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Regulatory effects of gut microbiota on breast health and human milk composition *via* gut-mammary gland axis

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ABSTRACT

The gut-mammary gland axis connects the communication between the gut microbiota and the mammary gland. Studies have reported that dysbiosis in gut microbiota is involved in the pathogenesis of breast diseases such as mastitis and breast cancer. In addition, different diets, including the supplementation of probiotics or prebiotics, which are closely related to the alteration of gut microbiota, were found to affect the nutritional contents of human milk and contribute to the development or alleviation of breast diseases. These studies suggested that the gut microbiota might be a new target for the regulation of human milk components or breast diseases. In this article, we summarized recent research advances in the gut-mammary gland axis and discussed some of the effective mechanisms and pathways involved, including distal translocation of gut microbiota, circulation of metabolites across the blood-milk barrier, the delivery of immune cells and their secreted antibodies to the mammary gland. This article also provides new strategies for preventing women's breast diseases and improving the composition of human milk through the gut-mammary axis.

1. Introduction

The mammary gland is unique organ of mammals[1]. On the one hand, the mammary gland plays a vital role in the health of women. It is the target organ of glands such as pituitary gland, ovary and adrenal cortex, affected by the hormones secreted by these glands (such as prolactin, estrogen, etc.)[2-3]. On the other hand, nutrients and immune substances are transmitted to the offspring through the secretion of milk, thus promoting the growth and development of the offspring[4].

In recent years, studies have found that breast disease and human milk composition can be regulated by supplementation with probiotics, indicating a close link between gut microbiota and the mammary gland, known as the gut-mammary gland axis[5-6]. The gut microbiota has received much attention due to its important role in metabolism, immune regulation, and protection of the host from intestinal pathogens[7]. Tryptophan metabolites derived from the gut microbiota can enhance the intestinal barrier and regulate intestinal homeostasis by binding to the aryl hydrocarbon receptor (AhR) or pregnane X receptor (PXR)[8-9]. In addition to this, butyrate derived from the gut microbiota can regulate the production of interleukin-22 (IL-22) by natural lymphocytes (ILC) and $CD4^+$T cells, thereby protecting the gut from inflammation[10].

Many related studies on the gut-mammary gland axis have been reported in the literature, but the specific roles and potential pathways of the gut microbiota in the mammary gland and human milk have not been systematically summarized. This review summarized the recent advances in the study of the gut-mammary gland axis and its related pathways. Finally, we discussed recent findings in probiotic modulation of breast diseases and human milk composition.

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2. Mammary gland

2.1 Anatomical structure and physiological functions of the mammary gland

The mammary gland is a complex, branched tubule alveolar structure. It is composed of various types of cells, including epithelial cells, fibroblast cells, adipocytes, endothelial cells, and immune cells. These cells work together to maintain the normal function of the mammary gland, with the mammary epithelial cells serving as the main functional unit responsible for producing and transporting milk[11]. The mammary gland is a dynamic organ that is affected by many factors, including various hormones such as estrogen, progesterone, prolactin, and growth factors such as epidermal growth factor and insulin-like growth factor[12-13]. These hormones promote glandular development during puberty and induce the formation of branching, epithelial and lactating organs at the end of pregnancy. After delivery, the baby's sucking stimulates the pituitary gland to secrete prolactin and oxytocin to maintain lactation. After weaning, local cytokine production and decreased prolactin secretion lead to large-scale breast cell loss and glandular degeneration[14].

2.2 Composition and function of human milk

The mammary gland plays a crucial role in lactation and milk production, which are essential for infant growth and development[4]. Human milk mainly includes: 1) macronutrients consisting of lipids, proteins, and carbohydrates; 2) micronutrients consisting of vitamins, minerals, etc.; 3) other substances, such as various bacteria, immunomodulatory components, and hormones[15]. Human milk has a dynamic composition that changes throughout the entire lactation period, encompassing distinct stages including colostrum, transitional milk, and mature milk[16]. The milk produced by the mammary gland in the first few days after childbirth is colostrum, which is secreted in lower quantities, but has higher protein content and a lower carbohydrate and fat content than mature breast milk. 7–14 days after delivery, colostrum becomes a transitional milk, characterized by higher yields and lower protein and immunoglobulin content while increasing lactose, fat and water-soluble vitamins to meet growth needs. Finally, 14 days after delivery, the composition of the mature milk remained relatively similar[17]. The macronutrients in human milk mainly provide nutrients to the infant to support growth and development[18]. Micronutrients can be involved in the regulation of infant neurodevelopment[19]. Lactoferrin, which is the most abundant whey protein in human milk, promotes intestinal cell proliferation, differentiation, and maturation, as well as modulates host immune responses[20]. Other immunomodulatory components in human milk, such as immunoglobulins, bind to pathogenic bacteria, toxins and viruses to protect the offspring from adhesion and invasion by pathogens[21]. A study discovered that Rb, Zn, and Sr in human milk are positively correlated with neurodevelopment indicators, indicating that these trace elements in human milk can affect infant neurodevelopment[22]. Some microbes in human milk can shape the early gut microbiota of the offspring through vertical transmission from mother to offspring[23]. In addition, human milk oligosaccharides (HMOs), the third most abundant nutrient after lactose and protein, can effectively promote neurodevelopment by changing the concentration of important metabolites and neurotransmitters in the brain and can also be used as substrates for gut microbiota, promoting the colonization of beneficial bacteria and enhancing the gut barrier function of offspring[24-26]. Moreover, these components of human milk that shape the gut microbiota in early infancy are all regulated by maternal diet[27-28].

3. Role of gut microbiota in women's health and the gut-X axis

3.1 Role of gut microbiota in women's health

The gut is the most important digestive organ and the largest immune organ in the human body[29]. It is made up of the mucus layer, epithelial cells, immune cells residing in the lamina propria, and the symbiotic bacteria that populate it[30]. However, the tens of thousands of gut microbiota in the gut make up a huge microbial reservoir, and they play an important role in the metabolic changes and immune regulation of the host[31]. Gut microbiota can metabolize nutrients and produce signaling molecules to regulate the function and differentiation of immune cells, they can also coordinate with some immune cells to resist intestinal pathogen infection or inflammatory diseases[32-35].

