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Review

Cross-Kingdom Interaction of miRNAs and Gut Microbiota with Non-Invasive Diagnostic and Therapeutic Implications in Colorectal Cancer

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Abstract: Colorectal cancer (CRC) has one of the highest incidences among all types of malignant diseases, affecting millions of people worldwide. It shows slow progression, making it preventable. However, this is not the case due to shortcomings in its diagnostic and management procedure and a lack of effective non-invasive biomarkers for screening. Here, we discuss CRC-associated microRNAs (miRNAs) and gut microbial species with potential as CRC diagnostic and therapy biomarkers. We provide rich evidence of cross-kingdom miRNA-mediated interactions between the host and gut microbiome. miRNAs have emerged with the ability to shape the composition and dynamics of gut microbiota. Intestinal microbes can uptake miRNAs, which in turn influence microbial growth and provide the ability to regulate the abundance of various microbial species. In the context of CRC, targeting miRNAs could aid in manipulating the balance of the microbiota. Our findings suggest the need for correlation analysis between the composition of the gut microbiome and the miRNA expression profile.

Keywords: colorectal cancer; biomarkers; microRNAs; gut microbiota; dysbiosis

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1. Introduction

Colorectal cancer (CRC) shows slow progression since it takes several years to develop from a benign adenoma and progress into a malignant adenocarcinoma [1]. This lengthy process makes it possible to use screening programs and prevent the disease in the early stage when the treatment is more effective and leads to better health outcomes. Unfortunately, there are many shortcomings with the current screening approaches, such as colonoscopy, which is invasive, time-consuming, and unpleasant, but it is still the gold standard procedure [2]. Currently, the implementation of population-based screens for CRC, such as colonoscopy or flexible sigmoidoscopy, is associated with low compliance rates, and non-invasive immunochemical fecal occult blood tests (iFOBTs) have become globally acknowledged screening methods for CRC detection [3,4]. However, their sensitivity in the detection of early premalignant colorectal adenomas (CRAs) or early stage CRC is poor, and it has been reported that almost 40% of CRC cases could be undetected [5–7].

Early CRC detection enhances the overall survival, prognosis, and curability of CRC patients [8–10]. Thus, introducing non-invasive and sensitive tests for the early detection of CRC lesions is fundamental to reducing the number of unnecessary colonoscopies and preventable deaths. Multi-panel biomarkers (e.g., genomic, transcriptomic, proteomic, inflammatory, and microbiome) combined with non-invasive sample collection from peripheral blood or stool are promising for early CRC detection. Due to its attractive characteristics (e.g., abundance and stability), microRNA (miRNA) seems to be a reasonable liquid-biopsy-based biomarker of malignant processes [11,12]. On the other hand, the gut microbiome composition has also been suggested as a potential marker of tumorigenesis [13]. Since the microbiota may affect important physiological and pathophysiological processes and, at the same time, interact with host miRNAs, the evaluation of both multi-omics biomarkers could provide a novel approach for early cancer diagnosis or patient follow-up. Although bacteria-induced cancer progression is still not fully understood, it is known that some species are able to facilitate tumorigenesis in an miRNA-dependent manner. We summarize the CRC-associated crosslinks between miRNA and the host-microbiome composition to highlight biomarkers that could provide potential biomedical applications in oncology.

2. microRNAs in Body Fluids

miRNAs are short (approximately 22 nt long) non-coding RNA (ncRNA) molecules of endogenous origin [14]. By binding to various genomic regions, they regulate the expression of genes involved in not only normal healthy conditions but also in the pathogenesis of severe diseases, including cancer [15]. Since miRNAs may be encapsulated in exosomes or associated with proteins (e.g., AGO2 or NPM1), they are well preserved and resistant to RNase-mediated degradation in body fluids [16]. Moreover, they were shown to be stable during long-term storage and even after repeated freezing and thawing [17]. Such biological characteristics predispose miRNA molecules to be ideal biomarkers for non-invasive liquid-biopsy-based cancer assessment strategies.

The study by Chen et al. was the first study to demonstrate the presence of miRNAs in human serum and plasma [18]. Moreover, specific expression patterns of serum miRNAs for various diseases, including CRC, have been identified. Ng et al. made the first systematic and comprehensive analysis of miRNA applicability and found miR-17-3p and miR-92 to be significantly elevated in CRC patients while recommending plasma miR-92 as a novel diagnostic biomarker for CRC [19]. Motivated by potential biomedical applications, such conclusions unleashed extensive research on miRNAs in body fluids (Figure 1).

