

Lactobacillus Molecular Biology: From Genomics to Probiotics

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Lactobacillus is a genus of Gram-positive facultative anaerobic or microaerophilic bacteria. In humans they are symbiotic and are found in the gut flora. *Lactobacillus* species are used for the production of yogurt, cheese, sauerkraut, pickles, beer, wine, cider, kimchi, chocolate and other fermented foods, as well as animal feeds such as silage. In recent years much interest has been shown in the use of lactobacilli as probiotic organisms and their potential for disease prevention in humans and animals.

This major new work focuses on recent research on the molecular biology and genomics of *Lactobacillus*. Written by an international team of scientists the volume is an essential reference for all medical researchers, dairy technologists, microbiologists and biotechnologists in the academic and industrial sectors. Topics covered include phylogenetics, taxonomy, comparative genomics, functional genomics, the intestinal microflora, surface proteins, stress responses, interaction with the immune system, probiotics, anti-cancer potential, and much more. Essential reading for all scientists involved with lactic acid bacteria or probiotic research and a recommended book for all microbiology laboratories.

Reviews:

"... an interesting blend of fundamental and applied topics relevant to the use of these important organisms in research and industry. Fundamental aspects covered in the book are taxonomy, metabolism, stress response, genomics, and surface proteins of lactobacilli. Also included are chapters on applications of *Lactobacillus* strains and their potential as probiotics in the treatment of diseases such as cancer or urinary tract infections." *from Biotechnol. J. (2009)*

"... contributions from respected international scientists, many of which are leaders in their respective fields, this book constitutes an authoritative resource about both fundamental research and applications of lactobacilli. ... essential and up to date information for anyone interested in the biology of lactobacilli. The book will clearly be of interest to microbiologists, nutritionists, food scientists, and medical practitioners alike, and it is a valuable contribution to the probiotic literature." *from Biotechnol. J. (2009)*

"*Lactobacillus Molecular Biology. From Genomics to Proteomics* is an essential reference for medical researchers, microbiologists and biotechnologists, especially, dairy technologists." *from Mercedes Berlanga, University of Barcelona writing in Int. Microbiol. (2008) 11: 294-295.*

"the chapters are edited competently and constitute outstanding independent reviews ... very informative and provides a comprehensive overview of the genus *Lactobacillus*" *from Knut Heller, Kiel writing in Biospektrum (2009) 15: 348.*

"intended for medical professionals, but the conclusions are exciting enough to convince anyone to eat more yogurt." *from SciTech Book News June 2009 p. 66*

"... a useful guide to how microbiology is developing ... a wide range of important topics ... production is beautiful, with clear diagrams, a nice typeface and two text columns per 17x25 cm page ... a most valuable text" *from Microbiology Today 2009*

Chapter 1 History of Probiotics and Living Drugs

Åsa Ljungh and Torkel Wadström

Chapter 2 Phylogenetics and Taxonomy

Effie Tsakalidou, G. Huys and Bruno Pot

Chapter 3 Comparative and Functional Genomics of the Genus *Lactobacillus*

Jan-Peter Van Pijkeren and Paul W. O'Toole

Lactobacilli are members of the Lactic Acid Bacteria group and constitute an ecologically and phylogenetically very diverse group. Some strains are of industrial importance since they are applied in a range of fermentation

processes, whereas other strains are exploited for their probiotic properties. To date, ten *Lactobacillus* genomes encompassing nine species have been sequenced, and their genome content broadly reflect the diversity of this genus. With the exception of members of the "acidophilus-complex", there is no long range synteny based on whole-genome alignments. The species are diverse in their metabolic capacity, and some species appear to be in an ongoing phase of specialization, largely determined by preferred ecological niches. Each of these species produces proteins which enable them to compete or survive within their preferred habitat. A repertoire of diverse adhesins has been functionally characterized in several gastrointestinal-associated lactobacilli. The comparative genomics of different *Lactobacillus* strains has revealed novel insights in the complexity of this diverse genus.