At present, more and more studies have reported that gut microbiota can regulate female health by interacting with sex hormones[36], insulin[37], and other hormones[38]. The gut microbiota has a profound impact on all stages of female reproduction, including the development and maturation of follicles and oocytes, fertilization and embryo migration and maturation, and even plays a crucial role in the regulation of hormones throughout pregnancy and lactation[39]. In addition, the imbalanced gut microbiota may lead to a variety of female diseases, such as cancers (breast, cervical, and ovarian cancer), reproductive system diseases (polycystic ovary syndrome, endometriosis) and postmenopausal diseases, such as menopausal obesity and Alzheimer's disease[40].

3.2 Association of gut microbiota with peripheral organs through gut-X axis

The crosstalk between the gut microbiota and peripheral organs has become a hot topic. Gut microbiota and peripheral tissues and organs form the gut-X axis through various pathways such as metabolism, hormones, and immunity[41-42]. New information from animal and human studies shows that changes in the gut microbiota play a big part in neuroinflammation, changes in the cerebrovascular system, abnormal protein clumping in the brain, and a weaker blood-brain barrier[43]. These changes may induce an increased risk of some related diseases under the gut-brain axis, such as Alzheimer's disease[44], Parkinson's disease[45], stroke[46], and autism[47], etc. A growing body of evidence has highlighted the relevance of the gut microbiota to lung immunity, termed the gut-lung axis[48-49]. Disruption of gut microbiota increases susceptibility to airway diseases, including infections and allergies[50-51]. The gut microbiota plays a key role in the response to pulmonary infections caused by bacteria by regulating innate and adaptive immune responses[52]. In addition to the

role the gut plays in the lung, mice with respiratory tract infections also indirectly induced intestinal immune damage and altered the gut microbiota, forming reverse crosstalk[53]. In addition, metabolites of gut microbiota, such as trimethylamine oxide[54] and endotoxin[55], which are absorbed into the circulation system, were found to promote the risk of cardiovascular diseases. According to the gut-skin axis, Bifidobacteria can upregulate tryptophan metabolism by producing indole derivatives to activate AHR-mediated immune responses and relieve atopic dermatitis symptoms[56]. Intestinal dysbiosis is also involved in the occurrence of liver inflammatory diseases through the lipopolysaccharide-Toll-like receptor 4 (TLR4)-NF-κB signaling pathway and metabolites such as deoxycholic acid through the gut-liver axis[57]. Furthermore, metabolites of gut microbiota, such as short-chain fatty acids (SCFAs), inflammatory factors and estrogen were found to affect the uterine[58], ovarian[59], and other functions of the female reproductive organs. Notably, recent studies have highlighted a close link between the gut and the mammary gland. Some specific bacteria are able to regulate the host immune system and tumor immunity of the breast by producing effective metabolites that promote estrogen metabolism, and diet, probiotics and prebiotics can play an important anticancer role in breast cancer[60].

4. Regulatory mechanism of the gut-mammary gland axis

4.1 Microbial translocation

4.1.1 Alteration of the gut microbiota during pregnancy

Pregnancy will cause changes in maternal metabolism, immunity and other aspects to adapt to and support fetal growth and development, accompanied by changes in the oral, vaginal, and gut microbiota[61–66]. Previous studies have shown that changes in various sex hormones during pregnancy can have a certain impact on gut microbiota through the brain-gut axis[67]. Nuril-Ohayon et al.[68] demonstrated that progesterone can regulate the composition of gut microbiota associated with pregnancy, leading to an increase in the relative abundance of *Bifidobacterium*. Many studies have reported changes in gut microbial diversity during pregnancy through high-throughput sequencing, which have important implications for maternal and infant. The relative abundance of *Proteobacteria* and *Actinobacteria* increased significantly in most pregnant women as the individual progressed from the first to the third trimester. *Clostridium*, belonging to Firmicutes, is overrepresented in the first trimester, while Enterobacteriaceae and *Streptococci* dominate in the third trimester[69-70]. In addition, in the later stages of pregnancy, maternal fecal inflammatory markers increase, low-grade inflammation occurs in the intestinal mucosa, and insulin resistance increases, which makes it more prone to many pregnancy complications, such as overweight and gestational diabetes mellitus (GDM), and has adverse effects on the mother, especially on the composition of human milk[71].

4.1.2 Microbes in human milk

Maternal microbiota is the main source of infant microbiota, which is rapidly colonized after birth. The difference in gut microbiota between breastfed and formula-fed infants reflects the importance of human milk microbiota[72-73]. In general, in breastfed infants, Bifidobacteria and *Staphylococcus* are the dominant microbes, while in formula-fed infants, the dominant microbes are *Enterococci*, Coliforms and Clostridia[74]. There is a lot of evidence that human milk microbiota changes at different stages of lactation. As reported by Cabrera-Rubio et al.[75], *Weisella*, *Leuconostoc*, *Staphylococcus*, *Streptococcus*, and *Lactococcus* were the most abundant genera of bacteria present in colostrum. And levels of *Leuconostoc*, *Weisella*, *Lactococcus* and *Acinetobacter* were higher in milk samples collected 1–6 months postpartum. Another study also showed that the total amount of bacteria in human milk and the abundance of *Bifidobacterium* and *Enterococcus* were significantly increased in the late lactation period, influenced by the lactation stage[76]. This is consistent with the increase in Bifidobacteria after the regulation of pregnancy hormones in the maternal gut microbiota described above[68]. It is suggested that there is a certain relationship between the maternal gut microbiota and the human milk microbiota. In addition, human milk microbiota can be affected by a variety of other factors. Increased number of *Lactobacillus* in colostrum for mothers with a higher body mass index (BMI). Similarly, mothers with a higher BMI at 6 months postpartum had more *Staphylococcus* and less *Bifidobacterium* in human milk[75]. Maternal diet is usually the main factor affecting BMI, so the effect of BMI on human milk microbiota may be achieved through diet-induced changes in maternal gut microbiota.

