Microbiome—Microbial Metabolome—Cancer Cell Interactions in Breast Cancer—Familiar, but Unexplored

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Abstract: Breast cancer is a leading cause of death among women worldwide. Dysbiosis, an aberrant composition of the microbiome, characterizes breast cancer. In this review we discuss the changes to the metabolism of breast cancer cells, as well as the composition of the breast and gut microbiome in breast cancer. The role of the breast microbiome in breast cancer is unresolved, nevertheless it seems that the gut microbiome does have a role in the pathology of the disease. The gut microbiome secretes bioactive metabolites (reactivated estrogens, short chain fatty acids, amino acid metabolites, or secondary bile acids) that modulate breast cancer. We highlight the bacterial species or taxonomical units that generate these metabolites, we show their mode of action, and discuss how the metabolites affect mitochondrial metabolism and other molecular events in breast cancer. These metabolites resemble human hormones, as they are produced in a "gland" (in this case, the microbiome) and they are subsequently transferred to distant sites of action through the circulation. These metabolites appear to be important constituents of the tumor microenvironment. Finally, we discuss how bacterial dysbiosis interferes with breast cancer treatment through interfering with chemotherapeutic drug metabolism and availability.

Keywords: breast cancer; microbiome; estrogen deconjugation; lithocholic acid; secondary bile acids; cadaverine; TGR5; FFAR; TAAR; mitochondrial metabolism; OXPHOS

1. Breast Cancer, a Leading Cause of Death among Women

Breast cancer is the most common cancer among women, with the estimated age-adjusted annual incidence of breast cancer in Europe in 2012 being 94.2/100,000 [1], with similar numbers in the United States (US) or the United Kingdom (UK) [2,3]. The estimated age-adjusted annual mortality is 23.1/100,000 for breast cancer in Europe [1]. In 2019, in the US, the number of newly diagnosed

invasive breast cancer cases is estimated to be 268,000, while the newly diagnosed in situ cases are estimated to be around 62,930 [2]. In 2019, 41,760 women out of these numbers are expected to die of breast cancer in the US [2]. The five year survival of breast cancer is over 80% in developed countries due to screening programs and the consequent early detection [4].

Several risk factors for breast cancer had been described, nevertheless the majority of the newly diagnosed women have no obvious risk factors [3]. The risk for breast cancer increases over the age. The majority of the patients are diagnosed after menopause, after the age of 50. The incidence rates for in situ breast cancer in the UK were the highest in people that were aged 65–69 (2013–2015) [3]. Extended female hormone exposure by the use of hormone-replacement therapy or early menarche or late menopause also increases the risk for breast cancer [3]. Mutations in the *BRCA1* and *BRCA2* genes represent a predisposing factor for breast cancer [5], similarly to a family history of breast cancer or personal history of neoplastic diseases or breast cancer [3] Finally, dense breast is an independent risk factor of breast cancer [1,6]. Physical activity, successful pregnancies, and lactation are protective factors [2,3].

In Western countries there are organized screening programs from the age of 40–45 to 65 years of age for women with bi-annual intervals [7–10]. The first step in screening is mammography, followed by ultrasonography in breast cancer-suspect individuals [1]. The final diagnosis is based on needle biopsy. Breast cancer screening does not reach the whole target population, for example, in Hungary only around 50% of the target population undergoes screening [7].

The treatment schemes for breast cancer include the surgical procedures, chemotherapy, targeted therapy, endocrine-, and radiotherapy. Chemotherapy regimens contain anthracyclines, cyclophosphamides, taxanes, antimetabolites (5-fluorouracil, gemcitabine, capecitabine), and navelbine that targets mitotic tubules [1]. Targeted therapy in breast cancer is used in the management of HER2 positive cases and it involves monoclonal antibodies against the HER2 receptor (trastuzumab, pertuzumab, and trastuzumab-emtansine, in which the humanized HER2 antibody is conjugated to DM1, a tubulin toxin) and the tyrosine kinase inhibitor lapatinib [11]. Endocrine therapy, which involves selective estrogen receptor modulators (SERMs), aromatase inhibitors, and gonadotropin-releasing hormone (GNRH)-analogs, is the standard treatment for hormone-receptor positive breast cancer [11]. There are new inhibitors with potential use in breast cancer therapy, such as poly(ADP-ribose) polymerase (PARP) inhibitors [12–14] or the inhibitors of CDK4/6 (cyclin-dependent kinases) [15].

For further information regarding the clinico-pathology of breast cancer, we refer the Readers to the relevant guidelines [1,16] and draw the attention of the Readers to use the most up-to-date version of the guidelines.

2. The Dysregulation of Metabolism in Breast Cancer

Breast cancer cells show characteristic pathological changes in metabolism and, in line with that, the pathological metabolism of the host (e.g., obesity, metabolic syndrome, type II diabetes) increases breast cancer risk that we discuss below briefly; for comprehensive reviews, see [17–21] and Table 1.

Originally, Otto Warburg suggested that cancer cells switch for "aerobic glycolysis" that are characterized by increased glycolytic flux and decreased mitochondrial oxidation that supports the high proliferative capacity of cancer cells [22]. Indeed, breast cancer cells were shown to exert features of Warburg metabolism [23], and in line with that, reverting Warburg metabolism can slow down the proliferation of breast cancer cells or declutch cell death, too [24]. Later, besides changes to glycolysis and mitochondrial oxidation, other metabolic pathways were shown to be upregulated in breast cancer [25], such as glutamine metabolism [26], lipid and fatty acid [27–31], glutamine-serine pathway [26,32,33], protein translation [34], or cholesterol metabolism [21]. These changes are the consequences of a complex rearrangement of the cellular energy sensor web, such as the activation of hypoxia-inducible factors (HIFs) [35,36], mammalian target of rapamcyin (mTOR) [37–40], estrogen-related receptors [41], estrogen receptors [19], phosphatidyl-inositol-3 kinase (PI3 kinase) [42,43], AMP-activated protein kinase

(AMPK) [44,45], peroxisome proliferator-activated receptor cofactor-1α and β (PGC1α and PGC1β) [46,47], or nuclear respiratory factor 1 (NRF1) [46].

Metabolic changes have important pathological roles, as these changes have important roles in supporting proliferation [24,48], angiogenesis [49], or epithelial-to-mesenchymal transition (EMT) [50,51]. It is also very likely that two risk factors of breast cancer, obesity or type II diabetes, at least in part, increase risk through predisposing for changes towards pathological metabolism in (cancer) cells [52–57]. Breast cancer metabolism is an attractive new target for chemotherapeutic interventions [19]; furthermore, changes to metabolism in breast cancer can be used to monitor the efficiency of chemotherapy [58] and changes to cancer cell metabolism can be exploited to overcome chemotherapy resistance [19,59,60].

There are four molecular (intrinsic) subtypes of breast cancer: luminal A (ER+, low proliferative capacity), luminal B (ER+, high proliferative capacity), HER2-enriched (ER−, HER2+), and basal-type (triple negative breast cancer, TNBC) [61]. All of the subtypes have metabolic alterations and there is compelling evidence that it is possible to discriminate between the intrinsic subtypes as a function of changes to metabolism [30] (see Table 1). These results also highlight the strong contribution of pathological metabolism of breast cancer cells to proliferative capacity and aggressiveness.

