NEWS & VIEWS

PHYSIOLOGY

Obesity and gut flora

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The intestinal bacteria in obese humans and mice differ from those in lean individuals. Are these bacteria involved in how we regulate body weight, and are they a factor in the obesity epidemic?

Much has been said and written about the sequencing of the human genome, and the research avenues that it has opened up. But our own genome is not the only one with which we need to be concerned. In particular, trillions of bacteria — collectively referred to as the microbiota — reside in our gastrointestinal tracts (Fig. 1), and each brings its own genome to this genetic party.

Reports by Gordon and colleagues[1,2] on pages 1022 and 1027 of this issue explore the potential relationship between the types of microbiota found in the gut and the regulation of body weight. Although there is no doubt that human genetics plays a large part in determining body weight[3], it is equally undisputed that the increase in prevalence of obesity over the past 25 years cannot be attributed to changes in the human genome[4]. The inference is that other factors are responsible, such as the availability of inexpensive, calorically dense foods, or the reduction in physical activity in our daily lives. The work described by Gordon and colleagues[1,2] raises the possibility that our gut bacteria are another factor that contributes to differences in body weight among individuals.

Diverse evidence points to the importance of biological control systems that result in a close match between caloric intake and caloric expenditure. For the vast majority of humans (including obese individuals), caloric intake exceeds caloric expenditure by less than 1%, but even these small differences can accumulate over years to lead to detrimental increases in body weight[4]. The body's ability to match caloric intake to caloric expenditure is the result of the brain's ability to monitor the amount of fat in the body through changes in the levels of circulating hormones. One such hormone is leptin, the levels of which increase with increasing body fat[5]. Leptin deficiency in mice and humans results in unrestrained caloric intake and low caloric expenditure, with a consequent rapid increase in body weight[6]. Similarly, falling leptin levels are a primary reason for the difficulty in maintaining weight loss.

The two reports[1,2] compare the genetic material collected from the microbiota in the gut of lean and obese mice and humans to assess the relative abundance of various types of bacterium. The two predominant populations of microbiota in both the mouse and the human gut are members of the bacterial groups known as the Firmicutes and the Bacteroidetes (Box 1, overleaf). The authors[1] studied a small number of obese humans, and found that the proportion of the genetic material from Firmicutes was higher than the proportion in lean individuals. Moreover, when obese individuals lost weight over a year, the proportion from Firmicutes became more like that of lean individuals.

In the second report[2], the authors describe how differences in the microbiota of lean and obese mice confirmed this result, with obese mice having a higher proportion of intestinal Firmicutes. Importantly, the microbiota of obese mice was rich in genes encoding enzymes that break down otherwise indigestible dietary polysaccharides. These differences seem to have functional consequences, as obese mice had more fermentation end-products and fewer calories remaining in their faeces than lean mice. Thus, the bacteria in obese mice seemed to assist their host in extracting extra calories from ingested food that could then be used as energy.

These two results collectively suggest that obesity alters the nature of the intestinal microbiota, but they do not prove that different relative proportions of bacteria can lead to different body weights. To test this possibility, the authors performed a clever experiment in which the microbiota of obese, leptin-deficient mice was transferred to lean, microbe-free recipient mice[2]. Over a two-week period, mice given the microbiota from obese mice extracted more calories from their food and had a modest fat gain that was statistically

Figure 1 | Home for an abundant microbiological flora. The human gut and (inset) a scanning electron micrograph of part of the small intestine, with some bacterial inhabitants picked out in green.

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Box 1 | The Firmicutes and the Bacteroidetes

The Firmicutes and the Bacteroidetes are divisions — or phyla — within the domain Bacteria. The microbiota of the human gut is dominated by their members, most of which are benign, although a few are pathogenic.

The Firmicutes is the largest bacterial phylum. It contains more than 250 genera, including *Lactobacillus, Mycoplasma, Bacillus* and *Clostridium*. There is considerable variety in the phylum. For example, the *Clostridium* species are obligate anaerobes (that is, they absolutely require anoxic conditions), whereas members of *Bacillus* form spores and many of them are obligate aerobes. *Streptococcus pyogenes*, the well-known cause of 'Strep. throat', is also a member of the Firmicutes.

The Bacteroidetes include about 20 genera. In the human gut, *Bacteroides* is probably the most abundant single genus, and *Bacteroides thetaiotaomicron* is one of the most abundant organisms. Species of *Bacteroides* are obligate anaerobes that are benign inhabitants of the gut. However, they are opportunistic pathogens that can cause disease if they gain access to the peritoneal cavity, for example following surgery or a perforated ulcer. Members of the Bacteroidetes are found in the intestinal tracts of many warm-blooded animals, but are also abundant in soil and sea water. **M.B. & R.J.S.**

greater than that of mice receiving microbiota from lean mice. Taken together, these data suggest that differences in the efficiency of caloric extraction from food may be determined by the composition of the microbiota, which, in turn, may contribute to differential body weights.

