

Research progress in the pathogenesis of breast cancer mediated by breast and intestinal flora

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Abstract: Breast cancer is the most common cancer of women and is the leading cause of death-related deaths in global female cancer. The flora is undoubtedly the second genome of the human body, playing the role of a "symbiotic creature." The breast and the intestine flora bond between cancer cells and their local environment. The flora affects breast cancer by regulating hormone metabolism, chronic inflammation, and immune system reaction. Other studies have found that diet, obesity, antibiotics, and probiotics can play an essential anti-cancer effect in breast cancer. Therefore, this article summarizes the latest research progress on the pathogenesis of breast and intestinal flora in breast cancer pathogenesis. The breast and intestinal flora are expected to become a hub for further diagnosis and treatment of breast cancer.

1. Introduction

Human beings are a complex ecosystem with trillions of microorganisms. The gastrointestinal tract's flora carries a collective genome called the superstitious group, which is 150 times larger than the human genome^[1]. There is a complex interaction between the mammary gland and breast cancer tissue and the occurrence of breast cancer, treatment reactions, and resistance. Breast cancer has become the highest incidence in women and is also the most common cause of global female cancer death^[2]. A history of estrogen levels, diet, obesity, personal or family breast disease, genetic susceptibility, and environmental factors will increase the susceptibility to breast cancer. Among them, the human symbiosis group has become a research hotspot. It not only promotes the development of breast cancer but also has anti-cancer effects. The disorders of flora composition in the intestinal and breast tissues have caused changes in the biological behavior of breast cancer. As a link between cancer cells and their local environment, breast and intestinal flora disorders can play a role in the development of breast cancer through estrogen-dependency mechanisms and non-estrogen-dependency mechanisms. These bacteria and their metabolites are involved in the change of tumor microenvironment, immune-inflammatory reaction, diet, and obesity regulation. Functional disorders may be in a "biological disorder" state that may create a related micro-environment with a high risk of cancer and lead to adverse treatment. Therefore, we should take the

breast and intestinal flora as the two critical factors to maintain health and monitor the changes in breast diseases, and explore and understand the mechanism of intestinal and mammary flora. Provide new ideas and methods.

2. Intestinal tract-breast flora disorders and guidance of the occurrence and development of breast cancer

The flora in the breast may originate from the skin, intestine, breast, and breast milk^[3] or activate CD18+ cells and dendritic cells through the intestinal-breast pathway^[4]. Metabolic products are transferred from the gastrointestinal tract to the breast through the gastrointestinal tract. In addition, stool transplantation can change the composition of the intestinal tract and breast flora, providing evidence for the intestinal-breast signal axis^[5]. Studies^[6] have found that the diversity of flora diversity in breast cancer samples is lower than the normal breast tissue next to cancer. The diversity of breast flora is a crucial indicator for assessing the community composition between patients with breast cancer and healthy subjects. Endocrine therapy is the most critical systemic treatment method for patients with HR(+), but its effectiveness is often limited by primary and secondary drug resistance. Studies^[7] have found that there are complex interactions between the incidence of breast flora and breast cancer and the treatment response and resistance, which may bring new ideas to endocrine therapy resistance. The latest study^[8] found that breast cancer tissue can be observed to increase the *Bacteroides fragilis*, *Bacteroides fragilis* toxin can cause hyperplasia of breast epithelial cells, and the intestinal and mammal bowel toxin fragile bacteria can be available. Promote the growth and metastatic potential of triple-negative breast cancer(TNBC). Therefore, a flora, which has apparent differences in normal breast tissue and breast cancer tissue, may become a potential impact of carcinogenic mechanisms or treatment intervention.

3. Intestinal flora participating in estrogen metabolism

The occurrence of breast cancer is closely related to the metabolic metabolism of the intestinal flora. The two are connected by Estrobolome, the genetic collection of the intestinal flora in estrogen^[9]. The flora with metabolic estrogen contains β -glucuronidase and β -glucosidase, which can increase the overall estrogen level and increase the risk of breast cancer. Estrogen levels or types of compounds can change the composition of intestinal flora and mediate breast cancer^[10]. Therefore, the interaction between the flora composition with the endogenous hormone and the estrogen-like compound may synergistically affect breast cancer development. Studies^[11] have found that *Bacteroides* have a very high degree of glucosamine and diversity. It is mainly metabolized with plant estrogen and can reduce the risk of breast cancer. However, some studies^[11] have found that β -glucuronidase enzymes that inhibit intestinal flora do not prevent the occurrence of breast cancer, which is different from most research results. Subsequent studies^[12] found that β -glucuronidase bacteria mainly exist in the two advantageous subgroups of the *Clostridium septum* cluster and *Clostridium coccoides*. Although the intestinal flora of patients with breast cancer mainly express β -glucuronidase, which bacteria are still controversial? Therefore, the interaction between β -glucuronidase and intestinal flora in breast cancer still requires subsequent experiments to confirm further.

