World Journal of Genetics & Molecular Biology

Iris Publishers

Research Article

Potential Candidates of miRNA Biomarkers and Their Biological Function in Colorectal Cancer

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Received Date: January 11, 2024

Published Date: February 05, 2024

Abstract

Colorectal cancer (CRC) remains a lethal malignancy in the world. Unfortunately, there is no unique signature biomarker available for CRC. Therefore, we aimed to critically analyze miRNAs associated with CRC with a specific emphasis on biological pathways and gene networks. A comprehensive literature search in PubMed, CINAHL, Wiley Cochrane Library, and Web of Science databases of miRNAs in CRC was performed. Gene targets for miRNAs were computationally predicted using established miRNA target-prediction programs: MicroInspector, miRanda, PicTar, RNA22, DIANA, RNAhybrid and TargetScan. To detect the potential pathway of miRNA target genes, we also performed the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. Molecular targets for each miRNAs were retrieved and the validated miRNA-target interaction network was obtained from the CyTargetLinker plugin in the Cytoscape environment. Of 94 human miRNAs found to be associated with CRC, we identified 35 upregulated and 59 downregulated. Gene target prediction analysis of miRNAs resulted from Venn diagram revealed 5309 genes for downregulated and 5070 genes for upregulated miRNAs; with 1155 genes for common miRNAs. We also found significant pathways associated with target predictions of upregulated miRNAs [TFG-B signaling (p-value 9.34E-12), FoxO signaling (p-value 3.31E-06), Hippo signaling (p-value 2.6E-04)]. Furthermore, MAPK (p-value 2.79E-08), ERbB signaling (p-value 6.69E-08), PI3K-AKT (p-value 2.87E-06) pathways were associated with genes of downregulated miRNAs. Interestingly, unique signature miRNAs associated with CRC were identified; miRNA-184 for total miRNAs, miRNAs 135b-3p and 191-3p for upregulated miRNAs, while miRNAs 296b-3p and 198-3p for downregulated. We performed interaction gene networks and target predictions for each miRNA identified. Our study reveals a selected number of miRNA signatures are associated with CRC by targeting biological pathways. This miRNA signatures may not only provide candidate biomarkers but also demonstrate likely and plausible mechanisms toward CRC.

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths worldwide and the third most common malignancy in the world [1]. Several factors contribute to the high mortality rate, including the absence of obvious symptoms in the early stages of CRC as well as the lack of cancer prevention strategies in developing countries, which causes a significant economic and psychological burden for people throughout the world [2, 3]. The incidence of non-hereditary CRC has been shown to be increased in patients with obesity, diabetes, high alcohol consumption and smoking history [2, 4]. CRC has been linked to diets consisting of low consumption of fruits, vegetables, fiber, fish, vitamin C, dairy

products, and with high consumption of foods containing red and processed meat [5]. Considering the high mortality and morbidity associated with CRC, a clear understanding of the pathophysiologic mechanisms that lead to CRC development as well as novel diagnostic and therapeutic methods is critically necessary.

Many biological molecules have been identified to play a significant role in the pathogenesis of CRC including miRNAs, small RNA molecules composed of 18–24 nucleotides that regulate the translation and stability of specific target mRNAs [6, 7]. CRC tumors often exhibit dysregulation of miRNAs when compared to normal tissue. MicroRNAs play an important role in CRC initiation, progression, and development through manipulation of cell stemness, angiogenesis, apoptosis, and the epithelial–mesenchymal transition (EMT) of tumor cells [7]. Researchers have used stool and serum levels of miRNAs to distinguish CRC patients from healthy controls, indicating that they have diagnostic significance in CRC [7, 8]. According to several studies, miRNA expression or polymorphisms associated with miRNA are associated with CRC diagnosis or prognosis [9-12]. Furthermore, miRNAs have been shown to be associated with molecular pathways such as PI3K / Akt, ErbB, MAPK, Hippo and Wnt, which have been identified to play a significant role in CRC pathogenesis [13-17]. In addition to potential diagnostic and prognostic roles in CRC, miRNAs have also been identified as potential candidates in therapy. Several studies have identified miRNAs mimics and inhibitors to have anti-CRC functional effects based on the molecular pathways which they target [10, 12, 18, 19].

Given the identified involvement of miRNAs on all fronts of CRC including pathogenesis, diagnosis, prognosis, and potential therapy, it is imperative to fully understand their role within this deadly disease. Consequently, there is an urgent need for novel diagnostic and prognostic biomarkers for the early diagnosis of CRC. In this review, we aim to critically review and analyze miRNAs which have been associated with CRC, with a specific emphasis on the biological pathways which they affect to assess the clinical utility of miRNA panels as diagnostic biomarkers for CRC.

Methods

Data collection

We searched PubMed and the Cochrane Database of Systematic Reviews (CDSR) through Wiley from 2016 to 2022 for keywords “miRNA”,” micro-RNA”, “colon cancer”, “colorectal cancer”, “CRC”. Through this search, we were able to identify 94 unique miRNAs [[10,11,14–18, 20–117]]. We also identified upregulated and downregulated miRNAs out of the total miRNAs. The experimental design is illustrated in Figure 1.

