THE GUT IS TEEMING WITH LIFE

TEXT: TIM SCHRÖDER

Bacteria are almost everywhere. We encounter them as pathogens or causative agents of infections. But they are our indispensable helpers. For example, without intestinal bacteria we would not be able to digest our food so effectively. A diverse microbial community – known as the microbiome – has co-existed with humans for hundreds of thousands of years. Ruth Ley and her team at the Max Planck Institute for Biology, Tuebingen are researching how microbes have influenced human evolution.

Our body is a veritable biotope – not for plants or animals but rather for bacteria: billions of microbes settle on – and in – our bodies. It may sound a bit unsettling, but it is essential for our survival. These commensal organisms fend off harmful pathogens, help us with digestion, and provide us with vital trace elements. Some bacterial species have co-existed with humans since we left Africa and colonized almost all of the Earth's continents tens of thousands of years ago. So it's not dogs – but rather bacteria – that are humans' best friends and most faithful companions!

Helicobacter pylori, the bacterium that causes stomach cancer, is one microbe that has been with humans from very early on. But Helicobacter is not the only bacterium that has co-evolved with humans. "Our findings suggest that a whole range of other intestinal bacteria tracked with our ancestors out of Africa," says Ruth Ley, research scientist at the Max Planck Institute for Biology, Tuebingen. Many of them are quite beneficial for humans. For example, the intestinal bacterium *Prevotella copri*, or Eubacterium *hallii*, both common inhabitants of the gut.

As humans encountered and adapted to new environments as we colonized the globe (adapting to new climatic conditions, novel pathogens, or agriculture and animal husbandry), our genetic make-up changed. Our microbes have undergone genetic changes as well. When mutations occurred in the human genome, changes often occurred in the genomes of bacteria as well. Ruth Ley and her team at the Max Planck Institute in Tuebingen are looking for evidence that the evolution of gut bacteria and archaea has tracked with the evolution of their hosts. "We're seeing a fascinating interplay between bacteria and humans," says Ley.

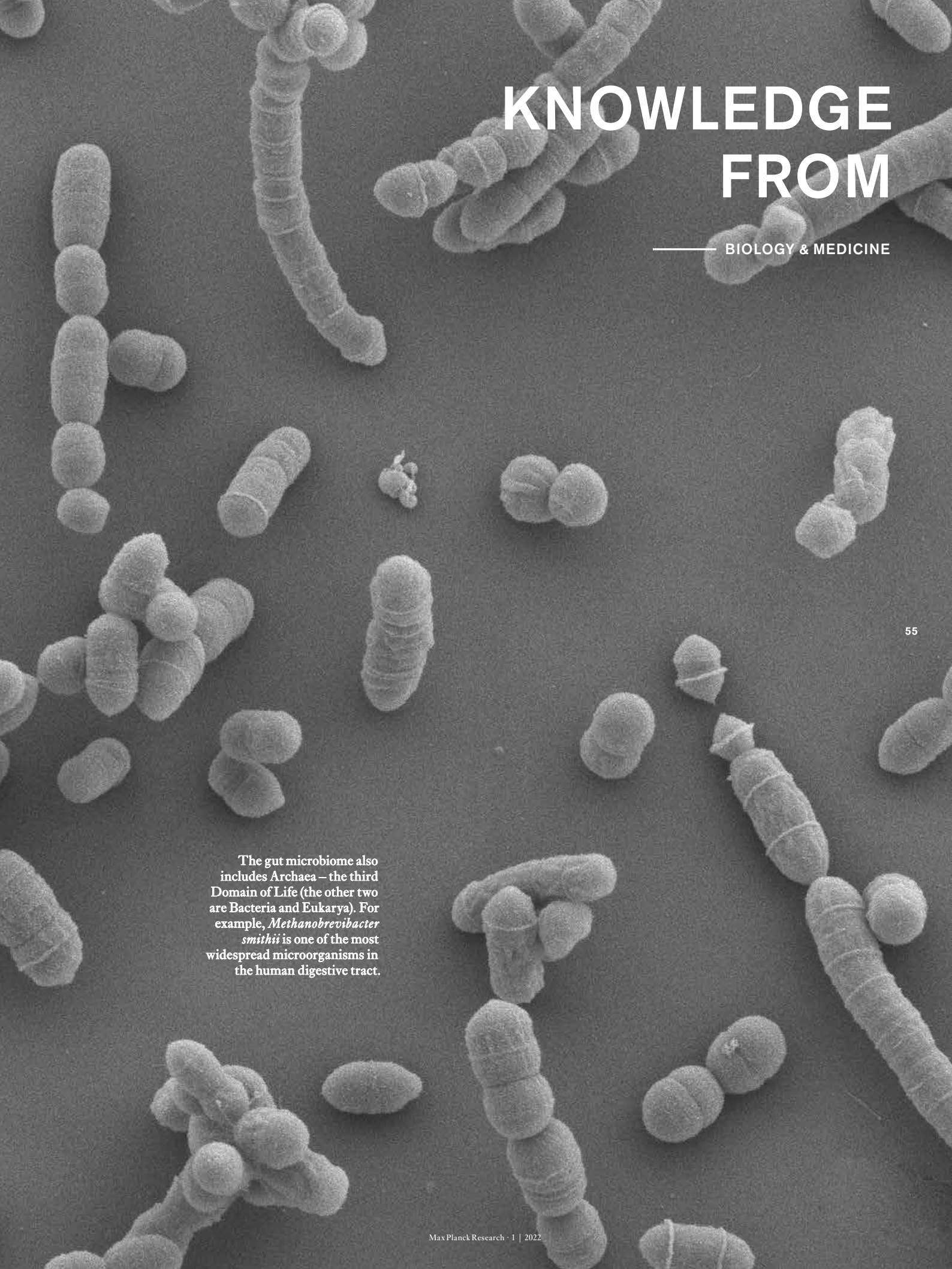
Scientists are able to read and reconstruct the migration history of humans based on their genetic make-up. "Geneticists have created a map of human genetic adaptions to new envi-

