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REVIEW

Targeting gut microbiota as a possible therapy for mastitis

Xiaoyu Hu[1] · Shumin Li[1] · Yunhe Fu[1] · Naisheng Zhang[1]

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Abstract

Mastitis, a disease that affects both dairy herds and humans, is recognized as the most common source of losses in the dairy industry. Antibiotics have been used for years as the primary treatment for mastitis. However, abuse of antibiotics has led to the emergence of resistant strains and the presence of drug residues and has increased the difficulty of curing this disease. In addition, antibiotics kill most of the microbes that are present in the digestive tract, leading to imbalances in the gut microbiome and destruction of the ecosystem that is normally present in the gut. Gut microbiota play an important role in the host's health and could be considered the "second brain" of the body. In recent years, the gut microbiota and their metabolites, including lipopolysaccharide (LPS) and short-chain fatty acids (SCFAs), have been shown to participate in the development of mastitis. LPS is the main component of the cell walls of gram-negative bacteria. Overproduction of rumen-derived LPS injures the rumen epithelium, resulting in the entry of LPS into the blood and damaged liver function; once in the blood, it circulates into the mammary gland, increasing blood-barrier permeability and leading to mammary gland inflammation. SCFAs, which are produced by gut microbiota as fermentation products, have a protective effect on mammary gland inflammatory responses and help maintain the function of the blood-milk barrier. Recently, increasing attention has been focused on the use of probiotics as a promising alternative for the treatment of mastitis. This review summarizes the effects of the gut microbiome and its metabolites on mastitis as well as the current of probiotics in mastitis. This work may provide a valuable theoretical foundation for the development of fresh ideas for the prevention and treatment of mastitis.

Keywords Gut microbiota · LPS · SCFAs · Blood-milk barrier · Mastitis

Introduction

Mastitis, a type of inflammation that occurs in the mammary gland, can be induced by mechanical irritation, microbial infection, and chemicophysical injury, and is a highly prevalent disease in dairy cows and humans. Mastitis is considered extremely important to the dairy industry worldwide because it causes economic losses due to reduced milk production, discarded milk, decreased likelihood of conception, premature culling, and treatment costs [40]. It is estimated that 15% of milk production per cow is lost due to the effect of mastitis [98]. In addition, mastitis is also a serious animal welfare issue because it is associated with pain, reduced well-being, and behavioral changes in the affected animals [73]. Antibiotics have long served as a major tool in the treatment of mastitis, but the cure rate is not very high, and side effects often occur. Thus, detailed knowledge of mastitis and identification of an effective solution to address the issue of how to prevent and treat mastitis is urgently needed to safeguard economic benefits within the dairy farming industry.

Gut microbiota, which are present in a large variety and in huge quantity, are an essential part of animals. The symbiotic relationship between host and bacteria is maintained by a highly intricate and extensive ecosystem [41, 59]. After Gordon found that gut microflora influence fat conservation, it was gradually realized that perturbations in gut microbiota not only contribute to intestinal disease but are also closely associated with certain metabolic illnesses such as diabetes, non-alcoholic fatty liver disease, colitis, obesity, and other diseases [39, 57, 123, 126]. A precious study showed that gut microbiota plays a protective role in chickens infected with influenza virus subtype H9N2

✉ Yunhe Fu
fuyunhesky@sina.com

✉ Naisheng Zhang
zhangns@jlu.edu.cn

Shumin Li
li.812275953@qq.com

[1] Department of Clinical Veterinary Medicine, College of Veterinary Medicine, Jilin University, Changchun 130062, Jilin Province, People's Republic of China

[128]. In addition, a significantly lower abundance of gut microbiota was observed in patients during the course of infection with Shiga toxin–producing *E. coli* (STEC) [32]. Furthermore, another study showed that gut microbiota protect against pneumonia induced by *Streptococcus pneumoniae* [97], suggesting that there may be a relationship between gut microbiota and infectious diseases such as mastitis. Many subsequent studies have proven that gut microbiota play a role in mastitis through their metabolites such as lipopolysaccharide (LPS) [48, 134] and short-chain fatty acids (SCFAs) [117, 118]. Rumen-derived LPS crosses the rumen epithelium and enters the bloodstream, subsequently passing through organs and tissues all over the body [35]. During the lactation stage, a great deal of the LPS in the blood enters the mammary gland, finally leading to mammary gland inflammation [134]. SCFAs, which are produced by bacterial fermentation of dietary fiber in the gut, have anti-inflammatory property; they have been shown to inhibit the production of pro-inflammatory cytokines and to decrease the pathological damage in mammary gland induced by LPS [118].

Sophisticated as an organism is, sophisticated coordination among tissues and organs ensures a well-arranged environment inside the body. In specialized compartments of the body, the movement of molecules between the blood and tissues is hindered by the so-called gatekeepers or barriers [96] such as the blood-milk barrier [120]. The commensal microflora provides the host with a barrier against the invasion of pathogens through maintaining the blood-milk barrier [103]. Evidence shows that changes in the gut microbiota can result in proliferation of specific pathogenic bacteria that produce higher levels of LPS within the digestive tract and that these bacteria then enter the mammary gland [132]. In addition, injecting LPS into the mammary gland decreases the threshold for PMN to cross the blood-milk barrier, triggering substantial PMN accumulation in the mammary gland [56]; this is clinically manifested as elevated SCC (somatic cell count) and increased susceptibility to mastitis. SCFAs are the most important energy source for the blood-tissue barrier [49]. Treatment with SCFAs was shown to inhibit the changes in the blood-milk barrier induced by LPS though regulating changes in associated tight junction proteins or HDACs [117, 118].

This review focuses on our current understanding of the role of the gut microbiota, especially its metabolites LPS and SCFAs, on the development of mastitis and on the role of probiotics in the treatment of mastitis. It may very well lead to a new approach to preventing and treating mastitis through modulation of the gut microbiome. It is hoped that this theory will also offer new insight into dealing with other infectious diseases.

