My Microbiome and Me

Zhao Liping combines traditional Chinese medicine and studies of gut microbes to understand and fight obesity

SHANGHAI, CHINA—In some ways it’s a familiar story. In 1987, Zhao Liping married Ji Liuying, a college classmate. Within 2 years, they had a daughter and Zhao finished his Ph.D. Under new pressure and eating richly—Ji is a good cook—the microbiologist put on weight. By 1990, when he started an environmental microbiology lab at Shanxi Academy of Agricultural Sciences in Taiyuan, China, Zhao had grown from 60 to 80 kilograms. Later, on a postdoctoral fellowship at Cornell University, he put on another 10 kilograms. By the time he returned to China in 1995, his waist measured a corpulent 110 centimeters and his health was poor.

But in 2004, he read a paper that eventually changed the shape of his career—and his body. Jeffrey I. Gordon, a microbiologist at Washington University School of Medicine in St. Louis, Missouri, and colleagues showed a link between obesity and gut microbiota in mice (Science, 29 May 2009, p. 1136). Zhao was curious whether that link extended to himself and decided to find out. In 2006, he adopted a regimen involving Chinese yam and bitter melon—fermented prebiotic foods that are believed to change the growth of bacteria in the digestive system—and monitored not just his weight loss but also the microbes in his gut. When he combined these prebiotics with a diet based on whole grains, he lost 20 kilograms in 2 years. His blood pressure, heart rate, and cholesterol level came down.

Faecalibacterium prausnitzii—a bacterium with anti-inflammatory properties—flourished, increasing from an undetectable percentage to 14.5% of his total gut bacteria. The changes persuaded him to focus on the microbiome’s role in his transformation. He started with mice but has since expanded his research to humans.

Zhao—now a slim, soft-spoken 49-year-old with flat-top hair and a square jaw—has become an unlikely spokesperson for a burgeoning field. In 2010, he presented his weight-loss story at the Human Microbiome Project meeting in St. Louis, Missouri, at the invitation of George Weinstock of Washington University in St. Louis. Gordon’s research had set off a flurry of new studies, but Weinstock says scientists had reached something of an impasse. The “field had been standardized to some extent by the early researchers following the same path,” Weinstock says, and Zhao’s willingness to dive in and experiment on himself “brought a breath of fresh air.” Even more refreshing was that Zhao presented his findings in a “detached, agnostic, scientific way,” Weinstock adds. “He was not religious about it at all.”

Now associate director of Shanghai Jiao Tong University’s Shanghai Center for Systems Biomedicine, Zhao oversees several clinical studies that look at the role of the microbiome in diabetes, obesity, and liver function. But his work remains grounded in his personal story—which friends say reflects a willingness to explore uncharted territory through raw trial and error. “As a scientist,” he says, “you should work on questions for which there is very little evidence but that you believe are important.”

Uncertainty about cause and effect is what plagues the field right now. It is difficult to prove, for example, that *F. prausnitzii* facilitated Zhao’s slimming and didn’t just show up once his gut was healthy. “The list of the diseases that the microbiome may play a role in is just growing and growing,” says Lita Proctor, director of the U.S. National Institutes of Health’s Human Microbiome Project in Bethesda, Maryland. “But the problem is that we’re only able to look at associations of the microbiome with disease and aren’t yet able to conduct cause-and-effect studies. What we’re witnessing is a very young field trying to figure out ‘Okay, what’s the right way to approach [these] data?’ ”

For Zhao, the way involves transferring his weight-loss program to hundreds of human subjects and drawing on animal studies to decide what metabolic parameters to monitor in people. While his ultimate goal is to establish a molecular pathway connecting the microbiota to obesity, his e-mail signature reads: “EAT RIGHT, KEEP FIT, LIVE LONG, DIE QUICK.”

Faith in traditional medicine

Zhao grew up in a small farming town in Shanxi Province. Like most Chinese born on the eve of the Cultural Revolution, he and his two younger brothers had a simple upbringing. His father was a high school teacher and his mother worked in a textile factory. Both of his parents were firm believers in traditional remedies. Zhao remembers watching his father try to fight a hepatitis B infection by drinking a pungent, murky herbal concoction twice a day.

