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Linking microRNA to metabolic reprogramming and gut microbiota in the pathogenesis of colorectal cancer (Review)

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Abstract. Colorectal cancer (CRC), an emerging public health concern, is one of the leading causes of cancer morbidity and mortality worldwide. An increasing body of evidence shows that dysfunction in metabolic reprogramming is a crucial characteristic of CRC progression. Specifically, metabolic reprogramming abnormalities in glucose, glutamine and lipid metabolism provide the tumour with energy and nutrients to support its rapid cell proliferation and survival. More recently, microRNAs (miRNAs) appear to be involved in the pathogenesis of CRC, including regulatory roles in energy metabolism. In addition, it has been revealed that dysbiosis in CRC might play a key role in impairing the host metabolic reprogramming processes, and while the exact interactions remain unclear, the link may lie with miRNAs. Hence, the aims of the current review include first, to delineate the metabolic reprogramming abnormalities in CRC; second, to explain how miRNAs mediate the aberrant regulations of CRC metabolic pathways; third, linking miRNAs with metabolic abnormalities and dysbiosis in CRC and finally, to discuss the roles of miRNAs as potential biomarkers.

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1. Introduction

Colorectal cancer (CRC) is ranked as the third most common cancer worldwide, with ~1.9 million new cases reported in 2020. It is also the second leading cause of cancer-related deaths, with an estimated 930,000 fatalities in the same year (1). Recent statistics predicted 152,810 new CRC cases and 53,010 deaths in the United States alone in 2024 (2). Globally, ~5.25 million individuals are living with CRC, with new cases expected to rise to 3.2 million by 2040 (3). Additionally, a troubling increase in CRC cases has been observed in Asia, which now has the highest CRC incidence (51.8%) and mortality (52.4%) per 100,000 population worldwide (4).

Both environmental influences and genetic factors contribute to an individual's lifetime risk of developing CRC (5-7). Most CRC cases are sporadic, considered to result primarily from environmental influences, without family history or evident genetic predisposition (5). Unhealthy lifestyle choices, such as insufficient physical activity and high alcohol consumption, increase the risk of CRC. Furthermore, dietary habits, including low intake of vegetables and protective micronutrients as well as high consumption of highly refined carbohydrates and fatty foods, are positively associated with CRC incidence (7-9).

The link between diet and gut microbiome composition is significant (10,11), affecting the physiological state of the colonic system. Bacterial degradation of carbohydrates can potentially produce harmful oxidative by-products that contact the colonic mucosa. High-fat diets boost liver cholesterol and bile acid production, which intestinal flora can convert into potential carcinogens (12,13). Given this evidence, it is unsurprising that obesity has been recognised as a risk factor for CRC. A meta-analysis study of patients with CRC revealed that 19.3% of patients with CRC receiving surgical resection were classified as obese (14). Studies suggested that obese women with a body mass index (BMI) of ≥30 had a 1.93-fold higher risk of developing early-onset CRC compared with those with a BMI of 18.5-22.9 (15,16). Meta-analysis studies suggested higher BMI is associated with an increased risk of CRC in both men and women (16,17). Obesity is also linked to poorer survival outcomes in patients with CRC. Obese patients with metabolic syndrome had a 1.45-fold higher risk of overall mortality and a 1.49-fold higher risk of CRC-related mortality compared with non-obese patients without metabolic syndrome (18).

The gut microbiota interacts with host cells to regulate nutritional absorption, metabolism, immunity, tissue development and carcinogenesis (10,11). Alterations in the composition and function of the intestinal microbiota are linked to the onset of intestinal diseases, including CRC (10,19). Gut bacteria are implicated in the early stages of CRC, contributing to the development of adenomatous polyps (20). Specific bacteria species, such as *Fusobacterium nucleatum*, *Escherichia coli* and *Bacteroides fragilis* are associated with colorectal carcinogenesis (11,19). Although studies have established a connection between gut microbiota with CRC, the specific mechanisms mediating these interactions remain unclear. Interestingly, a recent study suggested that gut microbiota carcinogen metabolism may be a contributing factor to the chemical-induced carcinogenesis of cancer (21). Certain microbial metabolites are implicated in CRC by inducing inflammation, DNA damage, and activating tumorigenic pathways (22,23). Understanding these interactions facilitates novel diagnostic and therapeutic strategies targeting gut microbiota for cancer management and prevention. Metabolic reprogramming, a hallmark of cancer, is crucial in CRC pathogenesis (24). This process involves adaptive changes in tumour cell metabolism to meet energy production needs, maintaining cellular balance, proliferation and differentiation (25). Metabolic reprogramming supports CRC rapid cell proliferation by fulfilling their energy and nutrient demands (26). Cancer genes and their signalling pathways regulate metabolic reprogramming through mechanisms involving glucose, glutamine and lipid metabolism, increasing aerobic glycolysis, lipid synthesis and decomposition disturbances, and cell proliferation (27). Clinical studies indicate that hyperactivated energy metabolism and dysregulated signalling pathways contribute to poor prognosis of CRC (28).

While various signalling molecules play roles in tumour pathogenesis, increasing evidence shows that microRNAs (miRNAs or miRs) significantly alter the energy metabolism of tumour cells through various metabolic pathways by targeting key enzymes and signalling pathways (29). These pathways include the regulation of the tricarboxylic acid (TCA) cycle, aerobic glycolysis and fatty acid (FA) synthesis, which are crucial for tumour cell survival and proliferation (30,31) and also affect the stromal and immune cell components of the tumour microenvironment (32). These small, non-coding RNAs regulate the translation and stability of specific target mRNAs, acting as tumour suppressors or oncogenes. They are involved in cellular regulation, development, differentiation, proliferation, apoptosis and metabolism. Yuan *et al*'s (32) review concluded that miRNAs critically mediate the interaction between host and microbiota. They also suggested that nutrient availability in the CRC microenvironment influences these interactions. Another study reported that the microbiota affects miRNA expression in the caecum (33). These findings highlight a reciprocal influence between microbiota and miRNAs.

The present review aims to elucidate miRNA interactions with metabolic reprogramming and microbiota in CRC. These intestinal miRNAs are derived mainly from the host and the food. Intestinal epithelial cells, through shedding or exosome excretion, are the primary sources of host-derived miRNAs. Food-sourced miRNAs absorbed by the host can influence the host gene expression (32). Understanding these interactions and their impact on CRC development, progression, metastatic spread, and antitumour drug resistance is vital for designing effective prevention programmes, improving early detection methods, and developing targeted therapies.

2. Metabolic abnormalities in CRC

During oncogenesis, CRC cells undergo metabolic reprogramming, leading to abnormal glucose, glutamine and lipid metabolism. Metabolic reprogramming is increasingly known as a hallmark of numerous cancer types, essential for sustaining rapid cell proliferation and the ensuing high demand for energy and biosynthetic precursors necessary for tumour development.

Glucose metabolism. The initial uptake of glucose by cells occurs through glucose transporters (GLUTs). Once inside the cell, glucose is phosphorylated to glucose-6-phosphate (G6P) by hexokinase (HK). Phosphofructokinase then catalyses the conversion of fructose-6-phosphate to fructose-1,6-bisphosphate, a process positively regulated by PI3K through the enhancement of glycolytic flux. Finally, pyruvate kinase (PK) governs the final step of glycolysis. In the absence of oxygen, pyruvate produced during glycolysis is converted to lactate by lactate dehydrogenase (LDH) (34). The first indication of a metabolic difference between normal and cancer cells was identified in 1924 by Otto Heinrich Warburg, who identified an abnormality in glucose metabolism. This phenomenon, known as the 'Warburg effect', describes the tendency of cancer cells to prefer glycolysis for adenosine triphosphate (ATP) production over oxidative phosphorylation, even when oxygen is available (35). Through aerobic glycolysis, the highly proliferative cancer cells obtain glycolytic intermediates such as lipids, nucleotides and amino acids to support their rapid proliferation, division and continued survival (35).