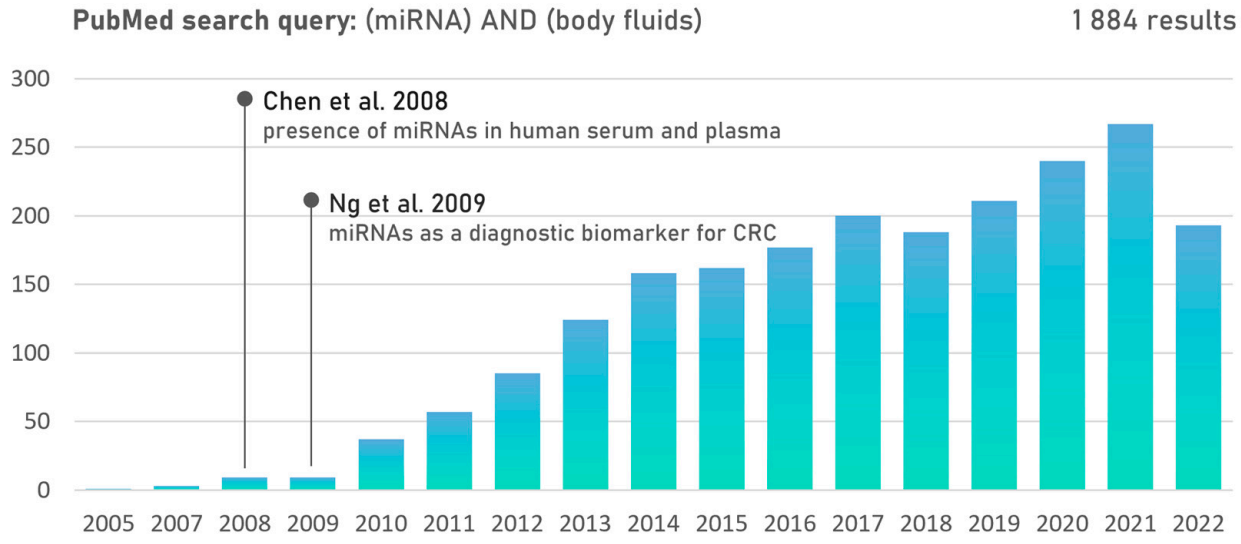

Figure 1. PubMed publication records searching for the terms (miRNA) AND (body fluids) suggest emerging research interest in cell-free miRNAs since 2009 [18,19].

2.1. Role of miRNAs in CRC Development

The aberrant expression of miRNAs was shown to play a role in the initiation and progression of CRC. The functions of dysregulated miRNAs appear to be context-specific, having a dual role in tumor development. A comprehensive list of both tumor-suppressive and tumor-promoting miRNAs associated with CRC development was depicted in the review by Ding et al. [20]. Several miRNAs act as oncogenes by inhibiting the expression of tumor-suppressor genes; thus, they are known as "oncomiRs" [21,22]. One of the most widely studied oncomiRs is miR-21, which mediates colorectal tumorigenesis by regulating the mitogen-activated protein kinases (MAPK) pathway and WNT/β-Catenin signaling through targeting PTEN, PDCD, and DKK2 [23]. The expression levels of miR-21 allow the discrimination of patients with CRA and CRCs from healthy volunteers, suggesting it is a promising biomarker for colorectal neoplasia screening. In favor of liquid biopsy, miR-21 is released by cancer cells and was shown to be abundant in plasma and serum [24,25]. Another oncomiR example associated with CRC and CRA is miR-135b, whos detection in stool samples has been proposed as a non-invasive biomarker for CRC and CRA [26], while targeting miR-135b was suggested as a possible treatment strategy for reversing oxaliplatin resistance in CRC [27]. Although some oncomiRs (e.g., miR-21, miR-155, and miR-224) have been reported to be consistently upregulated in the circulation of cancer patients, the specificity of these miRNAs is still questionable as they have been connected to inflammation and showed elevated levels in inflammatory diseases [28,29].

On the other hand, miRNAs may also provide tumor-suppressive characteristics through downregulating oncogenes associated with proliferation, apoptosis, invasion, and migration. A well-studied representative is miR-34a, which suppresses CRC metastasis by targeting Notch1/Jagged1 and thus regulates their downstream molecules vimentin and fibronectin [30]. In accordance, tumor-derived exosomes encapsulating miR-34a were shown to promote apoptosis and inhibit the migration and tumor progression of CRC cells [31].

However, research on the role of some miRNAs in oncogenesis is contradictory. For example, RAC1-activation-promoting cellular invasion [32], as well as RAC1 inhibition suppressing cell proliferation, invasion, and epithelial-to-mesenchymal transition [33] via miR-142-3p, has been described. Another example is miR-155, which was demonstrated as a tumor suppressor in CRC by targeting CTHRC1 [34]. In contrast, Zhang et al. have shown that the upregulation of miR-155 could promote the migration and invasion of CRC cells through the regulation of claudin-1 expression [35], and Wan et al. indicated it as a potential contributor to the progression and growth of CRC by enhancing the Wnt/β-catenin pathway in an HMG-box-transcription-factor-1-associated mechanism [36].

The contradicting levels of miRNAs in different CRC studies may be partially explained by a dynamic relationship between miRNAs and competitive endogenous RNAs (miRNA sponges). The colon and rectum are highly dynamic environments that respond to various environmental factors and thus require a rapidly modulable nature, providing the ability to induce or negate the effect of mRNA translation. Such conditions predispose ncRNA to be an ideal molecule for enabling the miRNA-mediated mRNA degradation and competitive sequestration of miRNAs, leading to gene downregulation and upregulation, respectively [37].