Table 1. Metabolic changes in the intrinsic subtypes of breast cancer. Empty squares stand for no data. Abbreviations: ASCT2/SLC1A5, amino acid transporter-2; ER, estrogen receptor; GDH/H6PD, glutamate dehydrogenase; GLS1, glutaminase 1; HER2, human epidermal growth factor 2 receptor; PgR, progesterone receptor; SLC, solute carrier transporters.

	Breast Cancer	Luminal A	Luminal B		HER2+	TNBC (~Basal-like)	Ref.
			HER2−	HER2+			
Receptor Status according to [1]	N/A	ER+, HER2−, Ki67 low, PgR high Low-Risk Molecular Signature (If Available)	ER+, HER2−, either Ki67high or PgR low High-Risk Molecular Signature (If Available)	ER+, HER2+, any Ki67, any PgR	HER2+, ER−, and PgR−	HER2-, ER-, and PgR−	[1]
Cholesterol and oxysterol metabolism	Lipid and cholesterol metabolism supports tamoxifen resistance. Increases in serum cholesterol is a risk factor for breast cancer.	27-hydroxycholesterol supports the growth of ER+ breast cancer cells	27-hydroxycholesterol supports the growth of ER+ breast cancer cells	27-hydroxycholesterol supports the growth of ER+ breast cancer cells			[62–68]
Glycolysis	upregulated	low	intermediate/low	intermediate/low	intermediate/low	high	[69–72]
Pentose-phosphate pathway	upregulated	low	low	low	high	highest	[73]
Glutamine-proline-glycine metabolism	upregulated to serve energy homeostasis and protein and nucleotide biosynthesis	SLC6A14, SLC7A11 upregulated	High expression of glutamine-proline enzymes in Mychigh tumors SLC6A14, SLC7A11 upregulated	High expression of glutamine-proline enzymes in Myc high tumors SLC6A14, SLC7A11 upregulated	highest expression of GLS1, GDH, ASCT, SLC7A5, SLC1A5 upregulated highest level of glutamine metabolism among the intrinsic types	SLC7A11, SLC1A5 upregulated increased glutamine uptake	[37–39,74,75]
Protein translation	upregulated	highest	high	high			[76–78]

The discovery of differences between the metabolism of cell types of breast cancer makes the landscape of the metabolic changes more complex. Namely, cancer stroma cells (dubbed non-tumorigenic cancer cells) or cancer-associated fibroblasts indeed rely on Warburg metabolism; however, the metabolism of cancer stem cells is dominated by mitochondrial oxidation [49,60,79–88]. Cancer stem cells in breast cancer have two different forms, the mesenchymal-like cancer stem cells are CD44+/CD24−, while the epithelial-like cancer stem cells are aldehyde dehydrogenase 1 family, member A1 (ALDH1) positive [89,90]. The inhibition of mitochondrial oxidation can increase the proportions of cancer stroma to stem cells, facilitating the efficiency of conventional chemotherapy that primarily targets stromal cells [86,91–93]. Larger proportions of stem cells than ER+ positive cancers characterize TNBCs [82,83]. In support of that observation, the TCA cycle is more active in TNBC as compared to the ER+ cases [94,95]. There is accumulating evidence that the metabolism of circulating cancer cells change to a more oxidative phosphorylation-dependent metabolism [19].

The actual shape of cancer cell metabolism is sharply regulated by the tumor microenvironment: the abundance of collagen [96], the circulating cytokines [97], or the adipocytes surrounding the tumor [52] are all major determinants of cancer cell metabolism. In this review, we add a new component to this list, bacterial metabolites, which are produced by the gut microbiome.

3. Microbiome Dysbiosis in Breast Cancer

Dysbiosis denotes an abnormal composition or maladaptation of the microbial community (the microbiome) of a given organism or a given compartment of the organism. Dysbiosis disrupts the normal function of the microbial community through hampering the symbiotic relationships in the community (e.g., cross-feeding). Dysbiosis can occur when the composition or the bacterial biomass changes (i.e., the proportions of certain species change within the community) [98]. Dysbiosis characterizes several neoplastic diseases [99–104], including breast cancer [91,105–124]. Although the largest microbial community of the human body resides in the gastrointestinal tract, when discussing dysbiosis in breast cancer, the breast's own microbiome also has to be taken into account. This, yet, ill-characterized, bacterial community that is found in the milk-ducts of the breast also exhibits dysbiosis in breast cancer. Studies have shown dysbiosis in the breast microbiome [105–115] (Table 2) and in the fecal microbiome [91,116–123] (Table 3).

Table 2. Studies investigating changes to the breast microbiome in breast cancer. Abbreviations: ER, estrogen receptor; CNB, Core needle biopsies; HER2, herceptin receptor/erbB receptor; NAF, Nipple aspirate fluid; PR, progesterone receptor; SEB, Surgical excision biopsies; TNBC, Triple negative breast cancer.

Sample Type and Sample Size	Method	Observations	Changes to the Microbiome	Ref.
Breast tumor tissue and paired normal adjacent tissue from the same 20 patient (ER positive)	Pyrosequencing 16S V4 rDNA	The amount of bacteria, measured by the copy number of 16S rDNA, is not significantly different in paired normal tissue from breast cancer patients and healthy breast tissue from healthy individuals. The amount of bacteria, measured by the copy number of 16S rDNA, is significantly reduced in breast cancer tissue.	The most abundant phyla in breast tissue were *Proteobacteria*, *Firmicutes*, *Actinobacteria* and *Bacteroidetes*. *Methylobacterium radiotolerans* is relatively enriched in tumor tissue and *Sphingomonas yanoikuyae* is relatively enriched in paired normal tissue.	[105]
Breast tissue from 81 women with and without breast cancer from Canada and Ireland. Canadian patients: benign (*n* = 11), cancerous tumors (*n* = 27) and healthy individuals (*n* = 5) Irish patients: breast cancer (*n* = 33) and healthy individuals (*n* = 5)	Ion Torrent V6 16S rRNA sequencing and culture	Breast tissue contains a diverse population of bacteria. Geographical difference exist between breast tissue microbiome of Canadian and Irish subjects.	*Proteobacteria* and *Firmicutes* (specifically the class *Bacilli*) were the most abundant phyla in breast tissue. The most abundant taxa in the Canadian samples were: *Bacillus* (11.4%), *Acinetobacter* (10.0%), *Enterobacteriaceae* (8.3%), *Pseudomonas* (6.5%), *Staphylococcus* (6.5%), *Propionibacterium* (5.8%), *Comamonadaceae* (5.7%), *Gammaproteobacteria* (5.0%), and *Prevotella* (5.0%). The most abundant taxa in the Irish samples were: *Enterobacteriaceae* (30.8%), *Staphylococcus* (12.7%), *Listeria welshimeri* (12.1%), *Propionibacterium* (10.1%), and *Pseudomonas* (5.3%). Higher abundance of *Escherichia coli* was detected in women with cancer than in healthy controls.	[110]
Triple negative breast cancer (TNBC) samples (*n* = 100)	PathoChip array	There are unique microbial signatures in triple negative breast cancer.	Multiple viruses and other microorganisms were detected in triple negative breast cancer samples. Bacterial signatures: *Brevundimonas diminuta*, *Arcanobacterium haemolyticum*, *Peptoniphilus indolicus*, *Prevotella nigrescens*, *Propiniobacterium jensenii* and *Capnocytophaga canimorsus* (see in [107])	[107]
Nipple aspirate fluid (NAF) from healthy women (*n* = 23) and from women with breast cancer (*n* = 25)	16S V4 rRNA gene sequencing	Microbiome composition of NAF from healthy control and breast cancer are significantly different. Beta-glucuronidase levels are higher in NAF from breast cancer than from healthy control.	The most abundant phyla in NAF were *Firmicutes*, *Proteobacteria*, and *Bacteroidetes*. In NAF from breast cancer genus *Alistipes* was more abundant and an unclassified genus from the *Sphingomonadaceae* family in NAF from healthy women.	[108]