Sources and species of milk microbiota

Milk is a highly nutritious food that can be obtained from mammals, including cows, goats, and humans. It has long been thought that the mammary gland is naturally free of resident bacteria and that the milk produced by a healthy mammary gland is germ-free; the observation that breast milk contains microorganisms was originally attributed to contamination by skin bacteria from the mother's areola or bacteria present in the oral cavity of the offspring [116]. The use of traditional culture-dependent methods proved that the bacteria found in mammary gland teats belong to four main phyla, *Firmicutes* (76%), *Proteobacteria* (17.8%), *Actinobacteria* (4.9%), and *Bacteroides* (1.3%). In addition, the phyla *Planctomycetes*, *Verrucomicrobia*, *Cyanobacteria*, *Chloroflexi*, and unclassified bacteria were found by a clone library sequencing-based method to be present at low levels. In addition, some bacteria, such as *Solobacterium*, *Clavibacter*, and *Arcanobacterium* spp., were detected on the teat surface but were found in milk [114]. Raw cow's milk has the potential to contain a large number of bacteria, including a significant LAB population that includes *Lactococcus*, *Streptococcus*, *Lactobacillus*, *Leuconostoc*, and *Enterococcus* spp. [24, 70]. Using a high-throughput DNA sequencing method, Masoud et al. identified a total of 256 bacterial species in milk: among these, *Streptococcus thermophiles* and *Lactococcus lactis* dominated, representing 43.7% and 19% of reads, respectively. Other microbiota in the milk, including *Acinetobacter*, *Aeromonas*, *Brevibacterium*, *Corynebacterium*, *Lactobacillus*, *Pseudoalteromonas*, *Pseudomonas*, and *Staphylococcus*, represented between 1.3 and 3.7% of the reads [71].

Over the last few years, however, with the development of detection methods based on more sensitive molecular methods of microbial identification, the theory that the healthy udder is germ-free has been challenged. In particular, the application of molecular DNA analysis has yielded results suggesting that commensal microbial communities exist within every mammary gland, healthy or not [81]. This may explain why some studies have found that some bacteria including *Lactococcus*, *Lactobacillus*, and *Enterococcus* as well as *Leucobacter*, *Deinococcus*, and *Paracodus* are present in milk but are not detected in the environment [112]. *Bifidobacteria*, a strict anaerobe, was present in milk, but it could not survive in the skin and is an unlikely source. In addition, microbiota from the mother's intestine are also found in breast milk [45]. These findings suggest that microbiota present in other anatomical locations may enter the mammary gland in some way. Importantly, several studies have demonstrated the existence of an entero-mammary pathway through which some intestinal luminal microbiota are transported to the mammary gland through the mesenteric lymph nodes [86].

Although the detailed mechanism by which microbiota cross the intestinal barrier and reach the mammary gland has not been completely clarified, it is likely that immune cells, especially dendritic cells (DCs), are involved in the translocation of gut bacteria into breast milk [89]. DCs are able to take up nonpathogenic bacteria from the gut and subsequently

carry them to the lactating mammary gland by opening the tight junctions between enterocytes without damaging the integrity of the epithelial barrier [25, 89]. Generally, the presence of occludin in DCs may be sufficient to loosen the epithelial tight junctions, and this destabilization is followed by the rapid formation of new junctions between the epithelial and the infiltrating DCs. When stimulated by target bacteria, DCs are recruited from the blood and are activated. They then upregulate the expression of occludin and distribute it to the cell surface and dendrites. This allows DCs to compete for epithelial occludin and open tight junctions. The infiltrating DCs then face the gut lumen and can directly sample bacteria [89]. DCs can retain live gut bacteria for several days and carry them to the mesenteric lymph nodes by passing through the lymphatic circulation; these bacteria can then be spread to distant organs, including the lactating mammary gland [67, 113]. In addition, research has suggested that the changes in hormone levels that occur in the later stages of pregnancy and during early lactation affect the expression of enterocyte tight junctions, leading to the taking up of gut microbiota by the mother due to an increasingly permeable intestine. These migrant gut bacteria are engulfed by lymphoid cells that home to the engorged breast and enter the milk, from which bacteria are released. There is evidence that numerous circulating lymphoid cells containing engulfed bacteria are present in lactating mothers, and labeled bacteria placed in the gut of lactating rodents were found in the animals' breast milk [116]. In addition, the blood circulation was involved in the transfer of cells from gut-associated lymphoid tissue to the mammary gland. The bacteria and their genetic material were present in peripheral blood mononuclear cells and breast cells and were found in human lactation breast milk [25]. In addition, many studies have reported that live lactic acid bacteria are present in the blood of human subjects [47, 82]. Other studies have suggested that isolated *Lactobacillus salivarius* CECT 5713 and *Lactobacillus gasseri* CECT 5713 found in human milk have the ability to translocate across a Caco-2 cell monolayer mediated by DCs [91]. After pregnant mice received a labeled *Enterococcus faecium* M1a strain, this bacterium was isolated from milk samples [92].

Some recent studies have focused on the source of milk microbiota in ruminants. Using culture-independent methodology, the author tested the microbial composition and diversity of organisms derived from the milk, blood, and feces of healthy lactating cows. The results showed that *Ruminococcus*, *Bifidobacterium*, and the *Peptostreptococcaceae* family were present in all three types of samples from the same animals [129]. In addition, the results of a study comparing the microbial communities present in blood, feces, and uterine samples from the same cows at 0 and 2 days postpartum using deep sequencing and qPCR showed that major uterine pathogens such as *Bacteroides*, *Porphyromonas*, and *Fusobacterium* were some of the core genera present in blood and feces and in the vagina. In addition, uterine pathogens showed a strong and significant interaction with each other in the network of blood microbiota. These data indicate that blood harbors a unique microbiome that includes the main uterine pathogens and blood maybe as a route of transmission of uterine pathogens from the gut to the uterus in cows [44]. This evidence supports the existence of an endogenous entero-mammary pathway in ruminants; however, the detailed mechanism by which bacteria are transported to the circulation and to the mammary glands of ruminants is not clear.