2.2. Non-Invasive miRNA Biomarkers for Early CRC Diagnosis

Tissue-based studies have found several differentially expressed miRNAs involved in the cascade of colorectal carcinogenesis that may serve as diagnostic biomarkers for CRC patients [38]. Those miRNAs circulating in body fluids provide promise as non-invasive biomarkers accessible through liquid biopsy (Table S1). Several serum miRNAs were suggested for reliable differentiation between CRC patients and control groups, including miR-17, miR-19a, miR-20a, and miR-223 [39]; a panel of miR-31, miR-141, miR-224-3p, miR-576-5p, and miR-4669 [40]; or a panel of exosomal miR-19a, miR-20a, miR-143, miR-145, miR-150, and let-7a [41]. For example, a promising diagnostic panel combining miRNAs (downregulated miR-144-3p, miR-425-5p, miR-1260

and upregulated miR-19a, miR-19b, miR-15b, miR-29a, miR-335, and miR-18a) detectable in plasma or serum samples demonstrated a sensitivity and specificity over 90% [42]. Thus, a multimarker evaluation seems beneficial for increasing the sensitivity and/or specificity of screening tests.

Another complicating factor in the search for biomarkers is the observation that the expression levels of miRNAs exhibit dynamics through the stages of CRC. Systematic increases in the levels of miR-21, miR-31, miR-20a, and miR-135b were observed in plasma during various stages of CRC [43]. These changes were particularly noticeable during the transition from an adenoma to a malignant tumor and the onset of lymph node metastasis, ultimately leading to distant metastasis, as evidenced by high serum levels of miR-200c in stage IV CRC patients [44]. Notably, similar patterns of significant changes in miRNA expression were observed in the alterations of the microbiome in CRC patients [45,46]. However, the current understanding lacks mechanistic studies to confirm or disprove the causality between these miRNA changes and microbiome alterations in the different stages of CRC.

Fecal sampling is also a non-invasive alternative for miRNA detection. Several miRNAs, including miR-223, miR-451 [47], miR-29a, miR-135b, and miR-224, are detectable in feces and may facilitate the non-invasive screening or diagnosis of CRC [48]. Fecal miR-106a was shown to be a useful marker to identify CRC patients with false-negative iFOBT results. Thus, miRNA tests combined with iFOBT may improve the sensitivity of CRC detection [49]. However, as gut bleeding is a clinically prevalent phenomenon of CRC, blood in stool may affect fecal miRNA levels to a varying extent and may substantially impact the interpretation of the clinical data. Considering the propensity of gut bleeding in CRC, the observed upregulation of some fecal miRNAs in CRC patients may be attributed predominantly to blood in their stool. Thus, the effect of blood in stool on the levels of fecal miRNA markers should be considered in the future design of clinical fecal miRNA profiling studies [47].

Promising studies have assessed miRNAs as potential biomarkers for several conditions [50]. Unfortunately, each scientific group used a different laboratory-specific pre-analytical setup for sample collection, total RNA extraction, cDNA synthesis, reverse transcription, and quantitative real-time polymerase chain reaction (qPCR) analysis. This lack of consensus in protocols does not allow for tracking and reproducing setups between labs [51,52]. Since the pre-analytical processes such as normalization and quantification could be different, the careful assay optimization and standardization of internationally accepted protocols are needed for a successful comparison of results produced by other laboratories [53–56].

3. Dynamics of Gut Microbiota Composition

The human microbiome is composed of a wide range of microorganisms, including viruses, fungi, archaea, and bacteria, with bacteria being the most numerous group [57–59]. The human body contains more than 100 trillion microbes [60,61], most of which (approx. 10^{13}–10^{14} microorganisms) occur in the intestines and are composed of more than 1000 different bacterial species. Interactions between the host and the microbiome are dynamic and depend on several genetic and environmental factors, such as age, geographic location, ethnicity, and lifestyle (e.g., diet, alcohol or drug intake) [62–66]. Intestinal microorganisms are essential in human physiology and metabolism, immune system modulation, and the competitive exclusion of enteropathogenic bacteria [60,61]. When the balance between the microbiome and the host is disturbed, dysbiosis occurs, causing severe problems, including cancer development [67,68]. Mechanisms by which a dysbiotic microbiome may contribute to CRC include changes in the immune system regulation, chronic inflammation, or the modification of various food component metabolisms, which may lead to toxic metabolite or genotoxin production [69–71]. Considering the bacterial driver–passenger model in CRC development, bacteria are divided into directly procarcinogenic (drivers), causing changes in the tumor microenvironment, and indirectly procarcinogenic

(passengers), which proliferate as opportunistic pathogens in the tumor-associated microenvironment. Interactions between microorganisms and the host may contribute to the activation of signaling pathways, leading to the development and subsequent progression of tumor growth [72].

Gut-Microbiota-Driven CRC Development and Progression

Although the composition of the intestinal microbiome is known to be individual and vary over time, the two most common phyla are Firmicutes and Bacteroidetes, which account for approximately 90% of all the bacteria present in healthy adults. Other members of a healthy microbiome in the colon include *Eubacterium*, *Bifidobacterium*, *Fusobacterium*, *Lactobacillus*, *Enterococcus*, *Streptococcus*, and Enterobacteriaceae [73–75]. Testing of stool and tumor samples from CRC patients has revealed differences in microbiome composition when compared to healthy controls. These differences were mostly in the taxons *Bacteroides fragilis*, *Streptococcus gallolyticus*, *Enterococcus faecalis*, *Escherichia coli*, *Fusobacterium nucleatum*, *Parvimonas*, *Peptostreptococcus*, *Porphyromonas*, and *Prevotella* (Table 1) [71,76–80]. The microbial composition also varies depending on the stage of the disease. For example, *F. nucleatum* or *Solobacterium moorei* strains are extensively represented in the early and metastatic stages of CRC, while *Atopobium parvulum* and *Actinomyces odontolyticus* strains are more prevalent in patients with CRA and intramucosal carcinomas [46,76]. Thus, the development of the CRC is not caused by one specific microorganism but involves a set of different bacteria whose harmful influence outweighs the influence of beneficial species. A reduced proportion of these beneficial bacteria, such as *Clostridium butyricum* or *Streptococcus thermophilus,* has been observed in patients with CRC [81–83]. The detection of significant microbiome changes in patients with CRC can serve not only as a biomarker for disease screening but also as a predictor of the response to treatment or as a way of determining the prognosis of individual patients [84]. However, a major barrier to analyzing the gut microbiome as a cancer biomarker is often non-compliance due to the undesirable nature of stool sample collection, which can be challenging for a patient [85].