4.1.3 Bacterial translocation from gut to mammary gland

In recent years, the source of human milk microbiota has been controversial. There is evidence that the maternal gastrointestinal microbiota and the maternal breast skin or infant oral microbiota may facilitate the colonization of microbiota in human milk[77]. However, the identification of microbes similar to those in the gut from human milk suggests the possibility of the translocation of gut microbiota to the mammary gland[78]. As previously mentioned, a healthy pregnancy with an increased bacterial load and marked changes in gut microbiota composition as well as hormones provide a huge opportunity for gut microbiota translocation to the mammary gland[79]. Traditionally, the translocation of pathogenic bacteria to distant organs is mediated by lymphatic tissue. For example, after a *Salmonella* infection, $CD103^+$ dendritic cells (DCs) sense the presence of the pathogen, patrol the small intestine epithelium, and recruit more DCs in a TLR and chemokine-dependent manner. The newly arrived DCs extend their dendrites toward the duct by penetrating the tight connections between intestinal cells, and DCs use the intraepithelial dendrites to effectively phagocytic *Salmonella* for delivery to peripheral tissues[80-81]. Translocation of maternal gut microbiota to mammary gland, including human milk, is also the result of active migration of DCs between intestinal lamina propria, Peyer's patches, isolated lymphoid follicles, and mesenteric lymph nodes (Fig. 1A). After sampling symbiotic bacteria from the maternal gut during pregnancy or after birth, DCs spread through the lymphatic system and reach the internal mammary lymph nodes[82]. De Andrés et al.[83] transformed *Lactococcus lactis* MG1614 and *Lactobacillus salivarius* PS2 with plasmids containing the lux gene to produce a luminescent response to the lux operon gene. The transformed strain was then

orally administered to pregnant mice, which could be isolated from breast milk or breast biopsy tissue and tested for the lux gene by PCR. Perez et al.[84] suggested that human milk and peripheral blood contain limited amounts of live bacteria and bacterial DNA that may be transported from the mother's gut to the mammary gland *via* endogenous cellular pathways (mononuclear macrophage) at the end of pregnancy. Although this evidence demonstrates the transfer of gut bacteria to breast tissue, the specific conditions under which it occurs and which specific components of bacteria can be identified and transferred are unclear.

Secreted immunoglobulin A (SIgA) is one of the most abundant immunoglobulin subtypes in mucous membranes and plays an indispensable role in resisting pathogen invasion[85-86]. SIgA can be recognized by bacterial lipopolysaccharide (LPS), capsular polysaccharides, and flagellin to form SIgA coated bacteria[87]. It can envelop some harmful pro-inflammatory microorganisms, leading to various diseases[88]. It can also coat beneficial bacteria to maintain mucosal homeostasis and promote immune development[89-90]. In addition, the gut and human milk of the mother are rich in SIgA, which can cover a specific bacterial spectrum[90]. Analysis of the microbiota and SIgA-coated bacteria in maternal stool, human milk samples, and infant stool samples by 16S rRNA amplicon sequencing revealed that *Bifidobacterium longum* was the key SIgA-coated bacteria transferred from the maternal gut to human milk[91]. Taken together, SIgA mediating specific bacteria becomes another route for intestinal bacterial translocation to the mammary gland (Fig. 1A).

4.2 Circulation of gut-derived metabolites

4.2.1 Changes in the intestinal function during lactation

After the start of lactation, in order to support the synthesis and secretion of milk and meet the nutritional needs of the offspring, the maternal demand for energy increases, and the gut will undergo huge changes, including changes in its own tissue structure and hormone metabolism[92-94]. For example, the number of cells in individual crypts in the intestine of lactating mice increases, and this change results in an increase in the wet weight of the mice intestine[95]. In the early stage of lactation, the absorption and uptake of nutrients *via* the intestine increases, and the dietary protein in the mother's diet passes through the maternal intestinal epithelium, enters the blood circulation, and is transported to the milk through the mammary gland, thus passing to the newborn[96]. In addition, some gastrointestinal hormones, such as peptide-YY (PYY) and glucagon-like peptide-1 (GLP-1) in the colon, were increased during lactation[93]. In conclusion, this adaptive change in the intestinal tract during lactation provides great convenience for the transport of metabolites and hormones of the gut microbiota.