<div align="center">**Table 2.** *Cont.*</div>

Sample Type and Sample Size	Method	Observations	Changes to the Microbiome	Ref.
Breast tissues from patients with benign (*n* = 13) and invasive breast cancer (*n* = 15). The invasive cancers were stage I in 10 patients (67%) and stage II in 5 (33%). Tumors were histologic grade I in 43% and grade II in 57%. The invasive cancers were all ER and PR positive, and a minority (29%) were HER2 positive.	16S V3-V5 rDNA hypervariable taq sequencing	Breast tissue microbiome is different in women with malignant disease and in women with benign disease.	The most abundant phyla in breast tissue were *Firmicutes*, *Actinobacteria*, *Bacteroidetes* and *Proteobacteria*. Breast cancer malignancy correlated with enrichment in taxa of lower abundance including the genus *Fusobacterium*, *Atopobium*, *Gluconacetobacter*, *Hydrogenophaga*, and *Lactobacillus*.	[109]
Breast tissue from 58 women: benign (*n* = 13), cancerous tumors (*n* = 45), and healthy individuals (*n* = 23)	16S V6 rRNA sequencing	Different microbiome profile exist between breast tissue from healthy women and women with breast cancer. Normal tissues from women with benign tumors are more similar to normal adjacent tissues from cancer patients than to normal tissues from healthy women.	Breast cancer patients had higher relative abundances of *Bacillus*, *Enterobacteriaceae* and *Staphylococcus*. *Lactococccus* and *Streptococcus* were higher in healthy women than in breast cancer patients.	[106]
Breast tissue from 39 breast cancer patients (*n* = 17 tumor, *n* = 22 normal) and breast tissue from 24 healthy patients	16S V3-V4 rRNA sequencing	Microbiome of tumor and paired normal tissues from the same breast cancer patient are similar. Breast tissue from cancer and non-cancer patients have significantly different microbiome.	Decreased relative abundance in the genus *Methylobacterium* (phylum *Proteobacteria*) was found in breast cancer patients.	[111]
Breast tissue from tumor (*n* = 668) and normal adjacent tissue (*n* = 72) from The Cancer Genome Atlas (TCGA)	16S V3-V5 RNA sequencing data	The microbial composition is associated with alterations in the host expression profiles.	The most abundant phyla in breast tissues are *Proteobacteria*, *Actinobacteria*, and *Firmicutes*. *Proteobacteria* was increased in the tumor tissues and *Actinobacteria* abundance increased in non-cancerous adjacent tissues. *Mycobacterium fortuitum* and *Mycobacterium phlei* are species differentially abundant in the tumor samples. Geneset enrichment suggested that *Listeria* spp was associated with the expression profiles of genes involved with epithelial to mesenchymal transitions. *H. influenza* was associated with the proliferative pathways: G2M checkpoint, E2F transcription factors, and mitotic spindle assembly.	[112]

Table 2. *Cont.*

Sample Type and Sample Size	Method	Observations	Changes to the Microbiome	Ref.
Breast cancer tissues [ER or PR positive (*n* = 50), HER2 positive (*n* = 34), triple positive (*n* = 24), triple negative (*n* = 40)] and breast tissue from healthy individuals (*n* = 20)	PathoChip array	There are unique viral, bacterial, fungal and parasitic signatures in each breast cancer type. Triple negative and triple positive samples showed distinct microbial signature, while the ER positive and HER2 positive samples shared similar microbial pattern.	Unique and common microbial signatures in the major breast cancer types are summarized in Table 1 in [113] All four breast cancer types had dominant signatures for *Proteobacteria* followed by *Firmicutes*. *Actinomyces* signatures was also detected in each breast cancer types.	[113]
Fresh tissue samples of both cancer and paired healthy tissues from core needle biopsies (CNB; *n* = 12) and surgical excision biopsies (SEB; *n* = 7). 3 patients underwent both procedures	hypervariable region of the 16S-rRNA gene (V3)	More similarities than differences exist between tumors and adjacent normal tissues from CNB and SEB specimens. There are more differences between subjects than between healthy and cancerous tissues collected from the same patient.	In breast tissue *Proteobacteria* are the most abundant phylum followed by *Firmicutes*, *Actinobacteria* and *Bacteroidetes*. Presence of genus *Ralstonia* is associated with breast tissue. The relative abundance of *Methylobacterium* was different in certain patients.	[114]
Breast tissue from benign (*n* = 22) and malignant (*n* = 72) breast cancer patients (Chinese cohorts)	16S V1-V2 rRNA sequencing	Microbiome profile is different in benign and malignant diseases. Microbiome composition is different in histological grades of malignant breast tissue. There is a specific correlation of microbial biomarkers and microbial pathways with advanced disease. Glycerophospholipid metabolism and ribosome biogenesis pathways were upregulated in grade III tumor compared to grade I and II. Flavonoid biosynthesis was significantly lower in grade III compared to grade I and II.	The enriched microbial biomarkers in malignant tissue included genus *Propionicimonas* and families *Micrococcaceae, Caulobacteraceae, Rhodobacteraceae, Nocardioidaceae,* and *Methylobacteriaceae*. The relative abundance of family *Bacteroidaceae* decreased and the relative abundance of genus *Agrococcus* (family *Microbacteriaceae*) increased with the development of malignancy. Genus *Propionicimonas* and five families *Micrococcaceae, Caulobacteraceae, Rhodobacteraceae, Nocardioidaceae* and *Methylobacteriaceae* were abundant in malignant disease compared to benign disease.	[115]

Table 3. Studies investigating changes to the gut microbiome in breast cancer. Abbreviations: AM, Akkermansia muciniphila; bai, bile acid inducible operon (wherein the *baiH* ORF codes for 7-HSDH, a key enzyme in lithocholic acid biosynthesis); BMI, body mass index; CadA, acid-inducible lysine decarboxylase; ER, estrogen receptor; HAM, high AM relative abundance; HER2, herceptin receptor/erbB receptor; LAM, low AM relative abundance; LdcC, constitutive lysine decarboxylase; PR, progesterone receptor.