Additionally, there is growing evidence that fungi play an important role in oncogenesis. Two large meta-studies recently showed that there are cancer-type-specific fungal communities even in colon cancers. Tumors and their adjacent tissue from the colon are dominated by *Candida*, *Malassezia*, and *Saccharomyces* genera, although in general, fungal abundances are lower than those of bacteria [86,87].

Table 1. Comparison of bacterial species identified from stool and tissue samples in patients with CRC and healthy individuals.

Bacterial Species	Presence in CRC Patients	Oncogenic Mechanism	Reference
Bacteroides fragilis	up	Wnt signaling activation, toxigenic	[88–90]
Enterococcus faecalis	up	pro-inflammatory signaling	[91–93]
Escherichia coli	up	Wnt signaling activation, genotoxicity	[94–96]
Fusobacterium nucleatum	up	Wnt signaling activation	[77,79,91,97,98]
Solobacterium moorei	up	unknown	[79,99]
Streptococcus gallolyticus	up	pro-inflammatory signaling	[100,101]

4. miRNAs in Host-Gut Microbiota Communications

Host and gut microbiome interactions can be mediated by proteins, metabolites, and ncRNAs, e.g., miRNA, circular RNA, and long non-coding RNA (lncRNA) [102,103]. Recent evidence has revealed a bidirectional interaction between miRNA expression and the human gut microbiota composition [104] (Figure 2). Several cancer-related bacteria, including *F. nucleatum*, *E. coli*, *B. fragilis*, and *Faecalibacterium prausnitzii*, were shown to modulate miRNA levels in CRC cells, thus playing a critical role in the disturbance of intestinal homeostasis (Table 2). Commensal bacteria can produce extracellular vesicles carrying RNA molecules with a gene expression regulatory ability that can be delivered to host cells and regulate the expression of genes regulating the efficacy of cancer

therapy [105]. On the other hand, specific host miRNAs can be taken up by bacteria, where they regulate microbial gene expression and subsequently may promote gut dysbiosis [106]. Although the mechanism is poorly understood, specific microbiome–miRNA interactions are able to mediate gastrointestinal cancer development or cancer therapy resistance, and thus bacterial-strain–miRNA correlations could represent a novel diagnostic or therapeutic strategy.

