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Gut Microbiome-Host microRNA Interactions in Cancer Development and Immune Regulation: A Case of Colorectal and Breast Cancer

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Abstract: Breast and colorectal cancers represent primary malignancies that researchers worldwide analyze for genetic along with environmental risk elements to build therapeutic methods for better cancer outcomes. The most prevalent cancer in women is breast cancer along with colorectal cancer ranking second and third respectively among females. Adults across the globe most often experience these cancer types yet the present scenario shows rising incidence rates among younger patients. These early-onset tumors often start in the advanced stages of their aggressive type and produce a poor clinical outlook for patients. Past research initially concentrated on identifying genes which might help explain cancer origins but this approach changed in recent years. Scientific research has demonstrated that genetics and epigenetics together with environmental elements strongly affect cancer predisposition. Due to recent paradigm shifts in scientific inquiry researchers performed diverse investigations to analyze host microRNA response patterns and validated microbiota-gut communication systems which significantly influenced disease occurrence and state. These factors directly affect the disease's final results. Immunosuppression stands as a major worrisome consequence among all identified unfavorable effects of this disease because at present such patients remain susceptible to numerous infections. Recent scientific research found microbiome along with microRNA to substantially affect immunosuppression. The review tracked host microRNA activity alongside gut microbiome changes during disease development to determine their influence on immunosuppression in patients. Understanding the microRNA and microbiome interaction mechanisms with disease presentation effects on immune function would enable future therapeutic development opportunities targeting host microRNA and patient gut microbiome functions. The combination of inhibitory-miRNA therapies with miRNA mimic-based therapeutics and immune checkpoint blockade therapies and bacteria-assisted tumor-targeted therapies helps manage cancer. This study simultaneously investigated noninvasive biomarkers that could help with both cancer diagnosis and treatment plans and prognostic assessment.

Keywords: Breast Cancer, Colorectal Cancer, miRNA, microbiota, immunosuppression.

Introduction: Breast cancer (BC) is the most frequent malignancy among females and remains the major cause of cancer-related mortality, with an expected 685,000 deaths recorded in 2020. Globally, roughly 2.3 million new instances of female breast cancer were reported in 2020, representing 11.7% of all cancer cases and accounting for nearly one in four cancer diagnoses among women. [1,2]. Breast cancer is divided into four molecular subtypes, which are considerably impacted by age: luminal A (ER+ and/or PR+, HER2-), luminal B (ER+ and/or PR+, HER2+), human epidermal growth factor receptor 2-enriched (ER-, PR-, HER2+), and basal-like (ER-, PR-, HER2-). These subgroups indicate differences in incidence, therapeutic response, disease progression, and survival outcomes. [3]. While breast cancer risk normally increases with age, a large number of instances are being found among younger individuals internationally.

Although early-onset breast cancer is uncommon, it accounts for 7% of all breast cancer cases and nearly 40% of malignancies diagnosed in women aged 15–39. A positive family history of cancer is the most significant personal risk factor, driven by a high genetic susceptibility. Germline mutations in BRCA1 and BRCA2 are major factors, with BRCA carriers not only being at a heightened risk of early-onset breast cancer but also facing a 16–35% greater potential of getting contralateral breast cancer. Young premenopausal breast cancer generally manifests at advanced stages and is associated with aggressive subtypes that have a poor prognosis. Triple-negative (ER-, PR-, HER2-) and HER2-positive (HER2+) breast tumours with high-grade proliferation are particularly fatal in younger individuals. Compared to older women, individuals with early-onset breast cancer had shorter survival rates, contributing to increased breast cancer mortality. Among elderly patients, Luminal A, the least aggressive subtype with a favorable prognosis, is widespread in those over 50, whereas Luminal B, a more aggressive subtype with high-grade proliferation, is often detected in persons older than 70.

Approximately 90% of breast cancer occurrences are random, with no clear hereditary susceptibility. Consequently, additional variables have a substantial role in the development of irregular breast cancers, especially in new non-BRCA carriers without a family history or genetic linkages. Hormonal imbalances, obesity, and eating habits are among the primary risk factors that greatly impact the condition. Additionally, new research has identified the possible function of the gut microbiome and host microRNA (miRNA), either independently or via complicated pathways, in contributing to BC development.

Colorectal Cancer

CRC is the 3rd most common cancer diagnosed in both sexes, ranking as the 3rd most common in men and the

2nd most common in females. [9]. in 2020, an estimated 1.9 million new cases of CRC were reported, along with approximately 935,000 deaths, accounting for up 10% of all cancer diagnoses and deaths worldwide. CRC incidence is growing constantly, and especially in Asia and in the East Asian countries. [10,11]. Especially evident is such trend in developing countries with the average HDI; rapid social and economic change along with acceptance of Westernized way of life cause rising CRC prevalence and mortality rates. Conversely, countries with a higher HDI have witnessed the outcome of CRC improving due to enhanced early detection strategies, increased adoptions of polypectomy, and innovation in the care given before and after surgery that has resulted in decreased CRC incidence and mortality. [12.13]. Cancer statistics in the United States show an increased incidence of young-onset colorectal cancer (20–49 years of age), which constitutes nearly 10% of all CRC cases. Specifically, young-onset colon and rectal cancers constitute 11% and 18%, respectively, compared to persons aged 50 and older. [14]. In the Asia-Pacific region, which is characterized by urbanized lifestyles dominated by westernization and has a larger population of young people, the incidence of young-onset colorectal cancer is also increasing, similar to trends in Western countries. [15]. Risk factors include obesity, sedentary lifestyle, and diet rich in meat, high calorie and fat, low in fiber content. [16]. Besides, differences in aggressiveness, tumor staging, and clinical outcomes were documented for young-onset versus late-onset colorectal cancer patients. 17. Early detection plays a crucial role in enhancing the diagnosis and prognosis of CRC because it offers adequate surgical intervention prior to the beginning of metastases. The 5-year survival percentage for individuals with advanced-stage IV CRC declines to 14%, whereas patients detected at an early/localized stage had a survival rate of 90%. This significant disparity underlines the importance of early identification and effective surgical therapy in improving survival results.[18].