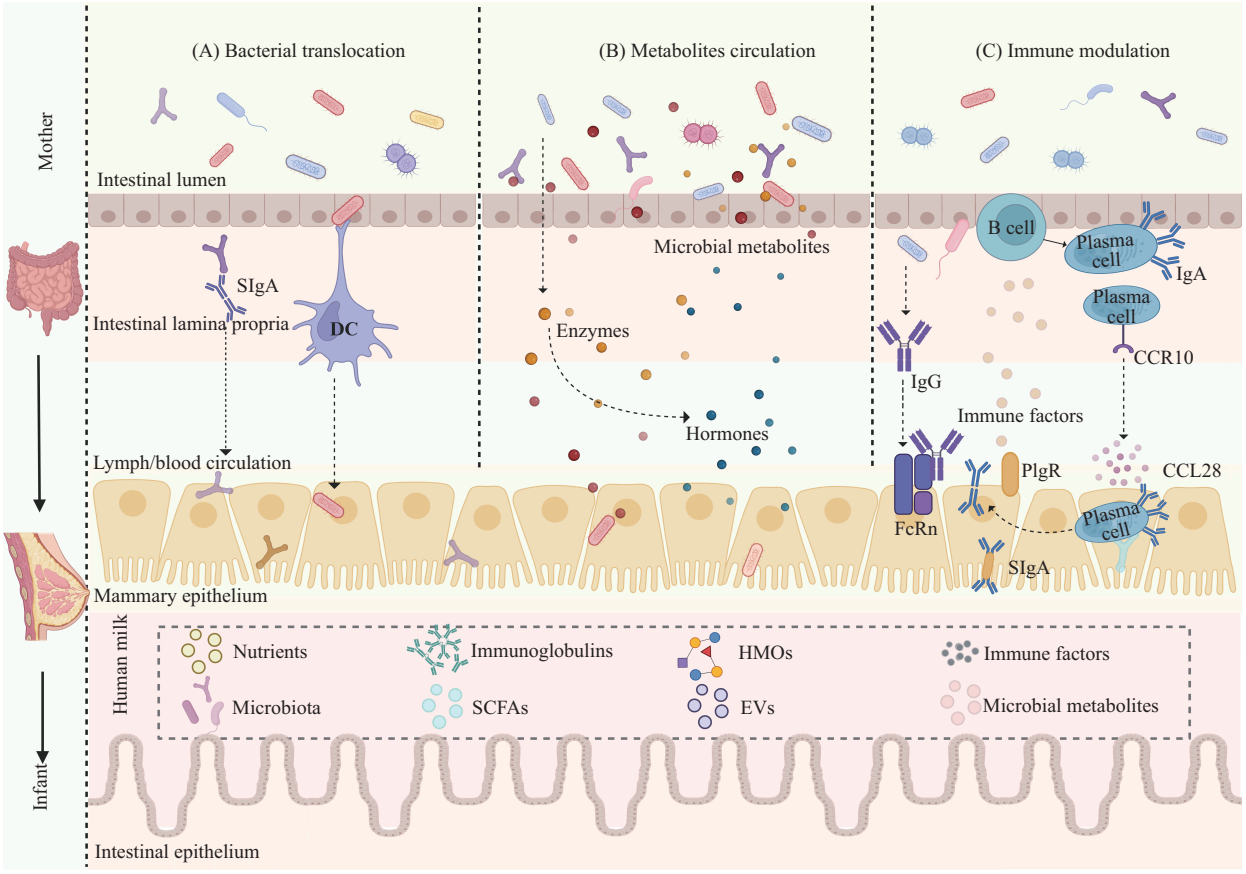

Fig. 1 The regulatory mechanism of the gut-mammary gland axis. (A) Commensal bacteria in the gut are transmitted to the mammary gland *via* SIgA-coating and DCs. (B) Gut microbiota can produce various metabolites or enzymes that are able to enter the blood circulating and across the blood milk barrier to regulate breast health and milk composition. (C) Some immune cells or immune factors in the gut can regulate the mammary gland. FcRn on breast tissue mediates gut microbiota-induced transfer of maternal IgG to human milk. IgA-secreting cells in the maternal gut migrate by expressing CCR-10 in combination with CCL-28 in the mammary gland.

4.2.2 Modulation effect of gut microbiota on hormones

The interaction between the gut and the mammary gland involves metabolic regulatory networks. Estrogen is a steroid hormone that plays a crucial role in female reproductive development[97-98]. In the female reproductive tract, estrogen can maintain a healthy vaginal environment by increasing the tight connections of the vaginal epithelium, enhancing the secretion of mucus, and regulating the abundance of *Lactobacillus*[99-100]. In addition, diseases such as endometriosis, polycystic ovary syndrome, infertility, breast cancer, and other diseases are mostly regulated by estrogen[101-103]. Studies have shown that high estrogen levels in postmenopausal women can lead to an increased risk of breast cancer[104-105]. The gut contains a number of microorganisms with β-glucuronidase and β-glucosidase activity that can uncouple estrogen to its active form[106-108]. Therefore, various dietary factors such as dietary fiber consumption, lead to changes in the gut microbiota and thus affect the content of estrogen, which may be an important mechanism of gut-mammary gland interaction[109-111].

Gut microbiota disorders have been shown to be associated with many metabolic diseases, such as GDM and overweight[112]. Maternal milk secretion is regulated by prolactin. Impaired glucose in GDM may change prolactin secretion, thereby affecting milk yield[113]. Furthermore, obesity is considered to be a state of inflammation and glucose and lipid metabolism disorders. Metabolites in human milk are altered in obese women, and this alteration may be influenced by the obesity-induced proinflammatory state or by its hormones, but the exact mechanism remains unclear[114-115].

4.2.3 Transport of metabolites in the gut microbiota

The microbiota is the main source of human metabolites. As the ultimate downstream products of microorganisms, metabolites regulate the various health of the host organism[116]. When the gut microbiota is disturbed, the excessive production of LPS can damage the intestinal barrier function, leading to LPS entering the blood and circulating into the mammary gland, increasing the permeability of the blood-milk barrier, and leading to mammary inflammation. SCFAs produced by the gut microbiota have a protective effect on mammary inflammation and help to maintain the function of the blood-milk barrier[117]. In addition to its effects on inflammation, changes in the gut microbiota-derived metabolome also affect cancerization in distal organs outside the gut[118]. Kovács et al.[119] found that a variety of gut microbiota, such as *Akkermansia*, Lachnospiraceae, *Ruminococcus* and *Bacteroidetes* produce various SCFAs, such as acetate and butyrate, by decomposing hard-to-digest carbohydrates, so as to promote the antibacterial activity of macrophages or the damage of breast cancer cell pairs through reactive oxygen species formation and mitochondrial damage. A subgroup of gut bacteria was found competent to convert tryptophan to indole, pyruvate, and ammonia by expressing tryptophanase, thereby increasing the diversity of indole-containing compounds in serum[120]. In addition, indolepropionic acid can selectively target breast cancer cells by activating AHR and PXR receptors and inducing oxidative stress responses[121]. Other bacterial metabolites that have cancer-inhibiting effects in breast cancer include lithocholic acid and cadaverine[118,122]. Bile acids (BA) are noted in breast cysts. However, BA is usually present in the intestine, Javitt et al.[123] orally administered deuterium-labelled chenodeoxycholic acid to patients and found that it appeared in breast cyst fluid within 9 days, proving that BA in breast cyst fluid came from the intestine rather than circulating steroid precursors metabolized by breast tissue itself. However, the mechanism by which BA is transferred between plasma and the mammary gland is not known, but these findings shift the focus of the gut-mammary axis to the pathogenesis of the disease (Fig. 1B).

4.3 Intestinal immune regulation

4.3.1 Transmission of immunoglobulin from the gut to the mammary gland

SIgA-producing cells are mainly plasma cells in the lamina propria of the gastrointestinal tract[124]. It has been observed that during pregnancy and lactation, IgA-secreting cells in the maternal gut migrate by expressing chemokine receptor (CCR)-10 in combination with chemokine ligand (CCL)-28 in the mammary gland[125]. The IgA monomers secreted by plasma cells are linked by polypeptides called J chains, which are then recognized and transported by the polymeric Ig receptor (pIgR) located on the basolateral membrane of mammary epithelial cells[126-127]. In addition, Usami et al.[128] found that Peyer's patches promote IgA plasma cell migration to the mammary gland in the presence of certain resident microorganisms, such as *Bacillus acidifaciens* and *Pseudomonas buccalis*. Therefore, the transfer of SIgA-producing plasma cells from the gut to the mammary gland may have greatly facilitated the formation of SIgA-coated bacteria.

