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Characteristics Of Biological Indicators Of Lactobacilli Providing Their Colonization Resistance Of The Genital Tract Of Women Of Fertile Age

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Abstract

This scientific review expands the understanding of the mechanisms of colonization resistance of the vaginal mucosa by lactobacilli of the female reproductive tract, which are based on adhesion to epithelial cells, the production of lactic acid, hydrogen peroxide and bacteriocins. Changes in these properties of the vagina lead to a disruption of the vaginal normocenosis, which can lead to the onset of gynecological diseases such as colpitis, cervical intraepithelial neoplasia, and cervical cancer.

Keywords: Reproductive tract, microbiota, lactobacilli (LB), bacterial vaginosis (BV), STI (sexually transmitted infections), lactic acid, hydrogen peroxide (H2O2), bacteriocin, adhesion, epithelial cells, glycogen, adhesins.

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1. Introduction

Lactic acid and some other low-molecular metabolites, such as acetic and succinic acids, hydrogen peroxide, and ethanol, synthesized by lactobacilli are non-specific, meaning they are secreted by cells regardless of the growth stage or the presence of foreign bacteria in the environment.

Compared with lactobacilli-dominated vaginal microbiomes, bacterial vaginosis exhibits marked changes in the organic acid metabolite profile. Specifically, lactic acid concentrations decrease significantly, from approximately 110 mM to less than 20 mM, while short-chain fatty acid levels increase significantly: acetic acid from 0–4 to 40–120 mM, propionic acid from less than 1 to 2–4 mM, butyric acid from less than 1 to 2–4 mM, and succinic acid from less than 1 to 20 mM. Additionally, amine levels increase, which may contribute to elevated vaginal pH.[12,8,19]

Vaginal lactic acid is present in the form of L- and D-isomers, primarily produced by lactobacilli; less than 15% of L-lactic acid is synthesized by vaginal epithelial cells. Pure cultures of Lactobacillus crispatus and Lactobacillus gasseri produce both D- and L-isomers, while Lactobacillus iners produces only the L-isomer, and Lactobacillus jensenii produces only the D-isomer. [30].

To maximize the antibacterial properties of lactic acid, lactobacillus-based probiotics need to acidify the vagina to a pH of ≤3.9 to achieve a state in which the protonated form of lactic acid predominates. Unlike H2O2, lactic acid at physiological concentrations , even at pH 4.5, mediates a potent 106 - fold reduction in the viability of

17 different bacteria associated with BV, without affecting the viability of four vaginal Lactobacillus species. spp . [21].

Antimicrobial activity against bacteria that cause sexually transmitted infections is mediated by lactic acid, not H_2O_2. Lactobacillus crispatus and Lactobacillus gasseri produce lactic acid, not H_2O_2, to inactivate Chlamydia trachomatis. [14].

Lactic acid synthesized by lactobacilli stimulates the activation of T-helpers type 17, which belong to the subclass of TH lymphocytes, promotes the maturation of dendritic cells and induces the synthesis of γ-interferon [31].

S. Witkin et al. (2013) showed that women with a predominance of Lactobacillus iners in the vaginal microbiocenosis had low levels of lactic acid, which was subsequently confirmed by laboratory studies and genome analysis of this species [30].

Production of hydrogen peroxide (H2O2)

H2O2 is an oxidizing chemical that is toxic to catalase-negative bacteria, including most anaerobes. It exhibits potent antimicrobial activity in vitro, and colonization with H2O2-producing lactobacilli has been associated with a reduced incidence of bacterial vaginosis, preterm birth, and HIV infection [25]. Until recently, H2O2 was thought to be the primary antimicrobial factor produced by lactobacilli. However, previous studies of H2O2 were conducted under aerobic conditions, despite the hypoxic vaginal environment [17].

The concept of a leading antimicrobial role for H2O2 is not supported by a number of recent data. Under hypoxic conditions typical of the vaginal environment, lactobacilli produce extremely low amounts of H2O2 or do not synthesize it at all. Furthermore, hydrogen peroxide is effectively neutralized by the pronounced antioxidant properties of cervicovaginal fluid and semen. Physiological concentrations of H2O2 do not have bactericidal activity against microorganisms associated with bacterial vaginosis; moreover, exogenous administration of H2O2 has a more pronounced negative effect on the viability of vaginal lactobacilli than on bacteria associated with bacterial vaginosis [22].