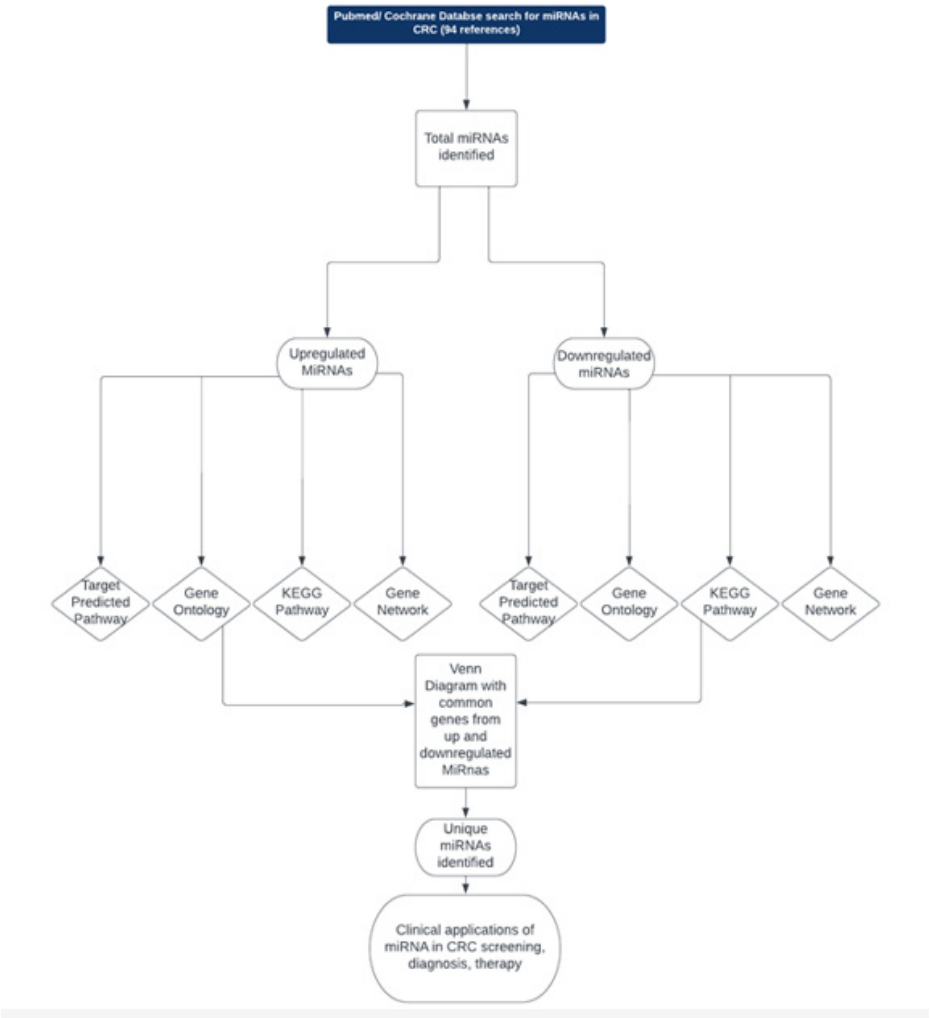

Figure 1: Schematic diagram illustrating the steps and tools used for the study.

Functional Annotation and miRNA Target Prediction:

Gene targets predication for differentially expressed miRNAs were initially computationally predicted using established miRNA target-prediction programs: Micro Inspector, miRanda, PicTar, RNA22, DIANA, RNA hybrid and Target Scan. The predicted genes of individual miRNA were uploaded to the online DAVID program (http://david.abcc.ncifcrf.gov/), DIANA program (http://diana.imis.athena-innovation.gr/DianaTools/index.php),gprofiler (https://biit.cs.ut.ee/gprofiler/gost) for their functional annotation and clustering analysis. To gain insights into the biological functions of these miRNA target genes, we performed the Gene Ontology (GO) classification. To detect the potential pathway of miRNA target genes, we also performed the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis.

Constructing Regulatory Network

Molecular targets for each miRNAs were retrieved and the validated miRNA-target interaction network was obtained from the CyTarget Linker plugin in the Cytoscape environment (15). CyTargetLinker, a Cytoscape apparatus, provides an extensible framework to integrate different regulatory interactions from databases including MicroCosm, Target Scan, miRTarBase, and ENCODE. The network containing interactions between differentially expressed (DE) Demi RNA and putative targets was constructed and visualized using Cytoscape (http://cytoscape.org) (16). Gene targets for all upregulated and all downregulated miRNAs were imported into the Venn Diagram to identify the unique set of genes of upregulated, downregulated, as well common gene prediction.

Results

Total miRNAs identified in CRC

We identified 94 unique human miRNAs from our study of 105 articles/publications related to colorectal cancer (Table 1).

Table 1: List of miRNAs identified in colorectal cancer pathogenesis.

hsa-mir-17-92	hsa-miR-452	hsa-miR-210	hsa-miR-296	hsa-miR-27b	hsa-miR-186-5p	hsa-miR-141-3p
hsa-hsa-mir-20	hsa-miR-494	hsa-miR-221	hsa-miR-22	hsa-miR-218	hsa-miR-181a-5p	hsa-miR-1271
hsa-mir-21	hsa-miR-501-3p	hsa-miR-107	hsa-miR-217	hsa-miR-206	hsa-miR-16-5p	hsa-miR-1258
hsa-mir-135	hsa-miR-590-3p	hsa-miR-223	hsa-miR-198	hsa-miR-126	hsa-miR-148a	hsa-miR-125
hsa-mir-144	hsa-miR-6803-5p	hsa-miR-4260	hsa-miR-184	hsa-miR-1249	hsa-miR-139-5p	
hsa-mir-92a	hsa-miR-92a-3p	hsa-mir-29a	hsa-miR-502	hsa-miR-1	hsa-miR-873-5p	
hsa-mir-106a	hsa-miR-942	hsa-mir-224	hsa-miR-30d	hsa-miR-708	hsa-miR-760	
hsa-mir-106b	hsa-miR-191	hsa-mir-143	hsa-miR-30a	hsa-miR-520e	hsa-miR-548c-5p	
hsa-miR-135b	hsa-miR-32-5p	hsa-mir-145	hsa-miR-216a	hsa-miR-519b-3p	hsa-miR-500a-5p	
hsa-mir-10b	hsa-miR-338-5p	hsa-mir-4478	hsa-miR-214	hsa-miR-330	hsa-miR-323a	
hsa-miR-135a	hsa-miR-590-5p	hsa-mir-1295b-3p	hsa-miR-20a	hsa-miR-324-5p	hsa-miR-4319	
hsa-miR-203a-3p	hsa-miR-6716-5p	hsa-mir-495	hsa-miR-885-3p	hsa-miR-302a	hsa-miR-362	
hsa-miR-301a-3p	hsa-miR-1229	hsa-miR-433	hsa-miR-6868-5p	hsa-miR-28-5p	hsa-miR-200b-3p	
hsa-miR-31-5p	hsa-miR-25-3p	hsa-miR-422a	hsa-miR-622	hsa-miR-204	hsa-miR-185	
hsa-miR-410	hsa-miR-125b	hsa-miR-338-3p	hsa-miR-375	hsa-miR-200	hsa-miR-143-3p	