There is also an important class of antibodies in human milk, called antigen-specific immunoglobulin G (IgG), which can promote intestinal immunity in infants and play a protective role against infections[129-130]. Gut microbiota induced maternal IgG is mediated by major histocompatibility complex (MHC) class I associated neonatal Fc receptors in metastatic epithelium present in breast epithelial cells and lymph nodes from serum to human milk and delivered vertically to the infant intestine, thereby inhibiting pathogen adherence and colonization[131-132].

4.3.2 Regulatory effects of gut microbiota on local immune cells and cytokines in the mammary gland

The imbalance of the gut microbiota can affect systemic immunity and induce inflammation. To investigate the effects of antibiotic-driven gut microbiota dysregulation on breast tissue, the researchers found through corresponding experiments that symbiotic bacteria dysregulation led to an increase in inflammatory factors in precancerous breast tissue, and that this inflammation persists in the presence of tumors[133-134]. In addition, gut dysbiosis was also found to associate with increased infiltration of myeloid cells, most of which are M2-polarized (tolerant) macrophages[133] (Fig. 1C).

5. The gut microbiota regulates the composition of human milk

5.1 Effects of different dietary patterns on specific human milk composition

Different dietary patterns can affect the composition of human milk. For example, triglycerides in human milk increase significantly

after high-sugar and high-fat diets, and the changes in high-sugar diets are all the more significant. Mothers on a high-sugar diet have an increased concentration of cholesterol in their human milk, and mothers on a high-fat diet have a higher concentration of lactose and a lower protein content in their human milk compared to mothers on a normal diet[135]. In recent years, the role of HMOs and human milk microbiota in promoting infant microbial colonization and immune development has attracted considerable attention[136-137]. Therefore, in this part, we concentrate on the effects of maternal dietary patterns on human milk microbiota and HMOs.

Altered dietary patterns lead to different gut microbiota[138-140]. Differences in the microbiota in human milk are caused by the transport of gut microbiota from different maternal dietary patterns through the gut-mammary axis[141-142]. Studies have shown a correlation between the nutrients in a mother's diet and the microbes in human milk. *Staphylococcus* and Bifidobacteria in human milk are linked to high carbohydrate intake, however, high intake of animal proteins and fats can lead to lower levels of Bifidobacteria and *Enterococcus* in human milk[143]. A study has shown that a maternal low-fiber diet (LFD) can lead to an increased degree of respiratory infection in infants, which is caused by LFD affecting the microbiome composition of human milk and infants' intestines, thereby reducing the expression of immune cell cytokines on neonatal intestinal epithelial cells. And this influence was restored after treatment with propionate producing bacteria isolated from the milk of mothers on a high-fiber diet[144].

In addition to the effects of human milk microbiota, diet also has an effect on HMOs in human milk. Compared with non-secretory mothers, the impact of diet on HMOs was more significant in secretory mothers. The concentration of total HMOs in the human milk of secreted women was negatively correlated with insoluble fiber, cellulose, hemicellulose, and polyphenol intakes, while some minor HMOs were positively correlated with it, such as fucosyllacto-*N*-hexaose and fucosyl-disialyl-lacto-*N*-hexaose. In addition, higher fructose and galactose intakes were associated with higher 2-fucosyllactose and lower 3-fucosyllactose[145]. Quin et al.[146] also found that intake of carbohydrates, including monosaccharides and dietary fiber was significantly positively associated with the relative levels of galactose and fucose present in HMOs, and the biosynthetic level of the sialic acid *N*-acetylneuraminic acid was significantly lower in HMOs in women who ate a lot of fruit. A clinical study investigated people on 2 different types of diets, the galactose/glucose diet and the carbohydrate/fat diet, found that the concentration of total HMOs binding fucose was lower in the glucose diet in the galactose/glucose group, and concentrations of HMO-bound fucose were significantly associated with the relative abundance of bacterial fucosidase. In the carbohydrate/fat cohort, the concentration of total HMOs binding sialic acid was lower in the high-fat diet. This suggests that the lactating mother's diet changes the HMOs composition of the milk, thereby shaping the functional milk microbiota and transmitting it vertically to the infant[147]. In addition, in an animal experiment, Wistar maternal mice fed a high-protein or high-prebiotic fiber diet throughout pregnancy and lactation also changed the content of HMOs in breast milk and the maternal gut microbiota but had no effect on the content of protein and fat in breast milk, and this change in HMOs are associated with susceptibility to disease in offspring[148].

Taken together, these results suggest that maternal diet influences certain components in human milk, such as microbes and HMOs, which in turn influences the intestinal microbial colonization and immune system development in infants.

5.2 Effects of exogenous probiotics or prebiotics on human milk composition

Probiotics are living microorganisms that, when given in adequate amounts, are beneficial to the health of the host[149]. Probiotics have been demonstrated to prevent allergic diseases, improve digestive disorders, and reduce the risk of obesity[150-151]. *Bifidobacterium* and *Lactobacillus* strains are the most widely used probiotics, and they are not only subdominant genera in the gut but also naturally present in human milk[152-153]. In recent years, Bifidobacteria and *Lactobacillus* have been added to many foods and dietary supplements as functional health products[154]. Multiple papers have shown that supplementing women with probiotics during pregnancy and breastfeeding can regulate the levels of milk composition and human milk immunomodulatory molecules, thus having an important impact on the health of newborns[155-156]. Studies have shown that maternal supplementation with probiotics in late pregnancy can affect the concentration of HMOs in colostrum, especially 3-fucosyllactose and 3-sialyllactose are significantly increased[157]. A randomized clinical trial found that large doses of multi strain probiotics given to women during the perinatal period affected the production of the maternal colostrum cytokine IL-6 and mature human milk IL-10, TGF-β, and neonatal intestinal mucosa SIgA, and improved symptoms of abdominal colic and functional reflux in infants[158]. *Lactobacillus fermentum* CECT5716 is a probiotic strain isolated from human milk[159-160]. Supplementation with *L. fermentum* CECT5716 in pregnant and lactating rats did not change the breast milk microbiota, but the strain was detected in 50% of the breast milk samples of the rats in the supplementation group, and probiotic administration led to beneficial changes in the fatty acid profile and immunoglobulin in breast milk[161].