Chapter 4 Studies of the Intestinal Microflora by Traditional, Functional and Molecular Techniques

Elisabeth Norin, Cecilia Jernberg, Hans-Olof Nilsson and Lars Engstrand

To resolve the complexity of a bacterial population sophisticated analytical methods and alternative genetic techniques are required. Traditional cultivation, microscopy and determination of fermentation/degradation products are still important. Future studies of the microbe-microbe and the microbe-host cross-talk will strengthen our knowledge about the composition and function of the microflora. We will discuss functional studies including the GAC-MAC concept, and the development of different molecular techniques, which provide microbiologists complementary methods to study complex microbial communities. The most commonly utilized targets are the genes coding for small subunit ribosomal (r) RNAs. The 16S and 23S rRNA genes contain conserved, variable and hypervariable sequences, making them suitable for studies of bacterial evolution and microbial community composition. Denaturing gradient gel electrophoresis and temperature gradient gel electrophoresis are gel-based techniques that separate double-stranded DNA molecules of identical size that vary in sequence and composition. Terminal-Restriction Fragment Length Polymorphism also provides a reproducible fingerprint of complex microbial communities. The recent development of sequence based methods including 454-pyrosequencing has improved sequencing technology and enabled genomics to take a quantum leap in terms of high throughput DNA sequence analysis facilitating completely new types of investigations. Finally, metagenomics, i.e. analyses of microbial populations by the use of genetic/molecular techniques as well as functional analyses, will be discussed.

Chapter 5 Surface Proteins of *Lactobacillus* Involved in Host Interactions

Jenni Antikainen, Timo K. Korhonen, Veera Kuparinen, Takahiro Toba and Stefan Roos

Specific recognition of host components is central in bacterial adhesion and colonization at host surfaces as well as in bacterial interaction with physiological and immunological processes of the host. Isolates of *Lactobacillus* express a variety of adhesive surface proteins, many of which are multifunctional adhesins or also involved in physiological processes in the bacteria. These adhesins can be grouped as S-layer proteins, proteins with the LPXTG surface-anchoring motif, surface-localized housekeeping proteins, as well as transporter proteins. Recognized targets for lactobacillar adhesins include epithelial and phagocytic cells, extracellular matrices, mucins, and circulating components. A more detailed, mechanistic knowledge of lactobacillar adhesion proteins will help to understand their role in colonization and to develop their probiotic use.

Chapter 6 *Lactobacillus* Stress Responses

Graciela L. Lorca and Graciela Font de Valdez

Within the lactic acid bacteria group, the genus *Lactobacillus* is widely used for food fermentation and preservation, and as food additives because its probiotic properties. Lactobacilli are usually exposed to harsh stress conditions such as starter handling and storage (freeze-drying or freezing), during food processing (heat, cold, high concentration of NaCl, and high hydrostatic pressure) and in their passage through the gastrointestinal tract (acidity and bile salts). The optimal performance of these strains depends on the stabilization of their survival potential and their metabolic activity. The purpose of this chapter is to summarize the current knowledge of the survival strategies developed by *Lactobacillus* in order to survive under stress conditions.

Chapter 7 Interactions of *Lactobacillus* with the Immune System

Denny Demeria and Karen Madsen

Lactobacilli have been used for centuries with the intent to produce a health benefit in the human host. Interactions between the host and lactobacilli involve lactobacilli-induced alteration of gene expression in gut epithelial and immune cells, with the subsequent modulation of both mucosal and systemic immune function. Effects of lactobacilli are concentration and species and strain-dependent. Lactobacilli are critical in establishing a state of immunological homeostasis within the host. Beneficial effects exerted by lactobacilli bacteria in the treatment of human disease may be broadly classified as those effects which arise due to activity in the large intestine and are related to colonization or inhibition of pathogen growth; and those effects which arise in both the small and large intestine, and are related to enhancement of the host immune response and intestinal barrier function.