Rumen microbiota

The rumen, the first compartment of the digestive tract of ruminants, is a very important digestive organ, and it contains a large amount of microbiota. The rumen microbiota are necessary for the proper physiological development of the rumen and for the animal's ability to digest and convert plant mass into food products; they also participate in the development of many diseases, making them highly significant to the host [43]. Thus, it is necessary to understand the changes in rumen microbiota that occur during an animal's lifetimes. During the first week after a calf's birth, the relative proportions of the rumen are considerably smaller than those in the adult, and the rumen lacks some of its functional components. Thus, it is considered nonfunctional at this time. With the growth of the calf, the volume and function of the rumen gradually increase, and these changes are accompanied by development of the rumen microbiota [10, 53]. One study showed that the major bacteria present in the rumen of newborn calves are aerobic and facultative anaerobic microbial taxa. Subsequently, these bacteria are gradually replaced by exclusively anaerobic taxa when the animal is between 6 and 8 weeks of age. Recently, Jami et al. [43] used 16S rRNA to identify and characterize the overall bovine ruminal bacterial populations in 1-day-old calves to 2-year-old cows. Of the 15 phyla detected in the samples, *Firmicutes*, *Bacteroidetes*, and *Proteobacteria* were the dominant phyla regardless of the age of the animals. The percentage and composition of phyla in animals of different ages varied considerably, as shown by the fact that *Firmicutes* were more abundant in 1–3-day-old caves than in animals of other ages; the vast majority of the reads belonged to the genus *Streptococcus*. The *Firmicutes* decreased in the 2-month-old animals and gradually increased as the animals increased in age. The phylum *Bacteroidetes* was less abundant in 1–3-day animals than in older animals. Of the minor phyla present in the tested animals, *Actinobacteria* and *Fusobacteria* were present in animals of all ages and were more abundant in 1–3-day-old calves. Other phyla, including *Tenericutes*, *Cyanobacteria*, and TM7, were present in higher percentages in older animals than in newborn animals (Fig. 1) [43]. Li et al. also characterized the rumen

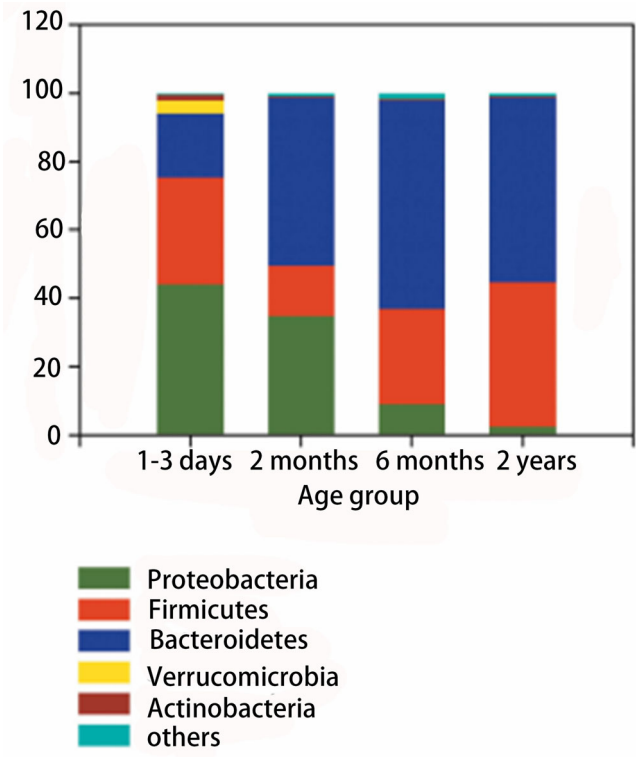

Fig. 1 Phylum level composition. Color-coded bar plot showing the average bacterial phylum distribution in the different age groups sampled

microbiota of pre-ruminant calves fed milk replacer using pyrosequencing of hypervariable V3–V5 regions of the 16S rRNA gene and a whole-genome shotgun approach. In total, 15 bacterial phyla were detected in the rumen microbiota of 42-day-old animals. Among these, *Bacteroidetes* was the dominant phylum (74.8%), followed by *Firmicutes* (12.0%), *Proteobacteria* (10.4%), *Verrucomicrobia* (1.2%), and *Synergistetes* (1.1%). In rumen samples from 14-day-old animals, 170 bacterial genera were detected, while 45 genera were found in the core microbiome of pre-ruminant animals [63]. The composition of the ruminal microbiota of cows in early (76 to 82 days milk [DIM]), middle (151 to 157 DIM), and late (251 to 257 DIM) lactation has also been studied. The major phyla in the rumen of all groups were similar to those found in previous studies and included *Bacteroidetes* (49.42%), *Firmicutes* (39.32%), *Proteobacteria* (5.67%), and *Tenericutes* (2.17%); the most abundant genera included *Prevotella* (40.15%), *Butyrivibrio* (2.38%), *Ruminococcus* (2.35%), and *Coprococcus* (2.29%) as well as *Succiniclasticum* (2.28%). In addition, lower-efficiency cows (low GFE, high RFI) harbored a higher percentage of *Anaerovibrio* and *Butyrivibrio*, and more efficient cows (high GFE, low RFI) possessed total ruminal communities with a higher abundance of *Coprococcus* [46]. A similar study showed that *M. elsdenii*, *C. catus*, and *Lachnospiraceae* are more abundant in the microbiomes of efficient animals; these organisms are a source of the valuable SCFAs propionate and butyrate [11]. In addition, yaks (*Bos grunniens*) and Tibetan sheep (*Ovis aries*) possess adaptations for living in a high-altitude environment. Characterization of the rumen microbiomes of these animals has shown that the VFA-yielding pathway markedly enriched in high-altitude ruminants, as shown by significant upregulation of the expression of rumen microbial genes associated with VFA transport [136].

The effect of gut-derived LPS on the mastitis

The effect of gut-derived LPS on the mammary gland inflammatory response

Mastitis is one of the most prevalent diseases of cows, especially high-yield ones. In clinical practice, mastitis has been found to occur in cows at a high frequency during the early and peak lactation period. To make it possible to harvest better dairy products, dairy cows used in the dairy industry are always fed a highly concentrated diet. However, the use of concentrated feed may alter the composition and quantity of the ruminal microbiome; in other words, it may perturb the gut microbiota.

LPS, one of the main elements of the cell walls of gram-negative bacteria, is an important factor that induces inflammation. Because a large number of gram-negative bacteria are present in the gut, the gut microbiota constitute a huge reservoir of this endotoxin [29, 78]. Many studies have focused on exploring the mechanism of LPS-induced inflammation. Long-time feeding HC diet often results in lower ruminal pH, which may lead to subacute ruminal acidosis (SARA) [58]. A number of signs of SARA in dairy cows, including inflammation, the presence of an acute phase response, laminitis, and liver abscesses, have been attributed to the translocation of free LPS in gram-negative bacteria from the digestive tract to the interior circulation [35, 87]. In addition, one study showed that translocation of LPS from the gastrointestinal tract into the bloodstream could induce a systemic inflammatory response that activated the TLR4 signaling pathway and was accompanied by chromatin decompaction and demethylation of the proximal TLR4 promoter [18]. It is widely known that the liver is the main site for clearance of circulating LPS [33]. In animals undergoing a systemic inflammatory response induced by feeding of an HC diet, the hepatic clearance rate of LPS was elevated, but the percentage of removed LPS decreased, accounting for an increase in the total entry of LPS into the liver [17]. Furthermore, crossing of rumen-derived LPS into the bloodstream increases the levels of the inflammatory cytokines TNF-α, IL-1β, and IL-6 in peripheral blood after long-term feeding of an HC diet to dairy cows. The increased levels of LPS in the portal and hepatic veins further injure the hepatocytes and inhibit liver function,

as shown by increases in the levels of TNF receptor–associated factor 6 (TRAF6), p-NF-κB, p38 MAPK, IL-1, and serum amyloid A (SAA) in the liver [35].