Prebiotics are substrates that are selectively utilized by host microbes and confer health benefits. It can be utilized and fermented by probiotics, thus promoting the reproduction and metabolism of intestinal probiotics[162]. Specific fiber components that have been identified with prebiotic activity are galacto-oligosaccharides, inulin-type fructans, and fructo-oligosaccharides at present[163]. Supplementation of maternal short-chain fructo-oligosaccharides during late pregnancy and lactation affects milk composition and offspring intestinal metabolome, including HMOs and lipid profiles of mature milk[164]. Prebiotic consumption by lactating mothers selectively alters the levels of four important immunomodulation factors in human milk[165]. Another study showed that prebiotic supplements can alter protein and miRNA levels in rat's milk[166]. These changes in human milk are crucial for the growth and development of breastfed babies (Table 1). However, the changes of breast milk composition after supplementation of probiotics and prebiotics are not exactly positive, and the trends of such changes are different in different lactation periods, so future studies may be based on different periods to explore.

Table 1
Research progress on the effects of probiotics and prebiotics on breast milk composition.

Effective probiotics and prebiotics	Changes in the composition of human milk	References
Lactobacillus rhamnosus GG, *L. rhamnosus* LC705, *Bifidobacterium breve* Bb99, *Propionibacterium freudenreichii* subspecies *shermanii* JS	Colostrum: 3'-sialyllactose, 3'-fucosyllactose ↑ 6'-Sialyllactose, lacto-*N*-tetraose, lacto-*N*-fucopentaose I, difucosyllacto-*N*-hexaose ↓	[157]
Lactobacillus paracasei DSM 24733, *Lactobacillus plantarum* DSM 24730, *Lactobacillus acidophilus* DSM 24735, *Lactobacillus delbrueckii* subsp. *bulgaricus* DSM 24734, *Bifidobacterium longum* DSM 24736, *B. breve* DSM 24732, *Bifidobacterium infantis* DSM 24737, *Streptococcus thermophilus* DSM 24731	Colostrum: IL-6, IL-10 ↑ Mature milk: IL-10, TGF-β1 ↑	[158]
L. fermentum CECT5716	Mature milk: palmitic acid ↓ α-Linolenic acid, linoleic acid, total polyunsaturated fatty acid, IgA↑	[161]
Short chain fructo-oligosaccharides	Mature milk: 3'GOS (Gal (β1–3) Gal (β1–4) Glc), Gal-Gal-Gal (β1–4) Glc (Hex4-U1), gal-Gal(β1–4) Glc (Hex3-U1), neutral core, total PMOs, triglyceride (24), diglyceride (2), monoglyceride (3) ↓ Triglyceride (2) ↑	[164]
Short-chain galacto-oligosaccharides, long-chain fructo-oligosaccharides	Mature milk: TGF-β1 ↓, Thymic stromal lymphopoietin ↓, IgG1 ↓ Soluble CD14 ↑	[165]
Oligofructose	Mature milk: protein, miR-203a ↑ miR-222, miR-200a, miR-103, miR-26a, miR-27a ↓	[166]

6. Gut-mammary gland communication in mammary gland-associated diseases

6.1 Mastitis

Mastitis, is a kind of disease that occurs frequently in lactating women, which brings immense trouble to mothers breastfeeding[167-168]. The causes of mastitis are very complex, such as genetic factors, postpartum medication, healthy diets, etc., but pathogenic microbial infections, especially *Staphylococcus aureus* and *Escherichia coli* have been considered to the main cause[169-171]. At this stage, someone has proposed a new concept, namely: "gastroenterogenic mastitis", the definition states that in addition to external pathogen infection, mastitis may also be infected through the gastroenterogenic pathogenic route[172].

Research has found that compared with healthy cows, gastrointestinal bacterial diversity of mastitis cows is reduced, *Lactobacillus* is decreased, *Enterococcus*, *Streptococcus*, *Staphylococcus* and proinflammatory metabolites are generally increased[173-174]. In addition, transplanting fecal microbes from mastitis patients into mice can facilitate mastitis[175]. After antibiotics were added to the mice, the intestinal microbiota was disturbed, the intestinal barrier function was impaired, and the intestinal microbiota or harmful metabolites migrated to the distal mammary gland through the damaged barrier, further aggravating mastitis in the mice[176].

Antibiotics are the primary treatment method for mastitis[177]. However, the safety of antibiotics in the treatment of mastitis remains to be investigated in current studies[178]. Therefore, alleviating mastitis through dietary fiber or probiotic intervention has become a new therapeutic means[179-182]. A fiber-rich diet such as inulin produces rich SCFAs, especially butyrate, through gut microbiota breakdown, which activates the antimicrobial defense mechanism of macrophages' histone deacetylase and thus alleviates *S. aureus*-induced mastitis[183]. In addition to activating the antimicrobial defense mechanism of macrophages, SCFAs can also inhibit the activation of NF-κB and NLRP3 pathways involved in the pathogenesis of mastitis, so as to achieve the coordination of multiple mechanisms to prevent the role of pathogens-induced mastitis[184]. Another study also found that oral isolation of *L. fermentum* CECT5716 from human milk samples had a good preventive effect on the incidence of mastitis in lactating women[185] (Table 2, Fig. 2).

6.2 Breast cancer

In recent years, the close relationship between the gut microbiota and the development of cancer has been widely concerned, and probiotics and their metabolites have been widely concerned due to their benefits to the body and potential anticancer activities[186-187]. Existing studies have reported that the occurrence and development of a variety of cancers are closely related to gut microbiota[188-189]. Breast cancer is one of the 3 most common cancers in the world besides lung cancer and colon cancer, and it is mainly divided into 3 subtypes according to the presence and absence of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor2 (ERBB2): hormone receptor positive (ER+/PR+), ERBB2 positive (HER2+), triple negative (ER−, PR−, HER2−)[190].

Several studies compared the gut microbiota between mastitis cancer patients and healthy individuals have found that compared with healthy individuals, breast cancer patients have significantly lower bacterial abundance and α-diversity, and an increased abundance of β-glucose-producing bacteria, which have enzyme activity that regulates estrogen[191-193]. This echoes the increase in estrogen in breast cancer patients[109]. This indicates that the gut microbiota may influence breast cancer risk by regulating metabolism and hormone circulation[194].