Sample Type and Sample Size	Method	Observations	Changes to the Microbiome	Ref.
Urine and fecal samples from men ($n = 25$), postmenopausal women ($n = 7$), and premenopausal women ($n = 19$)	Pyrosequencing of the V1-V2 region of 16S rRNA genes	The richness of the fecal microbiome was directly associated with systemic estrogens.	Non-ovarian systemic estrogens were significantly associated with fecal *Clostridia* taxa, including non-Clostridiales and three genera in the *Ruminococcaceae* family.	[116]
Urine and fecal samples from healthy postmenopausal women ($n = 60$)	Pyrosequencing of the V1-V2 region of 16S rRNA genes	Diversity of the gut microbiome were associated with patterns of estrogen metabolism.	Relative abundances of a number of taxa in the class *Clostridia* were directly associated with the ratio of estrogen metabolites to parent estrogen, while the genus *Bacteroides* was inversely associated with this ratio.	[117]
Urine and fecal samples from postmenopausal women with breast cancer ($n = 48$) and paired control women ($n = 48$)	Illumina sequencing and taxonomy	Postmenopausal women with breast cancer have altered fecal microbiota composition but estrogen-independent low diversity of gut microbiota.	Breast cancer patients had higher levels of *Clostridiaceae*, *Faecalibacterium*, and *Ruminococcaceae*; and they had lower levels of *Dorea* and *Lachnospiraceae*.	[118]
Fecal samples from breast cancer patients ($n = 31$). Clinical stages were stage 0 ($n = 15$), stage I ($n = 7$), stage II ($n = 7$), stage III ($n = 2$). Patients were ER positive/ PR positive (90%) and HER2+ (15%). 23 patients had a normal BMI and 8 were overweight	qPCR targeting 16S rRNA sequences	Microbiome composition in patients differ according to clinical characteristics and BMI.	In overweight patients, the number of total *Firmicutes*, *Faecalibacterium prausnitzii*, *Blautia* sp., and *Eggerthella lenta* bacteria was significantly lower than in the normal BMI patients. Total number of *Bacteroidetes*, *Clostridium coccoides* cluster, *Clostridium leptum* cluster, *Faecalibacterium prausnitzii*, and *Blautia* sp. were significantly higher in clinical stage II/III than in clinical stages 0/I. *Blautia* sp. is associated with a major histoprognostic grade.	[121]
Urine and fecal samples from postmenopausal women with breast cancer ($n = 48$) Clinical stages were in situ ($n = 11$), stage 1 ($n = 25$), stage 2 ($n = 10$), stage 3 ($n = 2$); 88% ER-positive and paired control women ($n = 48$)	16S V4 rRNA gene sequencing	Breast cancer patients have significant estrogen-independent associations with the IgA-positive and IgA-negative gut microbiota.	Breast cancer patients had significantly reduced alpha diversity and altered composition of both IgA-positive and IgA-negative fecal microbiota.	[119]

Table 3. *Cont.*

Sample Type and Sample Size	Method	Observations	Changes to the Microbiome	Ref.
Fecal samples from premenopausal breast cancer patients (*n* = 18), premenopausal healthy control (*n* = 25), postmenopausal breast cancer patients (*n* = 44), postmenopausal healthy control (*n* = 46).	Illumina sequencing	Composition of gut microbiome differ between postmenopausal breast cancer patients and healthy controls while did not differ significantly between premenopausal breast cancer patients and premenopausal controls.	Enriched species in postmenopausal breast cancer patients were *Escherichia coli, Citrobacter koseri, Acinetobacter radioresistens, Enterococcus gallinarum, Shewanella putrefaciens, Erwinia amylovora, Actinomyces* sp. HPA0247, *Salmonella enterica,* and *Fusobacterium nucleatum. Eubacterium eligens* and *Roseburia inulinivorans* were less abundant species in postmenopausal breast cancer patients.	[122]
Fecal DNA samples from postmenopausal women with breast cancer (*n* = 48) and healthy women (*n* = 48) The original patient cohort is published in [118].	qPCR (primers were designed for the known baiH ORF in different bacteria)	Abundance of baiH ORF in bacterial species was different in breast cancer patients compared to healthy control women.	The abundance of baiH of *Clostridium sordelli, Pseudomas putida* and *Staphyloccoccus aureus* was lower in breast cancer patients. A more pronounced decrease in the abundance of the baiH of *Bacteroides thetaiotaomicron* and *Pseudomonas putida* were detected in early stage breast cancer patients.	[120]
Fecal samples from women with stage 0 to II breast cancer (*n* = 32)/presurgical weight-loss trial	16S V4 rRNA gene sequencing	Body composition of early stage breast cancer women is associated with Akkermansia muciniphila (AM), microbiome diversity and interleukin-6 level.	Relative abundance of AM was lower in women with higher body fat. Alpha diversity was higher in women with HAM. Higher *Prevotella* and *Lactobacillus* while lower *Clostridium, Campylobacter,* and *Helicobacter* genera were detected in HAM vs. LAM patients. IL-6 was associated with species richness and body composition, but not AM.	[125]
Fecal DNA samples from postmenopausal women with breast cancer (*n* = 48) and healthy women (*n* = 48) The original patient cohort is published in [118].	qPCR (primers were designed for known CadA and LdcC genes in different bacteria)	Abundance of the DNA coding LdcC and CadA in bacterial species was different in breast cancer patients compared to healthy control women.	The abundance of *Escherichia coli* CadA and also *Escherichia coli, Enterobacter cloacae* and *Hafnia alvei* LdcC DNA slightly decreased in breast cancer patients. Decreased CadA and LdcC abundance was more pronounced in clinical stage 0 patients as compared to the pool of all patients. In the feces of stage 1 patients *Escherichia coli* LdcC protein levels were markedly lower than in the healthy women.	[91]

Obtaining nipple aspirate fluid or sterile biopsy are starting materials for the analysis of the breast microbiome that is then subjected to next-generation sequencing. The biomass of the breast microbiome decreases in breast cancer patients [105]. One explanation for the variability could be that the geographical difference creates notable changes in the composition of the microbiome, as pointed out in [110]. Changes to the breast microbiome are in correlation with the molecular subtype (hormone receptor+, HER2+, or triple negative), where the microbiome composition of the triple negative cases differs from other types [107,113]. Furthermore, the breast microbiome change as a function of the grade [115] and aggressivity [109] of the disease. These changes are translated into functional changes, as in the breast microbiome glycerophospholipid biosynthesis and ribosome biosynthesis processes are upregulated, while the flavonoid biosynthesis decreased as the grade of the disease increases [115]. It is of note that there are also characteristic changes to the virome and fungome of the breast [113].

