THE KEY ROLE OF HUMAN MICROBIOTA IN BREAST CANCER

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ABSTRACT: Sound evidence recognizes the microbiota as one of the major players in human health and disease, including cancer. Every human being is an holobiont, a shared human and microbial ecosystem, in which microbial composition is individually set by behaviours and environmental factors during the first years of life. Thereafter it is modulated by diet, physical activity, emotions and drugs (in particularly antibiotics and chemotherapeutics). As a consequence, a shift in medicine is needed toward a more comprehensive practice that takes into account every individual's genoma and, in addition, his or her metagenome, known as microbiome: a "microbiota revolution". As regards breast cancer (BC), a clear link between microbiota and oncogenesis is still to be confirmed. Specific microbes display unique features regulating their host niche in a number of body sites, which can result in an increased risk of cancer; in addition, gut microbiota composition plays a role in immune modulation within the intestinal barrier, affecting local and systemic inflammation, recognized drivers of cancer. Moreover, part of the bacterial gene mass inside the gut, constituting the so called “estrobolome”, influences the sexual hormonal balance and subsequentely may impact on the onset, progression and treatment of hormonal dependent cancers. Microbiota is also clearly involved in modulating the response to anticancer treatments, and above all to the emerging immunotherapy. Based on these premises, the microbiome is becoming a potential target, in order to enhance efficacy of antitumoral treatments as well as to lower their toxicity. The complex scenario that links microbiome composition to oncogenesis and response to anticancer treatments defines the frames of a new “oncobiotic” perspective.

KEYWORDS: Microbiome, Personalized Medicine, Integrative Oncology, Oncobiotic

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INTRODUCTION

Human microbiota includes organisms belonging to the domains of Bacteria, Archea, Eukarya and viruses, living in almost every site of our body (mostly in the gut, skin, vagina and mouth), in a number far exceeding our own human cells[1-3].

The increasing interest in structure and functions of human-associated microbial communities led the scientific community to build up a consortium, called "Human Microbiome Project (HMP), with the goal to analyse signature microbes in a large cohort of healthy subjects[4]. Each organ inside the body has its own specific microbiota composition, with a relevant inter-individual heterogeneity and different functions affecting physiologic activities, such as metabolism, immune system modulation and overall homeostasis.

Many factors, such as race, diet, maternal colonization, exercise, exposition to xenobiotics contribute to microbiome's individual composition, estabilished during the first years of childhood, and continue to influence its balance all life long[5-6].

Any perturbation of the microbiota's balance seems to have consequences for the host's homeostasis[7], potentially leading to metabolic disorders, allergies, inflammatory and autoimmune diseases[8].

Human microbiota plays a determinant role in the regulation of the innate and cell-mediated immunity, including the immune response against pathogenic organisms, through the intestinal barrier[5,9]. Microbes are also involved in metabolism of vitamins and xenobiotics, including anticancer drugs, modulating their pharmacokinetics, mechanism of action and toxicity[10].

Recently, sound evidences have linked microbiota to cancer development, progression and aggressiveness in different body sites, such as the stomach, colon, skin and lung, at least in 16–18% of cases [7,9,11,12,13,14,15,16,17], but its role in BC is still poorly understood.

Even though our knowledge is scarce, we know that metabolism, sexual hormones, stress management and immunity, in addition to breast tissue microenvironment, play a significant role in the onset and prognosis of BC.

In this review, we try to summarize the current evidence for the potential role of microbiota in each one of these aspects and explore correlations between gut microbiota and BC supporting a potential gut-breast axis (Fig.1).