Most CRC are irregular, constituting about 90% of all occurrences, with no apparent family history or genetic connection. The remaining 10% are categorized as family, having a documented hereditary propensity. [24]. Early-onset CRC is typically connected with hereditary cancer syndromes, which may be diagnosed in younger persons with a family history or supplementary risk factors, such as inflammatory bowel illness or genetic disorders like Lynch syndrome or familial adenomatous polyposis. Identifying these risk factors can lead to suggestions for preventative interventions, including weight loss, greater physical activity, a diet rich in vegetables, fruits, and whole grains, avoidance of alcohol and smoking, and increased vitamin D consumption to correct low levels. [14]. In contrast, spontaneous CRC arises because to the deregulation of many signaling pathways. [20]. Recognized carcinogenic mechanisms in sporadic CRC include chromosomal instability (CIN), CpG island methylator phenotype (CIMP), and microsatellite instability (MSI), all of which entail somatic genetic alterations. [21,22]. The most frequent route, chromosomal instability (CIN), accounts for 70% of sporadic CRC cases and occurs from the accretion of mutations in certain oncogenes and tumor suppresser genes, such as APC, KRAS, PIK3CA, BRAF, SMAD4, and TP53. [23].

Recent investigations have emphasized the relationship between host miRNA and the gut microbiota in colorectal cancer. These variables may have a substantial influence in CRC development, particularly in situations where there is no apparent genetic predisposition, and might contribute to the incidence of irregular colorectal cancer at a younger age.

Inter-Domain Communications Between the Gut Microbiome and Host miRNAs in Cancer Endogenous:

miRNAs function as regulatory small RNA molecules which use 3’-untranslated region binding to control gene expression in mRNAs. Interspecies interactions lead to modified proteins through three molecular pathways that involve mRNA disruption together with translation reduction and gene functionality silencing mechanisms. A single miRNA molecule connects to multiple mRNAs which regulate fundamental biological processes including cell growth and signaling and also DNA repair procedures and cell differentiation while mediating stress responses. [24]. The abnormal expression of miRNAs affects gene regulation and sets the stage for multiple diseases which include cancer. [25]. MiRNAs linked with cancer belong to one of two categories: oncogenic oncomiRs or tumor-suppressor TS-miRs. Several groups of microRNAs such as oncomiRs and TS-miRs play vital roles in cancer development as well as tumor metastasis and treatment resistance mechanisms. [26.27]. The field of metastasiRs (metastasis-associated miRNAs) directs metastasis processes whereas metastasis-suppressor miRNAs function to impede metastatic progression. [28,29]. The symbiotic relationship between human microbiota and microbiome brings fundamental benefits to essential body operations. Age together with lifestyle patterns and nutrition factors and environmental agents and hormone fluctuations along with presumed illnesses and host genetic makeups contribute to shaping the microbiota. [30] Specific parts of the gut microbiota provide beneficial functions that enable multiple host

activities including nutrient bioconversion and harmful microorganism defense and control of nervous system function and metabolic response and immunological stability. [31,32]. Gut microbiota dysbiosis describes a state where irregular microbial gut relationships arise leading to disruptions of typical microbial stability patterns. The disrupted microbiome leads to negative health effects which range from inflammatory conditions through infectious diseases and eventually into malignant disorders. Cancer initiation and progression appear to be influenced by modulated biological balance through microbiota alterations which affect host metabolites and genes as well as proteins expressed by hosts. [31]. When modifications occur to the immune system, they lead to obesity development and immune system damage. The altered microbiota affects lipid metabolism-related miRNA expression which results in simultaneous obesity and cancer development. [33]

Modern research shows a strong link exists between host miRNAs and gut microbiota. miRNAs control gene expression through host mRNA binding but the gut microbiota alters the expression levels of host miRNAs through MyD88-dependent pathways and microbiologic compounds that influence gene expression in the colon [34]. Lastly the host can modify gut microbiota by releasing miRNAs into extracellular vesicles which microorganisms ingest (Figure 1). The two-way interaction between miRNAs from host cells and gut bacteria regulates gene expression in hosts. [35]. Studied evidence establishes that dietary components consumed by hosts modify their miRNA expression levels which results in modified gut microbiota. Research has established that dietary agents can directly change the composition of microbiota through two key findings [36,37]. The concurrence of microRNA expression abnormalities and microbiota imbalance creates the foundations for various diseases including cancer.

Host miRNAs potentially interact with gut microbiota through expression-based communication to create new treatment possibilities for cancer which can be targeted via medication. The analysis of cancer metabolism relies heavily on miRNA levels as a primary druggable target in today's cancer research. The development of miRNA-based therapeutic approaches becomes possible through miRNA expression modulation which decreases oncomiR overexpression typical across malignancies while restoring tumor-suppressor miRs (TS-miRs) that tumors normally inactivate. miRNA inhibitor-based treatments lower oncomiR levels via antagomiRs (anti-miRs) and antisense anti-miR oligonucleotides (AMOs) and locked nucleic acids (The therapy using synthetic TS-miR sequences as mimics serves to reproduce endogenous TS-miRs that Dicer and Ago2 proteins detect. [38,39].