Lactobacilli capable of synthesizing H2O2 effectively prevent colonization of the vagina by microorganisms such as Prevotella bivia , Prevotella disiens , and Mobiluncus spp., which play a significant role in the development of vaginal microflora disorders. In the presence of myeloperoxidase, the viability of Gardnerella vaginalis decreases approximately 2000-fold. In women with vaginal dysbiosis, lactobacilli are detected in only 35% of cases, and only 11% of them contain strains that produce hydrogen peroxide, while in 96% of healthy women, all isolated lactobacilli are H2O2-producing. The sensitivity of microorganisms to the action of hydrogen peroxide is determined by a number of factors, including the level of metabolic activity, catalase activity of bacteria, as well as changes in the pH of the environment and other conditions [7].

It has been established that the presence of lactobacilli producing high levels of hydrogen peroxide is associated with a low incidence of bacterial vaginosis, premature birth and postpartum infectious complications [29].

Early clinical studies demonstrated that women with a dominant H_2O_2-producing lactobacilli population have a lower risk of developing a dysbiotic microbiota. These data indirectly suggest that the protective effect may be due to the presence of a vaginal microbiota predominantly represented by Lactobacillus spp., such as Lactobacillus crispatus , which is capable of synthesizing H_2O_2 under aerobic conditions [9].

So, Lactobacillus crispatus produce more hydrogen peroxide than other LB species and are therefore thought to contribute to the stability of normal vaginal microflora [24].

Bacteriocins

Bacteriocins are ribosome-synthesized peptides with antimicrobial activity against gram-positive and gram-negative bacteria, as well as some fungi. Unlike classical antibiotics, they are formed on ribosomes and have a relatively narrow spectrum of activity [26].

Depending on the spectrum of activity against target bacteria, lactobacilli bacteriocins are divided into two groups. The first group includes compounds with a narrow spectrum of action that cause the death of organisms similar to the producer strain. These include lactocin B and F27, amilovorin, pediocin N5P, thermophilin A, curvacin A, amilovirin L471, and enterococcin [26]. Bacteriocins of the second group have a broad spectrum of activity, inhibiting the growth of various gram-positive microorganisms, including Listeria monocytogenes , Clostridium botulinum , Clostridium sporogenes , Staphylococcus aureus ,

Pediococcus acidilactici , Bacillus spp., and Enterococcus faecalis . This group includes pediocin A, acidocin B, diacetin B1, curvacin FS47, lacticin 3147, plantiricin C, enterococcin, salivaricin, nisin, sarcacin 674 and mutacin [5].

In lactobacilli, bacteriocin synthesis is controlled by a complex of genes located on plasmids or within the chromosome. A characteristic feature of bacteriocins is that their production is generally inducible: it occurs only at a certain stage of population development or in the presence of competing bacteria of a different species or strain. In some cases, bacteriocin synthesis is regulated by a peptide inducer and is initiated only after its concentration in the medium reaches a certain threshold [2].

The introduction of prebiotics such as oligosaccharides into the medium can promote increased bacteriocin production.

The synthesis of bacteriocins by members of the normal microbiota is considered one of the mechanisms of quorum sensing, which ensures interbacterial communication, coordination of activity, and synchronization of collective behavior through the secretion of diffusible signaling molecules [13]. Strains producing "weak" bacteriocins gain the greatest advantage for survival in the biotope: their lower toxicity to competitors causes only moderate induction of bacteriocin expression in other microorganisms, which facilitates the formation of controlled competition and the maintenance of dynamic equilibrium in the population. This circumstance may also explain the predominance of producers of weak bacteriocins in natural microbial communities [20].

Among the bacteriocins actively used in modern applied research, plantaricin, lactocin and others are particularly distinguished.

Table 1 presents the types of LB and the bacteriocins they produce.

Table 1

Name of bacteriocin	Type LB
Helveticin	*L. helveticus*
Lactobrevina	*L.brevis*
Bulgaricin	*L.bulgaricus*
Lactocins B , F , G , M	*L. acidophilus*
Plantaricin	*L. plantarum*
Gasserin	*L.gasserii*
Salivaricin	*L.salivarius*

The ability to synthesize bacteriocin and resistance (immunity) to them is controlled by plasmids.

Bacteriocins are characterized by resistance to high temperatures and maintain activity over a wide pH range. They are colorless and odorless. At low concentrations, these peptides are capable of forming pores in cell membranes. However, bacteriocins are susceptible to degradation by proteolytic enzymes. [11].

Adhesion

The vaginal biocenosis is a complex microecosystem, the characteristics of which are determined not only by the composition of the microflora but also by the anatomical features of the vagina, the histological structure of its mucous membrane, and the biological properties of vaginal secretions. The vaginal mucosa is lined with stratified squamous nonkeratinized epithelium, devoid of glands, and comprises several cell layers: basal, parabasal, intermediate, and superficial. During cytolysis of the superficial epithelial cells, glycogen is released

from the cytoplasm and serves as a nutrient substrate, providing the energy and plastic needs of normal vaginal microflora [23].