Current data indicate that most CRC cells exhibit the Warburg metabolic phenotype, characterised by increased aerobic glycolysis. This metabolic profile is driven by the

overexpression of numerous genes and proteins involved in glucose uptake and glycolysis. GLUT1, in particular, is the most extensively studied and is strongly associated with neoplastic progression in the colon (36-38). GLUT1 is significantly upregulated in colorectal adenocarcinoma, and its expression correlated with poor tumour histology, higher stage, hepatic metastases and adverse survival in numerous clinical studies (39-41). Other glycolytic enzymes, including HK1 and HK2 (42,43), PK (44), LDHs (LDHA and LDH5) (45,46) as well as MCT4 (47,48), are all well documented to be upregulated in CRC. This high glucose dependency correlates with tumour aggressiveness and poorer prognosis in CRC (41,49,50).

The oncogenic adaptive response towards glucose metabolism is primarily mediated by hypoxia-inducible factor 1 (HIF-1), a transcriptional factor known to be involved in the pathogenesis of numerous types of cancer (51). HIF-1 is a heterodimeric complex consisting of HIF-1α and HIF-1β/Aryl hydrocarbon receptor nuclear translocator. The α-subunit is sensitive to oxygen levels and becomes stabilised in low-oxygen (hypoxic) environments. When stabilised, the active HIF-1αβ complex promotes the expression of various hypoxia-responsive genes by binding to the hypoxia-response element. This includes several glycolytic genes, such as GLUT1, LDHA and pyruvate dehydrogenase kinase 1 (41,52). The gene expression changes triggered by HIF-1α support the metabolic shift towards Warburg metabolism. HIF-1α overexpression has been linked to a poor prognosis in patients with CRC, as shown in numerous cohort studies (53-55).

Interestingly, metabolic shifts towards glycolysis are also evident in the early stages of CRC. The tumour suppressor gene Adenomatous Polyposis Coli (APC), frequently (>80%) mutated in sporadic CRCs, partly promotes tumorigenesis by enhancing glycolysis in CRC (56-58). Thus, metabolic reprogramming leading to enhanced glycolysis is a distinct characteristic of CRC, evident even at the disease's initiation.

Amino acid metabolism. Glutamine, the most abundant amino acid in the body, serves as a vital metabolic fuel for cancer cells. It is transported into cells by amino acid transporters such as ASCT2 or SLC1A5 and converted into glutamate in the mitochondria via glutaminase (GLS) activity. The resulting α-ketoglutarate replenishes the TCA cycle and is used for ATP generation. Altered glutamine metabolism is a hallmark of CRC. Patients show lower serum glutamine levels compared with healthy controls, likely due to the increased demand for glutamine by cancer cells (59,60). Pre-treatment glutamine levels can independently predict survival of patients with CRC, with lower serum glutamine levels linked to poorer overall survival and lower progression-free survival (60). This association is further supported by recent findings suggesting that glutamine deprivation may enhance the CRC migration and invasion by inducing the epithelial-to-mesenchymal transition (EMT) process (61). CRC cells show increased dependence on glutamine metabolism for proliferation and survival, with the viability of HT29 and HCT116 cells significantly decreased in the absence of glutamine (62). Glutamine-deprived cells exhibit significantly lower intracellular ATP levels due to suppressed glutamine consumption and glutamate production, and glutamine depletion triggers cell death and cell cycle arrest at the G0/G1 phase (63).

GLS1, which converts glutamine to glutamate, is crucial for CRC survival. GLS1 knockdown via short hairpin RNA significantly decreased cell viability and inhibited colony formation (64). Consistently, GLS1 knockdown impaired the CRC tumour growth in nude mice. Increased GLS1 expression in samples of patients with CRC correlates with low differentiation status and higher TNM stage (62).

Enhanced glutamine metabolism in DLD1, HCT116 and CaR1 colon cancer cells allows survival under glucose-depleted conditions. CRC cells increase glutamine metabolism to maintain TCA cycle activity when glucose metabolism decreases, leading to higher levels of amino acids, especially aspartic acid and asparagine. Increased glutamate dehydrogenase activity helps overcome glucose depletion in CRC (65). Indeed, dysregulated glutamine metabolism contributes to the energy homeostasis favourable to CRC progression.

Lipid metabolism. The dysregulation of lipid metabolism is now known as one of the key drivers of oncogenic processes, a metabolic phenotype shown to promote cancer development and therapeutic resistance in various cancers, including CRC (66). Normal healthy cells primarily metabolise circulating FAs obtained from dietary fat, with long-chain FAs accounting for ~70-80% of mitochondrial oxidative phosphorylation (67,68) for energy production. By contrast, cancer cells acquire the ability to increase the uptake of extracellular lipids and lipoproteins, leading to enhanced *de novo* lipid biogenesis and synthesis of cholesterol. Increased FA oxidation drives ATP generation to fuel cancer cells, while lipid metabolites from alternative FA metabolic pathways are essential for the formation of cell membrane, cell signalling, post-translational modification of proteins and storage of energy (69). During FA synthesis, FAs are produced from citrate and converted to acetyl-CoA by ATP citrate lyase in the cytoplasm. The rate-limiting step of FA synthesis involves the carboxylation of acetyl-CoA to produce malonyl CoA catalysed by acetyl-CoA carboxylase (ACC) (70). The end product of FA synthase (FASN) includes palmitate, a 16-carbon saturated FA (SFA), which serves as the substrate for desaturation and elongation reactions, producing various Fas (70). Metabolic intermediates of these processes are used to synthesise cholesterol and phospholipids for cell membranes and inflammation mediators such as prostaglandins. Notably, the excess lipids are subsequently stored in lipid droplets to be catabolised and generate ATP from mitochondrial FA oxidation in nutrient-deprived environments (71).

CRC frequently exhibit altered lipid profiles, impacting numerous lipid-associated pathways. Higher circulating FASN levels were reported in patients with stage III and IV CRC compared with stage I and II patients (72). High FASN expression is typically associated with a glycolytic phenotype and increased mitochondrial respiration, enabling CRC cells to sustain mitochondrial FA oxidation under metabolic stress (73). The downregulation of FASN in intestinal epithelial cells improves survival and decreases intestinal adenomas in a mouse model of APC-driven CRC (74). Apart from enhanced synthesis of palmitate, CRC also exhibits increased FA elongation with high membrane lipid saturation (75). The high abundance of SFAs, secondary to increased FASN activity, is incorporated into membrane phospholipids, rendering

cells less susceptible to free radicals and therapeutic penetration (76). Silencing lipid metabolic genes, including sterol regulatory element-binding proteins 1 and 2, crucial for FA and cholesterol synthesis, inhibited tumour growth in both *in vitro* and xenograft CRC models (77). Evidently, lipid biogenesis pathways correlate with CRC epithelial-mesenchymal transition, invasion and metastasis (78-81).