We used several computational databases for the target predictions of 94 miRNAs and identified 16,604 individual genes. To evaluate the biological role of the differentially expressed miRNA target genes, we performed a Gene Ontology (GO) classification enrichment analysis. Genes that showed a significance level $p<0.01$ were selected and tested against the background set of all genes with GO annotation using established computational algorithms. GO including cellular component, CC, (Figure 2a), biological process, BP, (Figure 2b), molecular function, MF, (Figure 2c), KEGG (Figure 2d) were identified. Among the cellular components (CC), the intracellular anatomical structure (p= 7.19E-62) and intracellular organelle (p= 9.91E-53) had the highest fold changes. For the biological processes, the regulation of transcription by RNA (p= 3.19E-50) and regulation of cellular processes (p= 5.75E-50) had similar fold changes and p-value, while in the molecular function, protein binding (p= 7.59E-37) and transcription regulator activity (p= 1.12E-32) had the highest fold change with significant p-value. Interestingly, we found in the KEGG pathway that proteoglycans in cancer (p= 5.01E-08) and signaling pathways of stem cells (p= 9.10E-08) had the highest significance and fold changes.

Gene ontology and KEGG pathways for total miRNAs identified in CRC. Panel (a) is cellular component, Panel (b) is biological processes, panel (c) is molecular functions, and panel (d) is KEGG.

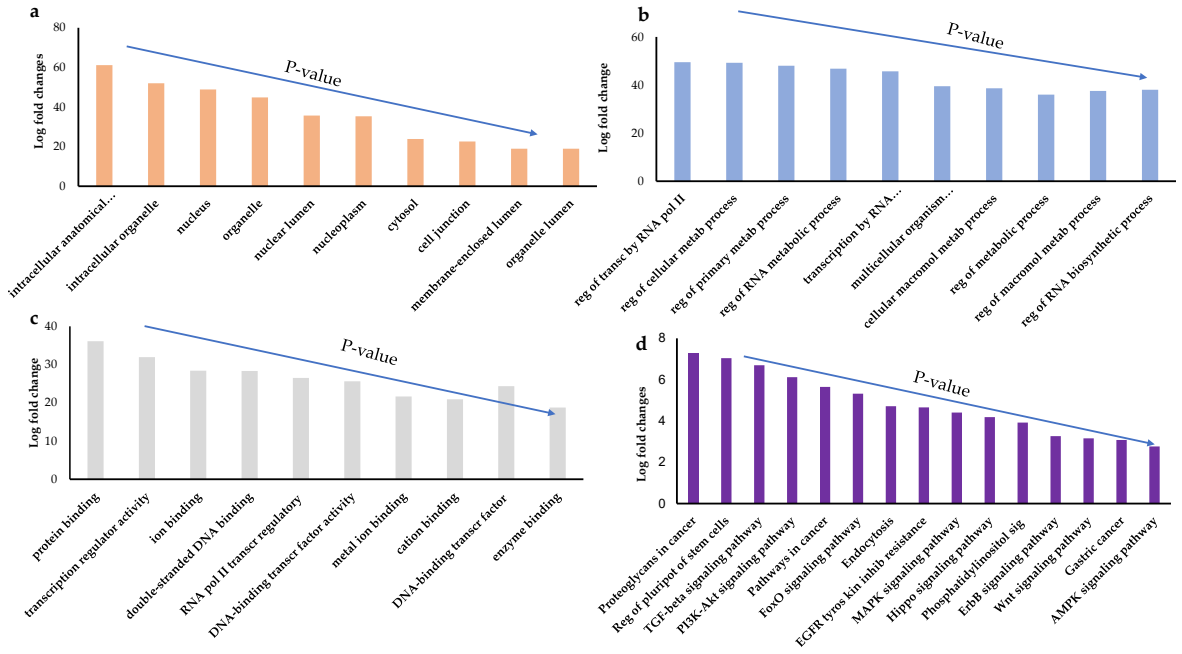

Figure 2: Gene ontology and KEGG pathways for total miRNAs identified in CRC. Panel (a) is cellular component, Panel (b) is biological processes, panel (c) is molecular functions, and panel (d) is KEGG.

Upregulated miRNAs in CRC

Next, we identified 35 unique upregulated miRNAs associated with CRC as shown in Table 2.