→

PHOTO: MPI FOR BIOLOGY, TUEBINGEN

KNOWLEDGE FROM

BIOLOGY & MEDICINE



The gut microbiome also includes Archaea – the third Domain of Life (the other two are Bacteria and Eukarya). For example, *Methanobrevibacter smithii* is one of the most widespread microorganisms in the human digestive tract.

ronments, and we are using that map to guide us in looking for corresponding genetic changes to the microorganisms living on and inside us: our microbiome," Ley explains.

A prime example of the interaction between humans and microbes is the digestion of lactose. Lactose is broken down in the small intestine by the enzyme lactase and provides energy for newborns during the nursing period. For almost all of human history, the milk content of our diet decreased considerably after the nursing period – and so did lactase production, as lactase was no longer needed in the digestion of the adult diet. This changed with the domestication of wild cattle, goats, and sheep some 2,500 to 10,000 years ago. "People were then able to use the milk from these animals as a source of food, i.e., energy into adulthood and throughout their lives," explains Ley. "In some populations, such as in Northern Europe, people who produced lactase into adulthood thus had a considerable evolutionary advantage." In fact, this so-called lactase persistence has become very common in regions with high milk consumption such as Europe, where gene variants that maintain lactase production throughout a person's lifetime are common.

Digestion of lactose

But the lactase enzyme is only one of the ways in which lactose can be broken down. Lactose can also be broken down by gut bacteria. One example are the bifidobacteria, bacteria common in mammals. While lactase breaks down lactose in the small intestine, bifidobacteria and other micro-organisms can also metabolize it. They either take it up whole, or they may for instance first break down lactose with the enzyme beta-galactosidase (also known as β-galactosidase) and then ferment the resulting fragments of glucose and galactose. However, bacterial breakdown provides less energy to the host than the breakdown of lactose by lactase and the direct absorption of glucose and galactose by the body. For people who consume milk, it is thus worthwhile – from an energetic standpoint – for the body to maintain its own lactase enzyme production beyond infancy, in order to perpetuate direct utilization of lactose.

People who produce lactase throughout their lives and not only during the nursing period essentially compete with bifidobacteria for the lactose. All others should consider themselves lucky that there are bifidobacteria that digest lactose for them. Without the microbes, the valuable sugar would pass through the intestine unused and be lost. People who produce little or no lactase as adults therefore also have higher concentrations of bifidobacteria than those who are lactase persistent (i.e., produce lactase throughout their lives).

When people who are lactase non-persistent experience diarrhea or abdominal pain after ingesting lactose from dairy products, this is called lactose intolerance. The cause is osmotic imbalances and/or gases produced during lactose fermentation by the microbiome. But this is not always the case: Ley's analyses show that in Vietnam and Gabon, 20 percent of people without sustained lactase production do not produce gases during lactose digestion. These people have more bifidobacterial, or other microbiota that digest the lactose without producing large amounts of gas. This observation suggests a treatment for lactose intolerance: one option would be to increase the population of specific bacteria in the form of probiotics. "However, you have to test the efficacy of such treatments and find out which species or strains work in which concentration," Ley explains.

