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Intestinal *Lactobacillus* in health and disease, a driver or just along for the ride?

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Metagenomics and related methods have led to significant advances in our understanding of the human microbiome. Members of the genus *Lactobacillus*, although best understood for essential roles in food fermentations and applications as probiotics, have also come to the fore in a number of untargeted gut microbiome studies in humans and animals. Even though *Lactobacillus* is only a minor member of the human colonic microbiota, the proportions of those bacteria are frequently either positively or negatively correlated with human disease and chronic conditions. Recent findings on *Lactobacillus* species in human and animal microbiome research, together with the increased knowledge on probiotic and other ingested lactobacilli, have resulted in new perspectives on the importance of this genus to human health.

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Introduction

Members of the genus *Lactobacillus* were long thought to be among the most abundant microorganisms in the human gastrointestinal (GI) tract and associated with good intestinal health. Following the development of culture-independent, DNA-sequence analysis methods, the numbers of autochthonous *Lactobacillus* were adjusted to $\leq$1% of the total bacterial population in the distal human gut. One consequence of this change is that the relevance of this genus to human health has come under scrutiny. In contrast, there is increased acceptance of the application of allochthonous probiotic *Lactobacillus* in fermented foods and supplements as probiotics to maintain health and prevent and treat disease [1,2]. Although human studies frequently show a benefit with probiotic administration [3], the importance of intestinal *Lactobacillus* remains under question.

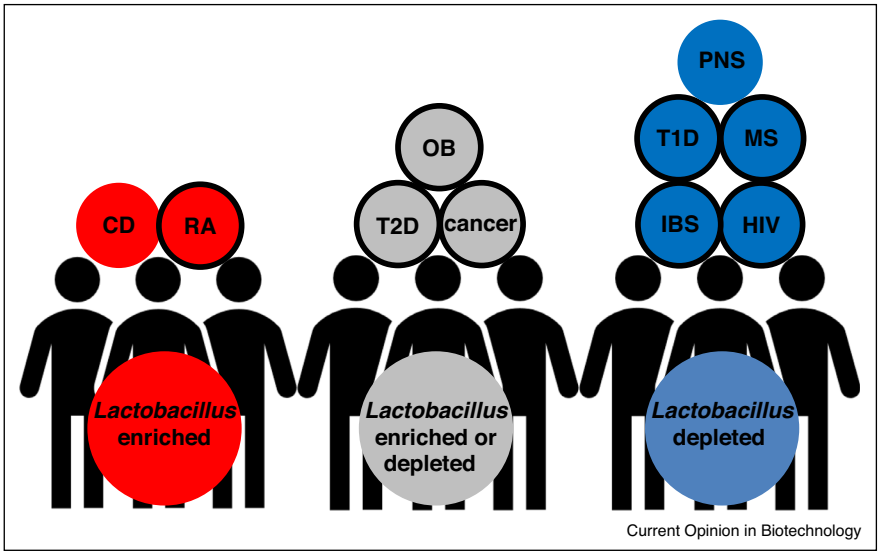
Human disease is increasingly correlated with fecal microbiota composition. Similarly, intestinal bacteria are frequently correlated with numerous other host (genetics, age) and environmental (diet, medication) factors. Such associations have been useful for identifying pathobionts associated with disease as well as taxa such as *Faecalibacterium prausnitzii* and *Akkermansia muciniphila* as beneficial members of the indigenous microbiota. Similarly, a number of recent publications in which culture-independent methods were employed (e.g. 16S rRNA gene amplicon sequencing) identified *Lactobacillus* as being significantly enriched in the distal gut during either health or disease (Figure 1 and Table 1). Because these approaches are largely untargeted, the outcomes provide an unbiased perspective on the relative importance of this genus weighed against other bacterial inhabitants of the GI tract. This review will address findings on the diversity and abundance of intestinal *Lactobacillus* resulting from gut microbiome studies and emerging mechanistic evidence of endogenous and ingested (probiotic) *Lactobacillus* species in the GI tract.