Out of the 35 upregulated miRNAs, we performed GO as mentioned above for the total miRNAs and we found the following: CC (Figure 3a) revealed that nuclear body (p=1.17E-49) and cell projection (p=3.90E-10) had the highest significance and fold change; BP (Figure 3b) showed that regulation of cellular processes (p=2.26E-47) and regulation of primary metabolism (p=1.21E-45) had the highest fold changes and significance; within MF (Figure 3c) , protein binding (p=2.19E-36) and ion binding (p=8.68E-35) had the highest significance and fold changes while KEGG (Figure 3d) revealed pathways in cancer (p=4.64E-07) had substantial fold change and significance (Figure 3a-d) respectively.

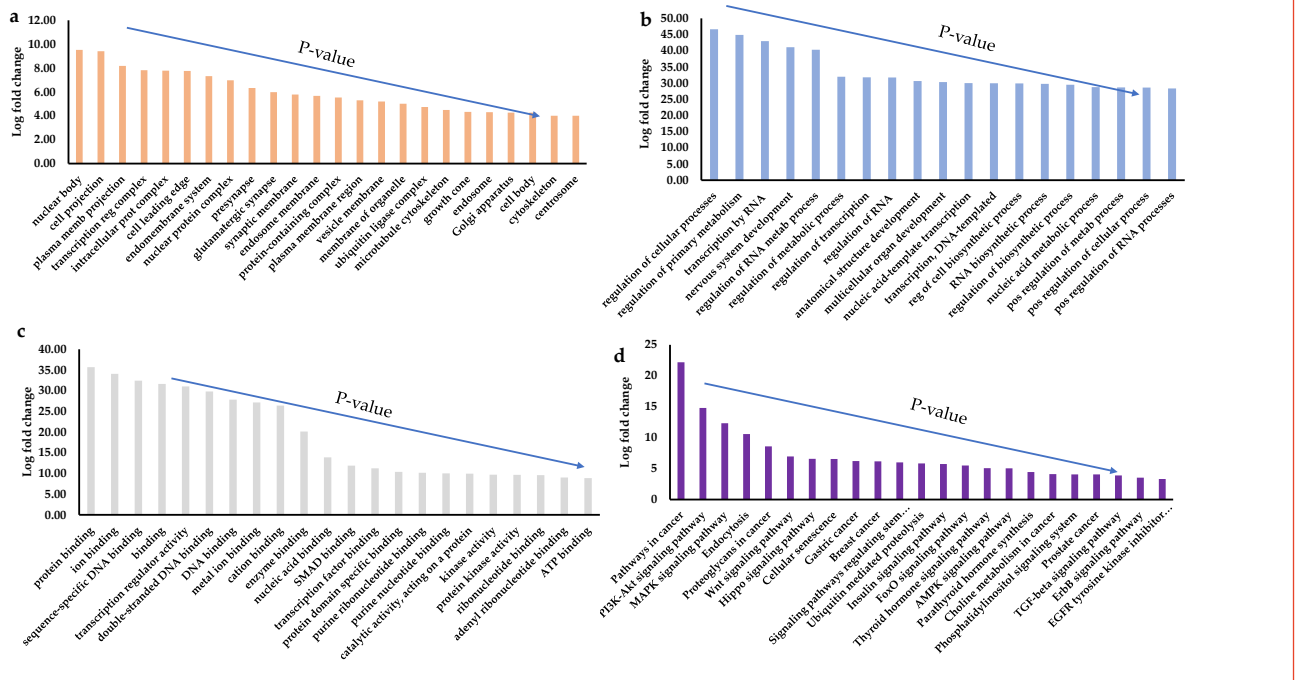

Figure 3: Gene ontology and KEGG of upregulated miRNAs in CRC. Panel (a) is cellular component, panel (b) is biological processes, panel (c) molecular functions, and panel (d) is KEGG.

Table 2: List of upregulated miRNAs identified in CRC pathogenesis.

hsa-mir-17-92	hsa-miR-135a	hsa-miR-92a-3p	hsa-miR-210
hsa-mir-20	hsa-miR-203a-3p	hsa-miR-942	hsa-miR-221
hsa-mir-21	hsa-miR-301a-3p	hsa-miR-191	hsa-miR-107
hsa-mir-135	hsa-miR-31-5p	hsa-miR-32-5p	hsa-miR-223
hsa-mir-144	hsa-miR-410	hsa-miR-338-5p	hsa-miR-4260
hsa-mir-92a	hsa-miR-452	hsa-miR-590-5p	
hsa-mir-106a	hsa-miR-494	hsa-miR-6716-5p	
hsa-mir-106b	hsa-miR-501-3p	hsa-miR-1229	
hsa-miR-135b	hsa-miR-590-3p	hsa-miR-25-3p	
hsa-mir-10b	hsa-miR-6803-5p	hsa-miR-125b	

Table 3 shows a list of the biological pathways identified from upregulated miRNAs target genes. We also highlighted the relevant pathways which are associated with cancer including: TGF-B signaling pathway (p=9.34E-12), fatty acid metabolism (p=8.36E-06), FoxO signaling pathway (p=3.31E-05), and Hippo signaling pathway (p=0.000263). Furthermore, we identified gene networks related to each of these selected pathways as shown in Figure 4 (A-D), respectively.