The rumen epithelium serves as an important biological barrier of immunity and acts as an important line of defense. Its main function is dependent on the rumen epithelium's multicellular structure, which includes the stratum corneum, the stratum granulosum, the stratum spinosum, and the stratum basale, as well as on the tight junctions that exist in the stratum granulosum [34]. It is indicated that in ruminants fed HC diets, there is an increase in the level of the immunogenic compound LPS and abnormal depression of pH in the rumen, leading to damage to the expression or function of the rumen epithelium [85]. When the integrity of the rumen epithelium is damaged, LPS in the rumen or pathogenic bacteria attached to the rumen epithelium may translocate across it, further leading to a systemic inflammatory response [50]. Evidence for diet-induced systemic inflammation is associated with the HC diet–induced disruption of rumen epithelial barrier function [64] as well as with increased permeability of the rumen epithelium [54], which allows microbes and immunogenic compounds to enter the portal circulation [50] and further leads to systemic inflammation [135]. To study the mechanism through which feeding of an HC diet increases the permeability of the rumen epithelium, the author used GO to analyze the identified DEGs. The results showed that feeding of an HC diet induced the expression of genes associated with inflammation and that the levels of inflammatory genes, including IL-1β, IL-2, IL-22, CCL19, CCL8, CX3CR1, CXCL6, INHBE, LEPR, PRL, and TNFRSF9, were significantly increased in rumen epithelium. The level of LPS was also increased by feeding an HC diet. Increased levels of LPS are closely connected with the inflammatory response of the rumen epithelium, as shown by the fact that LPS treatment increased the expression of TNF-α, IL-8, and IL-6 [135]. Rumen epithelial bacteria are directly attached to the rumen epithelium and are thought to be important for adaptation to the daily diet. Studies in which PCR-DGGE was used showed that HC feeding changed the composition of the epithelial microbiota, increased the proportion of *Bacteroidetes*, and reduced the proportion of *Firmicutes*, changes that are associated with damage to the rumen epithelium [94]. Recent studies demonstrated that feeding mice a high-fat diet could lead to increased serum LPS, resulting in mammary gland inflammation [104]. Other studies showed that rumen-derived LPS increased the levels of pro-inflammatory cytokines TNF-α, IL-1β, IL-6, and IL-8, and TLR4, NF-κB in the mammary gland during long-time feeding of a high-concentrate (HC) diet in cow [134], and increased the SCC in the cow mammary gland [48]. In our study, we also found that the serum LPS level was significantly increased in gut microbiota–depleted mice compared with that in wild-type mice. Fecal microbiota transplantation (FMT) to the gut of microbiota-depleted mice reversed this change. Changes in LPS levels were associated with changes in mammary gland inflammation. These unpublished results suggest that the development of mastitis in mice whose gut microbiota had been depleted was due in part to increased LPS levels.

These data suggest that changes in feeding or other stress factor lead to disturbances in the rumen microbiota. Changes in rumen microbiota cause the levels of LPS to increase significantly and lead to changes in the permeability of the rumen epithelium that allow LPS to pass through and enter tissues and organs via the bloodstream. The liver is the main organ responsible for the removal of LPS from the circulation. However, overproduction of LPS damages liver function and promotes the entry of LPS into the circulatory system through capillaries in tissues and organs, leading to chronic low-grade inflammation. Increased dairy production after birth increases blood flow; consequently, much more LPS enters the mammary gland, bringing about inflammation and increased susceptibility to mastitis [50].

The effect of gut-derived LPS on blood-milk barrier permeability

Dairy products harvested from cows suffering from mastitis contain increased somatic cell numbers (SCCs); SCC is the gold standard for the clinical diagnosis of mastitis as well as a reliable indicator of dairy quality [26]. Increased SCC corresponds to a reduction in the quantity and quality of dairy products. Based on previous research, the entry of a large volume of neutrophils (PMN), a major component of SCC, into mammary acini is the predominant reason for the elevation in SCC that occurs after infection of the mammary gland [83]. Therefore, the amount of PMN accessing mammary acini plays a paramount role in determining the severity and prognosis of mastitis. PMN must pass through the blood-milk barrier, which is made up of the vascular endothelium and the mammary epithelium, while crossing from the bloodstream to milk, a process that is under the control of the blood-milk barrier [133]. Disruption of the blood-milk barrier lowers the threshold against PMN crossing so that excessive numbers of PMN enter the mammary acini when the mammary gland has been irritated by pathogens. These PMN release high levels of inflammatory cytokines, leading to cytokine storm, the production of reactive oxygen free radicals, the activation of proteases, and consequent damage to the mammary gland [121] (Fig. 2).