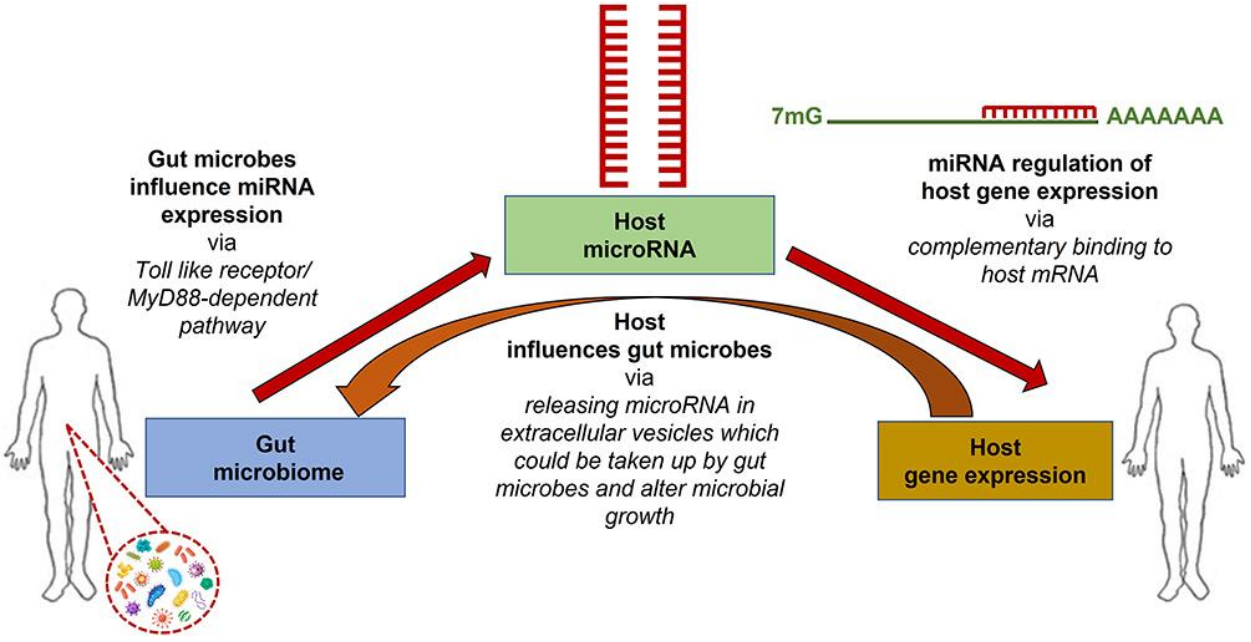

Figure 1: The process of communication between host gene expression and host miRNA activity with the gut microbiome proceeds across multiple domains ruling gene expression through miRNA binding to correct mRNAs and the gut microbiome alters miRNA expression through MyD88-dependent mechanisms and microbial metabolites. The host alters gut microbial composition through extracellular vesicle release of miRNAs that microbes absorb to modify their microbiome structure.

Research on expression-based interactions between gut microbiota and host miRNAs shows promise for developing cancer treatment pharmacological targets. Cancer metabolism and its associated druggable target expression levels of miRNA stand as the primary research focus at present. Controlling miRNA

concentrations enables the development of miRNA-derived cancer treatments through oncomiR suppression and restoration of TS-miR function which cancer cells naturally silence. Therapies that target oncomiRs with miRNA inhibitors employ different methods featuring locked nucleic acid (LNA) antagomiRs (anti-miRs) antisense anti-miR oligonucleotides (AMOs) and miRNA sponge. Therapeutic uses of miRNA mimics employ synthetic sequences derived from TS-miRs so Dicer and Ago2 proteins can recognize them for incorporation. [38,39].

Breast cancer shows interactions between gut microbiome and host miRNAs while miRNAs function as stable regulatory RNAs that exist in varying amounts within blood and plasma. A range of specific and indicative BC-specific circulating miRNAs have been detected for potential biomarker use in cancer evaluations. [40]. Testing the circulation of these miRNA biomarkers on patients with early-onset triple-negative breast cancer (TNBC) allows researchers to create minimal invasive and affordable novel biomarkers to aid in clinical diagnosis. Research on circulating miRNAs shows potential to enhance identifying cancer indicators and predicting outcomes in combination with treatment approaches. [41]. Tumor recurrence rates as well as overall survival and tumor staging have been linked specifically to these miRNA biomarkers thus making them useful biomarkers across different cancer subtypes. Research comparing tumor-derived miRNAs to non-tumor samples discovered elevated expression levels of miR-21, miR-106a, and miR-155 in tumors but simultaneous under expression of miR-126, miR-199a, and miR-335. Breast tumor tissue types present distinct relationships with the quantities of expressed miRNA molecules. The levels of expression of miR-21, miR-126, miR-155, miR-199a, and miR-335 relate to BC clinical factors along with histological tumor grades and sex hormone receptor status. [42]. Blood miR-21 measurements serve to distinguish breast cancer patients from healthy women and identify distant metastasis from locoregional recurrence of the disease according to two research reports. Research shows that high miR-21 gene expression at disease initiation directly influences breast cancer development potential which acts as a clear indicator at both diagnostic and prognostic stages of cancer progression. Estimates classify MiR-21 as an oncogene because this molecular factor allows tumor growth rates to increase by directing suppression against key tumor stabilizing genes TPM1 and PDCD4. [43]

Plasma levels of miRNAs show potential as biomarkers to identify and track cancer development early. The study results showed elevated levels of miR-21, miR-155, and miR-10b oncomiRs (oncogenic microRNAs) in breast cancer patients while Let-7a tumor suppressor miRNA levels in controls displayed decreased expression. The treatment procedures led to elevated levels of Let-7a and reduced concentrations of miR-21, miR-155, and miR-10b across patient plasma. The post-operative stages showed significant variation in levels of miR155 relative to the pre-operative stages which supports its potential as a biomarker and response indicator for Luminal A subtype treatment. [44]. Current research demonstrates a dual biomarker approach using miR-195 and miR-331 expression to separate metastatic from locally limited luminal A breast cancers.