CRC's lipogenic trait is associated with increased lipid droplets and upregulated FA oxidation. Lipid droplets serve as sites for prostaglandin E2 (PGE2) synthesis from arachidonic acid (82). Once transported out of the cell, PGE2 activates signalling pathways, which regulate essential processes, including inflammation, proliferation, migration, apoptosis and angiogenesis (83). Notably, lipid droplet accumulation also contributes to chemoresistance in CRC (84). The increase in FA oxidation in CRC promotes the survival of CRC cells, with the downregulation of CPT1C genes shown to suppress cell proliferation, inducing cell cycle arrest, and repressing cell migration (85). It is evident that increased mitochondrial uptake of FAs with CPT1A-mediated FA oxidation promotes metastasis (85), while CPT1C overexpression in the patient samples is linked with poor relapse-free survival (86). Upregulation of other genes essential for FA activation (long-chain acyl-CoA synthetase, ACSL) and mono-unsaturated FA production (stearoyl-CoA desaturase, SCD) were also shown to be associated with poor CRC prognosis (87). Taken together, these findings underscore the pivotal role of dysregulated lipid metabolism during CRC progression.

3. Linking miRNA signalling in metabolic abnormalities in CRC

Dysregulation of miRNA expression is implicated in the initiation and progression of tumorigenesis, having been studied in nearly all human types of cancer (88,89). Numerous studies have demonstrated that miRNAs tightly regulate altered metabolic pathways in cancers (31,90). In CRC, recent research has shown that changes in glucose, glutamine and lipid metabolism are associated with miRNA dysregulation (Table I) (91,92). Evidently, miRNAs are increasingly revealed to participate in cell metabolism by regulating the expression of genes, which in turn directly alter metabolic machinery or indirectly modulate the expression of key metabolic enzymes, acting as master regulators (49).

miRNA-mediated abnormalities in glucose metabolism. Studies have indicated that miRNAs associated with glucose metabolism are dysregulated in CRC. Several miRNAs affect glucose metabolism by regulating different enzymes or transporters in CRC cells. For example, miRNAs can control glucose uptake by directly modulating expression of GLUTs or through other regulatory mechanisms. Jin *et al* (93) observed that miR-195-5p expression is downregulated in CRC (93). Interestingly, miR-195-5p directly regulated GLUT3 expression in bladder cancer cells, decreasing glucose uptake and inhibiting cell proliferation (94). This interaction suggests a possible mechanism of miR-195-5p and GLUT3 in CRC. In CRC, GLUT3 promotes cell proliferation by enhancing glucose uptake and fuelling nucleotide synthesis under glucose-limiting conditions *in vitro* and *in vivo* (95). Additionally, miR-328 represses glucose uptake by targeting solute carrier family 2 member 1 (SLC2A1), encoding GLUT1. Indeed, reduced miR-328 expression in patients with CRC inversely correlates with the typically upregulated SLC2A1/GLUT1 expression in tumours (96). GLUT1 is a major GLUT in most cancer cell types, leading to increased glucose uptake (97).

Previous studies have also highlighted miRNA regulation of irreversible glycolysis steps. HKs, which catalyse the ATP-dependent phosphorylation of glucose to G6P, are overexpressed in CRC, contributing to aerobic glycolysis. miR-143 has been shown to target and downregulate HK2 in CRC cell lines. Loss of miR-143-mediated repression of HK2 promotes glucose metabolism in CRCs, shifting towards aerobic glycolysis (98). In accord, miR-143 is frequently reported as downregulated in CRC (99-101), with evidence that it significantly suppresses CRC cell proliferation by inhibiting KRAS translation (100). The embryonic form of PK, PKM2, is reportedly re-expressed in cancer cells to cause the dephosphorylation of phosphoenolpyruvate and formation of pyruvate, the last concomitted step of glycolysis. PKM2 provides tumour cells with a metabolic advantage by allowing the use of phosphometabolites upstream of pyruvate as precursors for synthesising nucleic acids, amino acids as well as lipids. miRNAs such as miR-124, miR-137 and miR-340, which are dysregulated in CRC, impede CRC growth by counteracting the Warburg effect through regulating alternative splicing of the PKM gene expression from PKM2 to PKM1 (102). High PKM1/PKM2 ratios inhibited the glycolysis rate and elevated glucose flux into oxidative phosphorylation (103).

In numerous tumours, after glycolysis, pyruvate is converted into lactate by LDH, with high LDH levels correlating with tumour aggressiveness (104). In human CRC specimens, miR-34a, miR-34c, miR-369-3p, miR-374a and miR-4524a/b negatively correlate with LDHA expression, reducing glycolysis, lactate production, ATP generation and cell proliferation (45). The miR-34 family, initially characterised as a p53 target gene in 2007 (105), has been identified as an important tumour suppressor, particularly miR-34a (106). P53-activated miR-34 suppresses the transcriptional activity of β-catenin-T-cell factor/lymphoid enhancer factor (LEF) complexes by targeting untranslated regions in a network of Wnt pathway-regulated genes, including WNT1, WNT2, β-catenin, LEF1 and LRP6 (107). Additionally, a study identified genetic loci newly associated with accelerated CRC progression in 3'-untranslated region of LDHA, which maps to the seed sequence recognised by miR-374a. Indeed, cancer cells overexpressing miR-374a have been shown to have lower levels of LDHA compared with those with miR-374a-MUT.

In addition to targeting key glycolytic enzymes, miRNA also regulates the glucose metabolism of CRC cells by directly altering the pyruvate dehydrogenase complex. Specifically, miR-26a was demonstrated to modulate CRC glucose metabolism by targeting PDHX, inhibiting the conversion of pyruvate to acetyl coA in the TCA cycle (108). miR-26a shows a higher expression in colon cancer tissues than in normal colon tissues (109) and promotes cancer cell metastasis potential by activating the AKT pathway through phosphatase and tensin homolog suppression *in vivo* (110). These findings suggest the role of miRNAs in regulating glucose metabolism in CRC progression.

Table I. Possible mechanisms of miRNA involvement in gut microbiota-regulated metabolism in colorectal cancer.

First author/s, year	Altered miRNAs	Target mRNAs	Altered microbial taxa	Effect on metabolism	(Refs.)
	Glucose metabolism				
Yuan *et al*, 2018	miR-106b-5p, miR-181-3p, mir-17~92 clusters, miR-182, miR-503	-	*Firmicutes*, *Bacteroidetes* and *Proteobacteria*	Glycan biosynthesis pathways	(138)
Feng *et al*, 2019	miR-4474, miR-4717	CBP	*Fusobacterium nucleatum*	Decrease expression of CREB-binding protein	(141)
Fei *et al*, 2012	miR-195-5p	GLUT3	-	Accelerate glucose input under glucose-limiting conditions	(94)
Santasusagna *et al*, 2018	miR-328	SLC2A1	-	Repress glucose uptake	(96)
Gregersen *et al*, 2012	miR-143	HK2	-	Shift towards aerobic glycolysis	(98)
Sun *et al*, 2012	miR-124, miR-137, miR-340		-	Regulate alternative splicing of the PKM gene	(102)
Wang *et al*, 2015	miR-34a, miR-34c, miR-369-3p, miR-374a, miR-4524a/b	LHDA	-	Decrease in glycolysis, lactate production, ATP generation	(45)
Kim *et al*, 2011	miR-34 family	p53, WNT1, WNT2, LRP6, β-catenin, LEF1	-	Suppresses the transcriptional activity of β-catenin-TCF/LEF	(107)
Chen *et al*, 2014	miR-26a	PDHX	-	Inhibits the conversion of pyruvate to acetyl coenzyme A	(108)
	Amino acid metabolism				
Chang *et al*, 2017; Xing *et al*, 2022	miR-203	GLS	*Faecalibacterium prausnitzii*	Regulate glutaminase protein	(147,148)
Heydari *et al*, 2019; Anderton *et al*, 2017	miR-18a	GCLC	*Lactobacillus acidophilus* and *Bifidobacterium bifidum*	Decreasing glutathione production from glutamate	(149,150)
Palomo-Buitrago *et al*, 2019	-	-	*Firmicutes* and *Bacteroidetes*	Downregulated upon glutamine supplementation	(153)
Zhou *et al*, 2010; Yang *et al*, 2023	miR-29a	GLUL	*Lactobacillus, Ruminiclostridium_9, Lachnoclostridium*	Increase epithelial permeability	(155,156)
Ternes *et al*, 2022	-	-	*Fusobacterium nucleatum*	Increased formate production and cancer glutamine metabolism	(145)
Dong *et al*, 2017	miR-137	ASCT2	-	Inhibited glutamine consumption	(111)
Gao *et al*, 2012	miR-23a	GLS	-	Increased glutaminolysis	(114)
Sengupta *et al*, 2020	miR-122	GLS	-	Downregulated glutaminolysis	(117)
Hatley *et al*, 2010	miR-21	-	-	Increased with K-ras activation	(120)

