (5). A higher ratio of Firmicutes/Bacteroides in obese individuals versus lean individuals has been confirmed in humans several times (6-8), and even though it has also been contradicted (9-11), this ratio is considered a prominent pattern in studies of obesity and the microbiome. It is worth noting that representation of species belonging to these phyla may be skewed by the varying methods of quantification used in such studies. A clinical trial in which obese individuals were randomized to either a carbohydrate-restricted or fat-restricted weight-loss regimen demonstrated that the abundance of Bacteroidetes increases as body weight decreases, and this phenomenon was emphasized in the individuals consuming a carbohydrate-restricted diet (12). Consistent with this observation, increases in Bacteroidetes (7), decreases in Firmicutes (13), or decreases in the Firmicutes/Bacteroidetes ratio (14) following weight loss have all been observed.

Another early observation made regarding differences between intestinal microbes from lean and obese individuals was that fecal samples from obese individuals contained a less diverse microbial repertoire than samples from lean individuals (6). Coinciding with diversity, individuals with low species richness in fecal samples have a higher prevalence of obesity compared to individuals with high species richness, and this correlates to desirable changes in several metrics of metabolic function (15).

In the interest of providing beneficial microbes via dietary supplements and identifying individual bacterial species as probiotic strains that may regulate body weight, several candidates have emerged. *Faecalibacterium prausnitzii* is a butyrate-producing, gram-positive organism belonging to the phylum Firmicutes and is associated with beneficial health outcomes (16). Because of its ability to release energy substrates from otherwise unavailable sources (fiber) and therefore contribute to calorie availability of food, a relationship between this species and overall body weight has been studied. One study that employed qPCR demonstrated no difference in *F. prausnitzii* abundance in obese individuals versus lean age- and sex-matched controls (17); however, this study did show a higher abundance of *F. prausnitzii* in women versus men, regardless of BMI. Hippe et al. (18) recently showed that lean individuals have a higher abundance of *F. prausnitzii* overall, but multiple phylotypes of *F. prausnitzii* exist and may differentially contribute to butyrate production and subsequently to body weight regulation. This reminds us that the role of an organism in modulation of health outcomes can be more complicated than simple abundance of the organism, an important theme across studies of the microbiome.

Akkermansia muciniphila was first isolated and characterized as an anaerobic, gram-negative rod bacterium belonging to the phylum Verrucomicrobia in 2004 (19). Originally identified for its potential to degrade mucin, a large component of the intestinal barrier, *A. muciniphila* has more recently been described to be negatively associated with obesity and type 2 diabetes (20-22). Leptin-deficient (*ob/ob*) mice display lower counts of cecal *A. muciniphila* (23). When mice were fed oligofructose, a prebiotic, *A. muciniphila* was restored to control levels in both high-fat-fed mice and *ob/ob* mice. This restoration of *A. muciniphila* corresponded to lower fat mass, lower serum lipopolysaccharide, and lower fasting glucose. Also, even though *A. muciniphila* is known to degrade mucin, high-fat-fed mice gavaged with this organism experienced a restoration of the intestinal mucus layer to the same thickness observed in control mice. Most recently, a higher *A. muciniphila* abundance has been correlated with several desirable metabolic parameters, including lower fasting glucose, less insulin resistance, and smaller adipocyte size in an overweight/obese population (24). The distribution of android/gynoid fat in that same population was most desirable in the group that had high species richness in combination with a higher abundance of *A. muciniphila*. The therapeutic implication for this organism in weight management is hopeful and continues to be studied.

In the process of assessing heritability of taxa using monozygotic and dizygotic twin pairs, Goodrich et al. (25) identified Christensenellaceae (gram-negative, anaerobic Firmicutes) as the most likely family of bacteria to be influenced by genetics. This robust study went on to investigate the potential health benefit of members of Christensenellaceae from many angles. Operational taxonomic units (OTUs) corresponding to members of this family, along with

Oscillospira spp. and *Methanobrevibacter smithii*, were more abundant in lean individuals versus overweight individuals in several datasets. The species *Christensenella minuta* was either added or not added to fecal samples from obese humans, and then these samples were transplanted into germ-free mice; as expected, the germ-free mice receiving obese microbes gained weight, and interestingly, the mice receiving *C. minuta* along with the obese microbes gained significantly less weight. This study demonstrates the potential of *Christensenella* to be a beneficial microbe in the context of body weight regulation.

Because of the attention that Bacteroidetes have received at the phylum level, individual species have been investigated for their relationship to body weight. OTUs corresponding to *Bacteroides thetaiotaomicron* (gram-negative) were positively correlated with a lean BMI (<20) in a Japanese population (8) along with *B. faecichinchillae*, *Blautia wexlerae*, *Clostridium bolteae*, and *Flavonifractor plautii*. Conversely, OTUs corresponding to *Blautia hydrogenotrophica*, *Coprococcus catus*, *Eubacterium ventriosum*, *Ruminococcus bromii*, and *R. obeum* were positively associated with the overweight group. It should be noted that the overweight individuals in this study were older than the lean individuals, and this could be a confounding factor. Of these, *B. thetaiotaomicron* has since been further explored; weight loss in humans reportedly did not affect abundance of *B. thetaiotaomicron* (14). *B. thetaiotaomicron* was not confirmed to be different between lean and obese individuals when quantified by qPCR in a small study (n=9) of young adults (26). This organism also does not seem to have effects on body weight or food intake in high-fat-fed rats (27). However, these authors proposed that *B. thetaiotaomicron* may require a particular substrate, such as lactitol, to provide benefit.

Ruminococcus bromii (gram-positive, anaerobic Firmicute), originally known to be important in ruminant animals, was only recently identified in human fecal samples (28). Like *B. thetaiotaomicron*, *R. bromii* has mixed reports of relationships to body weight. As stated above, *R. bromii* was reported to be more abundant in overweight adults (8). This organism, an established consumer of resistant starch, is currently being explored for its potential as an important modulator of harvesting energy from fiber (29). It is unclear whether this is a beneficial characteristic, as more efficient energy harvest from food by microbes is hypothesized to contribute to calorie intake and therefore weight gain (4).

It is widely accepted that intestinal microbes play an important role in weight regulation as well as many other health-related factors. However, the exact roles of individual microbes are largely unknown. Additionally, many variables contribute to the profile of microbes observed in the intestinal tract, and these must be elucidated to fully understand the interplay between microbes and human intestinal cells and subsequent effects on body weight.

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