A definitive distinction between luminal A and luminal B centers on miRNA cluster miR99a/let-7c/miR-125b elevation that prolongs the survival period for patients with luminal A cancer but only provides good clinical outcomes with high levels of miR-99a expression. This miRNA cluster functions as both a biomarker to separate luminal A from B while serving as a prognostic tool within luminal A for patients demonstrating low miRNA levels that indicate poor survival rates. [45]. Luminal B subtype pre-operative patients present elevated blood levels of miR-195 suitable for early diagnosis. Multiple miRNAs demonstrated tumor-suppressive effects against HER2 augmented EGFR1 pathway dynamics thus restraining cancer cell proliferation including miR-147 with miR-124 also revealing tumor-suppressive properties alongside miR-193-3p. The expression of miR-342-5p and miR-744 declines in HER2-positive BC tumors in comparison to HER2-negative breast cancers. The miRNAs Let-7f, Let-7g, miR-107, miR-10b, miR-126, miR-154, and miR-195 serve as specific biomarkers for HER2-positive breast cancer. Furthermore, miR-4734 and miR-150-5p demonstrate potential for use as predictive biomarkers. [46]. According to Zeng et al the diagnostic biomarker potential of miR-30a in plasma improves detection precision compared to conventional tests including cancerous embryonic antigen and cancer antigen 15-3 (CA15-3) through its reduced levels in BC patients. The levels of miR-30a provide major insights into the diagnosis of breast tumors with either ER or triple-negative features. Furthermore, some studies done on the behavior of miRNA were identified that miR-155 as a potential prognostic biomarker in TNBC patients, where elevated levels of miR-155 showed a protective action by reducing RAD51 expression and improving better clinical outcome for IR-based therapies in TNBC patients.43,58 Whereas miR-18b, miR-103, miR-107, and miR-652 levels interact with recurrence and deprived survival in TNBC.59 In addition, miR-376c, miR-155 and miR-17 are exposed as biomarkers in the early-stage, whereas miR-10b is a late- stage biomarker in TNBC,60 while up-regulated

miR- 532-5p might be employed as a possible biomarker for prognosis. [47]

Research demonstrates that TNBC types with poor prognoses show increased levels of miR-138 which demonstrates this protein's usage possibilities for both diagnostic testing and health condition assessments. Research shows miR-374 produces bigger tumors while miR-105 and miR-93-3p at elevated levels lead to poor patient survival. TNBC patients who develop chemoresistance show abnormal patterns of several specific miRNAs in their tissue samples. Resistance to chemotherapy and poor radiation response appear through low miR-200c levels while increased miR-181a expression associates with non-responsive neo-adjuvant chemotherapy treatment. [48] Numerous studies show how miRNA signatures support diagnostic and predictive and prognostic applications as biomarkers for cancer types especially TNBC specifically when occurring in people with early disease onset. [49]. Breast cancer studies Investigated Oncogenic microRNAs which drive breast cancer invasion and facilitate metastasis and cell migration during cancer growth and proliferation.65 Predominantly predictive microRNA markers associated with hormone therapy and targeted therapy and radiotherapy and chemotherapeutic agents and positive and negative prognostic markers, and diagnostic markers to identify early BC cases and BC molecular subtypes and histological subtypes, have been characterized.

Medical research into breast cancer microbiome relationships discovered that the microbiome signature of ER-positive and HER2-positive breast cancer tissues overlapped but triple-negative and triple-positive samples exhibited mismatched microbial patterns. Research data enables clinicians to create diagnostic tools while offering therapies for different cancer treatments. [50] Studies indicated that triple-negative breast cancer contained lowest microbial diversification while the ER-positive subtype displayed maximum diversity. Various bacterial genes present in the gut microbiome produce enzymes which break down estrogen. Endogenous estrogen combined with corresponding metabolic changes directly correlate with breast cancer risk rates in women who have ceased menstruating. Research shows endogenous estrogen plays a leading role in breast cancers because 70% of tumors in postmenopausal patients test positive for this receptor. [51] Thus, circulating estrogen and its metabolites modify the efficacy of the gut microbiome against breast cancer.71 Postmenopausal women have microbiota composition different from those of premenopausal women, creating different metabolites. In addition to that, during the postmenopausal period, microorganisms that had a synergistic effect during premenopausal would compete with each other. Zhao et al. mentioned that premenopausal women have higher abundances of Bacteroidetes and Roseburia spp. but lower abundances of Firmicutes and Parabacteroides. On the other hand, postmenopausal subjects had a lower Firmicutes to Bacteroidetes ratio, along with higher Escherichia coli and Bacteroides compared to premenopausal women. [52] Changes in endogenous estrogen concentration and composition of the gut microbiome differ between premenopausal and postmenopausal women, and this disequilibrium may promote breast cancer in postmenopausal via higher circulating estrogen levels. These roles of the microbiota in the initiation and progression of breast carcinomas could lead to new therapeutics in the future. Furthermore, it has been shown that the gut microbiome composition of BC women differs based on body mass, with obese BC women showing lower amounts of Firmicutes, Faecalibacterium prausnitzii, and Blautia sp. than normal-weight patients. It is also noted that the presence of some bacterial groups, such as the Clostridium leptum cluster, the Clostridium coccoides cluster, Faecalibacterium prausnitzii, and Blautia sp, correlates with the clinical stage; BC patients at stages II/III show a higher density of such bacteria than patients with stage 0/I. [53].