Table I. Continued.

First author/s, year	Altered miRNAs	Target mRNAs	Altered microbial taxa	Effect on metabolism	(Refs.)
	Amino acid metabolism				
Zhao *et al*, 2019; Wang *et al*, 2014	miR-375	PIK3CA	-	Increased the conversion of glutamine to α-ketoglutarate	(124,125)
	Lipid metabolism				
Hu *et al*, 2011	miR-106b family	p21	-	Involved in intestinal homeostasis	(177)
Hu *et al*, 2015	miR-17-92a cluster	p57	-	Reduced c-Myc expression	(178)
Haenen *et al*, 2013; Birt *et al*, 2013	-	-	*Faecalibacterium prausnitzii*, *Eubacterium rectale*/ *Roseburia spp*,	Production of butyrate; regulates the balance between fatty acid synthesis and oxidation	(164,165)
Krützfeldt *et al*, 2005; Esau *et al*, 2006	miR-122	SCD1, ACC1	-	Reduction in plasma cholesterol and reduce serum fatty acid synthesis	(131,132)
Cruz-Gil *et al*, 2018	miR-19b-1	ACSL1, ACSL4, SCD	-	Inhibit *de novo* lipogenesis, diminished β-oxidation, limiting the maximal mitochondrial respiration and impaired spare capacity	(81)
Gharib *et al*, 2020	miR-497-5p	ACSL5	-	Decrease intracellular lipid content	(133)

miR or miRNA, microRNA; GCLC, glutamate-cysteine ligase catalytic subunit; CBP, CREB-binding protein; ACSL, acyl-CoA synthetase; GLUT, glucose transporter; SCD, stearoyl-CoA desaturase; GLS, glutaminase; GLUL, glutamine synthetase; TCF/LEF, T-cell factor/lymphoid enhancer factor; SLC2A1, solute carrier family 2 member 1; ACC, acetyl-CoA carboxylase.

miRNA-mediated abnormalities in amino acid metabolism. Emerging evidence supports miRNA involvement in the regulation of glutamine metabolism. miR-137 was found to function as a tumour suppressor in CRC by downregulating glutamine metabolism. It directly targets and inhibits ASCT2, an amino acid transporter. miR-137 mimics significantly reduce glutamine consumption, decreasing intracellular α-KG levels by up to 40%. Consequently, downstream metabolites of glutamine metabolism, such as glutamic acid, N-acetylglutamic acid and L-aspartate, are depleted. Mice inoculated with HCT116 cells expressing miR-137 developed markedly smaller tumours compared with the controls (111). In patients with CRC, miR-137 is silenced in tumours (112).

GLS, the rate-limiting enzyme of glutaminolysis, is regulated by c-Myc via miR-23a. Myc increases glutamine uptake and metabolism in CRC (113) by inducing GLS and SLC7A5, a glutamine transporter protein. c-Myc suppresses miR-23a, which targets GLS, resulting in increased glutaminolysis (114). It has been observed that miR-23a expression is higher in patients with early-stage CRC compared with those in late stages (115). Interestingly, the miR-23a expression is also elevated in SW480 cells, compared with SW620 cells, which are derived from the lymph node metastasis of SW480 (116). This suggests that miR-23a may play a critical role in the early development of CRC and that its downregulation may be associated with cancer progression and metastasis. GLS is also directly regulated by miR-122 in the liver, where ectopic miR-122 expression downregulates glutaminolysis (117), although evidence of miR-122-regulated glutaminolysis in CRC has not been reported.

SLC25A22, a mitochondrial glutamate transporter, contributes significantly to glutamine metabolism reprogramming in cancer cells. SLC25A22 induces glutamine addiction in K-ras mutated CRC (118), which accounts for 30-40% of CRCs (119). Increased glutaminolysis in KRAS mutant CRC supports cell proliferation and invasion *in vitro* as well as tumour growth and metastasis *in vivo*. Of note, miR-21 expression increases with K-ras activation and modulates tumorigenesis *in vitro* (120). While miR-21 expression

is significantly higher in CRC tumours (121), no significant correlation exists between miR-21 and Kras-positive colorectal tumours (122).

Upregulation of GPT2, which continuously converts glutamine to α-ketoglutarate, underlies glutamine addiction in PIK3CA-mutated CRC cells. PIK3CA-mutant and wild-type (WT) proliferated at similar rates in media containing both glucose and glutamine, but parental cell lines succumbed faster than WT clones in glutamine-depleted media (123). *In vivo*, [$^{13}C_5$]-glutamine infusion in mice with subcutaneous xenograft tumours shows higher glutamine labelling in the TCA cycles of PIK3CA-mutant tumours than in PIK3CA-WT tumours (124). PIK3CA, which encodes phosphatidylinositol 3-kinase (PI3K) p110α catalytic subunit, is mutated in 20-30% of colon cancer and is regulated by miR-375. miR-375 is frequently downregulated in CRC when compared with the normal colon tissue, and its overexpression suppressed the proliferation of SW480 and HCT15 cells by reducing PIK3CA protein expression (125). These findings support the role of miRNAs in regulating glutamine metabolism.

miRNA-mediated abnormalities in lipid metabolism. Lipid metabolism produces essential metabolites necessary for protein modification and membrane biogenesis to satisfy the body's metabolic needs. The increasing interaction between miRNAs and various lipid metabolic processes, including lipophagy, lipolysis and lipogenesis has been increasingly shown to play a pivotal role in tumour survival. The miR-122, the pioneer miRNA associated with lipid homeostasis, is now increasingly linked to the development of numerous forms of cancer, including CRC (126-128). miR-122 has been shown to facilitate the metastatic progression of CRC in the liver, potentially associated with the suppression of essential genes that play a role in cancer metastasis and the inflammation pathways (129). The changes in miR-122 expression significantly affect cancer cells' migratory and invasive properties (130). miR-122 was originally demonstrated to affect the hepatic cholesterol and lipid metabolism. Inhibiting miR-122 results in a broad decrease in cholesterol levels in plasma by regulating the genes responsible for cholesterol biosynthesis (131). In addition, suppression of miR-122 was found to reduce serum FA synthesis by affecting numerous lipogenic genes. This includes a decrease in the activity of SCD1, a rate-limiting enzyme in lipogenesis, and a reduction in the function of ACC1, which regulates the production of malonyl-CoA (132).

