NEWS & VIEWS

MICROBIOLOGY

Genetic pot luck

Justin L. Sonnenburg

Without the trillions of microbes that inhabit our gut, we can't fully benefit from the components of our diet. But cultural differences in diet may, in part, dictate what food our gut microbiota can digest.

Imagine being served an exotic food that, because of its strange nature, can't be eaten using conventional utensils. Now imagine a person from the country from which the food originates handing you a cleverly designed implement that, taste notwithstanding, makes consumption of the food effortless (think durian fruit and machete, or baked beans and can-opener, if that helps). On page 908 of this issue, Hehemann *et al.*[1] report that resident bacteria in the human intestine have similarly acquired genetic material from a marine bacterium, enabling them to consume otherwise refractory components of dietary seaweed.

Our intestines are teeming with a dense and relatively complex community of microorganisms, collectively known as the intestinal microbiota[2]. This community consists of trillions of bacteria, most of which are long-term residents; the microbes we ingest with food are also transient members of this ecosystem. All are vying for limited resources, which are mostly derived from our diet. For instance, human enzymes cannot degrade many of the polysaccharides in dietary plants; these therefore pass to the distal portion of the digestive tract, where enzymes of our microbial inhabitants help to do the job.

Hundreds of microbial species in the intestine stand poised to access this 'high-carb' meal, suggesting that significant competition occurs for these coveted substrates. Indeed, genes dedicated to carbohydrate acquisition and degradation, such as those encoding glycoside hydrolase enzymes, are prominent in metagenomic data sets representing the microbiota's aggregate genome (the microbiome)[3]. Such genes are also enriched in the individual genomes of many species residing in the intestine, including members of the phylum Bacteroidetes[4]. So one apparent strategy for success in the intestinal ecosystem is to become proficient at using the dietary polysaccharides that your host consumes.

One way in which bacteria evolve is by acquiring genetic material from other organisms through lateral gene transfer[5]. If the acquired genes confer a fitness advantage, the bacterium will increase in abundance. For example, lateral transfer of genes that allow a bacterium to resist antibiotics means that it can survive in the presence of these agents. Of growing interest to those who study the intestinal microbiota is determining how gene transfer has shaped this community, and what environmental factors dictate whether the transfer is advantageous.

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Figure 1 | Hidden helpers. Marine microorganisms that live on seaweed — such as the nori used to wrap sushi — have contributed genes to the intestinal microbiome of Japanese individuals[1].

In studying a marine member of Bacteroidetes, *Zobellia galactanivorans*, Hehemann *et al.*[1] have identified and characterized a new class of glycoside hydrolase. This enzyme is responsible for cleaving a polysaccharide called porphyran, which is abundant in red algae of the *Porphyra* species. The authors' crystal structure of the enzyme bound to its carbohydrate substrate shows regions of the enzyme that are essential for specifically binding porphyran.

Searching all publicly available gene-sequence databases, Hehemann *et al.* noted that genes containing porphyran-specificity sequences were not found only in other marine bacteria. Surprisingly, predicted porphyranase sequences were also present in metagenomes derived from human faeces and in the genome of a resident human intestinal bacterium, *Bacteroides plebeius*. No other members of the numerous sequenced intestinal *Bacteroides* species carry similar genes, suggesting that *B. plebeius* acquired these genes (and other adjacently positioned marine polysaccharide-degrading genes) laterally from marine bacteria. But the question was: why would a bacterium living in the human intestine acquire and retain the genes for degrading an algal polysaccharide?

The team[1] noted that all six previously described *B. plebeius* strains were originally isolated from the faeces of Japanese individuals, so they turned to human faecal metagenomic data sets, some of which contained porphyranase sequences. The analysis revealed that these sequences are abundant in the intestinal microbiomes of Japanese individuals, but not in the microbiomes of residents of the United States. The authors conclude that seaweed, which is prevalent in the Japanese diet — including the abundant *Porphyra*-derived nori, used to wrap sushi — was probably the source of the microorganisms that introduced the useful genes (Fig. 1). Although it is not clear when in human history the transfer, or transfers, of these genes occurred, continuous consumption of seaweed is the likely selective force that drove the retention of this 'polymorphism' in Japanese microbiomes.

Searching huge metagenomic data sets[6] to understand what links environment, diet and the composition and function of microbiota is a great challenge; this study[1] provides a vivid example of how it can be achieved. In using solid mechanistic data as a basis for querying the rapidly accumulating sequence data related to the human microbiome, Hehemann and colleagues demonstrate how environment and diet can coalesce to

influence microbiota functionality. In addition, this study from a marine-glycobiology research group provides good evidence that the vast research resources being poured into microbiome-focused sequencing efforts will benefit the broader scientific community by driving discovery. With several well-established links between the intestinal microbiota and human health[7], such discovery will be crucial for realizing the medical potential and significance of our resident microorganisms in the coming era of personalized genomic medicine.