Ley's findings suggest that bifidobacteria were likely essential as metabolizers of lactose when humans began domesticating cattle, sheep, and goats. At that time, the microbe helped us to extract energy from the animals' milk. Then, over time, human gene variants emerged that allowed life-long lactase production, thereby making the work of the microbes redundant. "Unlike the co-evolution of cells and their organelles, this is not a classic co-evolution of two organisms that merge and become completely interdependent," Ley emphasizes. One example of such a particularly close form of co-evolution is mitochondria – organelles that supply cells with energy. It has been postulated that millions of years ago, one cell engulfed another – possibly an archaea – and permanently incorporated it. Since then, a lively exchange of genes has taken place between the cells of higher organisms and the mitochondria.

Mutual evolution?

"Although the genomes of humans and bacteria do indeed influence each other, we cannot rule out the possibility that they evolve separately. So far there is no evidence that humans and their gut microbes have co-evolved in the classic sense," explains Ley. In order to decipher the nature of such relationships, Ley compares the changes in the genomes of humans

SUMMARY

The human body is colonized by countless microorganisms. Without this so-called microbiome, we wouldn't be able to survive. For instance, the bacteria found in the intestine are indispensable for digestion and other key functions.

The evolution of humans is closely linked to the development of their intestinal bacteria. Researchers can reconstruct human migration patterns from similarities in their genetic histories.

PHOTO: JEAN-CLAUDE WINKLER PHOTOGRAPHY

At the Max Planck Institute for Biology in Tuebingen, Ruth Ley and her team are investigating how humans and the microorganisms in their gut mutually influence each other in their evolution.

with those of microbes. By doing this, she obtains information about the evolutionary relationships of the human hosts to their symbiotic partners in their intestines. Microbes that have evolved with humans have very similar branching patterns in their phylogenetic trees, i.e., evolutionary histories. "Sequencing DNA and decoding genetic information is only part of the work. The real challenge is compiling the data," says Ley.

For this, the researchers need human DNA and stool samples. From these stool samples, they can extract the genetic material of the intestinal bacteria (the microbiome's metagenome). "A great deal of research has been conducted exclusively in Western Europe. With our comparisons of the microbial genome comparisons in relation to human genomes, we are conducting pioneering research." It took Ley and her team three years to collect the genome data of close to a thousand people and their respective intestinal flora. Working with Peter Gottfried Kremsner, Professor of Tropical Medicine at the Tuebingen University Hospital, and his associates, Ley's team collected samples from more than 700 adults and 300 children in Vietnam, Gabon, and Germany. Working with collaborators, Ley has also assembled data in Britain, Cameroon and South Korea, in addition to data compiled from public sources. Comparing parents and children is important because intestinal bacteria are passed down over many generations.

The researchers have found that there are bacteria that are particularly loyal to human families and communities. Others quickly colonize new populations. Over time, a population's intestinal bacteria may become adapted to their foods, or other local environmental factors. "We are pursuing the idea that this has led to different populations of people having bacterial species that are precisely tailored to them – both to their genomes and to their diet," says Ley.

Utilization of starch

Ley is convinced that bacteria have played a far greater role in human evolution than previously thought – and not only as pathogens. For one thing, Ley's work has shown that bacteria enable us to use starch effectively. The seeds of important agricultural crops (e.g., cereals, rice, and corn, and also tubers) contain large amounts of starch. However, the forms vary in digestibility depending on the plant. After humans started to cultivate these plants, they suddenly had a first-class energy supplier at their dis-

→

posal. But only if they were also able to digest it. This requires sufficient quantities of the enzyme amylase. The digestion of the more easily digestible starch begins in the mouth by the amylase contained in the saliva. Starches that are more difficult to digest are broken down and fermented by bacteria in the digestive tract.