The fecal microbiome is also characterized by changes in breast cancer patients. The group of James J. Goedert published a series of studies illustrating that the diversity of the gut microbiome decreases in breast cancer patients as compared to healthy controls and the relative abundance of *Clostridiales* increase in patients [116–119]. Using the biobank set-up by the Goedert group [118], Miko and co-workers [120] and Kovacs and colleagues [91] assessed a subset of bacterial species and showed that the most drastic decreases were observed in early stage breast cancer (stage 0 and stage 1). These observations are supported be the observations of Luu and colleagues [121]; the log10 equivalent number/g stool of all *Bacteroidetes*, *Clostridium coccoides*, *Clostridium leptum*, *Faecalibacterium prausnitzii*, and *Blautia* species increased in stage II and III patients as compared to the stage 0 and I patients. In contrast to that, Zhu and co-workers [122] showed that the diversity of the gut microbiome changes differently in the pre- and postmenopausal breast cancer patients, furthermore the diversity of the gut microbiome increases in patients when compared to healthy controls.

There are correlative studies showing that antibiotic consumption, which decreases the diversity of the microbiome, increases the risk and recurrence of breast cancer [126–132]. Despite the non-mechanistic nature of these studies and the chance for uncontrolled confounding, these studies strengthen the observations that the decreases in the diversity of the microbiome increase the risk for breast cancer. Importantly, a recent murine study [132] showed that the use of a cephalosporin antibiotic (Cephalexin) accentuated the decrease in microbiome diversity that was induced by the tumor itself and induced tumor formation, suggesting a causative relationship between antibiotic use and breast cancer incidence, as well as strengthening the hypothesis of the reduced bacterial diversity in breast cancer. Cephalexin reduced the abundance of *Odoribacter* and *Anaeotruncus* (both are butyrate-producing bacterial groups), while increasing the abundance of *Bacteroides* [132].

4. Interactions between Microbiome and Breast Cancer Cells—Metabolites in Action

There are multifaceted bidirectional interactions between the host and the microbiome [133]. The host regulates the composition of its microbiome through its innate immune system or its feeding or hygiene behavior, but, in turn, as recent research strongly argues, the microbiome can also fine tune the (patho)physiology of the host [133–135]. A major pathway in microbiome-to-host signaling is the secretion of bacterial metabolites that enter the circulation and reach their target cells [136–139]. In that respect, the function of these bacterial metabolites is similar to human hormones, which are synthesized in an organ or gland (in this case, it is the microbiome) and they are transferred to other anatomical locations, where they exert their biological effects. Such blood-borne microbial metabolites were shown to modulate the behavior of breast cancer, lithocholic acid (LCA) [120,140–143], short chain fatty acids (SCFA) [134,144], cadaverine [91], or deconjugated estrogens [116,117]. These bacterial metabolites have profound impact on mitochondrial metabolism, nevertheless it is of note that metabolites also regulate other metabolic processes (e.g., lipid metabolism) [21] (For overview, please see Table 4 and Figure 1).

Table 4. Effects of the bioactive bacterial metabolites in breast cancer. Processes in green are upregulated by the metabolite, in red those, that are downregulated. Black text stands for ambiguous data. Abbreviations: ER–estrogen receptor; FFAR–free fatty acid receptor; TGR5/GPBAR1–G protein-coupled bile acid receptor 1; FXR–farnesyl X receptor; TAAR–trace amine-related receptor; OXPHOS–oxidative phosphorylation; EMT–epithelial-to-mesenchymal transition; HDAC–histone deacetylase; CSC–cancer stem cell; VEGF–vascular endothelial growth factor.

Metabolite	Receptor	Bacteria	Ref.	Bacterial Enzyme	Neoplastic Processes	Ref.
Reactivated estrogen	ERα ERβ	*Firmicutes* *Collinsella* *Edwardsiella* *Alistipes* *Bacteroides* *Bifidobacterium* *Citrobacter* *Clostridium* *Dermabacter* *Escherichia* *Faecalibacterium* *Lactobacillus* *Marvinbryantia* *Propionibacterium* *Roseburia* *Tannerella*	[116–118,145–147]	β-glucuronidase (*gus*/BC)	OXPHOS tamoxifen resistance metastasis, aggressivity hormone-induced apoptosis EMT proliferation, metastasis	[148,149] [150] [19,151] [152] [153,154] [21]
Short chain fatty acids Acetate Propionate Butyrate Lactate	FFARs	*Akkermansia muciniphila* *Lachnospiraceae* *Ruminococcus obeum* *Roseburia inulinivorans* *Bacteroidetes* *Negativicutes* sp. *Faecalibacterium prausnitzii* *Eubacterium rectale* *Roseburia faecis* *Eubacterium hallii* SS2/1 *Odoribacter* *Anaeotruncus*	[132,155–157]	diverse	OXPHOS (direct energy substrates) apoptosis HDAC inhibition macrophage antimicrobial activity	[158] [159] [160–163] [163]