Indeed, an aberrant lipid network involving ACSL/SCD contributes to the migratory and invasive properties in CRCs (80). It has been previously demonstrated that miR-19b-1 inhibits the process of *de novo* lipogenesis significantly. This is achieved by CRC cell invasion by directly targeting two members of the ACSL family, including ACSL4 and ACSL1, as well as SCD (81). Decreased expression of miR-19b-1 and increased ACSL/SCD levels in tumour samples were also correlated with a worse prognosis in patients with stage II and III CRC, indicating potential roles of ACSL/SCD in disease relapse (81).

In addition, miR-19b-1 reportedly compromised the respiratory capacity of CRC, enhancing the inhibitory effect of etomoxir on FA oxidation (81). By attenuating ACSL-mediated FA activation, increased miR-19b-1 would lead to decreased FA oxidation, hence limiting maximal mitochondrial respiration capacity. Further analysis identified the Wnt pathways as the most prevalent biological pathway associated with miR-19b-1 and the ACSL/SCD axis (81). Activation of Wnt pathway requires avoiding catenin degradation following inhibitory phosphorylation by GSK3β, which then leads to the invasion of gene transcription. The ACSL/SCD axis has been shown to increase GSK3β phosphorylation, activating Wnt signalling and, consequently, EMT (80); therefore, the downregulation induced by this miRNA over this network implies their important role in Wnt regulation. Furthermore, it has been observed that CRC cells also express a high level of ACSL5, and a previous study has established a reverse association between ACSL5 and miR-497-5p (133). Overexpression of miR-497-5p targets ACSL5, results in modulation of cell proliferation and development of CRC cells. Additionally, intratumoral injection of miR-497-5p into the CRC xenograft model reversed the growth of the tumour. The overexpression of miR-497-5p in CRC cells correlates with reduced tumour growth in xenograft models and is associated with improved clinical outcomes, including lower tumour differentiation and metastasis (133).

4. Linking miRNA signalling to gut microbiota in CRC

Bacterial diversity in the colon determines the status of metabolism in the colon. It is known that a healthy gut microbiome helps maintain energy homeostasis and metabolic processes, which can impact numerous oncogenic pathways, including inflammatory signalling and immune responses (134). Dietary composition is crucial in determining the metabolic output of the gut microbiota. The gut microbiota metabolises dietary nutrients, which in turn can also affect the composition of the gut microbiota. In an adult colon, the community of obligate anaerobic bacteria, dominated mainly by members of the classes *Clostridia* and *Bacteroides*, is responsible for breaking down various complex carbohydrates through hydrolysis (135,136). On the other hand, facultative anaerobic bacteria, such as the class *Proteobacteria*, do not use fibre but metabolise fermentation products to carbon dioxide in the presence of oxygen (137). The shift from obligate to facultative bacteria in the gut microbiota is considered to underpin numerous colonic dysfunctions. Therefore, the reciprocal interplay between the microbiota and the host often serves as the underlying mechanism elucidating the host-environmental axis in CRC progression.

Role of miRNAs in gut microbiota-regulated glucose metabolism. The miRNA expression levels are suggested to be correlated with gut microbiota abundances that determine the oncogenic fate of CRC cells via the glucose metabolic pathway. Yuan *et al* (138) demonstrated that 76 miRNAs were differentially expressed in CRC compared with normal tissues. These miRNAs were found to have a significant correlation with the relative abundances of several pathogenic bacterial taxa, such as *Firmicutes*, *Bacteroidetes* and *Proteobacteria* (138). These include miR-106b-5p and miR-181-3p as well as mir-17~92 clusters, miR-182 and miR-503, which are known to be oncogenic (138). *In silico* prediction has identified that these miRNAs specifically target the glycan biosynthesis

pathways (138). In the context of CRC, the significance of the interaction between bacteria and glycan is not clear. However, a previous study has suggested that the increased glycan production may lead to the recruitment of certain bacteria, such as *Fusobacterium*, to the location of the tumour and potentially impact tumour development (139). Furthermore, the differential correlation between enriched miRNAs and the subtypes of glycan biosynthesis pathway specific to each bacteria genus indicates that these bacteria may employ different mechanisms of attachment to adhere to the mucosal surface in response to their particular miRNA cluster signalling (140). This may serve as a mechanism by which the composition of species in the gut is influenced, especially during the stages of dysbiosis that lead to abnormal metabolic regulation in the colonic ecosystem.

In addition, previous studies have also suggested that increased levels of miR-4474 and miR-4717 in CRC tissues with positive infection of *Fusobacterium nucleatum* lead to decreases in the expression of CREB-binding protein (CBP), thereby promoting the progression of CRC (141). CBP exhibits a histone acetyltransferase activity and is involved in activating transcription by adding acetyl groups to specific lysine residues on histones and non-histone proteins (142). The expression of CBP was recently discovered to be correlated with the direct regulators of insulin-stimulated glucose uptake in adipocytes (143), suggesting its new role in glucose metabolism. Yet, its involvement in CRC development remains unknown. While there is an emerging understanding of how the microbiota composition affects glucose metabolism, understanding the role of miRNAs mediating these intricate regulations is limited and requires further investigation.

Role of miRNAs in gut microbiota-regulated amino acid metabolism. The gut microbiota has an impact on components of amino acid metabolism, including glutamine. Certain gut bacteria can utilise glutamine as a primary nitrogen source by breaking down the glutamine into ammonia and other metabolites (144). The gut microbiota utilises glutamine as the energy source for optimal survival and growth. Changes in the microbial composition significantly impact the total glutamine metabolism in the intestine, influencing the overall glutamine availability for CRC cells. For instance, the *Fusobacterium nucleatum* co-cultures with CRC cells taken from patients. This combination exhibits protumorigenic effects and induces metabolic reprogramming, leading to an increase in formate production and the metabolism of glutamine (145). Moreover, the metabolic reprogramming by intensifying glutamine metabolism can contribute to the development of resistance to cancer treatment (146). Several miRNAs have been identified as regulators of glutamine uptake and metabolism in cancer cells. When glutamine enters, it is converted to glutamate by GLS. The aforementioned enzyme is directly targeted by miR-203, which is frequently downregulated in melanoma (147). Interestingly, the production of butyrate by *Faecalibacterium prausnitzii* can inhibit the proliferation of CRC cells by increasing the expression of miR-203 (148). These interactions suggest that *Faecalibacterium prausnitzii* and miR-203 might have a similar role in glutamine metabolism toward CRC development. Moreover, the probiotics *Lactobacillus acidophilus* and *Bifidobacterium bifidum* were found to decrease the expression of miR-18a in CRC (149). miR-18a was also found to target glutamate-cysteine ligase catalytic subunit, rewiring glutamine metabolism by decreasing glutathione production from glutamate (150).