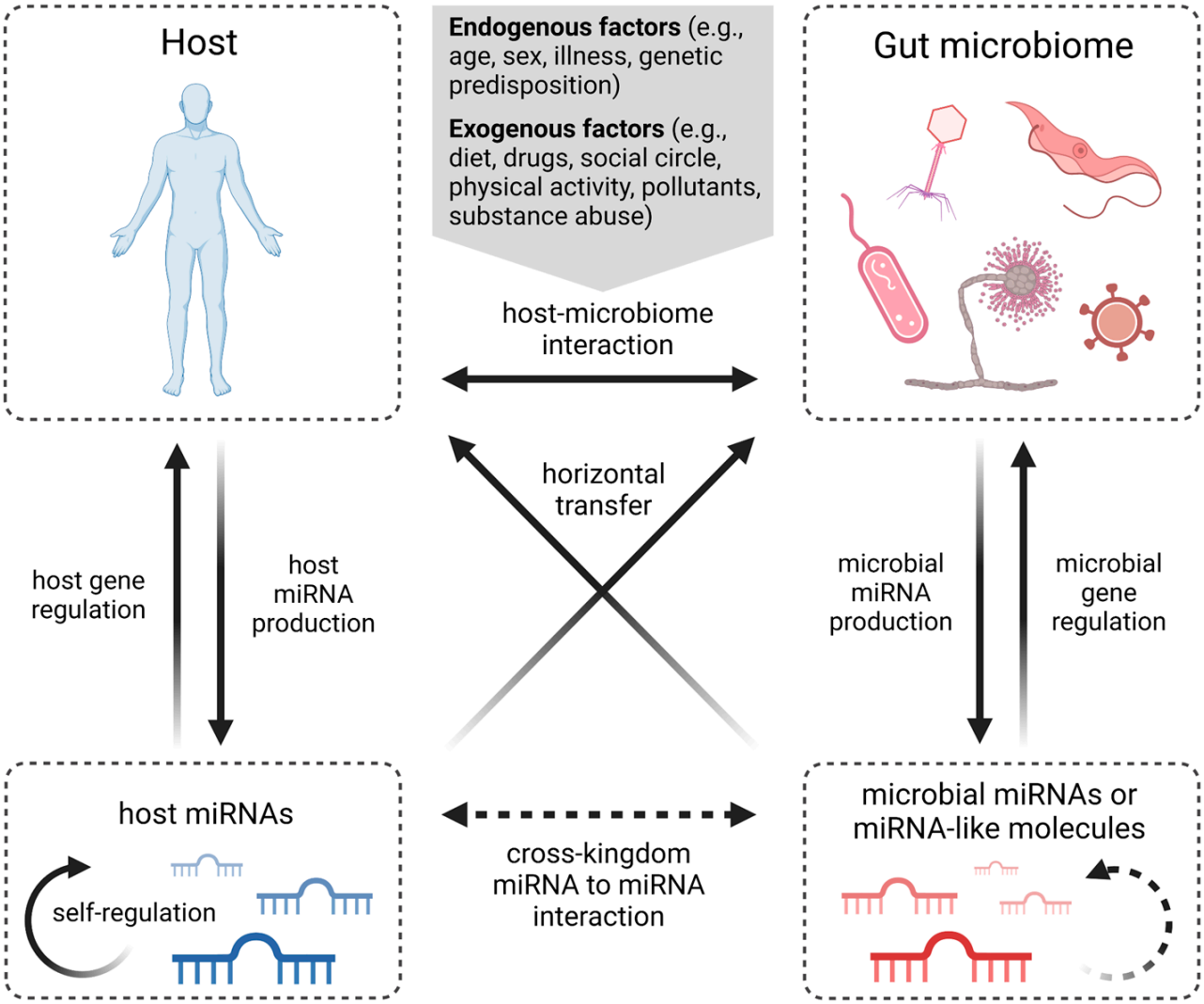

Figure 2. Known types of miRNA-mediated interactions between host and gut microbiota. Human-host–microbiome communication is affected by endogenous and exogenous factors. Both host and microorganisms produce miRNAs to regulate gene expression, while miRNA self-regulation has also been described. However, host-derived miRNAs have shown the ability to regulate microbiome gene expression, and microbial miRNAs and miRNA-like molecules can regulate gene expression of the host. Although self-regulation of microbial miRNAs, as well as interactions between host miRNAs and microbial miRNA molecules, can be hypothesized, these mechanisms have yet to be confirmed. Moreover, several cross-kingdom miRNA interactions have been described, but such communication in the gut microbiome is understudied (created with BioRender.com).

4.1. Microbiota–miRNA Interaction in Host Metabolism

A common denominator associated with CRC through miRNA interactions is the presence of *F. nucleatum*, an anaerobic oral commensal that is considered a pathogenetic factor contributing to multiple gastrointestinal disorders, including CRC [107]. Yu et al.

proposed a pathway of the *F. nucleatum*-mediated activation of TLR4 and MyD88 signaling, causing the genomic loss of mir-18a* and mir-4802 (molecules targeting the autophagy-related proteins ULK1 and ATG7, respectively), resulting in autophagy activation and consequently promoting chemoresistance to oxaliplatin and 5-FU in CRC patients [108] (Figure 3). Another molecule promoting oxaliplatin resistance in CRC is miR-135b-5p, which was shown to be upregulated in CRA and CRC cells together with the overabundance of *F. nucleatum* in the tumor microenvironment [109]. Its direct downstream target, MUL1, acts as a ubiquitin ligase and thus could degrade ULK1, resulting in protective autophagy induction [27]. On the other hand, a negative correlation between miR-135b-5p and TNF-α with a potential immunomodulatory effect in CRC development was observed [109] and was supported by an miR-135b-5p inhibitory effect on lipopolysaccharide-induced TNFα production in human macrophages [110].

An increased expression of miR-21, miR-17-5P, and miR-155, the molecules that can affect the metabolism of tumor cells, was also associated with the presence of *F. nucleatum* in CRC biopsy samples [111]. The upregulation of miR-21 takes place in a promoter-dependent manner by NF-κB stimulation via *F. nucleatum*-activated TLR4/MyD88 cascade. Subsequently, miR-21 reduces the expression of RASA1, leading to the activation of the MAPK signaling pathway and the consequent proliferation of CRC cells [112]. The NF-κB pathway in *F. nucleatum*-infected CRC cells was also shown to downregulate the expression of miR-1322, leading to CCL20 activation, subsequently promoting macrophage infiltration, simultaneously inducing M2 macrophage polarization, and enhancing CRC metastasis [113]. Prometastatic behaviors of cells can also be mediated through the activation of the Wnt/β-catenin pathway. *F. nucleatum* infection stimulates CRC cells to generate exosomes enriched in miR-1246, miR-92b-3p, and miR-27a-3p that are internalized by non-infected cells, where they silence GSK3β, which regulates β-catenin turnover, thus increasing the cell migration ability and promoting tumor metastasis [114]. In association with *F. nucleatum*-induced CRC progression, miR-4474 and miR-4717 were found to be upregulated. Feng et al. suggest their ability to target and downregulate the CREB-binding protein (CBP), which plays a crucial role in Wnt/β-catenin signaling, one of the key pathways in CRC development [115] (Figure 3).

Table 2. miRNA with altered expression in specific bacterial-infection-positive CRC.