Chapter 8 Lactic Acid Bacteria: Probiotics With Anti-Cancer Activities

Chandra Iyer and James Versalovic

Beneficial bacteria include *Lactobacillus* and *Bifidobacterium* spp. and other lactic acid bacteria (LAB) commonly known as probiotics. LAB possesses numerous potential therapeutic properties including anti-inflammatory and anti-cancer activities and other features of interest. In recent years, studies with *in vitro* cell culture and animal

models that clearly demonstrated protective effects of LAB for anti-tumor and anti-cancer effects. Dietary administration of LAB alleviated the risks of certain types of cancers and suppressed colonic tumor incidence, volume and multiplicity induced by various carcinogens in different animal models. Oral administration of LAB effectively reduced DNA adduct formation, ameliorated DNA damage and prevented putative preneoplastic lesions such as aberrant crypt foci induced by chemical carcinogens in the gastrointestinal (GI) tract of various animal models. LAB also increased the latency period and survival rates in test animals when challenged with carcinogenic agents. Reports also indicated that LAB cultures administered to animals inhibited liver, colon, bladder and mammary tumors, highlighting potential systemic effects of probiotics with anti-neoplastic activities.

Chapter 9 Lactobacillus in the Gastrointestinal Tract

John Keohane, Kieran Ryan and Fergus Shanahan

Probiotics are living organisms which when consumed have beneficial health benefits outside their inherent nutritional effects. Much has been written in both the medical literature and lay press about their potential benefits, some of it well validated by randomized controlled trials but other claims remain unsubstantiated. There is a growing body of evidence for the role of probiotics in gastrointestinal infections, irritable bowel syndrome and inflammatory bowel disease which will be discussed further in this chapter.

Chapter 10 Lactobacillus in the Vagina: Why, How, Which Ones and What Do They Do?

Gregor Reid

Of the 50 known species of *Lactobacillus*, at most 20 are able to colonize the intestine, and *L. iners* and *L. crispatus* appear to be the most commonly isolated in women in various countries around the globe. This consistency of isolation is all the more intriguing given the disparity of societal cultures and diet. For the most part, the origin of the lactobacilli is the woman's own intestinal microbiota, with passive transfer occurring along the skin from the anus to the perineum, vulva and vagina. The microbiota is disrupted by hormone levels, douching, sexual practices, the types of organisms ascending from the anus, and other factors such as alterations in innate immunity. The exogenous administration of certain strains of lactobacilli (probiotics) has been shown to reduce the risk of infection and help eradicate bacterial vaginosis. The mechanisms of action of the most documented probiotic containing *Lactobacillus rhamnosus* GR-1 and *L. reuteri* RC-14, appear to consist of physico-chemical displacement ability, as well as anti-infective compounds released from the cells, and immune-modulatory factors. Further development of these and other strains will lead to new approaches to help women retain and regain their vaginal health, and reduce their risk of various problematic, and in some cases, life threatening, conditions.

Chapter 11 From Probiotics, Prebiotics and Synbiotics to "Living Drugs"

Åsa Ljungh, Torkel Wadström

The human intestine harbours an immense collection of microbes which have co-evolved with us. Recent studies indicate that the gut microbes regulate energy harvest from the diet and participate in the peripheral body metabolism. Elie Metchnikoff understood that gut microbial dysbiosis severely affects many body functions, including a complex interplay of gut-brain interactions, now under intense study. Most probiotic strains belong to the genus *Lactobacillus*. The promising results of a first generation of probiotic microbes, evaluated in animal models as well as natural infections in animals and humans indicate a promising future for coming generations of probiotics. Antibiotic-associated, travellers' and pediatric diarrhea have been most studied, and more recently, inflammatory bowel disease and irritable bowel syndrome. The probiotic strains should be thoroughly characterized. Probably future probiotics will contain mixes of strains with complementary characteristics, tailor-made for different gastrointestinal diseases, vaginosis or as delivery systems for vaccines, immunoglobulins and other protein based therapies.