Studies show that only rare lactobacilli strains have the ability to ferment glycogen, but this ability is enhanced in the presence of human serum containing glycogenase. It is possible that most vaginal lactobacilli access carbohydrates through the physiological enzymatic breakdown of the polysaccharide by tissues or other organisms [2].

The maximum thickness of the vaginal epithelium is observed during high estrogen levels—in women of reproductive age, mid-menstrual cycle. During this period, the cell cytoplasm contains large amounts of glycogen. During the menstrual cycle, due to fluctuations in sex hormone secretion, periods of lactobacilli dominance alternate with periods of Gardnerella and Bacteroides predominance [1].

Bacterial adhesion to epithelial cells is a complex, multifactorial process involving both nonspecific physicochemical interactions and specific contacts between complementary molecules on cell surfaces. Bacteria with high adhesion capacity, compared to low-adhesion strains, more effectively stimulate the phagocytic activity of immunocompetent cells involved in the immune response. These factors, taken together, have a beneficial effect on the growth and development of the organism as a whole, increasing its resistance to infectious agents and promoting growth. During adhesion, lactobacilli select structurally normal epithelial cells located in the superficial layers of the mucous membrane; they “bypass” cells that are completely ready to be shed into the vaginal lumen and have already lost their nuclei [27].

The high adhesive capacity of lactobacilli to epithelial cells is ensured by the action of adhesins, which in representatives of the genus Lactobacillus can be represented by teichoic and lipoteichoic acids of the cell wall [3], exopolysaccharides with affinity for enterocyte receptors [32], as well as a complex of cell surface proteins [6]. In endogenous lactobacilli, adhesive properties are expressed to a greater extent compared to exogenous strains. By fixing on the surface of epithelial cells, lactobacilli form a continuous protective layer that prevents the attachment of other microorganisms to epithelial cell receptors and thereby ensures colonization resistance [4].

Lactobacillus iners possesses specific adhesive properties. This species is capable of adhering to epithelial cells and partially persisting in the presence of microorganisms associated with bacterial vaginosis due to its interaction with fibronectin, a glycoprotein on the surface of epithelial cells. It is difficult to displace even by pathogens. L.iners does not prevent the development of dysbiosis and, in some cases, can enhance the adhesion of pathogens. In vitro studies have shown that L.iners promotes the strengthening of the bond between cervical epithelial cells and Gardnerella vaginalis, a phenomenon not observed with other lactobacilli. In practice, this explains why CST-IV often develops into a state of bacterial vaginosis. [9].

Protein adhesion factors of lactobacilli are encoded by various genes localized both on chromosomes and on plasmids, which provides cells with the ability to adapt to interaction with the surface molecules of epithelial cells [7].

According to M.H. Coconier et al. [10], adhesion of Lactobacillus acidophilus is mediated by cell wall exopolysaccharides and is initiated by a promoting factor—a protein substance that is an exometabolite. The mucus binding domain (MBD) protein structures responsible for adhesion to mucin have been isolated and studied in nine species of lactic acid bacteria. The most complete MBD domains have been found primarily in intestinal lactic acid bacteria [16].

Due to their tight attachment to epithelial cells, lactobacilli are able to form their own biofilms, which prevents pathogen adhesion and protects cells from the damaging effects of infections. Both endogenous and exogenously introduced strains compete for "space" on the epithelium. For example, Lactobacillus acidophilus can displace Gardnerella vaginalis , Atopobium vaginae , Escherichia coli , and Staphylococcus aureus from the surface of genital tract cells, while Lactobacillus gasseri can displace G. vaginalis and Prevotella bivia. [28].

The molecular mechanisms that mediate lactobacilli adhesion to vaginal epithelial cells have not yet been fully elucidated. It is believed that lactobacilli adsorption is specific and is determined by the matching of receptors of a particular lactobacilli strain to receptors of the vaginal epithelial cells of a particular woman [15].

2. Conclusions

Increased interest in the status of lactobacilli in recent

years, including the morphological description of species in this group, requires systematization of existing knowledge—from a detailed study of the molecular mechanisms of genetic information transfer to their application in biotechnology and medicine.

In the process of adaptation to specific habitat conditions, lactic acid fermentation bacteria lost the ability to synthesize many metabolites, but acquired properties that ensure the effective colonization of their ecological niche, for example, the vagina, and competitiveness in it.

According to the data presented, all species of this genus that colonize the female reproductive tract are capable of producing bacteriocins, hydrogen peroxide, and lactic acid (D- and L-isomers).

It is the activity of these metabolites that determines the degree of strain antagonism and shapes the nature of interbacterial interactions.

Studying the biological properties of the identified endogenous lactobacilli species will enable the development of recommendations for the creation of local probiotics that meet modern requirements.

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