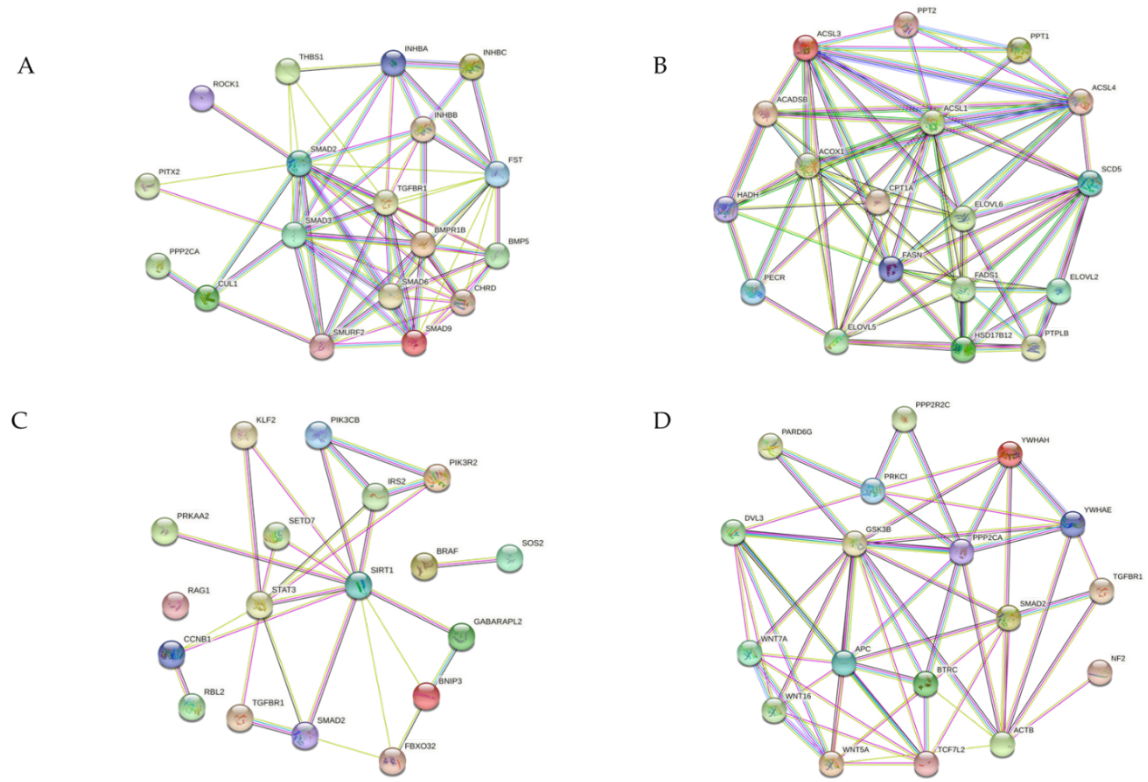

Figure 4: Gene network depiction of interactions between gene target predictions of upregulated miRNAs derived from TGF-B pathway (A), Fatty Acid metabolism (B), FoxO signaling pathway (C), HIPPO signaling pathway (D).

Table 3: List of the biological pathways identified from predicted target genes of upregulated miRNAs.

Pathway	p-value	# gene	#miRNAs
TGF-beta signaling pathway	9.34E-12	54	25
Fatty acid metabolism	8.36E-06	24	19
FoxO signaling pathway	3.31E-05	76	22
Hippo signaling pathway	0.000263	83	26
N-Glycan biosynthesis	0.001197	24	18
Axon guidance	0.001464	68	24

We further investigated the highlighted pathways (bold) from Table 3 for the top 20 significant target genes associated with each pathway as shown in Table 4. Interestingly we found unique miRNAs associated with these pathways. Namely, hsa-mir-135b-3p and hsa-mir-191-3p were identified, suggesting that these miRNAs may play an important role in those pathways.

Table 4: List of biological pathways of interest (derived from Table 3) affected by upregulated miRNAs with corresponding genes and miRNAs involved.

TGF-B signaling pathway		Fatty acid metabolism		FoxO signaling pathway		HIPPO signaling pathway	
Genes	miRNA	Genes	miRNA	Genes	miRNA	Genes	miRNA
FST	hsa-miR-203a-3p	FASN	hsa-miR-92a-3p	IRS2	hsa-miR-590-3p	ACTB	hsa-miR-203a-3p
TGFBR1	hsa-miR-494-3p	ACADSB	hsa-miR-25-3p	BRAF	hsa-miR-21-3p	GSK3B	hsa-miR-4260
ROCK1	hsa-miR-590-3p	ACSL3	hsa-miR-6803-5p	RBL2	hsa-miR-223-3p	DVL3	hsa-miR-301a-3p
INHBC	hsa-miR-223-3p	PTPLB	hsa-miR-4260	STAT3	hsa-miR-501-3p	WNT16	hsa-miR-590-3p
SMAD2	hsa-miR-135b-3p	SCD5	hsa-miR-144-3p	RAG1	hsa-miR-25-3p	TGFBR1	hsa-miR-92a-3p
SMAD6	hsa-miR-92a-3p	ACOX1	hsa-miR-135a-3p	TGFBR1	hsa-miR-494-3p	YWHAH	hsa-miR-32-5p
INHBB	hsa-miR-32-5p	PECR	hsa-miR-106a-3p	FBXO32	hsa-miR-301a-3p	PARD6G	hsa-miR-590-5p
SMAD9	hsa-miR-107	HADH	hsa-miR-107	CCNB1	hsa-miR-144-3p	WNT7A	hsa-miR-25-3p
THBS1	hsa-miR-338-5p	FADS1	hsa-miR-494-3p	SOS2	hsa-miR-92a-3p	SMAD2	hsa-miR-494-3p
PPP2CA	hsa-miR-301a-3p	CPT1A	hsa-miR-203a-3p	SMAD2	hsa-miR-32-5p	YWHAE	hsa-miR-106a-3p
SMURF2	hsa-miR-144-3p	PPT1	hsa-miR-32-5p	BNIP3	hsa-miR-135a-3p	BTRC	hsa-miR-223-3p
BMPR1B	hsa-miR-6716-5p	ELOVL5	hsa-miR-338-5p	PRKAA2	hsa-miR-590-5p	APC	hsa-miR-6716-5p
BMP5	hsa-miR-31-5p	PPT2	hsa-miR-223-3p	GABARAPL2	hsa-miR-338-5p	PPP2R2C	hsa-miR-338-5p
PITX2	hsa-miR-21-3p	ELOVL2	hsa-miR-221-3p	SIRT1	hsa-miR-6716-5p	PRKCI	hsa-miR-144-3p
SMAD3	hsa-miR-106a-3p	ACSL4	hsa-miR-31-5p	PIK3CB	hsa-miR-452-3p	PPP2CA	hsa-miR-107
CHRD	hsa-miR-6803-5p	ACSL1	hsa-miR-21-3p	SETD7	hsa-miR-1229-3p	TCF7L2	hsa-miR-221-3p
CUL1	hsa-miR-452-3p	ELOVL6	hsa-miR-452-3p	KLF2	hsa-miR-107	NF2	hsa-miR-31-5p
INHBA	hsa-miR-501-3p	HSD17B12	hsa-miR-301a-3p	PIK3R2	hsa-miR-106a-3p	BMP5	hsa-miR-191-3p