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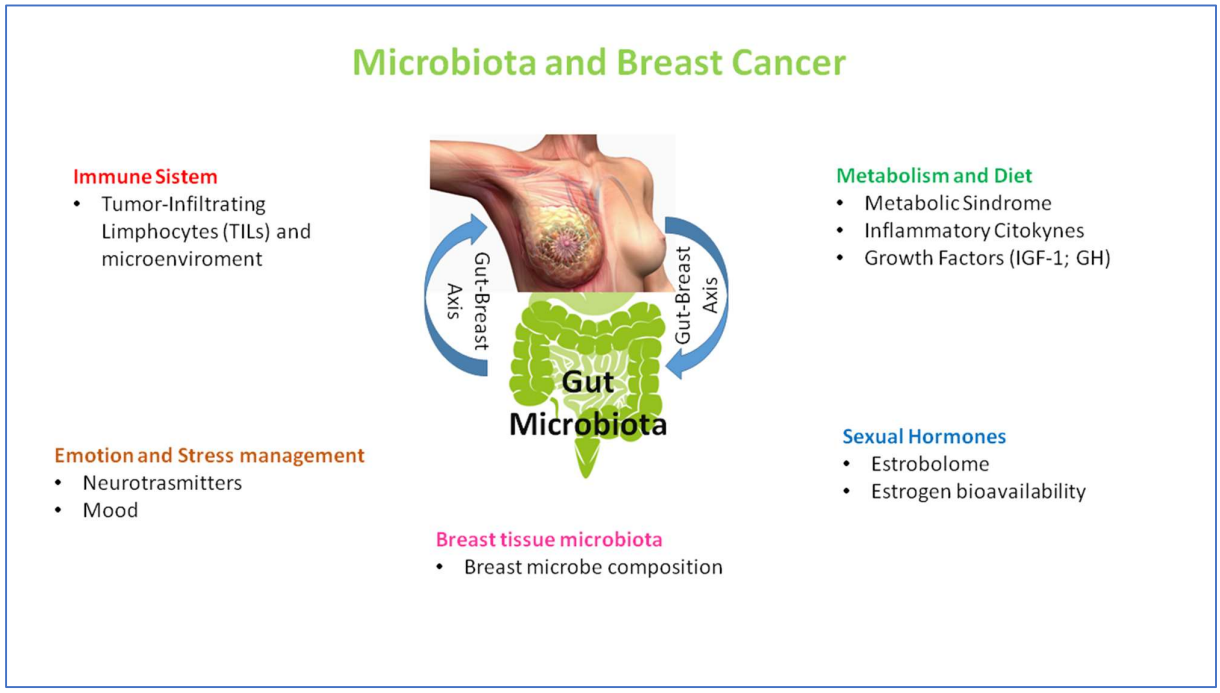

Fig. 1. Correlations between gut microbiota and breast cancer supporting a potential gut-breast axis.

MICROBIOTA AND CANCER

The cancerogenesis is the result of genetic and environmental factors, among which chronic inflammation, cytokines and oxidative stress play a key role[18,]. Gut microbiota is involved in many chronic inflammatory conditions[20] and is already recognized as an orchestrator in mechanisms related to tumor onset and progression, at least in animal models and gastro-intestinal cancers[21,22,23]. For instance, microbial products such as colibactin produced by *Escherichia coli*[24] and cytolethal distending toxin (CDT) produced by different proteobacteria, cause DNA damage in mammalian cells, promoting colorectal carcinogenesis[25,26].

Oncogenic type 1 strains of *Helicobacter pylori* produce a protein (Cag A) that, when injected into the host cell's cytoplasm, can promote cancer by acting on β-catenin, through the up-regulation of genes involved in proliferation, cell survival and migration, angiogenesis and carcinogenesis.
Numerous microbes, such as the colon cancer associated *Fusobacterium nucleatum*, activate NF-κB, a major regulator of inflammation within the tumor microenvironment[27].

Dietary fibre fermentation leads to the production of SCFAs (propionic, acetic and butyric acid are the most common ones), which reduce the inflammatory state of myeloid cells and regulate T cells in colon, improving intratumoral inflammation[28,29,30].

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In addition, several microbial enzymes, encoded by major taxa, including hydrolases, lyases, oxidoreductases, glucuronidases and transferases are involved in the metabolism of nutrients, food additives, drugs and environmental pollutants related to cancerogenesis[31].

More recently, emerging evidence links dysbiosis to cancer onset in extra-intestinal sites, by promoting systemic inflammation[32,33], modulating immune system and influencing host's metabolites derived from diet and xenobiotics.

Based on these premises, there is a growing interdisciplinary interest to achieve a deeper understanding of host–microbiome interactions for an integrative approach to cancer patients[34,35] .