A good student, Zhao earned a Ph.D. in molecular plant pathology from Nanjing Agricultural University. When he returned to Shanxi to start his lab, he focused on using beneficial bacteria to rein in plant pathogens...
One day, a veterinary scientist colleague asked for some strains of *Bacillus*, explaining that the bacteria helped control diarrhea in pigs and chickens. Zhao realized he was sitting on bacterial strains that might control infections in humans as well as plants.

Throughout the 1990s, Zhao dabbled in research on the pig microbiome, exploring the idea that bacterial strains might control infections in pigs, but couldn’t get funding. Meanwhile, his family’s health was falling apart. His plump father’s cholesterol levels spiked, and the elder Zhao suffered two strokes. Zhao’s two brothers had become obese as well. A few years later, Gordon’s paper provided what Zhao calls “the first evidence that gut microbiota can actually regulate host genes.” Thus it seemed plausible that this was a way the microbiome could affect health. He began using himself as a guinea pig to try to pin down what microbes might be involved in weight gain. Early microbiome research had raised more questions than it answered, however, and figuring out which of the hundreds of microbial species living in the average human gut might be involved was tricky.

He dug into Western literature on weight loss, but introducing a low-calorie diet and strenuous exercise didn’t make sense to him. “Nutritionally, your body is under stress,” he says. “Then you add to that physical stress. Maybe you can lose weight, but you might also damage your health.” Zhao thought of his father’s herbal concoctions and turned instead to the traditional medicine literature for inspiration.

Obesity and diabetes plagued members of China’s imperial court thousands of years ago, and the diagnoses of early doctors preserved in ancient materia medica resonated with Zhao. Traditional doctors “don’t have any idea about gut microbiota,” Zhao says. “But they think that the gut is the foundation for human health—and that the foundation is acquired after birth.” (The microbiome is acquired after birth, and there is increasing evidence that early colonization by the right bacteria is important for health later in life.)

Zhao pinned his hopes on medicinal vegetables commonly eaten in China, figuring upping his dose of these mild foods couldn’t hurt. As his waistline shrank, he undertook animal studies, trying to single out bacteria associated with obesity. For a study published online 12 April in *The ISME Journal*, he and colleagues switched mice from normal chow to a high-fat diet and then back to normal chow again while monitoring changes in their gut microbiota at 2-week intervals. They found about 80 bacterial species associated with a change in diet. More promisingly, the shifts in microbiota induced by a high-fat diet were completely reversible.

But microbiome studies on mice have their limitations (see sidebar, p. 1250). To establish a link between the human microbiome and obesity, Zhao knew he needed to study people: “The only successful example was myself,” he recalls.

**Testing in people**

In 2009, Zhao returned to Taiyuan to start his first clinical trial. By then, potential candidates for therapy abounded. Obesity was skyrocketing in China, particularly among children, and the incidence of diabetes had spiked from roughly 1% of Chinese adults in 1980 to nearly 10% today. After visiting several local hospitals, he had 123 clinically obese volunteers, with a body mass index of at least 30.

He put the patients on 9-week tailored programs that included prebiotic foods and had them come in for regular checkups and monitoring of gut microbiota and metabolic parameters. He followed 90 patients for an additional 14 weeks after the diet ended. At three points in the study, participants also gave stool samples, which Zhao and colleagues used to assess the microflora.

The 93 participants who completed the trial showed a median weight loss of about 7 kilograms. In their guts, meanwhile, toxin-producing bacteria decreased and beneficial bacteria increased. Encouraged by the results, Zhao added trials in three additional Chinese cities for a total of more than 1000 patients.

Zhao hopes the research will establish the molecular pathway that underlies shifts in metabolism. Studies by Patrice D. Cani of the Catholic University of Louvain in Belgium and others have shown that a clear
sequence of changes occurs in an animal’s gut after consuming a high-fat diet. Bad bacteria increase, the gut barrier becomes more permeable, and toxins increase in the bloodstream. The spike in toxins, in turn, triggers inflammation, which prompts a fall in the host’s metabolism. Zhao now hopes to see the reverse in his human subjects as they adopt healthier diets. “All these markers should show expected changes,” he says.

Zhu Baoli of the Chinese Academy of Sciences’s Institute of Microbiology in Beijing is an outspoken critic of what he describes as overblown claims surrounding Chinese medicine, which he dismisses as “just herbs.” But he says Zhao’s research is encouraging. He cites a study in Beijing focused on gut microbiota and diabetes in which Zhao and colleagues are looking for signature bacterial species connected to diabetes in humans. “He is headed in the right direction,” Zhu says.