This is a potentially revolutionary idea that could change our views of what causes obesity and how we depend on the bacteria that inhabit our gut. But a great deal remains poorly understood. Most notably, it is not clear whether such small changes in caloric extraction can actually contribute to meaningful differences in body weight. There are few data that substantiate the predicted increased caloric extraction in obese humans. Small but persistent increases in efficiency might potentially cause the accumulation of excess body weight over long periods, but these small differences are not the cause of obesity in leptin-deficient mice. These mice have a single gene mutation that prevents the production of biologically active leptin[7]. The resulting increased caloric intake and reduced caloric expenditure is many times larger than the small difference in extraction that could be produced by differences in the microbiota. In fact, the differences in body fat between mice given the 'obese microbiota' and those given the 'lean microbiota' are so small that they could be accounted for entirely by the tiny differences in food intake, rather than by differences in caloric extraction.

Another unknown is why and how the make-up of the microbiota is shifted by differences in body weight. Given that acquiring food from the environment can be both calorically expensive and potentially dangerous, it would seem to be most adaptive to extract as many calories from every bite of food as possible. Moreover, if caloric extraction does become more efficient, the regulatory system would dictate that the organism responds by reducing its caloric intake. If a host organism had the ability to change its microbiota so as to increase caloric extraction, it would seem most adaptive to do so when facing famine conditions and losing weight. However, the data indicate just the opposite — the microbiota seems to be more efficient in obese humans who already have the most stored energy, and shifts to being less efficient as the subjects lose weight[1].

There is also the issue of how conditions in the host organism could change the make-up of the microbiota. Low levels of leptin are a signal of starvation that triggers several changes in the neuroendocrine system that work to conserve calories[6]. Consequently, it would make sense that low leptin might also impart a signal to the microbiota to become more efficient at extracting calories from food. This hypothesis would fit the microbiota of the obese, leptin-deficient mice. However, in humans where obesity is associated with increased leptin, the same trends in microbiota composition are found, making it unlikely that the microbiota is responding to leptin directly. Moreover, it seems that when the bacteria are transferred to a lean mouse in which leptin is normal, the bacteria retain their 'obese' character over a two-week period. Thus, it is not clear how gut bacteria 'know' whether the host is obese or lean.

Gordon and colleagues' results[1,2] tempt consideration of how we might manipulate the microbiotic environment to treat or prevent obesity. But questions about how and why the composition of gut microbiota is regulated will have to be answered first. As we have discussed, those questions are many and various. The two papers nonetheless open up an intriguing line of scientific enquiry that will ally microbiologists with nutritionists, physiologists and neuroscientists in the fight against obesity. ■

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ASTROPHYSICS

A burst of new ideas

Bing Zhang

Gigantic cosmological γ-ray bursts have fallen into a dichotomy of long and short bursts, each with a very different origin. The discovery of an oddball burst calls for a rethink of that classification.

The events known as γ-ray bursts (GRBs) are the most violent and luminous explosions observed in the Universe. In the early 1990s, it became clear that they come in two distinct flavours: longer-duration bursts, typically longer than 2 seconds, with a spectrum of emitted radiation that peaks at lower ('softer') energy; and shorter-duration bursts with a more energetic, 'harder' spectrum[1]. Observations of burst afterglows in the past decade — particularly in the past year[2–4] — have seemed to show that this division is a clean one, and is firmly rooted in the progenitor of each type of burst. According to this picture, long bursts are associated with a young stellar population, marking the deaths of massive stars whose lifetime is short[5]. Short bursts, on the other hand, are associated with an old stellar population, and are probably powered by mergers of compact objects such as neutron stars or black holes[6].

In this issue, four papers[7–10] blow a hole in this cosy paradigm. They contain observations of a bright γ-ray burst, GRB 060614, that triggered NASA's GRB sentinel, the Swift satellite, at 12:43:48 UT on 14 June 2006. The burst defies pigeonholing within the current scheme.

Gehrels *et al.* (page 1044)[7] detail the circumstances of this peculiar burst's discovery. It is one of the brightest ever seen, and was soon located precisely not only by Swift's instrumentation, but also by other space- and ground-based telescopes. The burst is situated in the suburbs of a faint and relatively nearby dwarf galaxy[8]. Its duration, recorded by Swift as 102 seconds[7], characterizes it unambiguously