Besides the gut microbiome, a study on the mammary microbiome showed that the bacterial groups present in mammary tissue are not different from the surrounding normal tissue or tumours tissue. however, Escherichia coli's high profusion in BC patients relative to healthy controls indicated that it was promoting cancer. Several potential pathways through which microbes may influence the development of BC have been identified. These are metabolism function, DNA damage, genomic stability, and the regulation of chronic inflammation and immunology. Most microbiome detection research has instead depended on the sequencing method of a particular section of the bacterial 16S rRNA gene. Many studies based their work on qPCR or a DNA array, but other techniques have recently gained popularity: Breast cancer can result from the gut circulation of microbial and digestive materials because these substances disrupt numerous pathways that affect the host's gene expression or signal transduction. [54] Moreover, the host's food and lifestyle modify the gut microbiota population. If the diet has a negative impact on the composition of the microbiota, then it may rapidly drive malignancy development, even breast cancer. Various microbiota in the gut will cause an imbalance between various phylae, and the type of dietary fiber (soluble and insoluble) absorbed will affect

this. Probiotics and a well-balanced diet can help to improve the potential dysbiosis between Firmicutes and Bacteroidetes that may come up in the context of breast cancer. Triple-negative breast carcinoma, which presents more frequently in young breast cancer patients, is the most aggressive type of BC. Endocrine treatments and HER2-targeted drugs fail in TNBC, and chemoresistance typically develops after chemotherapy. Therefore, finding effective targeted therapies for TNBC based on modifying miRNA levels and/or microbiota status is expected to improve prognosis [55]

Interaction of Gut Microbiome and Host miRNAs in Colorectal Cancer

Many miRNAs are identified having potential biological and clinical implications in CRC. Aberrant miRNA expression is related to the disease course, prognosis, and survival of colorectal cancer. Differential expressions of miRNA have been reported between colorectal cancer tissue and normal colorectal epithelium; therefore, specific miRNAs enhance prognostic and predictive power as biomarkers in colorectal cancer. Where such miRNAs can predict the fate of the disease, as well as the reactions to chemotherapy and radio treatment in patients. Dysregulation of miRNA, would modify its role in numerous cellular pathways leading to cell proliferation, differentiation, apoptosis, and development, such as WNT/β-catenin route, EGFR pathway, TGF-β signaling system, and epithelial-to-mesenchymal transition. [56] Thus, identification of participation of miRNAs in the above-mentioned pathways will benefit the selection of CRC potential biomarkers and therapeutic strategies.

miRNA expression alterations in various phases of CRC, where a few of them express only in the late phase of CRC, such as miR-141, which is identified as a differential diagnostic biomarker and higher amounts of miR-141 in plasma are associated with poor survival of CRC patients.85 On the other hand, serum miR-21 has been identified as a potential marker for the early diagnosis and prediction of CRC. miR-21 is overexpressed in various cancers, such as colorectal cancer, which makes it a potential diagnostic biomarker for CRC.86 miR-21 expression is associated with TNM stage where higher miRNA expression is observed at later stages of CRC. [55-56] Overexpression of miR-21 enhances the tumor progression associated with poor survival and sensitivity to chemotherapy in patients. It functions as an oncogenic miRNA (oncomiR) that could modulate the expression levels of several cancer- associated genes, PTEN, TPM1, and PDCD.88 Besides, miRNA signatures could be used as diagnostic, predictive, and prognostic biomarkers for CRC. miR-31 is linked with BRAF mutation in CRCs, in which it is strongly correlated with aggressive phenotype, showing poor prognosis in patients, which implied that higher expression of miR-31 is related with BRAF V600E mutation in stage IV CRC patients. Moreover, a significant correlation of elevated expression level of miR-31 has been associated with poor survival. Besides, a significantly high elevation of expressions of miR-21 and 31 may also be seen in even precancerous colorectal adenoma, which may be targeted as a biomarker for screening CRC.[57].

Alternatively, host miRNA may influence the size and composition of bacteria in the gut microbiome of an individual. The researchers have conducted a number of studies which explored the association of miRNA expression with the microbiota in human CRC tumors and normal tissues.[34] Using modern technologies including metagenomic sequencing, research has revealed the gut microbiome association with the mechanisms of colorectal carcinogenesis, by the presence of a variety of microorganisms such as Fusobacterium nucleatum, Pepto-streptococcus stoma tis, and Parvimonasmicra, towards the development of CRC. Such susceptibility and development of CRC can be controlled by the makeup of the gut micro biome by controlling such processes as inflammation and DNA damage in the host by producing chemicals that either generate or inhibit tumors. Gut bacteria are present in varied locations, including the ascending colon, distal colon, proximal ileum, and jejunum within the intestine, where they play crucial functions, such as the production of vitamins and degradation of food chemicals. [57] Of several phyla of bacterial species isolated in the microbiome, the Firmicutes, and Bacteroidetes were shown to be highly abundant in the gut. Such overabundance of Firmicutes and Bacteroidetes and Proteobacteria were associated with differently expressed miRNA in colorectal cancer. Some studies have demonstrated that Bacteroidetes and Firmicutes phyla are highly associated with the levels of miR-141-3p, whereas Actinobacteria, Bacteroidetes, Cyanobacteria, and Firmicutes are associated with the levels of miR-200a-3p.

Dysbiosis/imbalance of the microbial community in the gut is associated with the development of CRC. CRC patients show to have an enrichment of many enteric bacteria such as Fusobacterium nucleatum, Bacteroides fragilis, Escherichia coli, and Enterococcus faecalis whereas a decreased number of microorganisms including Faecalibacterium, Blautia, Clostridium, Bifidobacterium, and Roseburia sp.[58] Such dysbiotic pattern revealed in gut microbiome in CRC patients from apparently healthy individuals that tends to enrich the opportunistic pathogen bacteria with detrimental

pro-inflammatory impact while reducing commensal bacteria population like the butyrate-producing bacteria. Butyrate-producing microorganisms are associated with protection against the development of CRC and colitis via the inhibition of tumor growth, induction of apoptosis, reduction of oxidative damage, and restriction of activity of co-carcinogenic enzymes. Conversely, with diminishing such beneficial bacteria population in gut, it advances the development of CRC. Some bacterial species, which are linked with cancer, are Fusobacterium nucleatum, enterotoxigenic Bacteroides fragilis, and colibactin-producing Escherichia coli. It has been found that the vast increase of Fusobacterium nucleatum in patients with early-stage CRC shows poor prognosis. In addition, latest studies identified a new B type, which is known as Enterotoxigenic Bacteroides Fragilis or ETBF. Fragilis strain that produces Bacteroides fragilis toxin (BFT), which activates specific cancer-promoting pathways in colon epithelial cells, resulting in colon inflammation linked to colorectal cancer. [59] Dysbiosis of the colon microbiome resulted in increased interleukin-17 driven inflammation, which promotes to the carcinogenesis of colorectal cancer in humans. Chronic inflammation is associated to carcinogenesis, where 20% of individuals classified with ulcerative colitis, leading to CRC development within 30 years of commencement.