Rob Knight, a microbiologist at the University of Colorado, Boulder, says he is looking forward to seeing results from Zhao’s clinical studies when they’re published. “Other studies of diet and the microbiome with fewer participants have yielded valuable and statistically significant results,” he says.

Large clinical studies involving prebiotics like those Zhao runs may be easier to carry out in China. At a bustling vegetarian restaurant in downtown Shanghai one night, Zhao feasts on seaweed, ginkgo, bamboo, Chinese kale, and Chinese yam. Chinese volunteers don’t blink when asked to eat such plants, he says. “They look at the list we give them and say, ‘Oh, this is food. No problem.’ ”

And because many of the substances are not yet accepted as food or medicines in Europe and North America, he adds, “it would take years to get permission to do clinical trials.”

But Zhao has his sights set beyond Asia, predicting this work will be more fruitful than genome studies in leading to antiobesity drugs. Weinstock agrees that the end goal of Zhao’s studies is to find active ingredients, not prove “that you can only treat people with the fungus that grows in the dung of some beetles.” In Zhao’s lab, he says, “it’s Western reductionist science meets traditional Chinese medicine.”

One promising compound Zhao and colleagues are looking into is berberine, the major pharmacological component of the Chinese herb Coptis chinensis, or huanglian. They have found that when rats were given a high-fat diet together with berberine, the rodents didn’t develop obesity or insulin resistance—and in their guts, populations of known pathogens decreased while those of known beneficial bacteria increased. Other gut species that changed in abundance haven’t yet been studied, and it’s not known whether they are linked to good or bad health. But Zhao is quick to acknowledge that this work is not going to produce a panacea. And, he adds, “we need to do a lot more work to understand how [berberine] will affect nutrition and metabolism.”

If Zhao does one day prove a link between gut microbiota and health, it will be bittersweet. His father, who suffers from inflammation and lingering effects from his strokes, is in his last days, and Zhao has spent much of the past few months at his bedside. “I wish I had done this research 10 years ago,” he says. “I could have helped him.”

—M.A.R.A. HVISTENDAHL

Pigs as Stand-Ins for Microbiome Studies

SHANGHAI, CHINA—The Chinese use pigs for just about everything, from processing waste to enriching the dinner table. Now they are testing piglets as a new model for human microbiome research. The past decade has seen an exponential rise in interest in how the microbes living in and on the human body affect health (see p. 1246). Studies often involve germ-free mice, but rodents have a very different physiology and gut microbiota than humans. Pigs, by contrast, have an anatomy and immune system closer to those of people—along with an omnivorous diet and a similar digestive tract.

For research published in 2007, Shanghai Jiao Tong University microbiologist Zhao Liping led a team that inoculated 28 germ-free piglets with the diluted excrement of a healthy 10-year-old boy to see whether the boy’s gut microbiota would thrive in the piglets’ guts. That happened with two groups of bacteria important to a healthy human gut, Bifidobacterium and Bacteroides. More importantly, when the researchers analyzed the piglets’ gut microbiota 12 days later and compared it with that of the human donor, conventionally raised piglets, and unrelated humans, the microbiota most closely resembled that of the donor—suggesting that it is possible to establish a human microbiome in piglets while maintaining their health and immunity.

Piglets with human gut flora have “great potential” for use in microbiome research, Zhao says. Sharon Donovan, a pediatric health researcher at the University of Illinois, Urbana-Champaign, agrees: “The piglet is an exceptional model for the human infant in terms of gastrointestinal, immune, and cognitive development.”

Several obstacles remain. Much less is known about pig genetics, so linking pig genes to the microbiome will be a challenge. Also, piglets are relatively expensive—about $120 apiece in China—and, like other animals, not always receptive to human microbiota. In another study by the Shanghai Jiao Tong scientists, seven out of 24 human-flora–associated piglets died because the bacteria they received from an otherwise healthy human donor’s stool contained a strain of pneumonia-causing bacteria, which scientists had missed. Nonetheless, says Imperial College London systems biologist Jeremy Nicholson, pigs inoculated with human microbiota get “closer to an animal model of human overall system behavior” than other animals. Humanized pigs, he adds, could be “the best thing you could do for human drug testing.”

—M.H.