Even breast cancer's onset and progression are regulated by genetic and environmental factors such as obesity, lack of exercise, alcohol, radiations, hormonal replacement therapy. Individual behaviors have also direct implications in microbiome composition, so that recent studies have highlighted the association between microbial alterations and those risk factors for BC, through metabolic and immunitary pathways[36] , hormonal balance and cancer microenvironment[37].

More recently, the role of breast tissue's microbiota in BC is emerging. Microbiome's signatures differ between a breast tumor and healthy tissue, but it is still unclear whether breast dysbiosis is a consequence or a cause of carcinogenesis[38,39,40,41]. Furthermore, the total bacterial DNA load was reduced in tumor versus paired healthy breast tissue, and inversely correlated with advanced disease. This evidence could suggest that more than single species associated with BC, like in the infective diseases model, cancerogenesis might depend on a multimodal model based on bacterial diversity and competition.

GUT-BREAST AXIS AND BREAST TISSUE MICROBIOTA

Despite the presence of a specific microbiota in human milk has been known for several years [42] , only in the last few years has breast tissue microbiota been evaluated irrespective of lactation and in correlation with cancer [43,44,45,46,47]. These works agree that breast tissues have a unique microbiota, distinct from other body sites, characterized by a predominance of *Proteobacteria* as the most abundant phylum, followed by *Firmicutes*[43,46].

In a study on 20 breast cancer patients, comparing tumoral breast tissues and the normal adjacent ones, the five most represented phyla were *Proteobacteria, Firmicutes, Actinobacteria, Bacteroidetes and Verrucomicrobia* and a greater amount of *Methylobacterium radiotolerans* was seen in tumor tissue, while *Sphingomonas yanoikuyae* was relatively enriched in non-cancerous one[44].

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A study analyzing breast tissue sampled with 16S rRNA sequencing from two populations of 81 women in Canada and Ireland found *proteobacteria* as the principal phylum. The most abundant taxa were quite different in the two populations, resulting *Bacillus* (11.4%) prevalent in the Canadian samples, while *Enterobacteriaceae* (30.8%) in the Irish women[43]. Costantini et al. showed that the genus *Ralstonia* is the most representative in breast surgical and needle biopsies performed in a Mediterranean population[49].

In other similar studies, it was seen that tumoral cells were colonized by *Streptococcus pyogenes* and *Lactobacillus rossiae*, which interfere in estrogen metabolism and cellular maturation. In addition, *Listeria fleischmannii* influences the genes regulating the epithelial-mesenchymal transition process, while *Haemophilus influenza,* which was found in the adjacent non-cancerous tissue samples, promotes the inflammatory immune response and tumor growth[48].

More recent studies showed that, in women affected by BC, the microbiota of normal breast tissues is more similar to adjacent tumour tissue than to the one sampled from healthy women[50], supporting the hypothesis that breast tissue dysbiosis may be antecedent to carcinogenic event[49] and could establish a microenvironment prone to cancer.

To date, there is no clear proof of how bacteria get to the breast tissue.
In addition to the entrance from the nipple, some studies suggest the presence of a gut-breast axis, along which the intestinal bacteria could reach the mammary gland[51].
This endogenous route of bacterial translocation should involve dendritic cells, which can sample bacteria directly from the gut lumen or after passing through the intestinal barrier, priming T cells in the Peyer's patches or after reaching the mesenteric lymph nodes[52].
Albesharat *et al* showed the same bacteria strains in maternal milk and faeces from mother and her child, suggesting a vertical transfer of intestinal bacteria from the mother's gut to her milk and subsequently to the new-born[53]. Further studies showed that mammary intestinal dysbiosis may lead to lactational mastitis, induced by opportunistic pathogenic bacteria outgrowing the commensal germs[54] and orally administered probiotics isolated from human milk may be proven more effective than antibiotics in treating mastitis itself[55]. Furthermore, the isolation of strains of *Enterococcus*, *Streptococcus*, *Staphylococcus*, and *Propionibacterium* in neonatal umbilical cord blood of caesarean-born babies further support the idea that bacteria can reach the mammary ducts via the bloodstream[56].
Following this pathway, a gut inflammatory process, driven by intestinal dysbiosis, through an impaired intestinal barrier or "leaky gut", may lead to systemic chronic condition and eventually to carcinogenesis, sustained by overexpression of COX2 and increased production of prostaglandins, as showed in several preclinical and clinical studies[57].