Association Between Breast and Colorectal Cancers

Some of the studies implied the potential for an association between breast cancer and colon cancer in females, with the likely relationship drawn between the extent of sex hormones and the occurrence of colorectal cancer. Prospective exposure of breast cancer patients to the higher levels of endogenous/exogenous sex hormones owing to parity, hormone/estrogen replacement therapy, and breast cancer treatments (tamoxifen) may enhance the prospective chance of getting colon cancer, which is yet contentious. Additionally, the study indicated that individuals with breast cancer were 60% more likely to have colon cancer. Another research conducted by Abu-Sbeih et al showed that patients with a previous history of BC may be at a higher incidence rate for the appearance of adenomatous polyps irrespective of the age of the patient and had a 5% chance of getting invasive CRC. Besides, it was emphasized that a decision about colonoscopy recommendation was based on the patient's age at the moment of BC diagnosis. Thus, for instance, appropriate colonoscopy screening is recommended one year after breast cancer detection in a patient who has more than 40 years old. [60]

Moreover, the relationship between these two cancers is further shown by the involvement of a common set of miRNAs and their expression during disease progression. As mentioned earlier, miR-21 is overexpressed in breast cancer patients boosting cell proliferation, migration, and invasion and hence works as oncomiR, whereas miR-31, miR-143, and miR-145 are known to be under-expressed in breast cancer patients reducing cell proliferation. [43-47] Though, the case with miR-21 and miR-31 in colorectal tumours shows a distinct behavior where the overexpression of those miRNAs may be found in colorectal patients supporting inflammation-associated carcinogenesis. In such cases, it is worthwhile to count the synergistic effects of miRNAs in such cancer types that might come up as second de novo malignancy in cancer survivors. Figure 2 shows the probable correlation with the prevalence of colorectal cancer in females having a history of breast cancer.

Involvement of Host miRNAs and the Microbiota in Immune Regulation of Cancer

miRNA participates in various processes of human physiology, such as differentiation, cell proliferation, development, and apoptosis. However, the development of tumours and treatment failure may be caused by the dysregulation of miRNA expression, biogenesis, and epigenetic regulation of miRNA genes. [61] Such cancer-derived miRNAs can modulate immune responses by creating an immunosuppressive tumor microenvironment while suppressing cancer immunogenicity, thus maintaining cancer cells from immune clearance. Immunomodulatory miRNAs (im-miRNAs) can influence cancer immune surveillance, which leads to immune escape of tumors. Such im-miRNAs are involved in modulating the immune response by modifying cancer antigen processing and presentation. For instance, miR-27 decreases the exposure of MHC class I to the cell surface in colorectal cancer. In addition, miRNAs can even control PD-1 expression and influence NK cells, thereby helping malignancies evade immune surveillance.[57] Furthermore, commensal gut microbiome components are also required for the maturation of innate and adaptive host immunity, preserving intestinal homeostasis, thereby providing detection and tolerance against opportunistic pathogen attacks and prevention of infection. However, alteration in the microbial community shifted immune checkpoint blockers to result in immunological dysregulation, thereby triggering inflammation-inducing bacteria, which enhances chronic inflammation leading to tumor development.[43] Several studies showed that gut microbiome may be involved with the functioning of the immune response by altering the expression of miRNA.

Alterations in the microbiota, miRNA transcriptome, among other factors such as chronic stress and some

therapy like chemotherapy trigger immunological imbalance in cancer patients that causes immunodeficiency/ immunosuppression.[49] This level of immunosuppression places them at vulnerability to infections produced by opportunistic pathogens like viruses, which for decades has remained a big concern to cancer patients and oncologists.