Of the many interesting issues raised by this work, one is the relative importance of microbiota adaptation that occurs during the evolution of host species, during the colonization of new environments, and coincident with dietary change[8]. Also, the efficiency with which the microbiota degrade polysaccharides relates to the calories the host can extract from its diet, potentially influencing the survival and fitness of both host and microbiota. Given that enhanced ability to obtain energy-rich food is considered to be one factor that has driven human evolution[9], it is likely that substantial microbiota adaptation has accompanied the dietary changes that have occurred throughout human history.

It remains to be determined how, during human evolution, changes in food production and preparation such as agriculture and cooking have influenced the intestinal microbiota. Exploration of the microbiota of diverse human populations (including traditional societies such as hunter-gatherers), studies of ancient samples derived from coprolites and mummified or fossilized hominins, and investigations into our great-ape relatives will together provide a picture of how the microbiota has shaped — and has been shaped by — our natural history.

Consumption of hyper-hygienic, mass-produced, highly processed and calorie-dense foods is testing how rapidly the microbiota of individuals in industrialized countries can adapt while being deprived of the environmental reservoirs of microbial genes that allow adaptation by lateral transfer. Conversely, global travel and trade are providing unmatched access to new types of food and perhaps new microbes harbouring novel genes destined for integration into our microbiome. So the next time you take a bite of an unfamiliar food, think about the microbial inhabitants you may also be ingesting, and the possibility that you will be providing one of your ten trillion closest friends with a new set of utensils. ■

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HUMAN EVOLUTION

Stranger from Siberia

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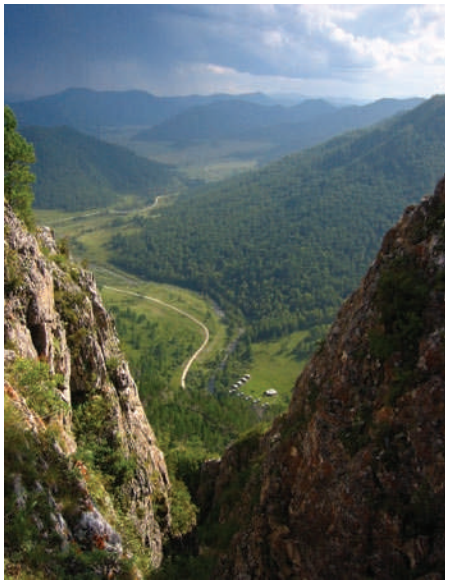
The sequencing of ancient DNA is generating dramatic results. The sequence from a bone fragment has revealed the existence of an unknown type of extinct human ancestor that lived in Asia 40,000 years ago.

Forty thousand years ago, the planet was more crowded than we thought. For decades we believed that there were just two members of the genus *Homo* living at that time. First, Neanderthals, which occupied large tracts of Europe and north Asia, although their days were numbered and within 15,000 years they became extinct. Second, early modern humans, members of our own species, who spread across Eurasia from the African homelands that they had left some 10,000 to 20,000 years earlier. This picture changed in 2003 when a third human species, the tiny 'Hobbit', *Homo floresiensis*, was discovered in Indonesia, the most recent of these fossils being only 13,000 years old.

Now, in a paper on page 894, Krause *et al.*[1] force a rethink of the recent human occupation of Eurasia by describing an unknown hominin — an extinct species of human ancestor — present in Asia around 40,000 years ago. Their discovery is remarkable not just for the insight it gives into the human past. For the first time a hominin has been described, not from the morphology of its fossilized bones, but from the sequence of its DNA*.



J. KRAUSE

Figure 1 | Occupation site. This view of the Altai Mountains is from just above Denisova Cave, where the fragment of bone analysed by Krause *et al.*[1] was discovered. The excavation field camp is visible in the valley below.

The DNA comes from a piece of finger bone discovered in Denisova Cave in the Altai Mountains of southern Siberia (Fig. 1). This cave was intermittently occupied by humans for 125,000 years. It is rich in stone tools and bone implements, but has yielded few human bones, most of them isolated finds such as that used in this study. With such incomplete specimens, the morphological information needed to identify the species to which a human bone belongs is impossible.

The finger bone came from a layer dated to between 48,000 and 30,000 years ago. DNA sequencing from fossils of this age is still quite an achievement, and would not have been possible without technical innovations developed by the same group in their work with Neanderthal DNA. These include methods for assessing whether a DNA fragment is genuinely ancient on the basis of its length and chemical damage, thereby solving the great conundrum for studies of ancient DNA by ensuring that the sequence obtained is not a contaminant from a researcher.

Krause *et al.*[1] focused on the DNA found in cellular organelles called mitochondria, as there are about 8,000 copies of this mtDNA per cell, compared with just two of the DNA in the nucleus, giving a greater chance of finding mtDNA in an ancient specimen. Using the next-generation sequencing methods that have been applied to Neanderthals[2], mammoths[3] and, most recently, the 4,000-year-old remains of an ancient Eskimo[4], a complete mtDNA sequence was assembled from the Denisova finger, with each nucleotide being read, on average, 156 times, so ensuring a high degree of accuracy. The uniqueness of the sequence was revealed when it was compared with that of modern humans and Neanderthals. It matched neither, even though both species were living in the Altai Mountains 40,000 years ago.

*This article and the paper under discussion[1] were published online on 24 March 2010.