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The chronic inflammation-based cancerogenesis seems to be driven by a multiagent and multifactorial process rather than a single germ mechanism.

Xuan and colleagues found that breast tumour tissues had a significantly reduced amount and richness of bacteria compared to healthy controls[47].

In a case-control study in post-menopausal women with BC, fecal microbiota showed less diversity and overall different composition compared to controls[58], suggesting an involvement of microbiome composition in BC cancerogenesis[47].

Even for non-malignant or premalignant breast diseases, such as mastitis or atypical ductal hyperplasia, lower microbial diversity seems to play a role, by promoting increased growth of opportunistic pathogens[54], which could pave the way for a potential use of breast tissue dysbiosis assessment as predictive tool and of prebiotics/probiotics in precancerous conditions, in order to prevent cancer development.

MICROBIOTA AND IMMUNE SYSTEM

Microbiota is a key player in the induction, training and functioning of the host's immune system.

The components of the innate and adaptive immune system, through a symbiotic relationship and a continuous cross-talk with different microbial communities, allow protective responses against foreign antigens and pathogens while providing tolerance to harmless antigens and commensal bacteria[59].

This alliance between immune system and microbiota takes place mainly in the skin and the gastrointestinal tract with its associated lymphoid tissue (GALT), where the largest populations of immune cells and commensal germs reside.

In the gut, the mucosal wall, constituted by the combined action of epithelial cells, mucus layer, IgA and antimicrobial peptides, has a fundamental role in recognizing healthy nutrients and potential noxae, avoiding the microbial translocation through the barrier and promoting the postnatal development of the immune system[60,61,62,].

When major changes in gut microbiota's composition and diversity occur, following stressful chronic conditions, poor diet, lack of exercise or antibiotics abuse, immune-mediated diseases, such as colitis and inflammatory bowel disease (IBD) may take place.

The compromised intestinal barrier in individuals with chronic gut dysbiosis leads to submucosal translocation of bacteria, triggering persistent activation of immune-mediated inflammatory responses, both at a local and systemic level, eventually

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leading to cancer of the colon and/or in extraintestinal sites. This cancerogenic process may be mediated by inflammatory cytochines, bacterial metabolites and regulatory T cells inhibition, but could also be due to direct translocation of pathogenic germs to distant organs and tissues.

The emergent role of immune microenviroment in BC, and above all of tumour-infiltrating lymphocytes (TILs), makes the tight relationship between microbiota and the interplay between proinflammatory and antinflammatory immune mediators a promising field of translational and clinical research in BC[65].

TILs are recognized as a prognostic indicator, for example in triple-negative BC (TNBC), and are associated with disease-free (DFS) and overall survival (OS).

Results from two phase III randomized adjuvant trials (ECOG 2197 and ECOG 1199) conducted on 481 cancer patients, with a median follow-up of 10.6 years, showed higher stromal TILs scores associated with better prognosis. In particular, for every 10% increase in TILs, a 18% reduction of risk of distant recurrence (p = .04), and 19% reduced risk of death (p = .01) were observed[66].

In recent times, immunotherapy is emerging as a promising strategy against hematopoietic and solid tumors which do not respond to conventional therapies[67,68].

The rationale of this treatment is that immune system surveillance can be reactivated by blocking the expedients used by cancer cells to evade the antitumor response[67,69,70].
Unfortunately, a significant heterogeneity of immune response to this kind of treatments exists; moreover, immune checkpoint inhibitors (ICI) may generate immune-related adverse effects, in particular colitis and pituitary gland inflammation in response to CTLA4 antibodies, and thyroid dysfunction and pneumonitis following blockade of the PD1–PDL1 interaction.
In this scenario, gut microbiota seems to play an important role, and a manipulation of the microbical colonies and their composition, through antibiotics, prebiotics or probiotics, can influence either the efficacy of immunotherapeutics[71,72,73,74] and their toxicity[75].