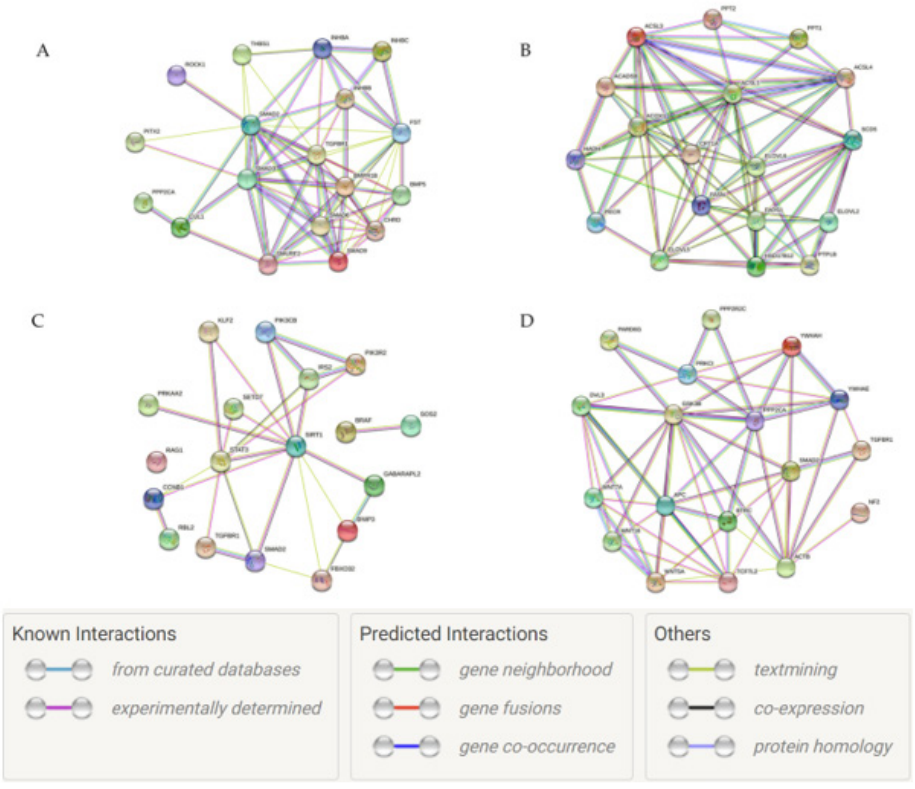

Figure 5: Gene ontology and KEGG of downregulated miRNAs in CRC. Panel (a) shows cellular component, panel (b) shows biological processes, panel (c) shows molecular functions, and panel (d) shows KEGG.

To gain a better understanding of the molecular mechanisms potentially involved in colorectal cancer, we explored the regulatory information networks (RIN) associated CRC using publicly available data warehouses to predict the potential targets using CyTargetLinker plugin in Cytoscape. Each regulatory interaction in the subnetworks consists of two nodes, a regulatory component (miRNAs) and a transcription factor (target gene) connected by one edge. The RIN for hsa-miR-135b-3p and has-miR-191-3p showed multiple gene targets as demonstrated in Figure 5.

Downregulated miRNAs in CRC

Next, we identified 59 unique downregulated miRNAs associated with CRC as shown in Table 5.

Table 5: List of downregulated miRNAs identified in CRC pathogenesis.

hsa-miR-296	hsa-miR-20a	hsa-miR-1	hsa-miR-186-5p	hsa-miR-4319
hsa-miR-22	hsa-miR-885-3p	hsa-miR-708	hsa-miR-181a-5p	hsa-miR-362
hsa-miR-217	hsa-miR-6868-5p	hsa-miR-520e	hsa-miR-16-5p	hsa-miR-200b-3p
hsa-miR-198	hsa-miR-622	hsa-miR-519b-3p	hsa-miR-148a	hsa-miR-185
hsa-miR-184	hsa-miR-375	hsa-miR-330	hsa-miR-139-5p	hsa-miR-143-3p
hsa-miR-502	hsa-miR-27b	hsa-miR-324-5p	hsa-miR-873-5p	hsa-miR-141-3p
hsa-miR-30d	hsa-miR-218	hsa-miR-302a	hsa-miR-760	hsa-miR-1271
hsa-miR-30a	hsa-miR-206	hsa-miR-28-5p	hsa-miR-548c-5p	hsa-miR-1258
hsa-miR-216a	hsa-miR-126	hsa-miR-204	hsa-miR-500a-5p	hsa-miR-125
hsa-miR-214	hsa-miR-1249	hsa-miR-200	hsa-miR-323a	

Out of the 59 downregulated miRNAs, we performed GO as mentioned above for the miRNAs and we found the following: CC (Figure 6a) revealed that intracellular organelle (p=2.85E-91) had the highest significance and fold change; BP (Figure 6b) showed that regulation of cellular processes (p=3.99E-51) and regulation of transcription (p=1.23E-50) had the highest fold changes and significance; within MF (Figure 6c), protein binding and ion binding (p=1.00E-83, 2.32E-34) had the highest significance and fold changes while KEGG (Figure 6d) revealed pathways in cancer (p=1.16E-12) and MAPK signaling (p=5.35E-11) had substantial fold changes and significance (Figure 6a-d) respectively.

