The earliest development of fermented foods, among the most ancient agricultural products, coincided with the rise of civilizations around the world. According to archeological records, wine was produced during the Neolithic Period from 8500 to 4000 BC, while beer and bread were mass-produced shortly thereafter. These foods, as well as others such as cheese, yogurt, and miso, are mentioned in ancient texts, including the Bible, the Iliad, and the Odyssey. Although modern preservation and processing methods reduced reliance on these products, fermented foods and beverages remain an important part of diets throughout the world.

In the United States, there is renewed interest in fermented foods for both their artisanal manufacture and their capacity to benefit human health. New companies are popping up to produce a wide range of fermented foods and beverages, including pickles, sauerkraut, sourdough bread, artisanal cheeses, yogurts and kefir, craft beers, and kombucha (fermented tea). These foods are not only popular, but they are also considered healthy. Indeed, in the absence of scientifically confirmed health benefits for most fermented foods, consumers are being told that some are “probiotic” and “prebiotic.” Many of these claims revolve around Lactobacillus species, which are widely used to ferment foods, and the role that these bacteria play as probiotics.

Lactobacillus and closely related lactic acid bacteria (LAB) are the most abundant bacteria consumed within regular US diets, with an individual consumer eating between $10^6$ to $10^9$ living bacterial cells from various fresh and fermented food sources each day. Adding probiotic Lactobacillus strains to that mix would provide an opportunity for increasing those numbers considerably. However, the study of host-microbe interactions of ingested probiotic bacteria in the intestine is a relatively new field, much in line with efforts to understand how the indigenous gut microbiome influences its host. Because Lactobacillus species are generally regarded as safe for consumption and do not permanently colonize the intestine, studying these bacteria serves as a gateway for investigating transitory host-microbe interactions in the digestive tract. Ultimately, doing so will help us to appreciate not only the microbes on our bodies but also those that join us at the dinner table.

The Microbiota of Fermented Foods

The production of fermented foods and beverages requires a variety of bacteria, molds, and yeasts. Depending on which foods are being fermented and under what conditions, different types of microorganisms tend to proliferate. Because of their metabolic and enzymatic activities, these different microorganisms are mainly responsible for the taste, texture, and aroma properties of the final fermented products.

Fermentations can be relatively simple, involving only one or two microbial species such as for yogurt or relatively complex, requiring both bacterial and fungal populations, sometimes...
growing simultaneously, or in other cases, as with cocoa, in succession. Recent studies using high-throughput DNA sequencing and other methods show that even “simple” fermentations can involve multiple microbial lineages, contain resident bacteriophages that regulate community composition, undergo elaborate microbial cross-feeding networks, and constitute dynamic habitats in which members may compete to succeed one another.

However, even with this breadth of starting materials, processing approaches, and microbial community structures, most fermented foods depend on LAB, which are saccharolytic members of the Firmicutes phylum that produce lactic acid and other organic acids as the primary end-products of fermentative growth. LAB genera found in foods include Lactobacillus, Leuconostoc, Lactococcus, Pediococcus, Weisella, Oenococcus, and Carnobacterium, with Lactobacillus being the most common.

**Lactobacillus Is Common in Food Fermentations and Gastrointestinal Tracts**

*Lactobacillus* species are essential agents for making a variety of plant, dairy, meat, and beverage products (Fig. 1). Currently, there are 217 recognized species of *Lactobacillus*, and the most well-known food-associated species include *L. plantarum*, *L. casei*, *L. brevis*, *L. rhamnosus*, and *L. delbrueckii*. A recent genome sequencing effort focusing on *Lactobacillus* and other LAB species identified more than 44,000 gene families. The number of gene families increased with each genome sequence, indicating that the genetic potential has not been completely uncovered for this genus.

Diversity within the *Lactobacillus* genus reflects the assortment of environments from which these species are found. In addition to fermenting foods, *Lactobacillus* colonizes human and animal digestive tracts. Side-by-side with *Bi-*
**Health Benefits of Fermented Foods**

Beyond their direct importance in fermentations, LAB alter foods in ways that benefit human health. For one thing, these bacteria metabolize sugars that are not well tolerated by some human populations. Further, they make organic acids and antimicrobial peptides that serve as barriers to the growth of spoilage and pathogenic bacteria. LAB fermentations also produce compounds such as folic acid or other B vitamins and conjugated linoleic acid that benefit consumers.

More recently, experts and consumers increasingly recognize that eating fermented foods may help to prevent a variety of chronic diseases. For example, the regular eating of fermented dairy products is associated with a significantly decreased risk for developing cardiovascular disease and type II diabetes mellitus. Consuming kimchi, a plant-based fermented food that is a staple in the diet of many Koreans, leads to an increase in insulin sensitivity and glucose tolerance in prediabetic adults.

