



Lactobacillus molecular biology. From genomics to probiotics

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The genus *Lactobacillus* is a member of the lactic acid bacteria (LAB), a group of gram-positive bacteria with low GC-content, anaerobic aerotolerant or microaerophilic, with obligate fermentative metabolism. As their name implies, they form lactic acid as their main fermentation product. LAB can be found in nutrient-rich environments, such as milk, meat, decomposing plant material, fermented food (yogurt, cheese, olives, pickles, salami, etc.), as well as in the oral cavity, gastrointestinal tract, and vagina of humans and other animals. They are generally used as probiotics, which are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. The pioneer in this application of LAB was Ilia Ilich Metchnikoff (1845–1916), who in 1908 was awarded the Nobel Prize of Physiology or Medicine (shared with Paul Ehrlich, 1854–1915, for studies on cellular immunity and phagocytosis). Metchnikoff proposed that the gut microbiota produces small amounts of toxic substances that damage the nervous and vascular systems and ultimately lead to aging. He suggested that the administration of bacteria present in fermented milk, i.e., lactic-acid-producing bacteria, could delay intestinal putrefaction while prolonging life and improving health in old age. Metchnikoff's theories were based on two observations: (i) the longer life expectancies of Bulgarian peasants, which Metchnikoff ascribed to the fact that they consumed large amounts of fermented milk products, and (ii) that the lactic acid produced by microbes prevented the growth of putrefactive organisms.

Lactobacillus molecular biology. From genomics to proteomics is an update on lactic acid bacteria, from genomic and biochemical characterization (Chapters 2, 3, 5 and 6), to biological effects in the host (Chapters 4, 7, 9 and 10), and finally, to potential clinical applications as probiotics (Chapters 8 and 11).

Since the original description of the genus *Lactobacillus* by Beijerinck (1901), more than 100 different species have been described. The genus *Lactobacillus* is the largest group within the family Lactobacillaceae. Current advanced molecular tech-

niques have shown lactobacilli to be the most heterogeneous genus among the lactic acid bacteria. This taxonomic heterogeneity is illustrated by the DNA G+C content, which ranges from 32 to 49.7%, far too broad for a single genus. Chapter 2 describes the phylogenetic subgroups of the genus *Lactobacillus*. While these have some historical meaning, they do not necessarily reflect fixed phenotypic behaviors or ecological links, i.e., the group described under the name *Lactobacillus acidophilus* comprises *L. acidophilus*, *L. crispatus*, *L. gasseri*, *L. johnsonii*, *L. delbrueckii* subsp. *bulgaricus* (formerly *L. bulgaricus*), etc.

Following sequencing of the genome of *Lactobacillus plantarum* WCFS1, in 2003, nine more *Lactobacillus* genome sequences have become available, i.e., that of *L. plantarum* WCFS1, a metabolically diverse organism with a relatively large genome of 3.3 Mb; *L. johnsonii* NCC533 (1.99 Mb); *L. acidophilus* NCFM (1.99 Mb), *L. sakei* strain 23K (1.88 Mb), *L. salivarius* UCC118 (1.82 Mb), *L. delbrueckii* ssp. *bulgaricus* ATCC 11842 (1.86 Mb), *L. gasseri* ATCC 33323 (1.89 Mb), *L. brevis* ATCC 367 (2.34 Mb), *L. casei* ATCC 334 (2.92 Mb), and *L. delbrueckii* ssp. *bulgaricus* ATCC BAA-365 (1.85 Mb) (Chapter 3). Members of the *Lactobacillus* appear to have primarily evolved towards their specific niche through genome decay rather than adaptation by acquiring genes for specialization. It is likely that the order Lactobacillales (includes the genera *Lactococcus*, *Enterococcus*, *Pediococcus*, *Streptococcus*, and *Lactobacillus*) specialized its adaptation to nutrient-rich environments, since in several species a number of genes related to biosynthesis have been lost whereas peptidases seem to have been acquired and genes encoding proteins involved in sugar metabolism and transport duplicated (Chapter 3).

Lactobacilli express a variety of adhesive surface proteins, some of them also involved in physiological processes in the bacteria. These adhesins include the S-layer proteins, proteins with the LPXTG surface-anchoring motif, the anchorless house-keeping proteins, transporter proteins, as well as proteins not belonging to any of those groups. Adhesion to host tissues is the first step in bacterial colonization as well as in bacterial interaction with physiological and immunological processes of the host. Greater knowledge of lactobacilli adhesion mechanisms would further our understanding of their role in colonization and persistence, and would facilitate their use as probiotics (Chapter 5).

Bacteria are critical in establishing a state of immunological homeostasis within the host. The beneficial effects exerted by lactobacilli are related to colonization of epithelial mucosa (competitive exclusion) and the inhibition of pathogen growth by the production of lactic acid or other compounds, such as, H₂O₂; those effects reflect the enhancement of the host immune response and the modulation of immune cell function (lymphocytes). It seems that the structure of the cell wall, including the amino acid sequence of structures such as lipoteichoic acid,

plays an important role in the immune response modulation; for example, the presence of alanine in the cell wall of LAB induces cytokine secretion. Immune responses to lactobacilli are dependent on the species used in the studies, the concentration of bacteria, and the compartment analyzed (anatomical zone) (Chapter 7).

Lactobacilli are members of the normal gastrointestinal microbiota of humans and other animals. The human fetus is considered to be microbiologically sterile, the first bacterial exposure taking place at birth, when the newborn comes into contact with the vaginal and intestinal microbiota of the mother and the microbiota of the surrounding environment. Following birth, the breast-fed infant gastrointestinal tract is rapidly colonized by a microbial consortium often dominated by bifidobacteria. This confers a substantial health benefit to the neonate by hindering pathogen colonization through competitive exclusion. In the mature gastrointestinal tract, only a small number of *Lactobacillus* species are true inhabitants (1–2% of the total gut microbiota) and most of the lactobacilli present are allochthonous members derived from fermented food, the oral cavity, or more proximal parts of the gut (Chapters 4 and 9). The dominant species in the vagina of healthy premenopausal women is *Lactobacillus*, specifically, *L. acidophilus*, *L. crispatus*, *L. gasseri*, and *L. jensenii*. The acidic environment of the vagina,

recognized as an important defense mechanism against the proliferation of different microbial pathogens, is maintained mainly by lactobacilli. Nevertheless, the composition of the vaginal tract's microbiota can be transiently altered by hormone levels, douching, sexual practices, menstruation, etc. (Chapter 10).

New molecular biological methods used to study the enormous complexity of the indigenous microbiota of the skin and mucosal surfaces have opened up new frontiers in the study of microbial interactions and the cross-talk between bacteria and their hosts in health and disease. An increasing public health concern is resistance to the antibiotics commonly used to treat infectious diseases. The high cost to develop new antimicrobials should increase interest in developing non-antibiotic approaches, including the use of bacteriophage and bacteriophage therapy (Chapters 8 and 11).

Briefly, *Lactobacillus molecular biology. From genomics to proteomics* is an essential reference for medical researchers, microbiologists and biotechnologists, especially, dairy technologists.

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