The main components of the blood-milk barrier are tight junction proteins. These proteins form a specialized structure in the top membrane of the mammary epithelium; the structure is located between the mammary acini and controls the inward and outward passage of water molecules, ions, and bacteria [125, 137]. Various components, including occludin, zonula occludens-1 (ZO-1), and junctional adhesion molecules, make up the tight junctions present in mammals [61]. The blood-milk barrier, the blood-brain barrier (BBB), and the blood-

testis barrier (BTB) share similar structures and functions. Some evidence suggests that the gut microbiota play an important role in the development of blood-tissue barriers such as BBB and BTB [15, 38, 74]. The maturation of the BBB and the BTB occurs slowly in germ-free mice and is accompanied by low expression of the tight junction proteins that constitute the BBB and BTB, such as claudin-5, occludin, and ZO-2. Fecal transplantation from healthy mice to germ-free mice increases the expression of these proteins [3, 15]. Research has shown that gut microbiota dysbiosis allows more LPS to enter the blood and that the expression of proteins relevant to tight junctions can be hindered by LPS, which finally devastates the blood-brain barrier [56, 117, 118]. When mastitis occurs in goats, cows, and other animals, the composition of occludin is altered, resulting in damage to the integrity of tight junctions [21]. In a mouse mastitis model, injection of LPS into the mammary gland was shown to cause changes in the expression of claudin-1, claudin-3, claudin-4, and claudin-7 that weaken the blood-milk barrier and lower the threshold for PMN crossing [56]. Our laboratory has assessed the effects of gut microbiota on blood-milk barrier permeability. The results demonstrated that the level of LPS was significantly increased in gut microbiota–depleted mice compared with wild-type mice, and these changes were accompanied by reduced expression of the tight junction proteins claudin-3 and occludin. However, administration of FMT to gut microbiota–depleted mice increased claudin-3 and occludin levels. FITC-albumin is an important factor that is used to evaluate the permeability of the blood-milk barrier [56]. We also tested the distribution of FITC-albumin in the alveolar lumen. We found that increased levels of LPS in microbiota-depleted mice caused increased distribution of FITC-albumin in the alveolar lumen and that FMT treatment of gut microbiota–depleted mice reversed these changes (unpublished observations). It is suggested that the increased levels of LPS caused by imbalances in the gut microbiota are closely associated with the function of the blood-milk barrier.

The role of SCFAs produced by gut microbiota on mastitis

The role of SCFAs produced by gut microbiota on mammary gland inflammatory response

Non-digestible carbohydrates, including cellulose, xylans, resistant starch, and inulin, are fermented to prove energy for the growth of microbiota and for the production of end products such as SCFAs [60, 108]. SCFAs are 1–6 carbons in length and are produced by fermentation of dietary fiber by the gut microbiota to butyrate, acetate, and propionate [2, 107]. It is well known that SCFAs provide approximately 70% of the energy source for ruminants, and they also serve as an important component of bovine milk [4, 42]. Although it has not been definitively determined through extensive bacterial isolation and metagenomics studies, some reports suggest that species differ greatly in their genetic makeup with respect to the enzymes that participate in SCFAs production [8, 20].

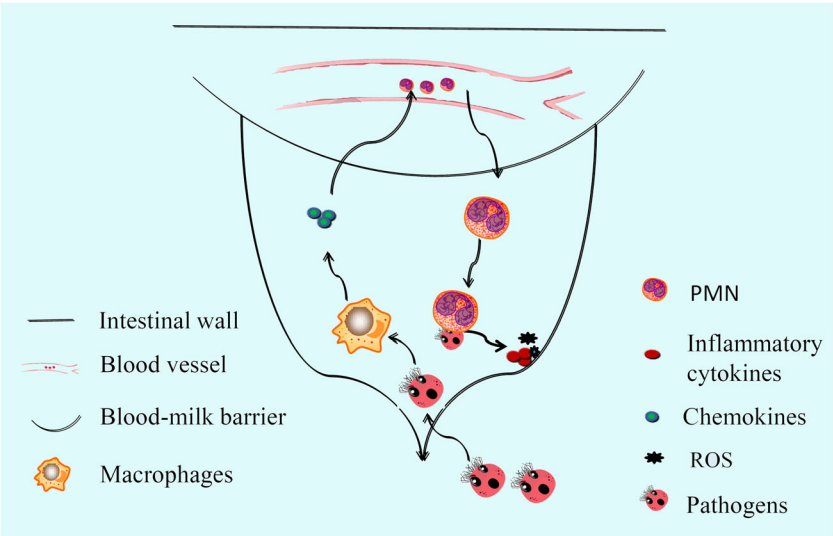

Fig. 2 The development of mastitis induced by pathogens. When pathogen escapes the defenses of the mammary gland teat, it enters the mammary gland and moves toward the milk pool. Macrophages are the primary immune cells that mediate the inflammatory responses of the body. They first contact and recognize the invading pathogen and then produce a large number of chemokines and some inflammatory cytokines. These further induce the accumulation of a large number of PMN in the infected mammary gland. In addition, these PMN release a large number of inflammatory mediators and ROS while removing pathogenic bacteria, leading to an inflammatory reaction in the mammary gland (mastitis). Importantly, to enter the mammary gland, PMN in the blood must cross a very important physiological barrier structure, the blood-milk barrier

Acetate is the main product produced by enteric and acetogenic bacteria, and it is produced at higher levels than propionate and butyrate [75]. Propionate is produced from sugar molecules such as pentoses, hexoses, and rhamnose by three pathways, i.e., the succinate, acrylate, and propanediol pathways [88]. Usually, *Bacteroidetes* and some *Firmicutes* are good producers of propionate. This process occurs mainly via the succinate pathway [51]. Butyrate production is required for additional enzymatic processes such as the extension of acetyl-CoA by butyryl-CoA:acetate CoA-transferase. Some bacteria, including *Roseburia*, *Eubacterium*, and *Anaerostipes* species and *Faecalibacterium prausnitzii*, are good producers of butyrate because the enzymatic modification process is activated in these bacteria [65, 66].

In mammals, these metabolites are produced in varying ratios; approximately 60% is acetate, followed by propionate (~ 25%) and, to a much lesser degree, by butyrate (~ 15%) [27, 90]. In bovine ruminal fluid, approximately 50% is acetate, ~ 27% is propionate, and ~ 23% is butyrate [124]. SCFAs are absorbed in the colon and rumen epithelium, are transported to the portal vein, cross into the blood circulation, and are transported to other organs. SCFAs enter cells by passive diffusion and by carrier-mediated transport mediated by molecules such as SMCT1/SLC5a8 and MCTI/SLCI6a1 [62, 77, 127]. SMCT1, the sodium-coupled monocarboxylate transporter I, is required for cellular uptake of SCFAs and related organic acids such as lactate and pyruvate [77]. MCTI is an H^+-coupled transporter of SCFAs and can also release organic acids. The transport of SCFAs by MCT1 is required to produce net chemical gradients of H^+ and monocarboxylates across the membrane [36]. SMCTI and MCT1 are present in many cells, including colonocytes, DCs, kidney cells, brain cells, strial marginal cells, smooth muscle cells, and intestinal epithelial cells [31, 51, 52, 99, 131].