While some fermented foods are pasteurized, roasted, or baked before being consumed, others, such as kimchi and fermented dairy products, serve as a source of living bacteria. These freshly eaten fermented foods can contain over $10^{10}$ LAB cells per serving, some of which survive transit through the gastrointestinal tract. While such food-associated LAB might support human health, the functionality of LAB in the digestive tract is better understood from studies of probiotic *Lactobacillus* strains.
Probiotic Lactobacillus

The World Health Organization defines a probiotic as a living microorganism that, when consumed in sufficient amounts, confers a health benefit on its host. The term probiotic typically is reserved for specific strains investigated in clinical studies. However, this definition can also encompass bacteria in yogurts that reduce lactose concentrations to levels that are acceptable to lactose-intolerant individuals.

*Lactobacillus*, in particular, are the most widely used and best-understood bacteria applied as probiotics for maintaining and improving human health. Some strains of *Lactobacillus* are effective at preventing and treating antibiotic-associated diarrhea and acute infectious diarrhea, alleviating lactose intolerance, reducing the risk for necrotizing enterocolitis in infants, and preventing pouchitis, a form of inflammatory bowel disease. Preclinical studies suggest that *Lactobacillus* might also be useful for preventing metabolic syndrome, reducing anxiety and depression, reducing atopic disease, and preventing bacterial vaginosis. Although the lactobacilli commonly applied as probiotics are typically different from those responsible for fermenting foods, studies of probiotic strains can help to explain how dietary LAB might improve conditions within the digestive tract as well as systemic health.

Probiotics work through three broad mechanisms in the human digestive tract: modification of the indigenous microbiota composition or function, stimulation of the immune system, and interaction with the epithelium. Beyond these general functional categories, there remains the
need to study the precise effectors made by probiotics and corresponding host pathways that respond to them. Thus far, the main Lactobacillus probiotic effectors are cell-surface-associated and secreted proteins as well as small metabolites and polysaccharides. Several of these effectors were shown to bind to receptors on intestinal cells to modify cell turnover, tight junction protein localization, and immune response pathways.

Factors Affecting Probiotic Lactobacillus

Various external factors influence Lactobacillus-host interactions within the gastrointestinal tract (Fig. 2). We are interested in understanding how LAB such as Lactobacillus adapt to and behave in foods and the digestive tract.

For example, dairy products are a natural habitat for certain LAB and a common means for delivering probiotic Lactobacillus in foods. When cells of L. casei are in milk, we find that proteins for modifying cell surfaces, metabolizing fatty acids, transporting and metabolizing amino acids, and transport of inorganic ions are abundant (Fig. 3). We find that these milk-associated proteins enable L. casei to survive in milk also help cells from this strain to persist in the murine intestine. Remarkably, ingesting L. casei in milk improves its capacity to reduce inflammatory responses. Such delivery vehicle-dependent differences in probiotic efficacy might apply to the behavior of Lactobacillus when delivered to human populations in fermented dairy products.

Other LAB are more commonly consumed in...
fermented plant foods. To measure how they adapt for growth on plant tissues, we studied *Lactococcus lactis*, another LAB commonly found in fermented foods. Transcript and metabolite levels of *L. lactis* after growth in a leaf tissue lysate of *Arabidopsis thaliana* showed that this LAB metabolizes sucrose, fructose, arabinose, ribose, cellobiose, and hemicellulose (Fig. 3). Cells of *L. lactis* growing in this plant tissue lysate also express genes encoding enzymes involved in oxidative stress pathways and for modifying cell envelope composition. Among these plant-inducible genes is a hybrid nonribosomal protein synthetase/polyketide synthase system. Such systems are responsible for producing secondary metabolites such as siderophores that can confer highly specific, plant-dependent traits, and in the case of *L. lactis* synthesize a molecule involved in reactive oxygen species tolerance, according to our preliminary results.

Once ingested, cells of LAB encounter new conditions that influence their behavior. Lactobacilli are metabolically active in the intestine, expressing genes that depend on intestinal location and the health status of the host. For example, when residing in the ileum of rhesus macaques, *L. plantarum* actively express genes encoding enzymes for degrading host-derived glycans such as sialic acid. This behavior appears to be conserved among other bacteria within the small intestine because the metatranscriptomes of the indigenous bacteria were also enriched with transcripts for fucose, aminosugars, and sialic acid metabolism pathways (Fig. 3).

In contrast, cells of *L. plantarum* respond differently when they are within the distal intestine. In this case, cells of *L. plantarum* more actively modify their cell surface composition and produce antimicrobial peptides (Fig. 3). Host diet further influences the activity and function of *L. plantarum* in the distal intestine.

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Suggested Reading