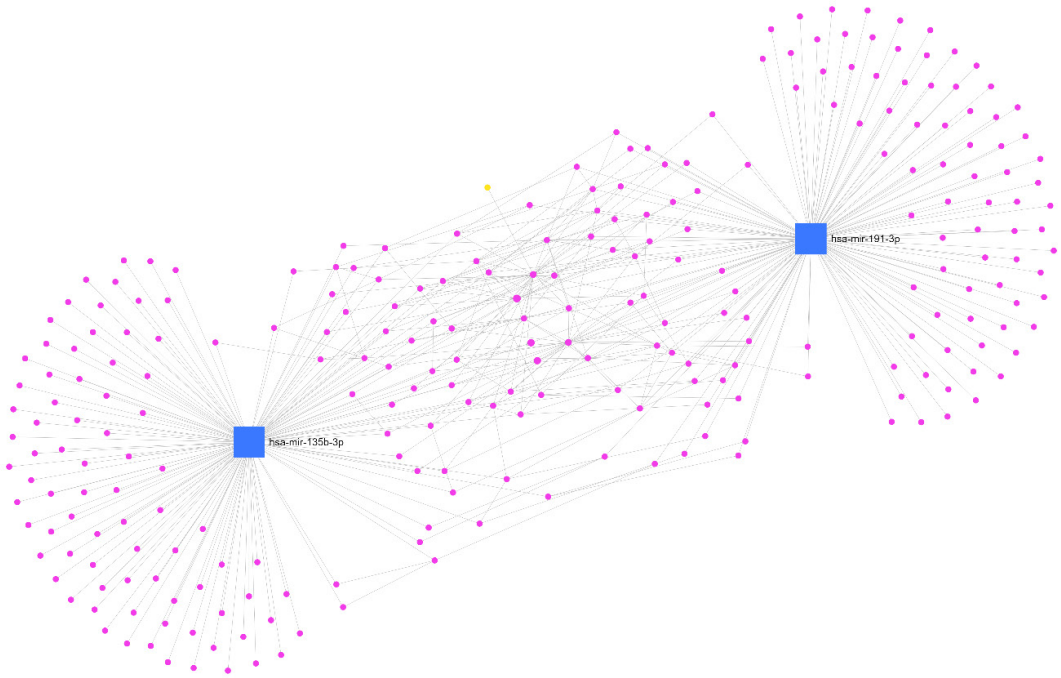

Figure 6: Gene ontology and KEGG of downregulated miRNAs in CRC. Panel (a) shows cellular component, panel (b) shows biological processes, panel (c) shows molecular functions, and panel (d) shows KEGG.

Table 6 shows a list of the biological pathways identified from downregulated miRNAs target genes. We also highlighted the relevant pathways which are associated with cancer including: MAPK signaling pathway (p=2.79E-08), ErbB signaling pathway (p=6.69E-08), PI3K-Akt signaling pathway (p=2.87E-06). Furthermore, we identified gene networks related to each of these selected pathways as shown in Figure 7 (A-D), respectively.