Alteration in glutamine level may also affect the gut microbiome as glutamine is an essential source of energy for the cells lining the gut, which helps maintain the health and integrity of the intestinal barrier. Research has shown that glutamine supplementation in mice increased IgA^+ plasma cells and secretory IgA concentration in the ileum, which is considered to be due to glutamine availability being altered in the gut microbiota (151). Other studies have shown that supplementation with glutamine protects against *Enterotoxigenic Escherichia coli* and enhances both innate and adaptive immunity activation (152). Glutamine supplementation has a notable impact on the gut microbiota, especially the composition of *Firmicutes* and *Bacteroidetes* in obese individuals. *Firmicutes*/*Bacteroidetes* ratio is known to substantially affect the maintenance of normal gut homeostasis, and a high ratio of *Firmicutes*/*Bacteroidetes* correlates with obesity and metabolic issues. Glutamine supplementation was observed to decrease the *Firmicutes*/*Bacteroidetes* ratio and reduce *Actinobacteria* in obese individuals (153). In CRC, the *Firmicutes*/*Bacteroides* ratio was considerably higher in patients with cancer and polyps compared with healthy controls (154). Glutamine supplementation was shown to upregulate miR-29a, which subsequently enhanced the permeability of epithelial cells by targeting the glutamine synthetase gene (155). Interestingly, transgenic mice overexpressing miR-29a reveal enrichment in gut microorganisms, such as *Lactobacillus*, *Ruminiclostridium_9* and *Lachnoclostridium* (156).

In addition to glutamine, the gut microbiota has been shown to produce metabolites derived from tryptophan that can regulate the metabolism of the host. These metabolites play a role in controlling the expression of the miR-181 family. It is important for regulating key pathways that affect adiposity, insulin sensitivity and white adipose tissue inflammation. These effects are observed in response to changes in diet and environment (157). Indeed, the dysregulation of tryptophan-derived metabolites and miR-181 expression in white adipocyte tissues was evident in a cohort of obese children. This supports the idea that the gut microbiota-miR-181 axis plays a role in mediating the metabolic and inflammatory processes that contribute to the pathogenesis of obesity-related disorders. It is noteworthy that miR-181 family members, especially the miR-181a-3p, are among the 76 miRNAs suggested to be oncogenic in CRC, according to a study conducted by Yuan *et al* (138). Given the established correlation between obesity and CRC, as outlined earlier in this section, it is speculative that the miR-181 family could be a double-headed spear in obesity-induced CRC. Microbiota has the ability to convert tryptophan into indole compounds within the gut lumen. This conversion has a role in regulating gene expression in host intestinal cells (158); thus, it is also interesting to investigate if dysregulation of this conversion could affect the miRNA expression towards oncogenesis.

Role of miRNAs in gut microbiota-regulated lipid metabolism. Most microorganisms prefer to ferment

carbohydrates over proteins. Hence, short-chain FAs (SCFAs), including acetate, propionate and butyrate, are the predominant by-products of bacterial fermentation (159,160). It has been demonstrated that SCFAs can be incorporated into carbohydrates and lipids and serve as sources of energy metabolism in the host (161). SCFAs are absorbed into the gut epithelium and provide 60-70% of the energy requirement needed by the colonocytes and 5-15% of the total calories needed by humans (162).

Colonocytes actively metabolise SCFAs in the order of butyrate > acetate > propionate as they circulate from the gut lumen to the hepatic vein. As butyrate is the most abundant among the SCFAs produced, it acts as the primary source of energy for the colonocytes (163). Butyrate is produced by two major bacteria, *Faecalibacterium prausnitzii* in the Clostrial cluster IV and *Eubacterium rectale*/*Roseburia* spp. Both bacteria account for 10-20% of the overall bacteria that may be identified in the faeces of healthy adults (164). Butyrate exerts numerous cellular processes by functioning as an inhibitor of histone deacetylase (HDAC) and as a ligand for G protein-coupled receptors. Metabolically, butyrate regulates the balance between synthesis and oxidation of FAs. Butyrate can be utilised to enhance lipid synthesis from ketone bodies or acetyl-CoA through the β-hydroxy-β-methylglutaryl-CoA pathway. Furthermore, butyrate can be oxidised into carbon dioxide through increased β-oxidation (165). Hence, it is unsurprising that up to 70% of ATP generated in an *in vitro* intestinal epithelial cell model is contributed by butyrate. Regulation of lipid biosynthesis and glycolipid metabolism by butyrate can also occur in the liver by being converted into FAs, cholesterol and ketone bodies (166).

Butyrate's beneficial effects are well documented, particularly in mitigating obesity and insulin resistance caused by a high-fat diet (167,168). Butyrate dietary supplementation in rodent models caused a shift from lipogenesis to FA oxidation. This action is considered to be mediated by a downregulation of PPARγ activity, which resulted in reversed insulin resistance and improvement in glucose homeostasis (169). Oxidative metabolism is enhanced in adipose tissues and the liver to increase the level of mitochondrial uncoupling protein 2 and the AMP/ATP ratio (170). However, butyrate has a paradoxical effect on inhibiting the proliferation of CRC cells while concurrently stimulating the proliferation of normal colonic epithelium (171). The dual effect of butyrate is attributed to a distinct metabolic characteristic of healthy colonocytes and CRC cells. While colonocytes metabolise butyrate through β-oxidation, cancer cells show a glycolytic phenotype. The latter contributed to accumulated butyrate that acts as an HDAC inhibitor (172) and consequently as a tumour suppressor. Additionally, patients with CRC reportedly have low SCFA stool levels and butyrate-producing bacteria (173). On the other hand, it has been demonstrated that carcinogenesis in CRC can be promoted by butyrate (174). Evidently, the butyrate paradox has been proposed due to the concentration of butyrate produced (175), with a low dose of butyrate promoting tumorigenesis and a high dose inhibiting it (176).

Butyrate produced from the fermentation of non-absorbed dietary fibre has been proven to benefit the host by exerting colonic chemopreventive effects. Butyrate negatively regulates the miR-106b family, comprising miR-106a/b, miR-17, miR-20a/b, and miR-93 in the colon cancer cells, which in turn induce p21 gene expression to reduce cell proliferation (177). The protective effects of butyrate against CRC were also shown to be contributed by the suppression of the oncogenic miR-17-92a cluster expression, which includes miR-92a, miR-18a and miR-19a/b, in addition to miR-17 and miR-20a (178). This has been shown to be mediated via the reduction in c-Myc, which regulates oncogenic miRNA biogenesis and consequently elevates p57 levels to stimulate apoptosis and diminish colon cancer cell proliferation. Indeed, it was found that the miR-106b family and miR-92a expression were increased in sporadic-type human colon cancers (177,178). Overall, the observation of the overlapping of miRNAs in between studies, namely miR-17-92a cluster and miR-106b family, suggested that a given miRNA family can work both upstream and downstream of microbiota (178). This plays a role in mediating the reciprocal regulation between host cells and microbes. Whether such miRNA has more profound oncogenic effects compared with those involved in uni-directional host-microbiota interaction, if any, is yet to be elucidated.

5. miRNAs as disease biomarkers

Being heavily implicated in host/microbiota metabolic reprogramming in oncogenesis, miRNAs could be valuable biomarkers to evaluate CRC stage and progression (179,180), assessing the aetiology of CRC (181), and estimating the risk of CRC recurrence and survival (182,183). With current CRC screening limitations, there is a need for less-invasive, cost-effective, and sensitive assays as an alternative to the existing gold standard of screening. miRNAs extracted from bodily fluids such as faecal and serum samples have the potential to serve as disease biomarkers for alternatives or improvements on CRC screening tests.