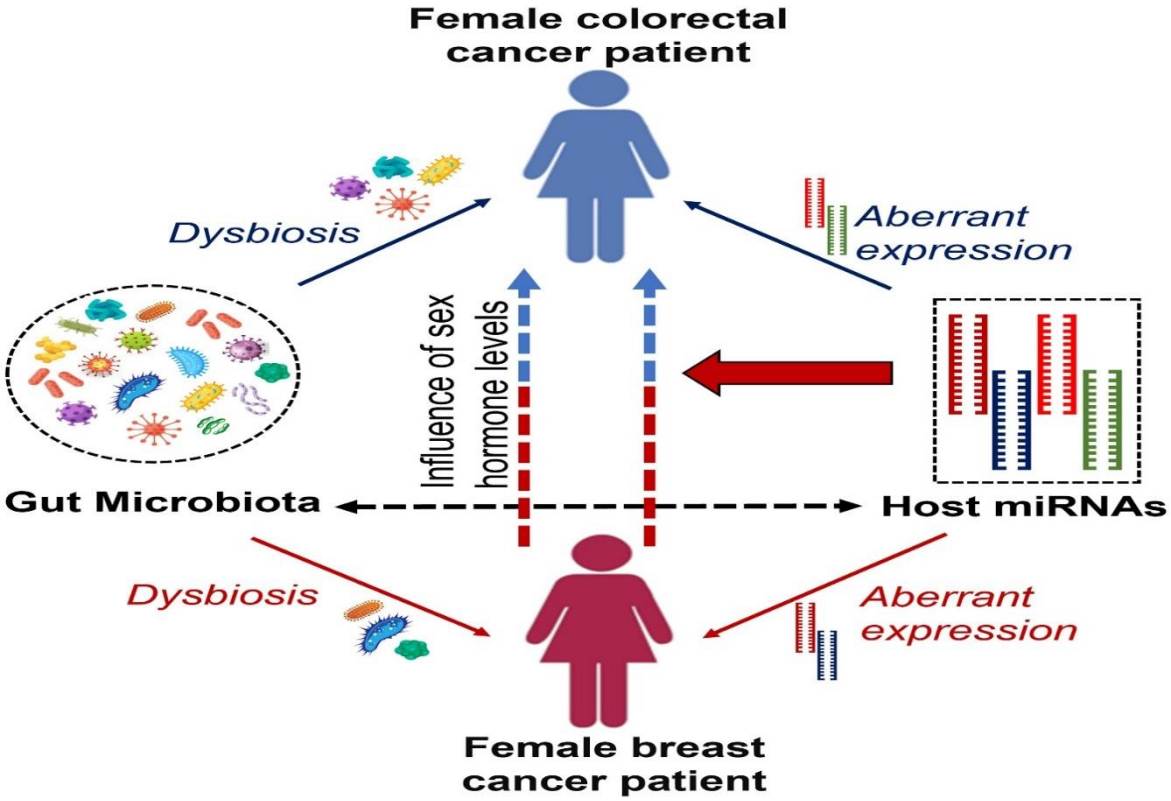

Figure 2 Incidence of colorectal cancer among breast cancer patients/survivors. Coherent cross-talk between the gut microbiome and host miRNAs is preserved in the host, but dysbiosis of the gut microbiota and inappropriate expression of many host miRNAs can trigger malignancies like breast and colon cancers. Alternatively, women afflicted with or who survived from breast cancer are known to suggest a susceptible risk of developing colon cancer. Levels of endogenous and/or exogenous sex hormones and differential activity of a certain common set of miRNAs induce colorectal cancer in females with breast cancer history.

Being a new coronavirus, the COVID-19, or coronavirus disease of 2019, is a sort of severe acute respiratory syndrome brought on by the SARS-CoV-2 virus, or severe acute respiratory syndrome-coronavirus-2, causing highly worse respiratory distress in immunocompromised persons than in immunocompetent persons. Such a development falls among the highlighted pathogenic attacks for everyone, especially for cancer patients. Virus virulence is more important in disease outcome; besides that, many other host- associated features including age, gender, obesity, smoking, and comorbidities including cardiovascular disease, diabetes mellitus, and cancer influence a lot regarding the serious consequence of the disease.[51] Cancer patients are recognized to be immunosuppressed individuals, and the condition is worsened by some kinds of treatment, making them susceptible to infections such as COVID-19, which could be opportunistic, resulting to serious effects in such patients. Studies in China showed a death risk of 6% of cancer patients who had COVID-19 infection than 1% of non-cancer patients. Susceptibility of cancer patients was deemed three times higher for COVID- 19 infections with a poor prognosis due to their immune-suppression caused by the disease and treatments administered compared to individuals without cancer.

Different cancer types are either more or less susceptible to viral infections, such as COVID-19. Colorectal cancer, for example, is more susceptible to COVID-19. Transmembrane serine protease 2 facilitates the activation of the coronavirus spike protein, thus increasing the entry of the virus into the target cell, and the angiotensin-converting enzyme 2 receptor assists the spike protein in its binding to the target cell. The increased expression of the two proteins in lung epithelium increases the risk of getting SARS-CoV-2. Outside the respiratory tract, ACE2 and TMPRSS2 are expressed in the human gastrointestinal system and

overexpressed in colorectal cancer. As such, the intestinal epithelium may serve as a target for COVID-19 virus infection that may be associated with increased incidence of infections in colorectal cancer patients. [51-54]

However, some miRNAs can bind to viral RNA and prevent its translation, thus having a deleterious effect on the viral genome. One study reported six separate miRNAs, which were identified as the potential regulators of human coronaviruses: miR-21-3p, miR-195-5p, miR-16-5p, miR-3065-5p, miR-424-5p, and miR-421.114 Alternatively, some miRNA such as miR-27b can modulate ACE2 receptor, through which coronavirus enter into the cells.115 Another study has demonstrated that miRNAs 200b-3p, 200 c-3p, and 429 can regulate ACE2, while TMPRSS2 is regulated by let-7c-5p, miRNA 98-5p, let-7 f-5p, let-7a-5p, let-7 g-5p, let-7b-5p, miR-4458, let-7e-5p, let-7i-5p, let-7d-5p, and miRNA 4500.116 These miRNAs can be useful therapeutic options in modulating the proteins involved in COVID-19 entrance, particularly in the gut, since ACE2 and TMPRSS2 are expressed at high levels in colorectal cancer. However, expression against the SARS-CoV-2 genome is reduced inversely with age; hence, the elderly population is unlikely to be reduced by COVID-19 via miRNA-based approaches compared to younger populations. [54]

In breast cancer, the re-activation of the DCC due to inflammatory responses within the microenvironment poses a danger as they had attained a dormant condition following successful treatment of the primary disease. DCC may be reactivated by breaking through the dormancy of metastasis, and in situations like the SARS-CoV-2 infection, damage caused in the respiratory tract invokes a series of immunological events which, in turn, provoke pro-inflammatory responses. Such responses regulate inflammatory responses and may induce the re-activation of DCCs, facilitating the growth of cancer cells. [61]

Promising Therapeutic Targets of Cancer

miRNAs are modifiers of the cell involved in several biological processes that include proliferation, cell signaling, differentiation, stress responses, and DNA repair. Moreover, miRNA plays a critical role in the development, activation, and effector functions of immune cells in innate as well as adaptive immunity. The innate immune system would provide the primary response to an infection, but adaptive immunity would allow such a response to expand. miRNAs can target major players in the innate immune systems, including natural killer cells, macrophages, and inflammatory cytokines and chemokines.[62] For instance, the oncomiRs, or oncogenic miRNAs, miR-21 and miR-155, have been shown to play a significant role in the mechanism of immune modulation involving breast cancer. It was shown that miR-21 displays a bi-directional role during carcinogenesis where it also facilitates an antitumor immune response and higher levels of miR-115 in immune cells suggest an anti-tumor immune response as well. Such miRNAs can be identified as a possible immunotherapeutic target for malignancies, such as creating inhibitory-miRNA therapeutics based on antisense antimiRs.