Gut microbiota, through TLR4 signalling, stimulate myeloid and tumor infiltrating cells for responsiveness to intratumoral treatment with the TLR9 agonist CpG-oligodeoxynucleotide (CpG-ODN)[73,76,77,78]. CpG-ODNs induce myeloid cells to

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produce proinflammatory citokines, such as tumour necrosis factor (TNF) and IL-12, in a proportional manner with the presence of Gram-negative *Alistipes* and Gram-positive *Ruminococcus* genera in fecal microbiota of mice. On the other hand, *Lactobacillus* genus is negatively correlated to these cytokines' production[79]. It was also seen that recolonization of *Alistipes shahii* after antibiotic therapy leads myeloid cells to regain the ability of producing TNF, while oral somministration of *L. fermentum* inhibits TNF synthesis[73].

In a study[80] including 249 patients with different types of cancer (melanoma, lung, kidney, bladder) treated with ICIs, patients affected by antibiotic-induced dysbiosis, with a significant reduction of the genus *Akkermansia muciniphila* in fecal samples, showed a general reduction of therapeutic response to anti PD-1 / PDL-1 and consequently a lower progression-free survival of the disease (PFS) and total survival (OS). To test the effective correlation between *Akkermansia muciniphila* and the response to ICIs, germ-free mice models, receiving faecal microbiota from respondents with marked presence of *Akkermansia muciniphila*, demonstrated a superior therapeutic response, a significant reduction in tumor size and increased immune cells accumulation in cancer microenvironment.

In a recent prospective study[81], Spencer et al showed that in 146 melanoma patients, probiotics and antibiotics use at baseline were associated with lower alpha diversity (AD) in stool samples ($p=0.02$) and patients with higher consume of plant based diet had higher odds of response to immunotherapeutics (OR=5.3, 95% CI: 1.02-26.3).

MICROBIOTA AND METABOLISM

Metabolic syndrome, obesity and insulin resistance significantly affect BC incidence and mortality, especially among post-menopausal women[82,83].

Gut microbiota composition is a major player of intestinal barrier integrity, inflammation and obesity, as shown in germ-free mice models after fecal transplant from obese people[84,85].

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For instance, a fecal abundance of *Ralstonia pickettii* was found increased in obese subjects with pre-diabetes and type 2 diabetes mellitus, and *Ralstonia pickettii*-treated mice showed reduced glucose tolerance. This led the authors to suppose that low-grade inflammation, potentially initiated by the intestinal microbiota, could be a driving force in the development of insulin resistance in obesity[86].

Microbial dysbiosis is involved in low-grade chronic inflammation-mediated carcinogenesis, at least in gastric and intestinal cancers[87], while a clear correlation with BC is still to be confirmed[88].
An association in mice between gastric infection by pathogenic Helicobaster hepaticus, TNF-alfa expression and rapidly growing tumors in mammary tissue has been showed[89], which is consistent with the findings of elevated TNF-alfa and poor BC outcomes in women.
Similarly, *Akkermansia muciniphila* levels and inflammatory cytokine IL6, associated with BMI in obese BC patients, lead to poorer clinical outcomes[90]. The loss of *Akkermansia muciniphila* allows the lipopolysaccharide (LPS) and other endotoxins to leak, through an altered intestinal barrier, into the blood stream, causing chronic inflammation in different districts of the body, including breast tissue.

On the contrary, abundance in the gut of *Bifidobacterium* and *Faecalibacterium Prausnitzii* following a plant based diet is associated with anti-inflammatory and anti-tumoral effects[91,92].

The gut microbiota is also involved in the production of a large amount of metabolites, that might interfere with cancerogenesis in extraintestinal cancers, including BC.

Most of these metabolites derive from aminoacidic metabolism, but the exact relations between proteic dietary intake and microbiome's manipulation are yet to be established.

Among the most studied microbiota derived metabolites, trimethylammine (TMA) and its oxidated form (TMAO) stand for a perfect example of diet-microbiota interaction: phosphatidylcholine and L-carnitine, aboundant in red meat, are metabolized in TMA by several intestinal bacterial species and oxidated by the liver to TMAO, whose plasma levels are associated to progression of atherosclerosis, platelet aggregation and certain cancer types, probably through inflammatory pathways[93,94,95,96].

Microbiota's composition and functions are modulated by nutrients introduced with diet: vegan people are endowed with a microbiota which poorly produces TMA, even when its precursors are occasionally consumed[93]. On the contrary, patients who undergo bariatric surgery show high levels of circulating TMAO, probably as a result of an aerobic gut environment, the perfect condition for the production of this metabolite[97,98,99,100].