Table 4. *Cont.*

| Metabolite	Receptor	Bacteria	Ref.	Bacterial Enzyme	Neoplastic Processes	Ref.
Secondary bile acids Lithocholic acid	TGR5 FXR	*Clostridiales*	[164,165]	7α/β-hydroxysteroid dehydroxylase (*baiH*)	apoptosis (in supraphyisiological conc.) proliferation VEGF production OXPHOS antitumor immunity EMT fatty acid biosynthesis movement, metastasis formation	[140,141,143,166] [120,167] [120] [120] [120] [120] [143] [120]
Amino acid degradation Cadaverine	TAAR1, 2, 3, 5, 8, 9	*Shigella flexneri* *Shigella sonnei* *Escherichia coli* *Streptococci*	[132,155–157]	Lysine decarboxylase (*LdcC*, *CadA*)	OXPHOS CSC movement, invasion EMT metastasis formation	[91] [91] [91] [91] [91]
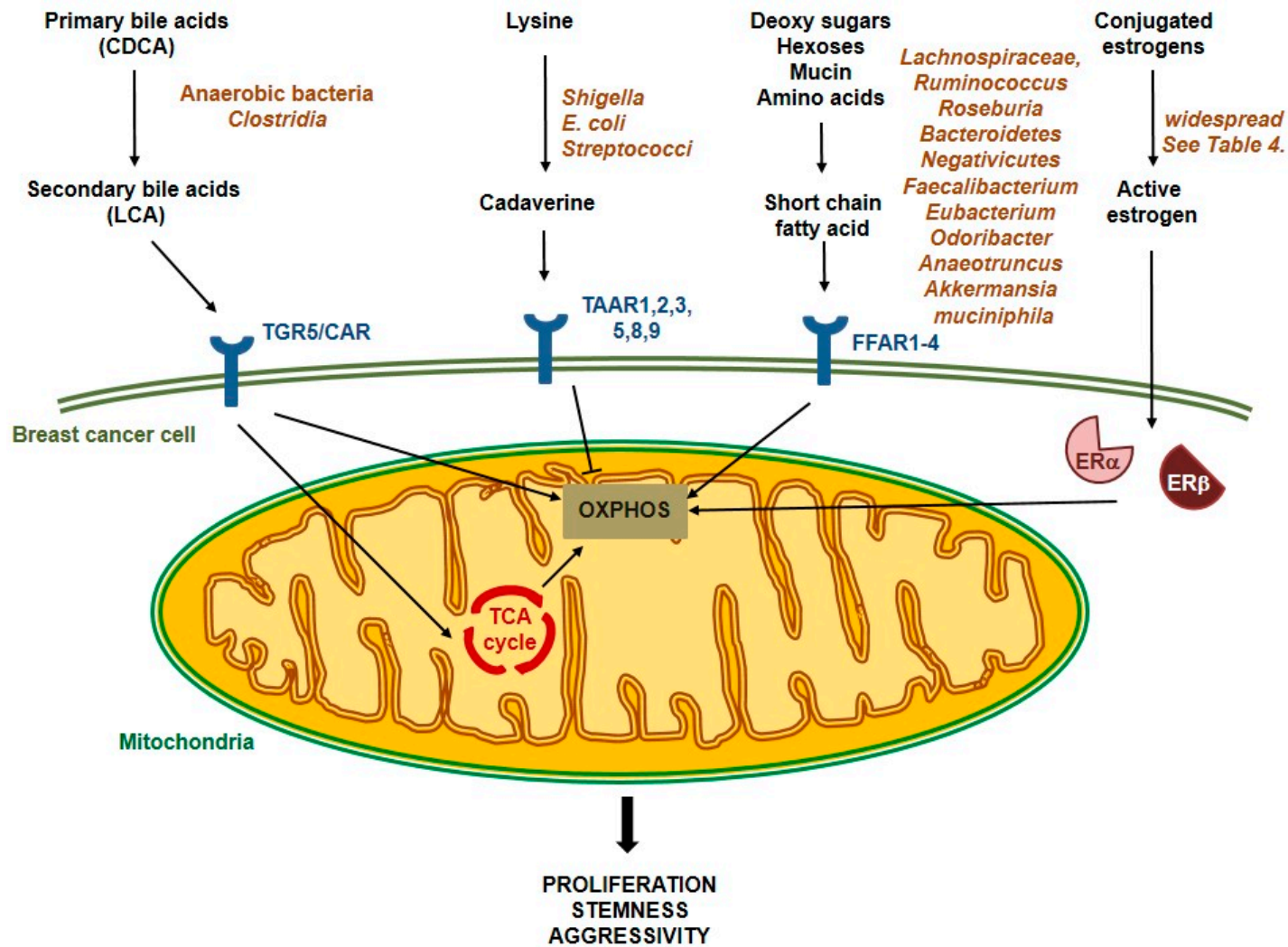
Figure 1. Schematic representation of the pathways elicited by bacterial metabolites that modulate mitochondrial metabolism in breast cancer.

4.1. Estrogen Deconjugation and Reuptake

The group of James J. Goedert showed that, in men and postmenopausal women, the gut microbiome is a key determinant of estrogen metabolism [116,117]. The microbiome has a vital role in estrogen metabolism, as bacteria can deconjugate excreted estrogens enabling their reuptake [168], in line with that, the urinary estrogen levels showed correlation with the richness of the fecal flora in men and in postmenopausal women [116,117]. Bacterial β-glucuronidases are responsible for the deconjugation of conjugated estrogens that are coded by the *gus* [145,146] and *BG* genes [147]. *gus* is widespread among gut bacteria, being more common among *Firmicutes*, while BG is more widespread, being present in *Bacteroidetes* and *Firmicutes* [147]. The following bacterial genuses were shown to express β-glucuronidases: *Collinsella, Edwardsiella, Alistipes, Bacteroides, Bifidobacterium, Citrobacter, Clostridium, Dermabacter, Escherichia, Faecalibacterium, Lactobacillus, Marvinbryantia, Propionibacterium, Roseburia,* and *Tannerella* [169]. Goedert and colleagues have provided strong functional evidence for the role of *Clostridiales* in estrogen reactivation [116,117] and showed that the relative abundance of *Clostridiales* increases in breast cancer patients [116–118]. Feeding regimes can modulate β-glucuronidase expression in the gut [146]. (Reactivated) estrogens act through estrogen receptors, and hence promote the progression of ER+ breast cancer through multiple pathways (Table 1).

Reactivation of estrogens enable their reuptake and increase serum estrogen levels [116–118], estrogen-evoked changes in the expression of mitochondrial genes were suggested to contribute to estrogen-induced carcinogenesis [170]. In line with that, both estrogen receptors (ER), ERα and ERβ, reside on the surface of mitochondria [171] and the ER-responsive sites were suggested to be present in mitochondrial DNA [170]. ERβ is directly involved in the expression of nuclear-coded mitochondrial proteins [172]. Endocrine-resistant tumors have higher mitochondrial respiration when compared to the tumors that are sensitive for endocrine therapy, which is due to the increased expression of NRF1 and TFAM1 [148,149]. Increased oxidative phosphorylation was shown to contribute to tamoxifen-resistance [150] and general therapy failure [173], support metastasis [19], and render the tumors more aggressive [151]. The flip-side of the induction of mitochondrial oxidation is the increased mitochondrial production of free radicals that is cytostatic and is dependent on ERβ [174,175]. When taken together, bacterial estrogen deconjugation can promote breast cancer progression.

4.2. Short-Chain Fatty Acid Production

The microbiome by the saccharolytic fermentation of non-digestible carbohydrates generate short-chain fatty acids (SCFAs, acetate, propionate, butyrate) [161,176]. Fermentation of the non-digestible carbohydrates yield formate, acetate, propionate, butyrate, and lactate [176]. A relatively small proportion of SCFAs are produced through amino acid degradation; the degradation of branched chain amino acids yield branched-chain fatty acids; nevertheless, the amount of branched-chain fatty acids is extremely low [176].

The capability for acetate production is widespread among bacteria, while the production of other metabolites is more restricted to certain species. *Akkermansia muciniphila* is a key player in propionate production from mucin [155], while *Lachnospiraceae, Ruminococcus obeum,* and *Roseburia inulinivorans* are responsible for the degradation of deoxy sugars (e.g., fucose, rhamnose) and hexoses by *Bacteroidetes* and *Negativicutes* sp. to produce propionate [157]. The majority of butyrate production is bound to *Faecalibacterium prausnitzii, Eubacterium rectale, Roseburia faecis, Eubacterium hallii,* and an unnamed cultured species SS2/1 [156], as well as the genera *Odoribacter* and *Anaeotruncus* [132]. It is also of note that the application of Cephalexin, which is an antibiotic that is frequently used as a pre-surgery premedication to breast cancer patients, reduced the abundance of *Odoribacter* and *Anaeotruncus* that are butyrate producer bacteria [132]. The abundance of *Akkermansia muciniphila,* which is a cross-feeder and propionate producer species, was associated with the richness of the gut microbiome in breast cancer patients [125].