Alternatively, gut microbiota has a high contribution towards the immunotherapy of cancer where these bacteria can influence immune activities through alteration of the immunological check point inhibitors. Most cancer immunotherapies work by restoring the functions of the immune cells by inhibiting immunological checkpoints and reconstituting the antitumor immunity of the immune cells.[63] Immune checkpoint blockade treatment (ICB) is one such potential immunotherapeutic approach for a few types of tumors where the gut microbiota has a pivotal role in the delivery of such drugs. The anatomic location of gut microbiota varies the efficacy of PD-1 and CTLA-4 blockades. Enterococcus, Ruminococcaceae, Akkermansia, and Bifidobacterium species enhance the efficacy of treatment of the blockade of PD-1. The genus Bacteroides shows a biphasic effect where some strains enhance the CTLA-4 blocking therapy and others negatively affect the efficacy of therapy.

Gut dysbiosis may support chronic inflammatory diseases like cancer, which allow unfavored able bacteria to reside in the gut and negatively impacts immunotherapy. Giving antibiotics or prebiotics along with symbiosis can improve colonization of the commensal microbiota within the gut through eliminating pathogenic microbes that is well-suited to creating antitumor immune activities. [63] Several new trends emerge in the modern world concerning cancer medicines, like using live or attenuated and/or genetically engineered microbes to treat cancer. Bacteria-assisted tumor-targeted treatment is one of the possible ways of using bacteria as gene or medicine delivery vehicles to treat tumours when bacteria alone work as an efficient anticancer agent. Some of the selected bacterial species, including Clostridia, Bifidobacteria, and Salmonellae, are used in animal models to express tumor suppressor genes, anti-angiogenic genes, suicide genes, or tumor- related antigens in a specific tumor. Moreover, bacteria are used as immunotherapeutic agents and their tox ins/enzymes in cancer therapy, which are powerful drugs in the future.

CONCLUSION

After considering all the important topics covered so far, the identification of relevant signatures related to gut microbiomes and host miRNAs highlighted their role in the development of cancer through dysregulation. Understanding these mechanisms of microbiome and miRNA dysregulation in various cancers is crucial for regulating the onset and spread of cancer. Beyond that, the diagnosis, prognosis, prediction, and recurrence of the disease may be traced using biomarkers from the gut microbiota and host miRNA profiles. It is essential, therefore, that the correlation potential of two cancers that are usually encountered together, such as breast and colorectal cancers, should also be accounted for when making prompt diagnosis at the onset and providing relevant treatment following this consideration since that might indicate synergy between both of these biomarkers for these types of cancer. The dysregulation of miRNA, along with the microbiota, even affects a cancer patient's immune responses to cause immunosuppression and increase the vulnerability to infections. Thorough knowledge of what the gut microbiome and miRNA do, particularly about its behavior in cancer conditions, would be highly beneficial in developing possible noninvasive biomarkers for the early detection of illness in order to minimize possible risks. As an alternative, knowing how the gut microbiota and host miRNAs communicate depending on expression can help in the development of druggable targets for cancer treatments such as miRNA-based therapies that decrease oncomiR expression while restoring TS-miR expression. Additionally, therapeutic targets can be created to improve gut health and produce antitumor immune activity by increasing beneficial bacteria and lowering harmful ones. Commensal microbial colonization in the gut can be improved by symbiotics, prebiotics, and antibiotics.

To improve the antitumor environment inside the tumor, genetically engineered bacteria either by themselves or with traditional approaches are under examination for potential future therapies. This technique is referred to as bacterium-assisted tumor-targeted therapy. Moreover, having insight into the composition of the microbiota can make use of immunotherapeutic methods, like the medicines which blockade immune checkpoint for cancer patients. In summary, it is important to understand how host miRNAs and the gut microbiota interact and behave, especially in relation to cancer diagnosis, treatment, and prognosis, while obtaining the necessary information to implement effective and efficient therapeutic approaches.

Abbreviations

BC, breast cancer; ER+, estrogen-receptor-positive; ER-,estrogen-receptor-negative; PR+, progesterone-receptor-positive; PR-, progesterone-receptor-negative; HER2+,human epidermal growth factor receptor 2-positive;HER2-, human epidermal growth factor receptor 2-nega-tive; miRNA, microRNA; CRC, colorectal cancer; HDI, Human Development Index; CIN, chromosomal instability; CIMP, CpG island methylator phenotype; MSI, micro-satellite instability; oncomiR, oncogenic miRNAs; TS-miRs, tumor-suppressive miRNAs; metastamiRs, metastasis-associated miRNA; antagomirs, anti-miRs; AMOs, antisense anti-miR oligonucleotides; LNA, locked nucleic acid; TNBC, triple-negative breast cancer, TPM1, tropo-myosin; CEA, carcinoembryonic antigen; CA15-3, cancer antigen, TUSC2, tumor suppressor candidate 2; EGFR, epidermal growth factor receptor, TGF-β, transforming growth factor beta; PDCD4, programmed cell death 4;BFT, Bacteroides fragilis toxin; ETBF, enterotoxigenic Bacteroides fragilis; im-miRNAs, immunomodulatory miRNAs, PD-1, programmed cell death protein 1; NK, natural killer; ACE2, angiotensin-converting enzyme2; TMPRSS2, transmembrane serine protease 2, DCC, dormant cancer cells; ICB, immune checkpoint blockade;CTLA-4, cytotoxic T-lymphocyte-associated protein 4.

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