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In a recent study, early stage BC patients had reduced abundance in fecal DNA of genes responsible for bacterial cadaverine production, as compared to healthy women; the microbiome derived cadaverine affects the behavior of BC cells, showing a tumor suppressor role[101].

In addition, short chain fatty acids (SCFAs), products of bacterial fermentation of complex polysaccharides in the distal gut, are well known modulators for cell invasion, apoptosis and outcomes in BC[102,103,104,105,106,107]. Other bacterial metabolites, such as lithocholic acid produced in the small intestine and colon by commensal germs, can stimulate oxidative and nitrosative stress, thus inhibiting BC progression and metastases and are involved in cellular signaling, by binding to G-protein-coupled bile acid receptor 1 (also known as TGR5) and receptor FXR[108,109,110]. Both TGR5 and FXR regulate important metabolic pathways, related to the risks of obesity, steatosis, impaired tolerance to glucose and insulin resistance, generally recognized as risk factors for BC[108,110,111,112,113,114].

ESTROBOLOME

Gut microbiome is one of the major regulators of circulating estrogens[115,116], which are involved in the onset, progression and outcomes of the majority of breast cancers[117,118]. Sexual hormones are normally conjugated and excreted by the liver into the intestinal lumen, where particular species of bacteria, constituting the so called "estrobolome", endowed with β-glucuronidase activity, may deconjugate estrogens, increasing their reabsorption through the entero-epathic circulation.

Common bacteria in human microbiota provided with the β-glucuronidase enzyme include *Collinsella, Edwardsiella, Alistipes, Bacteroides Bifidobacterium, Citrobacter, Clostridium, Dermabacter, Escherichia, Faecalibacterium, Lactobacillus, Marvinbryantia, Propionibacterium, Roseburia, Tannerella*[119,120,121] .

Changes in estrobolome composition induced by lifestyles and drugs, including antibiotics, modify systemic levels of estrogen and its metabolites, even in hormonal dependent BC patients and survivors[122,123,124]. Several studies link BC progression to the entero-hepatic circulation of estrogens[126], and an abundance of β-Glucuronidase signaling was identified in nipple aspirate fluid of BC survivors[126], while BC tissue shows higher concentrations of estrogen metabolites compared to normal breast tissue[127].

A small study comparing 10 premenopausal women, consuming a "Western diet" (with high fat intake), with 10 vegetarians with a high fiber and moderate fat diet, showed estrogen levels three times higher in vegetarians' feces and 15% to 20% lower in serum[128]. In another study, immigrants from Asia, consuming a low fat diet, had systemic estrogen levels 30% lower than American women eating a high-fat diet[129], possibly via the estrobolome, although additional factors including lifestyle, exercise and supplements may contribute[130].

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Intestinal bacteria can turn some plant lignans into mammalian lignans, enterodiol and enterolactone, which may act as selective modulators of estrogens with protective effects against BC[131,132], and improve survival in postmenopausal BC patients[133].

On the other hand, sex hormones affect the gut's microbiome and estrogen deprivation following menopause could be responsible for major modifications of microbiota composition later in women's life.

Furthermore, gut microbiota contributes to the metabolism of endocrine disrupting chemicals, such as bisphenol-A, affecting their plasmatic levels and toxicodynamics[135]. This mechanism might have a deep impact on clinical management of BC patients, since the emerging evidence of an association between exposure to endocrine disruptor chemicals, metabolic disorders, diabetes and cancer[136].

MICROBIOTA AND EMOTIONS

Emerging evidence is linking microbiome's composition with different outcomes in psycho-social behaviors and emotions[137], which evoke endocrine and metabolic responses involved in maintaining health, favoring adaptation to the environment and predisposition for chronic diseases.

Microbiota-gut-brain axis, a bridge between lifestyle habits, gastro-intestinal functions and mental health, includes several pathways and communicates via the immune system, direct enteric nervous system routes and bacterial metabolites.