The serum concentration of the total SCFAs fall into the 10–100 μM range, wherein acetate, propionate, isobutyrate, and butyrate make up the bulk [177–179]. SCFAs modulate numerous

cancer hallmarks, such as cell proliferation, apoptosis, cell invasion, gene expression, metabolism, among others, in breast cancer [144,159,180–182]. The main receptors of SCFAs are the free fatty acid receptors (FFARs) that are only situated on the cancer cells, but also on stromal cells (e.g., adipocytes) [180,183,184]. The effects of SCFAs can have positive (e.g., [144]) and negative (e.g., [184]) effects in breast cancer as a function of the context.

The knowledge on role of SCFAs in mediating metabolism in breast cancer cells is very limited. In breast cancer cells, even-chain short fatty acids, acetate, butyrate, or lactate can be directly utilized as energy substrates, in line with that, sodium-butyrate induces oxygen consumption in breast cancer cell lines [158] and the inhibition of the lactate metabolism sharply reduces the viability of breast cancer cells [185]. Furthermore, butyrate can induce apoptosis through inducing mitochondrial ROS generation [159]. SCFAs, most notably, butyrate, are histone deacetylase inhibitors that are a key feature for their anticancer activity [160–163].

4.3. Secondary Bile Acid Metabolism

Lithocholic acid is secondary bile acid that is synthesized from chenodeoycholic acid (CDCA) and ursodeoxycholic acid (UDCA), by the dehydroxylation at position 7 [165,186]. The genes that are involved in the degradation of secondary bile acids can be found in the bile acid-inducible operon (bai operon) [164]. The enzyme catalyzing the formation of lithocholic acid that is cytostatic in breast cancer is $7\alpha/\beta$-hydroxysteroid dehydroxylase (*baiH*) [165,186]. Anaerobic bacteria, mostly the *Clostridiales*, are responsible for bile acid transformation [164]. The bile acids in the breast are of the gut origin [187].

The capacity of the human body and the microbiome to synthesize LCA is largely reduced in breast cancer, which is the most dominant in early stages (stages 0 and 1) [120]. Serum lithocholic acid levels negatively correlate with Ki67 labelling index in breast cancer [167]. LCA, in concentrations corresponding to its serum or breast tissue concentrations (30–50 nM or < 1 μM, respectively [120,188]), exerts antineoplastic effects on breast cancer cells by inhibiting epithelial-to-mesenchymal transition, vascular endothelial growth factor (VEGF) production, metastasis formation, induced antitumor immunity, and elicited changes in metabolism [120]. In supraphysiological concentrations (>1 μM), LCA inhibits fatty acid biosynthesis [143], induces induced multidrug resistance proteins [166], and induces cell death [140,141,143,166]. LCA did not exert antiproliferative effects in its tissue reference concentrations on non-transformed primary fibroblasts [120]. A exert its antineoplastic effects through the G protein-coupled bile acid receptor 1 (TGR5) [120] and in supraphysiological concentrations through Farnesoid X receptor (FRX) [166]. Other secondary bile acids, deoxycholic acid (DCA) or ursodeoxycholic acid (UDCA), had no effect on breast cancer cells in the reference concentration [120].

Bile acid-induced activation of TGR5 was shown to induce OXPHOS in metabolic models [189–192], in good accordance with that, LCA can elicit anti-Warburg effects in breast cancer models. In breast cancer cells, LCA induces mitochondrial biogenesis through NRF1, AMPK, and PGC-1β; the same effectors are also induced in murine breast cancer models upon LCA feeding [120]. The induction of these energy sensors declutch transcription programs that induced the expression of mitochondrial proteins (cytochrome c, atp5g1, ndufb5) and consequently enhanced mitochondrial activity. both when, the TCA cycle was fed on acetate or on glucose suggesting enhanced glycolytic flux, too [120]. In parallel, oxygen consumption rates were also induced suggesting improved terminal oxidation [120]. Besides the regulation of oxidative phosphorylation, LCA induced mesenchymal-to-epithelial transition, antitumor immune response, and inhibited proliferation and metastasis formation [120] (see Table 1).

4.4. Amino Acid Degradation

Cadaverine is synthesized from lysine by the bacterial enzymes LdcC and CadA [193,194]. Human cells are also capable of synthesizing cadaverine; however, it seems that bacterial cadaverine production is dominant over human biosynthesis [91]. *Shigella flexneri*, *Shigella sonnei*, *Escherichia coli*, and *Streptococci* were shown to express cadaverine biosynthetic enzymes [195].

Cadaverine in concentrations corresponding to its serum reference concentrations (100–800 nM) [196,197] inhibited cell proliferation, epithelial-to-mesenchymal transition, cell movement and invasion, and tumor infiltration to the surrounding tissues [91]. Moreover, cadaverine changed metabolism in breast cancer cells and it reduced the proportion of ALDH1$^+$ cancer stem cells in 4T1 murine breast cancer cells [91]. Cadaverine exerted its effects through the trace amine-associated receptor-1, 2, 3, 5, 8, 9 (TAAR1, 2, 3, 5, 8, 9), of which TAAR1 was already associated with the inhibition of breast cancer growth [198]. The capacity of the microbiome to synthesize cadaverine is suppressed in breast cancer, most dominantly in early stage breast cancer (stages 0 and 1) [91]. Putrescine had no effect on breast cancer cells [91]; furthermore, cadaverine was not effective on primary, untransformed cells [91].

Cadaverine has been shown to reduce cellular oxygen consumption that is a readout of OXPHOS activity, rendering the cells more glycolytic [91]. The molecular mechanisms bringing about that phenotype has not yet been elucidated. In line with the more glycolytic phenotype of cells, the percentage of cancer stem cells was reduced upon cadaverine treatment [91]. In addition to these, cadaverine inhibited migration, invasion, and metastasis formation, as well as induced mesenchymal-to-epithelial transition [91].

5. Interference of the Microbiome and Anticancer Treatment

Bacteria of the microbiome can interfere with chemo- and radiotherapy in cancer treatment and management [199,200], which is also true for breast cancer. There are several aspects to the interactions between the microbiome and anticancer treatment; the microbiome can metabolize the chemotherapeutic drugs, inactivating or activating them, can modulate the immune system [201,202], can interfere with the side-effects of therapy, or the therapy can modulate the microbiome. Alexander and colleagues [203] suggested a framework, called TIMER (from Translocation, Immunomodulation, Metabolism, Enzymatic degradation, and Reduced diversity and ecological variation), to support a coordinated description of the interactions between the microbiome and cancer drugs. Below, we discuss the drugs that are relevant for breast cancer treatment.

Anthracyclines are synthesized by *Streptomyces* strains and can hence modulate the composition of the microbiome [204], for example, anthracyclines can be bacteriostatic on *Acinetobacter* species [205]. Several bacteria can metabolize anthracyclines (i.e., detoxify them) [206–208]; *Streptomyces* WAC04685 can deglycosylate and inactivate doxorubicin [209]. *Streptomycetes* can be found with a low prevalence in the human gut [210], making it likely that the microbiome can interfere with the bioavailability and pharmacokinetics and the pharmacodynamics of anthracyclines. Furthermore, upon anthracycline treatment, certain bacteria can cross the intestinal barrier to enter secondary lymphoid organs [203].