SCFAs modulate metabolic, nervous, inflammatory, and immunological functions primarily by activating G protein–coupled cell surface receptors (GPCR) such as GPR41, GPR43, and GPR109a as well as by inhibiting histone deacetylases (HDAC) [12, 28]. GPR41 and GPR43 are major receptors that can be activated by acetate, propionate, butyrate, and other SCFAs [16, 28], whereas GPR109a is mainly activated by butyrate [105, 106]. GPCR play an important role in immune responses regulated by SCFAs and are present on almost all cells in the immune system, including epithelial cells, neutrophils, and macrophages. Many studies have shown that SCFAs play an important role in the regulation of inflammation. There is evidence that butyrate and propionate inhibit LPS-induced TNF-α and nitric oxide synthase (NOS) expression through activating GPR41 and GPR43 receptors and GPR109A and that they inhibit HDACs in neutrophils [115]. Dietary fiber and its fermentation to SCFAs have been shown to have anti-inflammatory effects in asthmatic airways and this protective effect results in the upregulation of GPR41 and GPR43 gene expression [37]. Acetate-GPR43 interactions protect animals against dextran sulfate sodium (DSS)–induced colitis by inhibiting pro-inflammatory cytokine production by mononuclear cells [72]. Mice fed a high-fiber diet played increased circulating levels of SCFAs and were protected against allergic inflammation of the lung, whereas a low-fiber diet reduced circulating levels of SCFAs and aggravated this disease. Furthermore, treatment of mice with propionate improved the immunological environment in the lung and influenced the severity of allergic inflammation, and the protective effect of propionate was dependent on GRP41 [109]. Butyrate treatment inhibited inducible (iNOS), TNF-α, MCP-1, and IL-6 production by activation of GRP43 [80]. A role for GPR109A in immunity and inflammation has been suggested based on the observation that the expression of GPR109A is increased by treatment with cytokines such as IFNγ [95]. GPR109A protects against the inflammatory response in colonic macrophages and dendritic cells by inducing the differentiation of Treg cells and IL-10-producing T cells. Furthermore, GPR109A expression was shown to be associated with the butyrate-mediated induction of IL-8 in colonic epithelium [100]. Butyrate inhibited LPS-induced NF-κB activation in the colon of mice. The inhibitory effect of butyrate was dependent on GPR109A, shown by the fact that inhibition by butyrate did not occur in HCT116 cells transfected with GPR109A, which do not express [106]. Studies have also suggested that SCFAs exert anti-inflammatory properties by inhibiting HDACs in LPS-induced macrophages and dendritic cells. Treatment with butyrate and propionate was shown to inhibit TNF-α production through inhibition of activation of the NF-κB signaling pathway in LPS-stimulated mononuclear cells, and the effects of butyrate and propionate were similar to that of the HDAC inhibitor TSA [111]. In neutrophils, butyrate and propionate also inhibited TNF-α production and NF-κB signaling pathway activity through inhibiting HDACs after treatment of the cells with LPS [6].

In recent years, a protective effect of SCFAs on mastitis has been reported. Experiments conducted as part of a clinical investigation showed that the levels of some SCFAs in milk from clinical quarters differed from those in milk from control quarters. The data demonstrated that SCFAs levels were significantly lower and that the percentage of total neutral lipids was significantly higher in milk from clinical quarters compared with milk from control quarters [76]. Butyrate treatment reduced the internalization of *S. aureus* into bovine mammary epithelial cells (bMEC) by approximately 50% and increased the expression of tracheal antimicrobial peptide (TAP), β-defensin, and nitric oxide synthase (iNOS) [79]. Furthermore, it was also found that TSA, an HDAC inhibitor, inhibited pro-inflammatory cytokine production, suggesting that butyrate protects against LPS-induced mastitis through inhibition of HDAC [118]. Similarly, propionate was shown to reduce *S. aureus* internalization into bovine bMEC and to modulate antimicrobial peptide mRNA expression and

propionate also conferred protection against LPS-induced mastitis by inhibiting pro-inflammatory cytokine production and NF-κB signaling pathway activation, as well as inhibiting HDACs in mice [117]. The results of another study suggested that treatment with acetate dose-dependently inhibited *S. aureus* internalization into bMEC by inhibiting activation of the NF-κB signaling pathway [119]. Recently, Shen et al. conducted important studies of the effects of butyrate on HC-induced damage to dairy goat mammary gland and rumen epithelium. They found that the molar proportion of propionate was increased in dairy cows fed a highly concentrated diet, whereas the proportional concentrations of other SCFAs were unchanged [124]. However, treatment with sodium butyrate significantly reduced rumen epithelium LPS levels, TNF-α, IL-1β, IL-6, MMP-2, and MMP-9 levels, MPO activity, and p-p65 expression induced by an HC diet. Furthermore, severe injury to the rumen epithelium induced by an HC diet was also ameliorated by dietary sodium butyrate [23]. Feeding lactating goats an HC diet induces an inflammatory response and apoptosis of cells in the mammary gland, whereas addition of sodium butyrate to the diet of lactating goats reduced the level of LPS and pro-inflammatory cytokines, subsequently inhibiting NF-κB and caspase-3 activation and eventually suppressing apoptosis of mammary gland cells [19]. This evidence suggests that supplementation of the diet with SCFAs plays an important role in maintaining mammary gland health.

The role of SCFAs produced by gut microbiota in blood-milk barrier function

SCFAs also serve as a critical energy source for host physiological barriers such as the gut barrier, the blood-brain barrier, the blood-testis barrier, and the blood-milk barrier. Butyrate is an energy source for colonocytes that can regulate gut epithelial barrier maintenance [102]. It can also induce colonic mucus secretion through promoting Muc2 and glycosyltransferase expression and promoting autophagy [122]. In type 1 diabetes, elevated circulating SCFAs levels improve symptoms by limiting the number of autoreactive T cells, inducting the numbers of Tregs, and enhancing the gut barrier [68]. In germ-free mice, the expression of claudin-5 and occludin in the BBB and the expression of occludin and ZO-2 in the BTB were lower than the levels found in wild-type mice; however, the protein components of the tight junctions in these barriers were restored to control levels by microbial colonization or by butyrate alone [15]. This may have occurred through epigenetic modification in the form of enhanced histone acetylation stimulated by butyrate [2, 3]. In addition, the gut microbiota disturbance caused by changes in the gut after exposure to provocative dietary agents favored low-grade systemic inflammation and altered SCFA utilization in the brain, changes that may lead to increased BBB permeability [69]. Recent reports have also indicated that SCFAs play an important role in blood-milk barrier function. It was shown that treatment with butyrate and propionate inhibited LPS-induced mastitis by restoring blood-milk barrier function and inhibiting the NF-κB signaling pathway as well as through HDAC inhibition [117, 118]. In our studies, we also found that the levels of butyrate, propionate, and acetate were significantly reduced in gut microbiota–depleted mice treated with ampicillin, neomycin sulfate, metronidazole, and vancomycin compared with those in wild-type mice, and decreases in the levels of SCFAs were associated with increased blood-milk barrier permeability. In addition, addition of sodium butyrate and sodium propionate to the diets of both gut microbiota–depleted mice and wild-type mice significantly inhibited the increase in blood-milk barrier permeability induced by *S. aureus* (unpublished observations). This evidence suggests that SCFAs maintain the blood-milk barrier in a way that protects against the development of mastitis.