Many BC patients experience cancer-related distress symptoms, anxiety and depression, during and after oncological treatments[138]. Negative emotions and prolonged stress stimulate the production of pro-inflammatory cytokines and the release of corticotrophin, adrenaline, noradrenaline and cortisol by the hypothalamic-pituitary-adrenal (HPA) axis[139,140,141,142,143]. These stress-related hormones act as growth factors for pathogens such as *E. coli* (E. coli0157), *Yersinia enterocolitic* and *Pseudomonas aeruginosa* that increase the synthesis of pro-inflammatory cytokines[144].

While the influence of mind on gut's functioning is intuitive and well estabilished[145], the role that gut microbiota plays on mental health is less clear and self-evident. Yet, dysbiosis driven by alterations of the brain reward system and bad behaviors (namely, lack of exercise and overcomsumption of red meats and ultraprocessed foods) can be responsible for poor psycho-social outcomes and stress-related disorders[146,147,148].

Patients with functional gastro-intestinal disorders (FGIDs) produce a great amount of cortisol[149], are more prone to hypersensibility phenomena such as pain[150] and present higher levels of anxiety and depression.

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Pathogenic microbes, overgrowing in patients with dysbiosis, produce toxins, which are released into the blood stream[151,152,153], directly influencing mental health and mood disorders, such as butyrate-producing *Faecalibacterium* bacteria[154]. Gut microbiota is also able to produce other neurotransmitters, recognized through the faecal metagenome analysis, such as serotonin, norepinephrine, dopamine, 3,4-dihydroxyhenylacetic acid and gamma-aminobutyric acid (GABA), positively associated to anxiety and depression.

Scientific evidences suggest a link between mental health and other microbiome derived metabolites, like bile acids[155], acetic acid and propionic acid[156], volatile organic metabolites[157], fecal proteases[158], lactate, pyruvate[159], amino acids[160] (alanine, pyroglutamic acid), tyrosine, lysine, leucine[159], phenols[160], polyunsaturated fatty acids (PUFAs)[161] and short chain fatty acids (SCFAs)[162].

Several studies[163,164,165] have also shown that stress-induced and estrogen-induced visceral pain is linked to epigenetic modification at the spinal cord, mediated by SCFAs. In other terms, gut-microbial products can affect chromatin plasticity in host's brain, leading to potential changes in neuronal transcription and eventually host behaviours[166].

In an interesting study, gut microbiome diversity, assessed in fecal samples, was associated to better psycho-social outcomes in BS survivors, with less anxiety, depression and fatigue[167].

The increasing rates of long-term survival in women affected by BC impose quality of life and mental health as absolute needs to be addressed properly. Furthermore, an appropriate management of mental health issues in BC patients, frequently facing gastrointestinal disorders, psychological distress, anxiety and depression, is mandatory not only for their quality of life, but also for potential implications in cancerogenesis and oncologic outcomes, through processes mediated by immune imbalance and proinflammatory citokines. Based on these premises, a new frontier of research is studying how microbiota modulation could contribute to neuro-psychological adjustments[168,169] in BC women undergoing oncological treatments.

CONCLUSIONS

Many relevant evidences are unveiling profound links between human microbiota composition and several physiological and pathological processes, including cancer.

While gut dysbiosis is clearly linked by a cause-effect relation to many diseases and pathological conditions, it is still unclear whether the recent evidence of breast tissue dysbiosis represents a cause or a consequence of cancer.

The recognition of individual microbical profiles in every human being is driving a new model of precision oncology, tailored not only to genetic features of the subject

and the cancer itself, but also to his or her microbiome signatures, and will orientate preventive and predictive measures in the next future.

Given this key role of microbical communities and their plasticity, i.e. the possibility to be modulated through behavioral changes and antibiotic, prebiotics and probiotics, microbiota must be considered a potential target in order to enhance efficacy, reduce toxicities and alleviate side effects of antitumoral therapies.

In addition, microbiome manipulation becomes strategic in order to empower immunitary, metabolic, hormonal and psychological approaches to cancer patients and further improve oncologic outcomes.

As regards BC, microbiota is involved in several pathways, from intestinal patterns of metabolic syndrome, to immune system modulation, sexual hormones balance and bioavailability, stress management and directly through breast tissue dysbiosis.

Advancing this brand new oncobiotic science will probably lead us to significant improvements in the fight against cancer for the years to come.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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