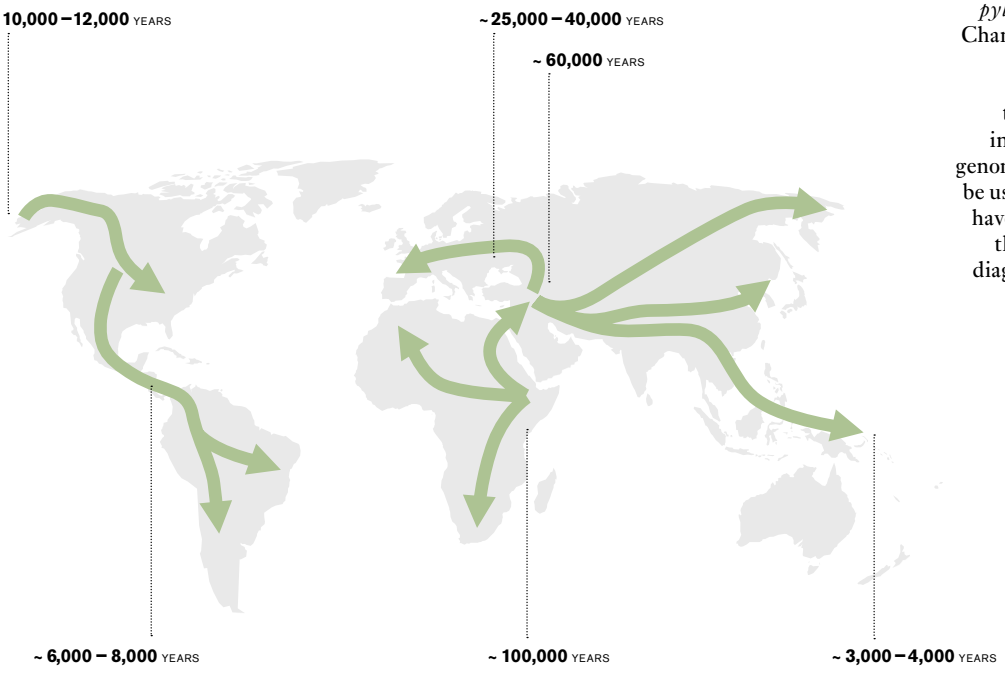
How the host and microbe divide up the breakdown of starch depends largely on a person's genetic make-up. If the gene for the production of salivary amylase is present several times in the genome, more starch can be broken down in the mouth. Humans with a history of living as hunter-gatherers have on average fewer copies of the amylase gene compared to humans with an agrarian background. But at that time, starchy foods likely made up a smaller proportion of their daily diet. With the cultivation of cereals, rice, and corn, it became more important to be able to efficiently digest starch. Duplication of the amylase gene resulting in a greater copy number may have given humans a fitness advantage because digestion via amylase in the mouth increased energy output compared with microbial fermentation.

Some people produce a lot of salivary amylase, while others produce only a little. Ley's work has shown that their microbiomes differ considerably. People with multiple copies of the amylase gene and produce more amylase in the mouth have high numbers of bacteria of the genus *Ruminococcus* – a bacterium that specializes in "resistant" starch that is difficult for the human alone to digest. Because these individuals break down simple starch almost completely in the mouth, only the resistant form remains for the microbiome. To make maximum use of this form of starch, a greater proportion of *Ruminococcus* are needed.

Ruth Ley and her team assume that *Ruminococcus* has given people with many copies of the amylase genes an evolutionary advantage because they can better utilize resistant starch: by digesting the simple starch with the help of salivary amylase and then fermenting the more complex starch with the help of intestinal bacteria. "Bacteria can likely influence the evolution of humans," Ley declares.

Such a parallel evolution of bacteria and their hosts is also likely in other mammals. Many pass on their bacteria from generation to generation through body contact or specific behaviors. In reptiles and birds, however, bacteria and hosts appear to evolve separately. Whether bacteria can also switch from one species to another is still an open question. For example, there are many strains of bifidobacteria, some of which live in the intestines of pigs. As Ruth Ley explains, "The question is, whether strains have been passed from one family to another and how faithful these bacteria actually are to humans – or whether some strains may have passed from one mammalian species to others."

←



When humans left their original home in Africa, they took microorganisms such as the bacterium *Helicobacter pylori* with them in their intestines. Changes in the human genome made it possible to adapt to new living conditions. Correspondingly, the genes of the microorganisms in the intestine also changed. The genome of the microbes can therefore be used to trace which paths humans have taken as they dispersed all over the Earth. The annual data in the diagram refer to global migration in the period before today.

GRAPHIC: GCO BASED ON AN MPG DESIGN

Sunrise reloaded

In the summer of 2022, Sami Solanki's balloon carried SUNRISE observatory will again take a closer look at the sun's magnetic fields.

The Foundation is proud to support the Max Planck Institute for Solar System Research and the 3rd flight of the largest and most powerful solar telescope that has ever left the ground. This unique view will enable an even better and more effective research on how the sun influences.

The Max Planck Foundation has supported the Max Planck Society for more than ten years by providing targeted funding for top-level innovative and cutting-edge research at the more than 80 institutes, enabling breakthroughs in frontier science. As a patron, you can make a crucial difference by creating additional scope to keep this research ahead of the curve in the international scientific competition. Join us!

Max-Planck-Foundation
Deutsche Bank
IBAN DE46 7007 0010 0195 3306 00

www.maxplanckfoundation.org

MAX PLANCK
Foundation