Bacteria	Altered miRNAs	miRNA Expression	Effect *	Reference
F. nucleatum	miR-4802; miR-18a*	down	▲ chemoresistance	[108]
	miR-21	up	▲ proliferation	[112]
	miR-34a; miR-135b	up	▲ inflammation; ▼ apoptosis	[27,109]
	miR-22-3p; miR-28-5p	down	▲ inflammation	[109]
	miR-4474; miR-4717	up	▲ CRC initiation	[115]
	miR-1322	down	▲ infiltration; ▲ polarization	[113]
	miR-1246; miR-92b-3p; miR-27a-3p	up	▲ migration	[114]
	miR-21; miR-17-5p; miR-155	up	NA	[111]
E. coli	miR-20a-5p	up	▲ proliferation; ▲ tumor growth	[116]
	miR-30c; miR-130a	down	▼ autophagy	[117]
B. fragilis	miR-155-5p; miR-200a-3p	down	▲ tumor growth	[118]
	miR-149-3p	down	▲ inflammation	[119]
F. prausnitzii	miR-92a	down	▲ apoptosis; ▼ proliferation	[120]
	miR-203	up	▲ apoptosis; ▼ proliferation; ▼ invasion	[121]

* Increased ▲/decreased ▼.

E. coli may also mediate CRC development by interacting with miRNAs. The majority of mucosa-associated *E. coli* isolated from CRC biopsies harbors the *pks* genomic island (*pks* + *E. coli*) responsible for the synthesis of genotoxic colibactin. Colibactin-producing *E. coli* increases cellular senescence characterized by the production of growth factors that promote the proliferation of uninfected cells and subsequently stimulate tumor growth. The underlying mechanisms involve *pks*+ *E. coli*-induced DNA damage, leading to an increased c-Myc expression. The proto-oncogene c-Myc encodes a transcription factor that

binds to the miR-20a-5p promoter, thus upregulating its expression. miR-20a-5p targets SENP1 and silences a translation of this key protein that regulates p53 SUMOylation, an essential post-translational modification in eukaryotic cells [116]. Xing et al. discussed the mechanism of how adherent–invasive *E. coli*-infected epithelial cells may increase the proinflammatory response, consequently activating the NF-κB pathway and leading to miR-30c and miR-130a upregulation, which induces defective autophagy via ATG5 and ATG16L1 silencing, respectively [117].

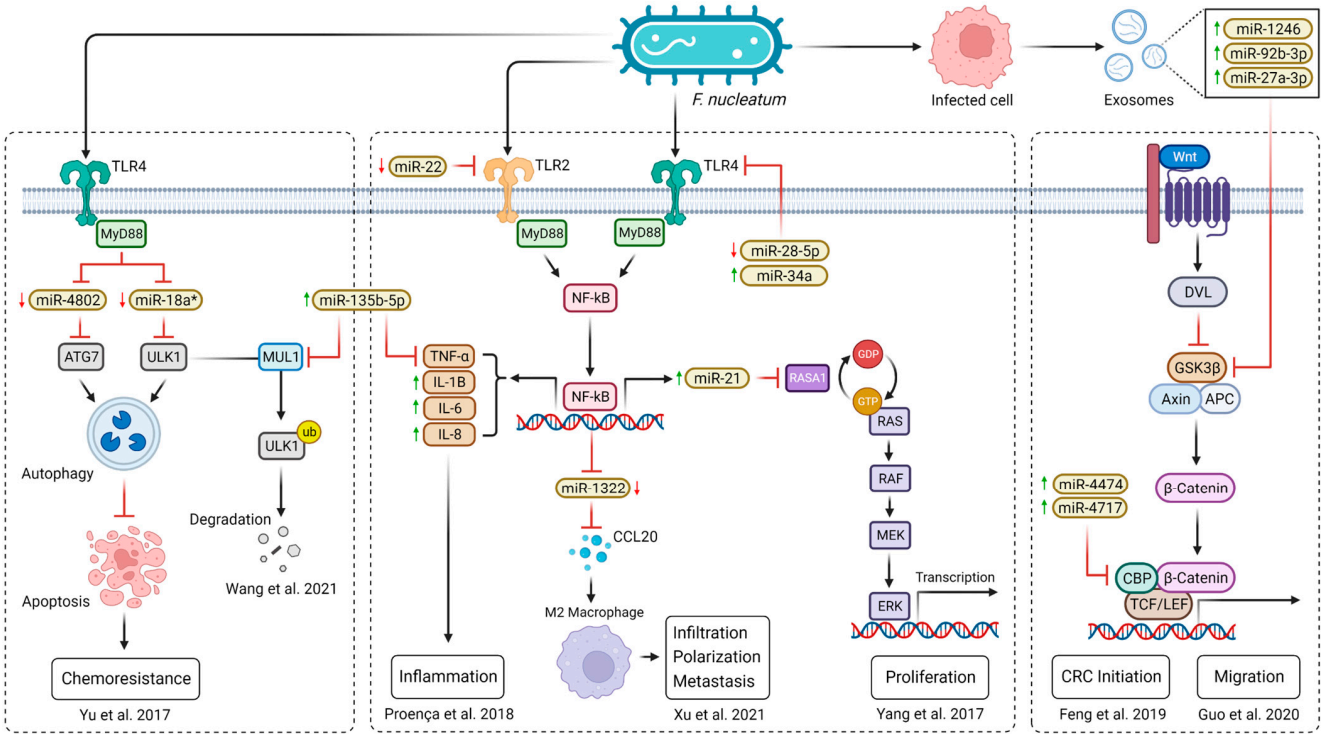

Figure 3. A scheme of *F. nucleatum*-mediated CRC development via miRNA interactions. However, not all the proposed miRNA interactions have yet been confirmed by functional studies [27,108,109,112–115]. Explanatory notes: red arrows (↓) represent decreased level; green arrows (↑) represent increased level; black arrows describe direct stimulatory modification or transcriptional activation of gene expression; red bunt-ended lines (T) describe direct inhibitory effect (created with BioRender.com).