Cyclophosphamides cause damage to the gut mucosa and, thereby, attenuate the barrier function that makes the gut leaky and gut bacteria can enter [211]. Rich microbiome is protective against cyclophospmamide-induced mucosal injury [212]; in fact, strains of *Lactobacillus plantarum* as a probiotic was shown to be protective against mucosal injury [213]. Bacteria (usually Gram-positive microorganisms, such as *Lactobacillus johnsonii*, *L. murinus*, *Barnesiella intestinihominis*, and *Enterococcus hirae* [203,214]) can enter secondary lymphoid organs and thereby shape the anticancer immune response of the host [202]. *Lactobacillus plantarum* HY7712 can ameliorate cyclophosphamide-induced immunosuppression in mice [215].

Selective estrogen receptor modulators (SERMs) (Tamoxifen, Raloxifen) tamoxifen can modulate the composition of the microbiome. SERMs can be toxic for *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* [216–218], *Porphyromonas gingivalis*, *Streptococcus mutans* [219], *Enterococcus faecium* [220], and *Bacillus stearothermophilus* [221]. To date, no bacterial drug metabolism was related to SERMs. Tamoxifen resistance was shown to be a reason of changes to cancer cell metabolism [63,149,222], which can be modulated by the microbiome.

Taxanes can be a subject to bacterial metabolism [223,224]. Moreover, taxanes may interfere with bacterial LPS in activating the immune system [225]. Finally, taxanes can interfere with the composition of the microbiome [226].

Antimetabolites, 5-fluorouracil (5FU), and gemcitabine were shown to interact with the microbiome. Both of the drugs are metabolized by the microbiome [227–233]. Bacterial enzymes can activate both drugs [203,233,234]; nevertheless, the bacterial deactivation of the active metabolites is equally important [203,229–231]. Although, studies in breast cancer or its models had not been performed, it is known that the bacterial metabolism of 5FU can influence the treatment efficacy of colorectal cancer [235]. Intratumoral bacteria (*Gammaproteobacteria*) were shown to be the key players in deactivating gemcitabine in colorectal cancer that was alleviated by the eradication of *Gammaproteobacteria* by ciprofloxacin [229]. A loss of gemcitabine cytotoxicity was also observed in Mycoplasma-infected cells in culture [230]. Geller and Straussman [232] identified *Gammaproteobacteria* in human pancreatic ductal adenocarcinoma tumors in elevated numbers than in healthy pancreas tissue that can regulate gemcitabine availability. This observation can be extended for breast cancer, as it is also a solid tumor inside the human body. Cytidine deaminase was shown to be responsible for gemcitabine inactivation [232]. Both 5FU and gemcitabine have bactericide properties [231,234,236,237] and, therefore, they modulate the composition of the microbiome. Capecitabine was not toxic on *E. coli* [231] and its effects on the microbiome is largely uncharacterized. 5FU-induced dysbiosis contributes to the severity of the 5FU-induced mucositis [238,239] that can be corrected by the use of probiotics [240]. 5FU mucositis can induce bacterial translocation through the intestinal barrier [241].

PARP inhibitors, which are drugs likely to be used in the future in breast cancer treatment [12–14], were shown to increase the diversity of the gut microbiome [242,243]. To date, there is no literature on the interplay between aromatase inhibitors, navelbine, GNRH-analogs, and the microbiome. It is of note that bacteria can also interfere with biological therapies; nevertheless, no interactions were found with the antibodies used in breast cancer targeted therapy [203]. Finally, the microbiome can modulate the severity of radiation-induced mucositis [244,245] and can protect against radiation-induced toxicity [246].

6. Applicability and Future Directions

Bacterial dysbiosis characterizes breast cancer, both in the breast tissue and in the gut [91,105–123,247]. Both the gut and breast microbiome sharply responds to the disease and display changes as a function of the histological variants, grade, or stage of the disease [91,107,109,113,115,120,121]. The role of the breast microbiome in carcinogenesis is unresolved, in contrast to that, the gut microbiome was shown to produce or modify metabolites (e.g., LCA, cadaverine, SCFAs, estrogens), which, through the circulation, get to distant sites, such as the breast, where they modulate cancer cell function. In that sense, these metabolites resemble human hormones, as they are produced in a "gland" (in this case, the microbiome) and are subsequently transferred to distant sites of action through the circulation. These metabolites appear to be important constituents of the tumor microenvironment.

All known bacterial metabolites have pleiotropic effects on breast cancer cells; nevertheless, almost all of them modulate mitochondrial metabolism. However, the actual effects are rather variable and there are inducers (e.g., estrogens or LCA) and inhibitors (e.g., cadaverine) of mitochondrial metabolism. Changes to mitochondrial metabolism is a double-edged sword in breast cancer. Switching for an anti-Warburg mitochondrial metabolism, comprising the upregulation of mitochondrial oxidation, can slow the proliferation of cancer cells and sensitize stromal cell for chemotherapy; however, in parallel, the induction of mitochondrial oxidation can tune cancer cells into cancer stem cells [85,86,93,248,249]. An example for that is cadaverine, which represses mitochondrial oxidation and, hence, reduces the percentage of cancer stem cells [91]. It is also of note that the substrate availability and substrate preference of cancer cells can also drive a switch between cancer stroma and cancer stem cells [250–252]. Consequently, a good understanding of metabolite-induced changes can enable us to use these metabolites in combatting breast cancer, either as stand-alone drugs or in combination with other chemotherapy regimens or mitochondrial drugs.

There is an intricate connection with feeding regimes and breast cancer risk [253], suggesting that it may be possible to create feeding regimes that maintain a "cytostatic microbiome" [134,135]—probiotics and changes to diet can influence SCFA serum levels [134]. Finally, there are natural dietary compounds

(e.g., polyphenols) that can also modulate the microbiome and mitochondrial metabolism [254]. Maintaining the microbiome in good shape can be also vital in the successful completion of chemotherapeutic regime in breast cancer treatment [238–240].

The microbiome may also have indirect effects on breast cancer. For example, the white adipose tissue has aromatase activity and, therefore, it can synthesize estrogen and thereby promote breast cancer. Pathological composition of the microbiome is also associated with obesity [255] and increases in the body mass index (BMI) are a risk factor of breast cancer [125,256]. There are other drivers of dysbiosis, apart from antibiotics or obesity, such as aging [257–260] or diseases (e.g., type II diabetes, polycystic ovary syndrome, non-alcoholic fatty liver disease, etc. [261–267]), which may explain the association of cancer events with these diseases. Bacteria in the microbiome can serve as sources of immunogenicity, similarly to the appearance of the counter-antibodies of the AB0 blood group system [268,269], and through that could modulate the activity of the immune system [202,214,270–273]. Finally, cachexia is also associated with dysbiosis [274–277].

We are still scratching the surface in understanding the role of dysbiosis in breast cancer. Nevertheless, there seems to be a meaningful, complex, and deep molecular network, below which can be exploited in the combat against cancer.

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