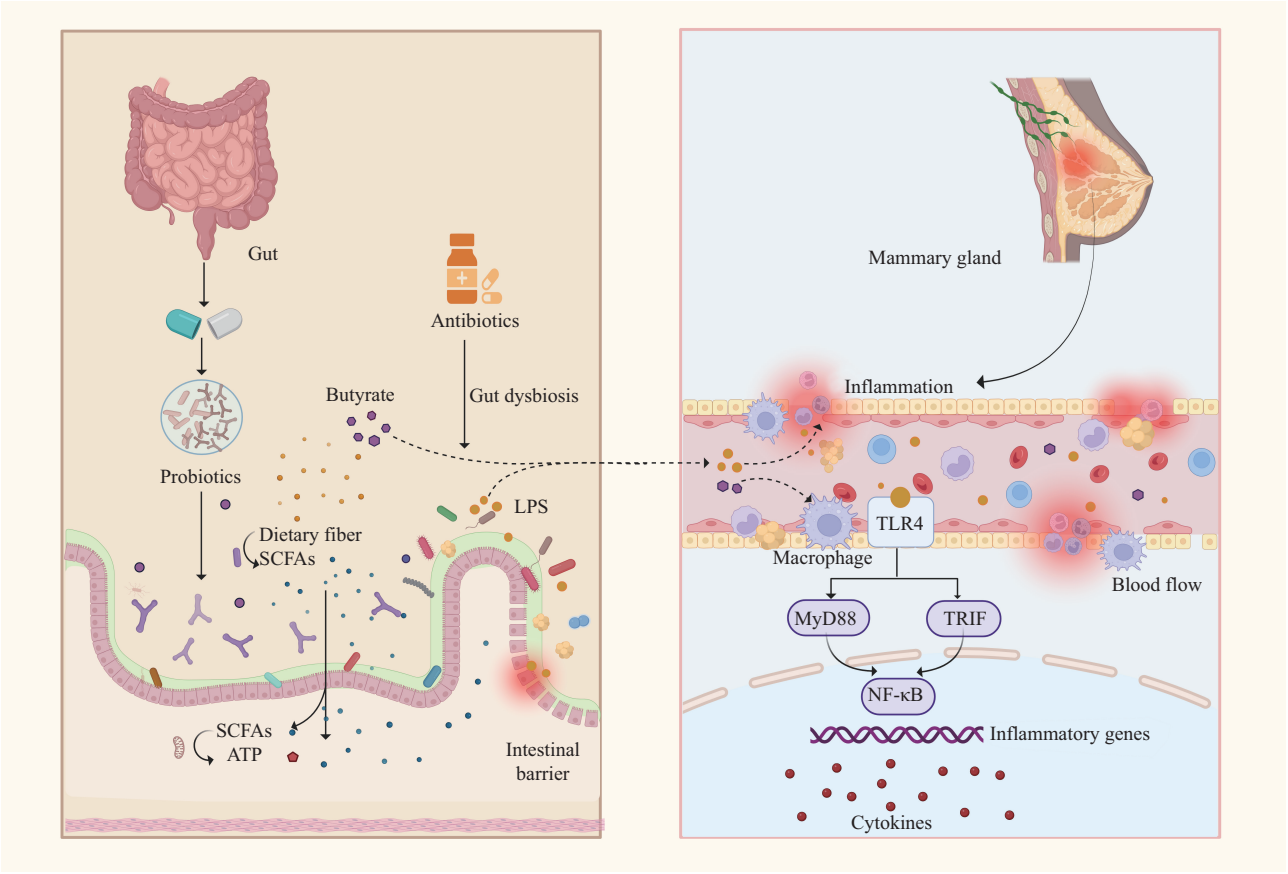

Fig. 2 The gut-mammary gland axis in mastitis. The intestinal microbiota is disturbed and the intestinal barrier function is impaired, and intestinal microorganisms or harmful metabolites migrate to the distal mammary gland through the damaged barrier, further aggravating mastitis. Alleviating mastitis through dietary fiber or probiotic intervention has become a new therapeutic means.

Table 2
Research progress on the effects of probiotics and prebiotics on breast diseases and therapeutic mechanisms.

Breast disease	Changes of gut microbiota	Effective probiotics and prebiotics	Therapeutic mechanisms	References
Mastitis	Bacterial diversity ↓ *Lactobacillus* ↓ *Enterococcus*, *Streptococcus*, *Staphylococcus* ↑	Inulin *Roseburia*, *L. fermentum* CECT5716	(1) Activating the antimicrobial defense mechanism of histone deacetylase in macrophages by producing SCFAs. (2) Inhibiting the activation of NF-κB and NLRP3 pathways involved in the pathogenesis of mastitis by Producing butyrate.	[173-174,183-185]
Breast cancer	Bacterial abundance ↓ *α*-Diversity ↓ *β*-Glucose-producing bacteria (*Clostridium*, *Faecalibacterium*, *Ruminococcus*, *Roseburia* genera and *E. coli*) ↑	Dietary fiber *B. longum*, *L. acidophilus*, *Enterococcus faecalis*, *Lactobacillus reuteri*, *L. plantarum*, *Akkermansia*, Lachnospiraceae, *Ruminococcus* and *Bacteroidetes*	(1) Promoting estrogen metabolism and clearance. (2) Stimulating host lymphocytes. (3) Upregulating levels of proapoptotic BAX and lytic PARP proteins and decreasing levels of anti-apoptotic Bcl-2 proteins in MCF-7 cells. (4) Butyrate produced by bacteria can inhibit the growth of cancer cells in a p53-independent manner and trigger apoptosis of MCF-7 cells through the Fas/Fas L system. (5) Promoting the antibacterial activity of macrophages or reactiving oxygen species formation and mitochondrial damage by producing SCFAs. (6) Activating AHR and PXR receptors and inducing oxidative stress responses to selectively target breast cancer cells by producing indolepropionic acid.	[119-121,191-193, 200-202,207-208]

The Mediterranean diet (MD) and the Western diet (WD) are deemed to be 2 distinct dietary patterns[195]. WD is high in calories and low in nutrients, tends to make women overweight or obese, and also increases the risk of breast cancer by increasing inflammatory factors[196]. However, according to a recent case study, adhering to a MD rich in fiber and low in fat may reduce the likelihood of breast cancer in pre and postmenopausal women, due to the effects of these substances on lowering estrogen levels, neutralizing oxygen free radicals, and protecting DNA from damage[197-199].