Several studies highlighted that those faecal miRNAs are promising biomarkers for the screening and diagnosis of CRC, as the faecal matter comes into close contact with the intestinal lumen and may contain cells exfoliated from malignant colonocytes (184). A study found that the miR-17-92a cluster and miR-135 were significantly increased in patients with CRC compared with healthy controls (184). Moreover, miRNAs derived from faecal matter could be used as predictive tools, as they could be used to identify patients with CRC or advanced adenomas. For example, faecal miR-221 and miR-18a were significantly upregulated in patients with CRC compared with healthy individuals (185). Additional miRNAs, including miR-135b (186,187), miR-20a (188), miR-92a and miR-144* (189), can be detected in the faecal matter and may serve as useful biomarkers for the screening and diagnosis of CRC. Indeed, faecal miR-135b exhibits high sensitivity and specificity for distinguishing patients with CRC from healthy controls, with sensitivity rates up to 96.5% and specificity rates up to 87.2% suggesting potential as a screening test for CRC (186,187). Similarly, a previous study also showed that faecal levels of miR-92a and miR-144* show favourable sensitivity and fair specificity for detecting CRC, making them promising non-invasive biomarkers (189). In another study, miR-92a has a higher sensitivity for distal CRC and advanced adenomas compared with proximal CRC and minor polyps (190). Expression levels of faecal miRNAs

Table II. miRNAs implicated as biomarkers for colorectal cancer diagnosis.

First author/s, year	Samples	miRNAs	(Refs.)
Koga *et al*, 2010	Faecal	miR-17-92a cluster **miR-135**	(184)
Yau *et al*, 2014	Faecal	miR-221 miR-18a	(185)
Wu *et al*, 2014; Li *et al*, 2020	Faecal	**miR-135b**	(186,187)
Yau *et al*, 2016	Faecal	**miR-20a**	(188)
Wu *et al*, 2012; Link *et al*, 2010; Bastaminejad *et al*, 2017	Faecal	**miR-21**	(190,195,196)
Choi *et al*, 2019	Faecal	**miR-92a** **miR-144***	(189)
Chang *et al*, 2016;	Faecal and plasma	miR-223 **miR-92a**	(191)
Koga *et al*, 2013	Faecal	miR-106a	(192)
Duran-Sanchon *et al*, 2020	Faecal	miR-421 miR-27a-3p	(193)
Tarallo *et al*, 2019	Faecal	**miR-21-5p** miR-200b-3p **miR-1290-5p** miR-4792-3p **miR-1246-3p**	(194)
Liu *et al*, 2019	Plasma	**miR-1290** miR-320d	(197)
Eslamizadeh *et al*, 2018	Plasma and tissue samples	**miR-21** miR-31 **miR-20a** **miR-135b** miR-145 miR-let-7g miR-200c	(198)
Ng *et al*, 2017	Serum	miR-139-3p	(199)
Tan *et al*, 2019	Plasma	**miR-144-3p** miR-425-5p miR-1260b	(204)
Guo *et al*, 2019	Serum	**miR-1246** miR-202-3p **miR-21-3p** miR-1229-3p miR-532-3p	(205)

Bold miRNAs indicate overlapping miRNAs between studies. miR or miRNA, microRNA.

are also able to increase the sensitivity in identifying patients with a high risk of CRC, which also showed a high expressional correlation between tissue and plasma (191). The aforementioned study has shown that in combined analysis of miR-223 and miR-92a, the sensitivity for detecting CRC was 96.8%, and the specificity was 75%. Furthermore, faecal miRNAs could be used together with current screening methods to increase the accuracy of CRC detection. Combining miR-106a extracted from the residuum of faecal occult blood test (FOBT) could reduce the rate of false negatives in CRC screening compared with FOBT alone (192). In another study, miR-421, miR-27a-3p and haemoglobin in faeces can provide more precise identification of patients with advanced adenomas or CRC more accurately compared with the concentration of faecal haemoglobin alone (193). Furthermore, miR-20a levels in faecal matter are not influenced by factors such as antibiotic use, making it a stable and reliable biomarker for non-invasive CRC screening (188). This shows that faecal miRNAs might be promising for clinical translation as a CRC biomarker.

The analysis of faecal miRNAs has attracted marked interest in recent years as faecal miRNA profiles can be

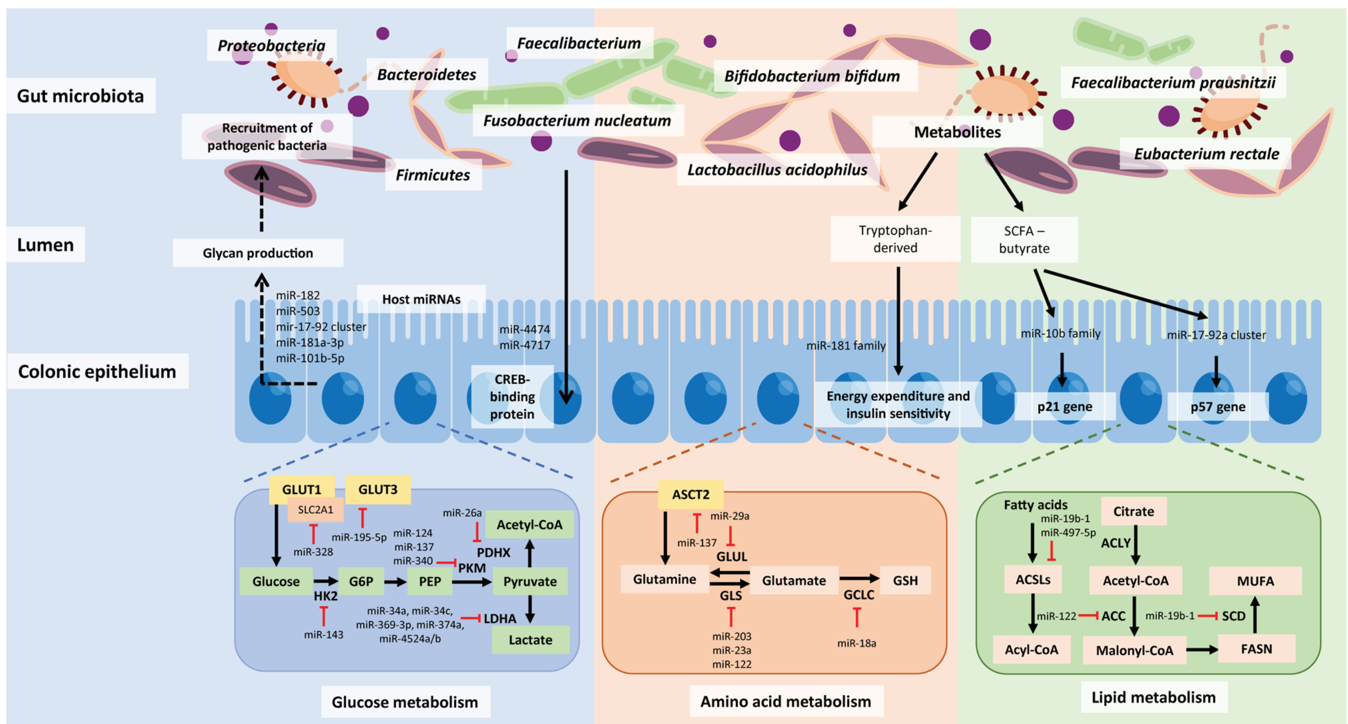

Figure 1. Host-miRNA-gut microbiota interactions in the metabolism of glucose, glutamine and lipids in colorectal cancer. miRNA or miR, microRNA; GLUT, glucose transporter; ACSL, acyl-CoA synthetase; LDHA, lactate dehydrogenase; GLS, glutaminase; GCLC, glutamate-cysteine ligase catalytic subunit; GSH, glutathione; SLC2A1, solute carrier family 2 member 1; MUFA, mono-unsaturated fatty acid; GLUL, glutamine synthetase; ACC, acetyl-CoA carboxylase.