Effect of probiotics on mastitis

Effect of probiotics on monogastric mastitis

According to the concept of mastitis as a manifestation of dysbiosis, i.e., an imbalance of the gut or rumen microbiota, the use of probiotics to re-equilibrate the microbiota appears as a possible corrective measure. Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer health benefits on the host [5]. Scientists have isolated various strains of probiotics from milk, and the presence of these organisms is thought to be protective against mammary gland infections or mastitis.

The use of probiotics to treat mastitis in breastfeeding women has been reported. Live culture treatment has the potential to be as effective at eliminating chronic subclinical infections as treatment with an antibiotic; 15 of 25 cases treated with the culture and 18 of 25 cases treated with an antibiotic did not exhibit clinical signs of the disease following treatment [55]. After 3 weeks of receiving *Lactobacillus fermentum* CECT5713 or *Lactobacillus salivarius* CECT5714, the mean bacterial counts in milk from the probiotic group were lower than those in milk from the control group; in addition, women receiving the probiotics experienced less pain and less frequent recurrence of mastitis than those assigned to the antibiotic group [7]. In a prevention experiment, it was shown that the incidence of mastitis in women who received *Lactobacillus salivatius* PS2 from approximately week 30 (25%) was lower than that in the control group (57%). When mastitis occurred, the bacterial counts in the milk from the probiotic group were markedly lower than those in milk from the control group [30]. In addition, a 16-week clinical trial showed that women receiving *Lactobacillus fermentum*

CECT5716 during lactation showed a decrease of 51% in the incidence of clinical mastitis. In addition, oral administration of *Lactobacillus fermentum* CECT5716 resulted in lower levels of *Staphylococcus* spp. than those in the milk of women in the control group [84].

Effect of probiotics on ruminant mastitis

The use of probiotics to treat bovine mastitis in the dairy industry has also been widely studied. *Lactococcus lactis* DPC 3147 is a food-grade organism that exhibits broad-spectrum antimicrobial activity against mastitis-causing pathogens in vitro [93]. *Lactococcus lactis* DPC 3147 combined with a bismuth-based treatment has a protective effect on mastitis caused by *Streptococcus dysgalactiae* and *S. aureus* in dry cows [93, 110]. Others also found that the use of resuspended freeze-dried *Lactococcus lactis* is as effective as an antibiotic in curing clinical mastitis [55]. Treatment of the mammary glands of uninfected animals with the lactococcal culture produced an immunomodulatory effect. It was shown that *Lactococcus lactis* treatment