It has been reported that the consumption of probiotics or prebiotics can alleviate the side effects of clinical chemotherapy and slow the development of breast cancer. For example, probiotic

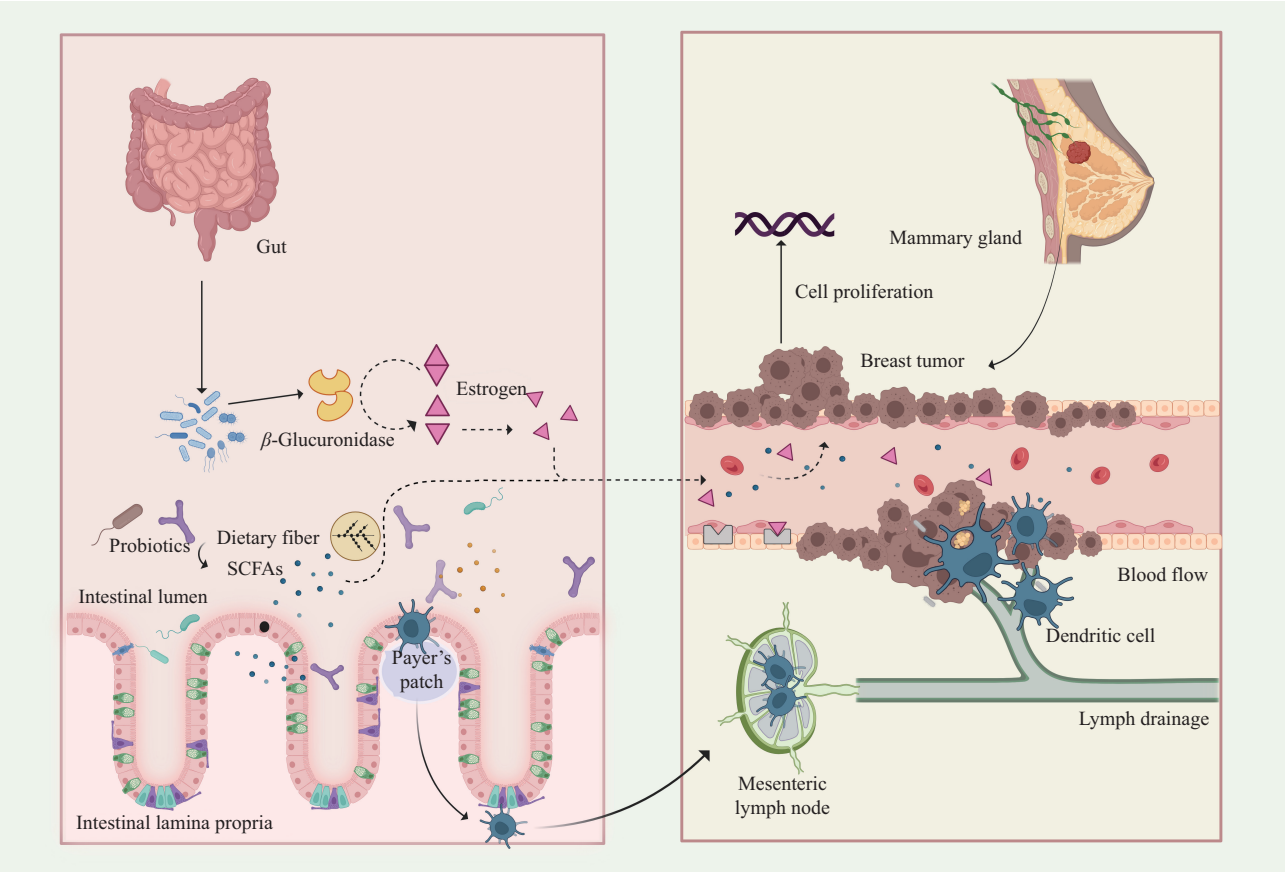

Fig. 3 The gut-mammary gland axis in breast cancer. The gut contains a number of microorganisms with *β*-glucuronidase and *β*-glucosidase activity that can uncouple estrogen to its active form, and high estrogen levels increase the risk of breast cancer. Various dietary factors such as dietary fiber and probiotics consumption can lead to changes in the gut microbiota, catabolic estrogen and the production of large amounts of SCFAs.

supplements reduce chemotherapy-related cognitive impairment in breast cancer patients[200]. *L. reuteri* stimulates host ILC to reduce the risk of breast tumors in HER2 mutant mice on WD[201]. Furthermore, dietary fiber intake may have a protective effect on breast cancer patients by promoting estrogen metabolism and clearance[202]. In addition, a number of studies have proved that probiotics and their metabolites have anti-proliferation activities of breast cancer cells through *in vitro* co-culture experiments[203-206]. Administration of *L. plantarum* resulted in upregulated levels of proapoptotic BAX and lytic poly-ADP ribose polymerase (PARP) proteins and decreased levels of anti-apoptotic Bcl-2 proteins in MCF-7 cells[207]. Butyrate inhibits the growth of breast cancer cells in a p53-independent manner and triggers apoptosis of MCF-7 cells through the Fas/Fas L system[208]. All these provide a reliable basis for the use of probiotics *in vivo* to treat breast cancer (Table 2, Fig. 3). However, probiotics and probiotic intervention therapy still face great challenges, such as the activity and duration of probiotics *in vivo*, precise composition, frequency of administration, etc., which need further clinical research.

7. Conclusion and prospects

In recent years, gut microbiota has become a hot topic due to their cross-talk with peripheral organs, especially between the gut and the mammary gland. The microorganisms in the gut or the immune cells regulated by the microorganisms can translocate to the distant breast tissue through DCs or mononuclear macrophages, and can also affect hormone endocrine synthesis by producing some metabolic substances, and then regulate the development and function of the mammary gland through blood circulation. In addition, diet as the main influencing factor in the gut microbiota, human milk composition and mammary gland status can be affected by different dietary patterns. In addition, the probiotics and prebiotics that have a good regulatory effect on breast diseases and human milk composition are not yet comprehensive. In the future, it may be necessary to further explore the specific internal mechanism of gut microbiota regulating breast function and human milk composition, and on this basis, screen more probiotics and prebiotics that are friendly to women and mothers. Supplementation of probiotics and prebiotics according to the gut-mammary gland axis to regulate breast health and human milk composition is a promising approach. This may provide a new method for the prevention and treatment of breast diseases in the future, and provide a new idea for some mothers with less and delayed lactation to improve the composition of human milk.

Conflict of interest

No potential conflict of interest was reported by the authors.

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