4. The influence of intestinal flora affects obesity and becomes the potential effect of breast cancer

Studies^[13] have found that obesity can change the metabolic pathway of the intestinal flora, and believes that the intestinal flora is expected to become a hub to regulate obesity and breast cancer.

The intestinal flora promotes obesity through multiple mechanisms, such as regulating the Fenol X receptor in the liver^[14] or the inhibitory of Fasting induced activating factor(Fiaf). Studies^[15] have found that the number of Faecalibacterium prausnitzii, Firmicutes, and Blautia.spp in overweight or obese women has decreased significantly, which shows that the changes in intestinal flora are significantly connected with obesity. Research ^[16]further discovers Normal weight and international BMI hierarchical Ingenuity:> 30–≤ 35 (KG/M2) or II obesity:> 35 kg/m2 bacterial flora composition has apparent differences, which proves BMI is related to the baseline intestinal flora. However, there is currently controversy on the formation of fungus that leads to obesity. Most studies have found that obesity is related to reducing Firmicutes and Bacteroides. On the contrary. Some research^[17] found that a particular intestinal type composed of high proportions of bacteria will increase general inflammation and obesity. In addition, different species are different, such as Lactobacillus Reuters, Lactobacillus casei, and Lactobacterium Plantarum, and obesity risks are positive and negative^[18]. At present, intestinal flora disorders are related to obesity and have potential effects in obese patients. Nevertheless, the composition of the flora that promotes obesity is difficult to define because there are complicated distinction variables such as host genes and diet. Presently, related research only proves that the intestinal flora composition has changed, and the formation of fungal flora composition and the development of breast cancer and its mechanism is still unknown. The subsequent research proves.

5. Diet changes the intestinal tract and breast flora to promote the occurrence of breast cancer

Eat in the complex interconnection between human flora, estrogen metabolism, and its impact on breast cancer recurrence and metastasis potential. Studies^[19] have found that The Bacterium lactis in the mammary tissue of the Mediterranean diet monkey is ten times that of the western diet monkey mammary tissue, which may increase the characteristics of anti-cancer. In addition, high sugar, high-fat, low-fiber, and low-activity diet will cause the number of bacteria containing high-level β -glucuronidase, the production of short-chain fatty acids decreases, and increases the risk of breast cancer^[20]. On the contrary, high dietary fiber avoids "intestinal leakage syndrome" and its related inflammation and promotes the production of short-chain fatty acids and intestinal alkaline phosphatases. Together, the two strengthen the colon mucosa's close connection and reduce carcinogenic potential. The latest study^[21] found that CloStridium Hathewayi is related to higher levels of total and soluble dietary fiber, positively related to the β -glucuronidase activity. In addition, lignin is a substance that suppresses estrogen synthesis and metabolism, anti-vascular generation, anti-metastasis, and epic-ending genetic effects, and play an anti-cancer effect^[22]. Eggerthella transformed into plant estrogen, such as enteric lids. The latest study^[8] found that feces were transplanted between mice in the control group or high-fat diet (HFD) and that HFD induced and promoted tumor effects. Therefore, there is a relationship between intestinal flora and diet, and the intestinal micro-environment can be regulated by dirt and dietary fiber population through diet and transplant dietary fiber. Progress may become a new way to prevent and treat.

6. The flora mediums to the development of breast cancer through immune and inflammation reactions

Human immune dynamic balance depends on the continuous skewers between the flora and the host's immune cells. By affecting the metabolism, inflammation, and immune response, the flora can regulate the occurrence and development of local and distant cancer. Studies^[23] have found that StaphyLococcus in breast cancer tissue is related to the negative cancer gene traf4. Pelomonas, Bradyrhizobium, and Vascular generating factors VEGF-A are positive and negative, respectively.