Abundance and diversity of intestinal *Lactobacillus*

Lactobacillus species have been isolated from the entirety of the human GI tract (oral cavity to feces) as well as the skin and vagina [4,5]. This genus is estimated to constitute 6% of the total bacterial cell numbers in the human duodenum [6] and approximately 0.3% of all bacteria in the colon [4] (Figure 2). These levels are similar to the numbers of lactobacilli found in pigs, ranging from 5% to 0.1% of total bacteria in the proximal [7] and distal [8] gut, respectively. *Lactobacillus* was found in higher quantities in rhesus macaques (up to 30% and 10% of all bacteria in the small and large intestine, respectively) [9]. Proportions of *Lactobacillus* in rodent models ranged between 30% and 60% of bacterial numbers in the ileum and approximately 25% in the colon [10,11] (Figure 2). *Lactobacillus* can also dominate the human vaginal microbiota (90 to 100% of total bacteria present) and is found on the skin, but in much lower relative abundance [5] (Figure 2).

Only a few out of the >200 known *Lactobacillus* species have been consistently and repeatedly associated with the human GI tract. Recently, this number was increased to over 50 *Lactobacillus* species that were repeatedly detected in the stools of healthy volunteers [12•]. The

Figure 1



Alteration of intestinal *Lactobacillus* in health and disease. Blue circles indicate *Lactobacillus* is depleted in disease compared to healthy controls. Red circles indicate *Lactobacillus* is increased in disease. Gray circles indicate *Lactobacillus* levels were found to be either increased or decreased with disease, depending on the study. Circles with black edges indicate a benefit for consumption of probiotics for treating disease. CD = Crohn's disease, RA = rheumatoid arthritis, OB = obesity, T2D = type 2 diabetes, IBS = irritable bowel syndrome, T1D = type 1 diabetes, PNS = prenatal stress, HIV = human immunodeficiency virus, MS = multiple sclerosis.

most abundant lactobacilli included *L. casei*, *L. delbrueckii*, *L. murinus*, *L. plantarum*, *L. rhamnosus*, and *L. ruminus*. Some of these species (e.g. *L. rhamnosus* and *L. murinus*) are rarely isolated from environments outside the intestine and are considered gut-autochthonous microorganisms. Other mucosal sites are colonized by distinct species (e.g. *L. crispatus* in the vagina) [13•]. There also appears to be host-specificity among some *Lactobacillus* species, as shown for linages of *L. reuteri* [14].

Infectious disease

Both human immunodeficiency virus (HIV)-infected humans and simian immunodeficiency virus (SIV)-infected rhesus macaques harbor reduced numbers of intestinal *Lactobacillus* [15,16] (Table 1). *Lactobacillus* depletion in rhesus macaques was associated with the loss of gut barrier-promoting T-helper 17 (Th17) cells and increased microbial translocation [16]. The potential of *Lactobacillus* to prevent or reverse intestinal damage during infection was demonstrated with the reduced interleukin-1β-mediated inflammation and improved barrier function upon inoculation of *L. plantarum* directly into ileal loops of SIV+ macaques shortly after SIV infection [17]. The intestinal epithelium in healthy animals responded similarly to *L. plantarum*, consistent with the finding that the ileal transcriptomes of *L. plantarum* were indistinguishable between SIV+ and SIV− animals [18]. In human populations, HIV+ patients on a multi-strain probiotic supplement containing strains of *Lactobacillus* and other genera contained higher numbers of memory Th17 cells in peripheral blood and in the intestine, and histological examination of colonic biopsies indicated increased intestinal barrier function [19].

Several recent animal studies have indicated a broader role for *Lactobacillus* in prevention and resolution of infectious disease. Tryptophan metabolites (indole aldehydes) produced by indigenous *L. reuteri* strains activate host aryl hydrocarbon receptors (AHR) to promote gut and vaginal epithelial barrier and antimicrobial responses required for limiting the expansion of *Candida albicans*, an opportunistic pathogen [20••]. Autochthonous *Lactobacillus* might also have a role in the resolution of infectious disease and recovery of immune homeostasis. Although *Yerstina enterocolitica* infection was cleared from toll-like receptor 1 (TLR1) knockout mice, the intestine was activated toward an inflammatory phenotype and the gut microbiota was enriched with *Desulfovibrionaceae* while containing lower numbers of *Lactobacillus* [21••]. Oral gavage with *L. reuteri* reduced anti-commensal antibodies, innate cytokines, and Th17 responses; thereby ameliorating immune hyper-reactivity [21••]. Conversely, post-*Yersinia pseudotuberculosis* infection lactobacilli were cultured from enlarged gut-associated lymphoid tissue and were associated with chronic lymphadenopathy, indicating that these bacteria might contribute to chronic, immune hyper-reactivity [22].

Irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD)

A meta-analysis of reports investigating the fecal microbiomes from IBS patients and healthy subjects concluded