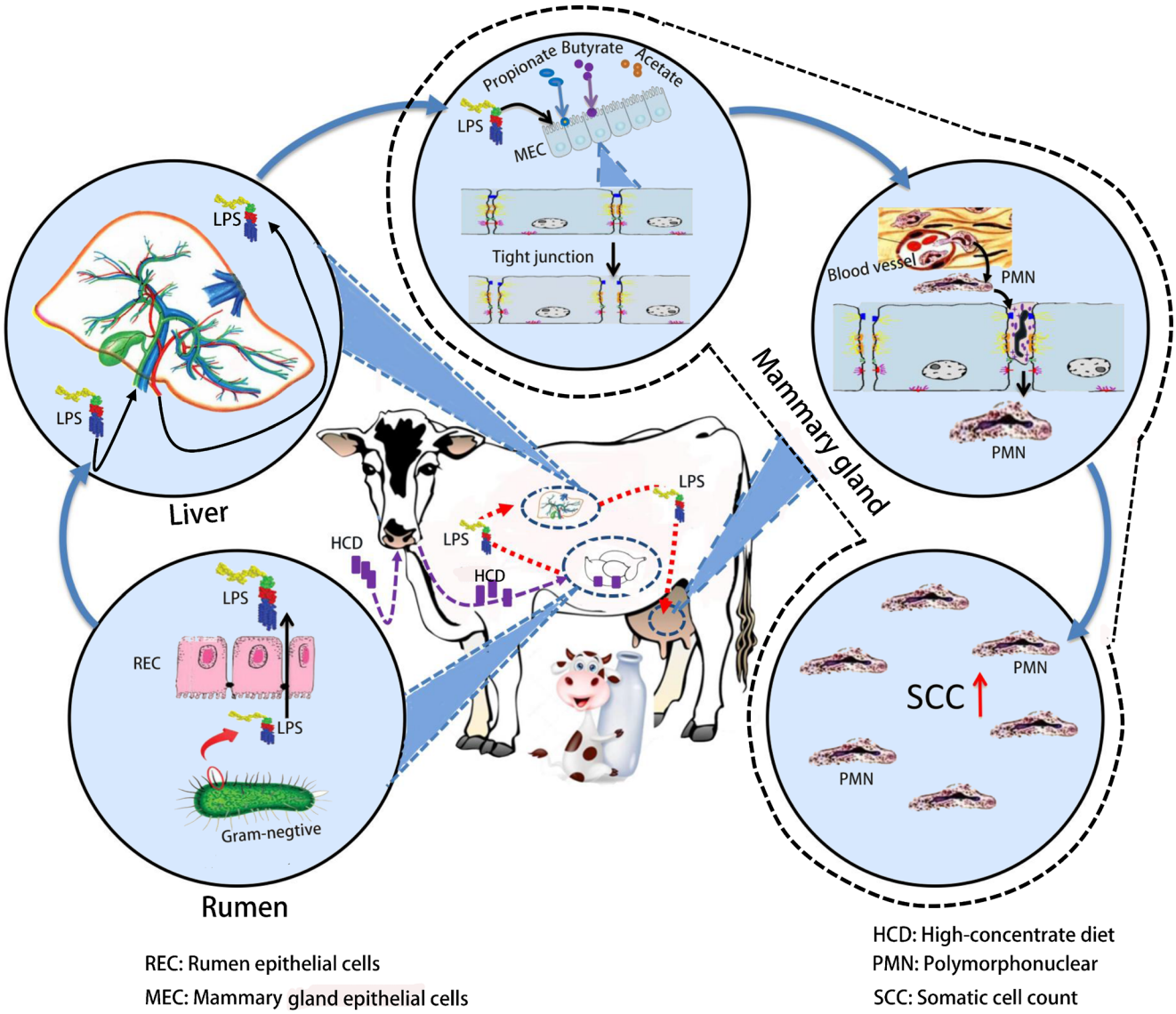

Fig. 3 The effect of gut microbiota on mastitis. The gut microbiota metabolites LPS and SCFAs are thought to be closely associated with the development of mastitis. Stressors, including feed alterations, disturb the regular gut microbiota, leading to the propagation of pathogenic bacteria that continually release LPS into the bloodstream through the rumen epithelium which may have been damaged by exposure to a lower pH. The gradually increasing levels of LPS injure the function of the liver, and LPS then enters the bloodstream. In lactating cows, the increased blood flow within the mammary gland enables much more LPS to enter the mammary gland tissue, decreasing the threshold for PMN crossing of the blood-milk barrier and finally increasing the SCC of the milk, a clinical diagnostic criterion for mastitis. In addition, SCFAs, especially butyrate and propionate, are the main energy source for the blood-milk barrier. Reducing the presence of SCFA-producing bacteria damages the function of the blood-milk barrier and further promotes the accumulation of PMN in the mammary gland when the mammary gland is stressed

resulted in substantial recruitment of PMN and lymphocytes to the infused quarters [22]. In addition, infusion with a live culture of *Lactococcus lactis* DPC 3147 leads to a rapid and considerable innate immune response, as shown by the increased expression of immune-related genes and high SCC levels. However, the immune response was short-lived, and SCC returned to pre-infusion levels within 1 week [9]. The use of single-molecule, real-time sequencing technology (SMRT) to measure changes in the bacterial community after treatment of cows with probiotic lactic acid bacteria (LAB) showed that LAB treatment reduced the number of mastitis-causing bacteria and improved the microbial environment of the cow teat. The results also suggested that SCC levels were lower after LAB treatment than after treatment with a commercial disinfectant [130]. Some isolated probiotics from milk have been shown to inhibit the growth of mastitis-causing bacteria in vitro, possibly through the production of bacteriocins [1]. Bouchard et al. isolated 165 lactic acid bacteria (LAB) from the bovine teat canal. Among these, they found that ten non-redundant LAB possess the ability to inhibit the mastitis-causing bacteria *Staphylococcus aureus*, *Escherichia coli*, and *Streptococcus uberis* and to reduce the colonization capacities of bovine mammary epithelial cells (bMEC), as well as possessing immunomodulatory properties. In addition, three strains exhibited high colonization capacity and moderate surface hydrophobicity, and nine strains exhibited anti-inflammatory properties in *E. coli*-stimulated bMEC [14]. *Lactobacillus casei* strains such as BL23 protect against invasion of bMEC by *S. aureus* by inhibiting the adhesion and internalization of *S. aureus* in a strain-dependent manner, suggesting that the inhibitory role of BL23 in *S. aureus* depends on interactions between *L. casei* cell surface components and bMEC [13]. Further research showed that the mutants serA1, srtA2, serC1, and srtC2 and a double mutant (srtA1-srtA2) of *L. casei* BL23 reduced its inhibitory capacity, especially in the case of the srtA2 mutant. In addition, a lower internalization capacity of *L. casei* srtA2 into bMEC was found. This proves the important role of sortase A2 in the inhibition of *S. aureus* internalization by *L. casei* BL23 [101]. To date, a large amount of evidence indicates that probiotics may provide an effective treatment measure and an alternative to antibiotics in the treatment of mastitis. Thus, the efficacy of probiotics in the treatment of mastitis should be evaluated.

Conclusion and Perspective

Mastitis is a benign inflammatory condition of the mammary gland with heterogeneous histopathological findings. Mastitis is recognized as one of the most common diseases affecting dairy herds. Bovine mastitis causes huge financial losses to the dairy industry due to reduced yield and milk quality, death, and treatment costs. Antibiotics have been used for years as the primary treatment for mastitis. However, the abuse of antibiotics has led to the emergence of resistant strains and the presence of drug residues, increasing the difficulty of curing this disease. In addition, administration of antibiotics kills most of the microbes in the digestive tract, leading to imbalances in the composition of the gut microbiota and destroying the normal exosystem within the digestive tract.

Gut microbiota play an important role in the development of mastitis, although the detailed mechanism of their action has not been reported. On one hand, changes in factors such as feeding will lead to rumen microbiota imbalance and reduced pH, impairing the integrity of the rumen epithelium and leading to entry of LPS into the rumen or the translocation of pathogenic bacteria across the rumen epithelium into the blood. When the liver is overloaded with endotoxins, substantial amounts of endotoxins escape detoxification, and flow into the capillary vessels pass through the bloodstream into organs and tissues all over the body, resulting in subclinical endotoxemia, a chronic systemic low-grade inflammation; under these conditions, the LPS circulating in the blood enters the mammary gland, especially during lactation. The increased level of LPS in the mammary gland damages the blood-milk barrier, lowering the threshold for PMN to cross the barrier. When stimulated in the mammary gland, a large number of PMN enter the gland and increase the susceptibility to mastitis. On the other hand, SCFAs, the end products of gut microbiota fermentation, are also involved in the development of mastitis. Although the detailed mechanism of the effect of SCFAs on mastitis has not been elucidated, SCFA treatment inhibits the development of mammary gland inflammation and reversed the blood-milk barrier permeability induced by LPS or *S. aureus* through inhibition of HDACs (Fig. 3). In addition, probiotic treatment has a protective effect against mastitis in both humans and animals. This suggested to us that probiotics or drugs that regulate the gut-mammary gland axis by increasing the production of SCFAs and inhibiting LPS may represent a new and promising direction in mastitis treatment. Hopefully, this theory will offer new insight into dealing with other infectious diseases.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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