Enterotoxigenic *B. fragilis* (ETBF) is a well-known tumor-inducing bacterium in the human gut that has been shown to induce tumor growth and promote inflammation by modulating lncRNA and miRNA molecules. ETBF-associated lncRNA1 (BFAL1) is highly expressed in CRC cells and provides an ability to competitively sponge miR-155-5p and miR-200a-3p molecules targeting the Ras homolog, the mTORC1 binding (*RHEB*) gene sequence. Thus, BFAL1 attenuates miRNA's suppressive function and subsequently increases *RHEB* expression, leading to the activation of the downstream mTOR signaling pathway [118]. ETBF may also induce colorectal carcinogenesis by downregulating plasma exosomal miR-149-3p and further promoting the PHF5A-mediated RNA alternative splicing of KAT2A in CRC cells. Cao et al. suggest targeting the ETBF/miR-149-3p pathway as a promising approach to treat patients with intestinal inflammation and CRC with a high amount of ETBF [119].

F. prausnitzii is a well-known tumor-inducing bacterium, reported as one of the main butyrate producers in the human gut. Scientific evidence indicates that butyrate reduces the expression of c-Myc, thus inhibiting miR-92a transcription and leading to increased levels of p57 with a tumor-suppressive activity. These actions diminish CRC cell proliferation and stimulate apoptosis [120]. Sodium butyrate was also shown to induce CRC cell

apoptosis and inhibit CRC cell proliferation, colony formation, and invasion through miR-203/NEDD9 cascade [121]. However, to our knowledge, the direct effect of *F. prausnitzii* on miR-203 expression in CRC cells has not been investigated yet.

4.2. Host-Derived miRNAs Affect Microbiome Gene Expression

The regulation of intestinal microbiota by host cells is, to a large extent, an unknown process. An analysis of recent studies by Rotschield et al. estimated the heritability of microbiota as between 1.8% and 8.1%, suggesting that the major influence on microbiome diversity and expression lies apart from diet on epigenetic modulation, possibly via miRNA [122]. The ability of host cells to reshape the intestinal microbiota via the miRNA pathway has been proven by Liu et al., who found that fecal miRNAs directly regulate specific bacterial gene expression and affect microbial growth in the gut [123]. The molecules miR-515-5p and miR-1226-5p were able to enter bacteria, co-localize with bacterial nucleic acids, and promote growth by altering the gene expression of CRC-associated bacterial species, such as *F. nucleatum* and *E. coli*, respectively. Animal studies have also demonstrated that particular host-produced miRNAs can suppress microbial growth. Knockout mice for CRC-associated miR-21 resulted in extensive growth of intestinal *Lactobacillus* sp., and a direct impact of human miR-21 on *Lactobacillus reuteri* growth reduction was also confirmed in vitro [124].

Since miRNAs (mainly derived from intestinal epithelial cells) are a normal constituent of human feces, they represent an important component of gut microbiota maintenance. However, different miRNAs provide different capacities to enter bacteria, leading to variation in their regulatory effects, so the mechanisms of the entry of miRNAs into bacteria and their subsequent processing require future investigation. Several studies have investigated the role of bacteria in CRC, but host–microbiome interaction ranges beyond bacterial species. However, to a lesser extent, the implication of the fungal microbiome in CRC development has also been discussed [125]. The pathogenic fungus *Candida albicans* was shown to communicate with human monocytes and induce the release of a human miRNA that promotes fungal growth. This mechanism represents an unexpected cross-species interaction and implies that the inhibition of specific miRNAs offers new possibilities for the treatment of human fungal infections [126].

4.3. Microbiome-Derived miRNAs Affect Host Gene Expression

It appears that microbiome-derived nucleic acids contribute to minute quantities of cell-free nucleic acids in human body fluids, indicating their potential as novel cancer biomarkers. They were detected in saliva, stool, blood, and plasma [127] and represent a new field for diagnostic research. One of the proposed mechanisms by which the gut microbiome influences the host transcriptome is the production of microbiota-derived snRNAs. Studies and tools that predict miRNA and miRNA-like molecules present in the genomes of microbiota are abundant, but only a fraction of them attempt to provide and verify the underlying molecular mechanisms.