differentially and specifically influenced by gut microbiome composition (194). A previous study revealed that the presence of host-microbiota dysbiosis and interactions in the gut of individuals with CRC can be observed by analysing altered small RNA faecal profiles, proposing miR-30-5p as a potential biomarker for adenomas following its high level of expression in this group. Furthermore, the level of faecal miR-21-5p, miR-200b-3p, miR-1290-5p, miR-4792-3p and miR-1246-3p were notably upregulated in the CRC group when compared with the adenoma and healthy groups, which could be considered attractive biomarkers (194). Moreover, miRNAs have great potential as a CRC biomarker due to their association with the activation of oncogenes and/or tumour suppressor genes, which are further regulated by miRNAs in the process of metabolic reprogramming. Various studies found that expression of miR-21 in faecal samples is upregulated in CRC compared with controls (190,195,196). For example, faecal miR-21 expression of patients with CRC was increased compared with healthy individuals, with a sensitivity of 86.05% and a specificity of 81.08%, and able to significantly differentiate between CRC tumour, node and metastasis stages III-IV from stages I-II (196). It is thus conceivable that those faecal miRNAs have a significant impact on regulating CRC metabolism, which later acts as a possible miRNA CRC biomarker.

miRNAs from plasma and serum are also recognised as biomarkers for early detection and diagnostic value for CRC screening. These circulating miRNAs include those freely circulated and released by tumour cells or those encapsulated within exosomes. Plasma miRNAs can be utilised for early detection as they can differentiate between healthy individuals and those with CRC or advanced adenomas. For example, plasma miR-1290 and miR-320d expression could differentiate between patients with adenoma and CRC and healthy individuals with high specificity and sensitivity (197). Additionally, plasma miRNAs are also able to distinguish different stages of CRC, where a study revealed that plasma miR-21, miR-31, miR-20a and miR-135b were significantly upregulated during higher stages of malignancy. On the contrary, miR-145, miR-let-7g and miR-200c exhibited significant downregulation with the higher stages of malignancy. Additionally, let-7g plasma levels showed a significant decrease in stage III patients compared with healthy controls (198). This was similar to serum miRNAs, where miR-139-3p expression demonstrated high sensitivity and specificity for both early and late-stage CRCs, as well as proximal and distal CRCs (199). Moreover, plasma and serum miRNAs were reported to be relatively stable upon prolonged incubation and remain protected from endogenous degradation (200-202). These results revealed the possibility of using plasma and serum miRNA expression patterns for evaluating the stage and progression of CRC.

While most of the studies shown in Table II were in the context of the role of miRNAs as biomarkers individually, none of the found miRNAs have been deemed as an ideal biomarker for CRC. Further investigations have focused on utilising panels of miRNAs as biomarkers to assess the prognosis of patients with CRC. This approach has the potential to enhance the sensitivity and specificity of CRC profiling (203). Using miRNA panels could enhance the efficacy of screening tests. A previous study identified a miRNA panel consisting of plasma miR-144-3p, miR-425-5p and miR-1260b, which were able to distinguish patients with CRC from healthy individuals with 93.8% sensitivity and 91.3% specificity (204). Similarly,

using five serum miRNA panels, miR-1246, miR-202-3p, miR-21-3p, miR-1229-3p and miR-532-3p effectively distinguished patients with CRC from healthy individuals with high levels of sensitivity and specificity, 91.6 and 91.7%, respectively (205). This indicates that the combination of different miRNAs leads to a more precise and accurate determination of CRC in the future.

6. Challenges and future prospective

Following the discovery that miRNAs could be identified in both extracellular and intracellular environments (206), their potential use as biomarkers has emerged as the primary focus of current cancer research, especially in the early detection of CRC (207). Although numerous studies have been conducted, there is still much to uncover regarding the standardisation and optimisation of miRNA-based predictive biomarkers and therapeutic approaches.

At present, miRNA detection and analysis within the clinical context show potential. While miRNA tests offer apparent clinical utility and are expected to enhance screening programs, they remain an emerging technology. The routine analysis of miRNAs is not commonly adopted in clinical practice due to various considerations, including the cost of assays and the requirement for specialised equipment, expertise and complex data analysis. It raises concerns regarding a potential increase in financial burden due to testing costs. Despite technological development that reduces costs over time, the financial burden associated with miRNA profiling might remain significant for routine clinical applications, especially in resource-limited settings. Therefore, early-stage technology assessments provide an opportunity to evaluate the key characteristics of test kits and programs crucial to achieve in terms of their clinical effectiveness and affordability for routine clinical use. As several new designs and technologies have been developed (208,209), analysis of miRNAs are expected to evolve and become more accessible and cost-efficient for screening purposes.

For clinical application, the most critical evaluation criteria for miRNAs as diagnostic and prognostic biomarkers are high sensitivity and specificity to minimise false-positive or false-negative diagnoses. An effective biomarker for a specific cancer type in clinical settings should exhibit significantly differential expression and be associated with patient outcomes. However, patient conditions and symptoms may modify the composition and concentration of miRNAs in the gastrointestinal tract (210), resulting in variability in outcomes. For instance, symptoms common in patients with CRC, such as indigestion and diarrhoea, could significantly impact the analysis of miRNAs, particularly those obtained from faecal samples. These factors are crucial to account for these factors when interpreting miRNA levels as biomarkers for CRC, as they may introduce confounding variables that could influence diagnostic accuracy. Therefore, a larger sample size is critical for distinguishing healthy individuals and patients with CRC accurately. Factors including age, sex, ethnicity, lifestyle, BMI, dietary habits and medical history further complicate the miRNA analysis, highlighting the necessity to address the limitations of small sample sizes. Comprehensive and diverse datasets of patients with CRC are crucial to ensure robust and reliable conclusions in clinical applications of miRNAs.

Despite these challenges and limitations, miRNA research is a promising advancement in CRC research, driven by progress in bioinformatics tools (211), high-throughput sequencing (212) and machine learning (213) that facilitate progress in miRNA-based biomarker identification. Technological innovations, including point-of-care devices (208,209) and microfluidic biosensor platforms (214), lead towards rapid and user-friendly miRNA detection. Furthermore, the assay utilised for the identification and quantification of miRNA species must be reproducible, scalable and cost-effective to be widely employed in CRC screening. By overcoming present limitations, miRNA-based biomarkers can potentially transform personalised biomarkers and improve early detection and management of CRC.

7. Conclusions

There is compelling evidence that metabolic abnormalities underlie the energy states and progression of CRC. Although much is known about the mechanisms and functional consequences of metabolic alterations in CRC, how these processes interact with diet, obesity and lifestyle remains unclear. Previous studies highlight that gut microbiota exerts a direct impact on the metabolism of glucose, glutamine and lipids of the host, further signifying the intricacies of the cancer cells with the colonic environment (Fig. 1). Given their functions as master transcription factors, miRNAs may be more significant as key signalling mediators in facilitating CRC-microbiota-host interactions. Further studies are required to delineate the signalling governed by miRNAs during the CRC progression. Only through a comprehensive understanding of these interactions miRNAs can be optimally utilised as predictive markers and targets of therapeutic strategies.

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Authors' contributions

IC, AHAJ, NABMS, WMFSBWMN, SCK and AAMF contributed to the drafting of the manuscript. IC and YYL conceptualised the study, acquired funding and drafted the manuscript. IC, AHAJ, NABMS, SCL, YYL and YALL contributed to the conception and design and critically revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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