Streptococcus and Propionibacterium are positively related to T cell activation genes. The lack of Staphylococcus and Propionibacterium in the cancer tissue is negatively related to the tumor immune function (symbols with poor prognosis PDGF-AA, PDGF-BB, and cancer gene TRAF4). The interaction between these flora and immune-related genes explains that the flora may affect breast cancer through immunity. The intestinal flora also increases TLR through PAMPS and activates NF-KB to cause continuous inflammation in the micro-environment of breast cancer ultimately. Chronic inflammation can affect the development of breast cancer by promoting inflammatory cytokines and immune cells such as TREG. Studies^[24] have found that changes in particular specific flora in the intestinal flora may lead to increased Treg production or reduction of pathogenic T cells, which may change the inflammatory response in the micro-environment of breast cancer. In addition, some bacterial metabolic products, such as butyl and propionic acid, have proven to play a powerful anti-inflammatory effect by regulating colon regulating T cells to achieve the role of inhibiting breast cancer development^[25]. Tannic acid can also directly enhance anti-tumor cytotoxic CD8⁺ T cell reactions by regulating the IL-12 signaling pathway. After oral administration of probiotics such as Bifidobacterium and lactobacillus, the immune system in breast cancer tissue can be supplemented and activated, promote the apoptosis of cancer cells, and play a positive role in the prognosis of breast cancer^[26]. However, the efficacy of probiotics in the clinical treatment of breast cancer is not apparent, and they cannot be used as an effective treatment plan for patients with breast cancer. In summary, the symbiotic human population may directly or indirectly regulate the process of immune response and inflammation and media the development of breast cancer.

7. The use of antibiotics leads to the development of breast cancer in the event of a flora

The use of antibiotics can cause intestinal flora disorders, which will help the reproduction of sexual pathogens. The use of antibiotics will lead to a structural imbalance of intestinal flora, which is conducive to the reproduction of opportunistic pathogens, and also affects the function of flora and the interdependence of host flora, which is harmful to host health. In the latest META analysis^[27], the type of antibiotics may be related to the risk of breast cancer. At the same time, there is a specific dose-dependency relationship between antibiotics and breast cancer. Excessive use of antibiotics will reduce the level of lignin-entering-enteric decide in plasma, or it may also be related to the reduction of Butyrate^[28]. In addition, an appropriate amount of antibiotics can reduce the risk of breast cancer by reducing estrogen to re-enter the intestinal-liver circulation level. At the same time, antibiotics also reduced the response to platinum-based chemotherapy and immunotherapy, which is related to the ecological balance that destroys the intestinal flora^[29]. The above shows that the complete flora composition plays a vital role in the effect of anti-cancer treatment. Compared with patients with low or low bacterial diversity, patients with a high diversity of sculpture flora are significantly longer in progress^[30]. Therefore, designing antibiotics for flora may help regulate the composition of gastrointestinal fungus to achieve a reaction to improve primary chemotherapy and immunotherapy while reducing the risk effect of breast cancer.

8. Flock composition is related to the staging type of breast cancer

The characteristics of the flora are also related to the molecular type of breast cancer. Some studies^[31] have found that, in TNBC, the incidence of diseases containing Arcanobacteriumhaemolyticum and Prevotellaceae is much higher than in normal tissue. In addition, the molecules derived from Plasmodium in the body and in vitro are related to the anti-breast cancer characteristics of adult mice. They may be used as the target of immunotherapy for TNBC. The intestinal flora is also related to the staging of breast cancer. The proportion of

FAECALIBACTERIUM Genus and Blautia is also different during different clinical stages and stages. Compared with patients with phase I breast cancer, Blautia in patients with phase III breast cancer is higher [24]. Among patients with high body fat, the prevalence of Akkermansia Muciniphila in stage 0-II breast cancer [32]. Patients with a higher or higher stage of breast cancer were found to have a higher G_Clostridium abundance [15]. Therefore, the composition of intestinal flora in the stage of breast cancer disease. In the future, the qualitative and quantitative analysis of the flora logo may provide helpful diagnosis, disease progress, and prognosis information for patients with breast cancer. It will help provide clues for designing new treatment strategies.

9. Conclusion

The diversity and steady state of breast and intestinal flora is the key to preventing breast cancer. It can play an anti-cancer role by stabilizing the ecological balance of flora to regulate the estrogen metabolism process, endocrine therapy resistance, obesity, and diet. Immunization, inflammatory reaction, and synergistic anti-cancer drugs mediated by the flora and its metabolites, as well as the participation of intestinal probiotics through oral or fecal transplantation in immune regulation, induction of tumor cell apoptosis, and reversal of flora ecological imbalance, may be potential targets for prevention and adjuvant treatment of breast cancer. Therefore, maintaining the ecological balance of the bacteria and removing the carcinogenic flora may be an important direction and hotspot for future research.

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