In recent years, studies discussing viral miRNAs affecting host expression have emerged [128–130]. The production of viral miRNA has been mostly observed in herpesviruses such as Epstein Barr virus (EBV) [131–134], human cytomegalovirus [135,136], herpes simplex virus 1 and 2 [137–140], and Kaposi sarcoma-associated herpesvirus [133], as well as human immunodeficiency virus [141–143], Ebola virus [144], and Merkel cell polyomavirus [145]. The EBV genome encodes a cluster of 22 viral miRNAs called miR-BamHI-A rightward transcripts (miR-BARTs). Meng et al. report that EBV-miR-BART18-3p may promote CRC development by upregulating LDHA-mediated metabolic processes and the FASN-mediated de novo lipogenesis pathway. The ectopic expression of EBV-miR-BART18-3p leads to increased migration and invasion capacities of CRC cells in vitro and causes tumor metastasis in vivo. High EBV-miR-BART18-3p expression is closely associated with the pathological and advanced clinical stages of CRC, and thus it might serve as a potential diagnostic marker and therapeutic target for CRC [146].

Considering non-bacteria microbiomes, fungi producing miRNA to interact with hosts are poorly explored. To our knowledge, there is no evidence for a direct interaction between gut fungi miRNAs and human gene expression machinery, but several records confirm the existence of cross-kingdom small-RNA-interference pathways that can affect host gene expression. The fungal miRNA-like molecule bba-milR1 produced by *Beauveria bassiana* has been found to suppress *Anopheles stephensi* immunity to enable fungal penetration of the mosquito integument [147]. The plant pathogenic fungus *Fusarium oxysporum* has been proven to regulate gene expression in chickpea via miRNA [148]. Fungal miRNAs were also detected in a mutualistic interaction between the mycorrhizal fungus *Pisolithus microcarpus* producing Pmic_miR-8, which allows the fungus to integrate deeper into *Eucalyptus grandis*' tissues and positively affects the maintenance of its mycorrhizal roots [149].

Studies generally discuss the mode of host miRNA expression regulated via the MyD88-dependent pathway or gut-microbiome-derived metabolites. However, there is scarce evidence for an interaction between gut microbial snRNAs and human gene expression machinery. Although miRNAs were found in various species of plants, animals, and viruses, little is known about miRNA-sized RNAs (msRNAs) in prokaryotes. The surrounding msRNA sequences in bacteria have been shown to have a structure similar to precursor miRNA molecules, and supporting analyses suggest that msRNA may be processed from longer RNAs in a way similar to miRNA maturation [150]. On the other hand, miRNAs act through RNA-induced silencing complex (RISC), which does not exist in bacteria. However, bacterial Hfq RNA chaperone mediates and stabilizes RNA–RNA interactions and provides a similar role as RISC [151]. Only a few studies have observed how bacterial msRNAs or miRNA-like molecules interact with macro-organisms. *Salmonella enteritidis* produces miRNA-like RNAs Sal-1 by exploiting host AGO2 protein in infected cells. The production of Sal-1 promotes the intracellular survival of *S. enteritidis* and helps to evade the host immune system [152]. Furuse et al. observed that miRNA-like RNA MM-H is produced by *Mycobacterium marinum* in infected macrophage cells, but they were unable to investigate its function in *M. marinum*-infected cells [153]. Small secretable RNAs were detected in the periodontal pathogens *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Treponema denticola*. Those small RNAs were exported in extracellular vesicles and suppressed the production of IL-5, IL-13, and IL-15 in T-cells [154]. These studies underline that further research is needed to understand how microbiomes are capable of interacting and affecting host expression by the means of miRNA-like molecules.

5. miRNAs and Gut Microbiota Therapeutic Implications

Due to the evident relationship between miRNAs and the development of colorectal cancer, further research focused on the possibilities of probiotics and targeted nutrition as novel therapeutic concepts must be conducted. It is well known that probiotics can regulate the expression of intestinal miRNAs [155] and that the host's diet affects the variety and abundance of the microbiota [156]. Among the probiotics studied to alter miRNA expression in colorectal cancer, *Lactobacillus acidophilus* and *Bifidobacterium bifidum* showed potential to upregulate miRNAs with tumor-suppressive properties and downregulate oncogene-associated miRNAs [157]. Moreover, animal studies have demonstrated the ability of *Bifidobacterium longum* to inhibit colorectal cancer by inducing miR-145 and miR-15a tumor-suppressive properties [158]. miRNAs identified as either downregulated or upregulated in CRC patients (Table S1) can provide potential therapeutic targets for miRNA-based therapy using miRNA mimics or antisense RNAs to restore or reduce endogenous miRNA levels, respectively. Among the main advantages of miRNA-based therapies might be their lower toxicity due to their natural occurrence in the intestine compared to currently used chemical substances [159]. However, the lack of miRNA specificity towards the target [160] and problems associated with the delivery of therapeutic agents to cells of interest [161] currently limit their therapeutic use in clinical practice.

6. Conclusions

Over the past decade, gut microbiota dysbiosis has been linked to many health disorders, including CRC. Since miRNAs were shown to regulate microbiome composition and play a critical role in intestinal homeostasis, specific microbiome–miRNA correlations can serve as non-invasive diagnostic biomarkers for CRC. Uncovering the interactions between CRC-associated miRNAs and microbiome entities such as bacteria, phages, viruses, or fungi expands our understanding of CRC cell biology and could help to identify novel therapeutic targets. Such cross-kingdom communication supports the idea of targeting miRNAs to aid in manipulating the balance of the microbiota. However, the mechanism of miRNA-mediated colorectal tumorigenesis considering microbial composition is still poorly understood, and for some microbial representatives it is not at all understood. Thus, further studies are necessary to elucidate the benefit of this potential non-invasive multi-omics biomarker approach.

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