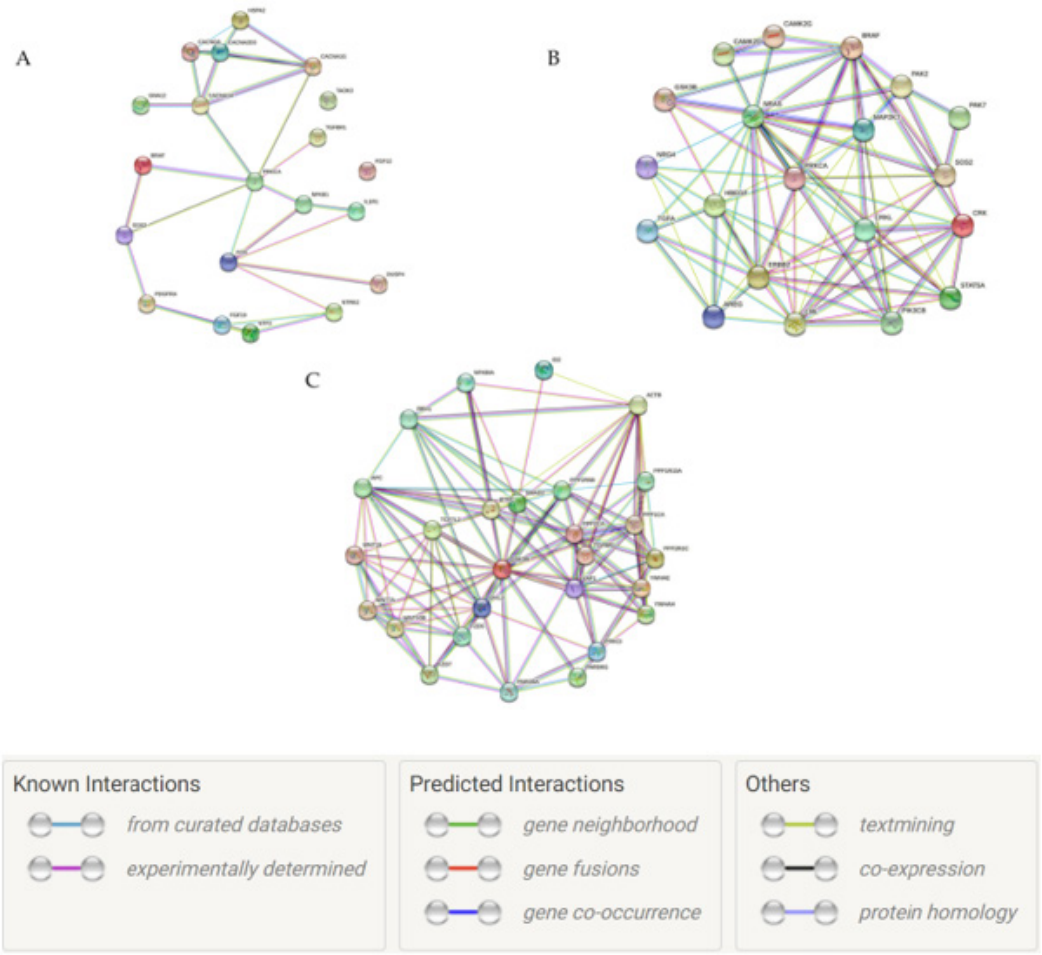

Figure 7: Gene network depiction of interactions between gene target predictions of downregulated miRNAs derived from MAPK signaling pathway (A), ErbB signaling (B), PI3K-Akt signaling pathway (C).

We further investigated the highlighted pathways from Table 6 for the top 20 significant target genes associated with each pathway as shown in Table 7. Interestingly we found unique miRNAs associated with these pathways. Namely, hsa-mir-296b-3p and hsa-mir-198-3p were identified, suggesting that these miRNAs may play an important role in those pathways.

Table 6: List of the biological pathways identified from predicted target genes of downregulated miRNAs.

Pathway	p-value	# gene	# miRNAs
MAPK signaling pathway	2.79E-08	158	26
ErbB signaling pathway	6.69E-08	60	25
PI3K-Akt signaling pathway	2.87E-06	197	28

Table 7: List of biological pathways of interest affected by downregulated miRNAs with corresponding genes and miRNAs involved.

PI3K-Akt signaling pathway		ErbB signaling pathway		MAPK signaling pathway	
Genes	miRNA	Genes	miRNA	Genes	miRNA

FZD7	hsa-miR-4260	CAMK2D	hsa-miR-186-5p	TAOK3	hsa-miR-520e
PPP1CA	hsa-miR-501-3p	BRAF	hsa-miR-200b-3p	BRAF	hsa-miR-519b-3p
ACTB	hsa-miR-590-3p	GSK3B	hsa-miR-134-3p	DUSP4	hsa-miR-186-5p
GSK3B	hsa-miR-494-3p	HBEGF	hsa-miR-216a-3p	HSPA2	hsa-miR-181a-5p
DVL3	hsa-miR-942-3p	PRKCA	hsa-miR-27b-3p	FGF12	hsa-miR-16-5p
WNT16	hsa-miR-452-3p	ERBB2	hsa-miR-1-3p	FOS	hsa-miR-548c-5p
FZD5	hsa-miR-25-3p	SOS2	hsa-miR-495-3p	NTRK2	hsa-miR-200b-3p
TGFBR1	hsa-miR-92a-3p	STAT5A	hsa-miR-214-3p	PRKCA	hsa-miR-224-3p
YWHAH	hsa-miR-32-5p	CBL	hsa-miR-500a-5p	NTF3	hsa-miR-495-3p
ID2	hsa-miR-203a-3p	CAMK2G	hsa-miR-22-3p	CACNG8	hsa-miR-502-3p
PARD6G	hsa-miR-338-5p	NRAS	hsa-miR-302a-3p	PDGFRA	hsa-miR-30d-3p
WNT7A	hsa-miR-144-3p	CRKL	hsa-miR-198-3p	CACNA1A	hsa-miR-30a-3p
YAP1	hsa-miR-135b-3p	NRG4	hsa-miR-218-1-3p	TGFBR1	hsa-miR-362-3p
SMAD2	hsa-miR-1229-3p	CRK	hsa-miR-362-3p	CACNA2D3	hsa-miR-185-3p
YWHAE	hsa-miR-590-5p	PIK3CB	hsa-miR-338-3p	FGF19	hsa-miR-141-3p
BTRC	hsa-miR-223-3p	PAK2	hsa-miR-6868-5p	NFKB1	hsa-miR-433-3p
APC	hsa-miR-301a-3p	MAP2K7	hsa-miR-141-3p	CACNA1G	hsa-miR-216a-3p
PPP2R2C	hsa-miR-6716-5p	TGFA	hsa-miR-224-3p	GNA12	hsa-miR-27b-3p
PRKCI	hsa-miR-221-3p	PAK7	hsa-miR-323a-3p	IL1R1	hsa-miR-330-3p
WNT10B	hsa-miR-6803-5p	AREG	hsa-miR-296b-3p	SOS2	hsa-miR-200a-3p

Similar to upregulated miRNAs, we explored the regulatory information networks (RIN) associated CRC for uniquely identified downregulated miRNAs using publicly available data warehouses to predict the potential targets using CyTargetLinker plugin in Cytoscape. The RIN for hsa-miR-198-3p and has-miR-296b-3p showed multiple gene targets as demonstrated in Figure 8 however also showed a strong interaction with target gene UBC.

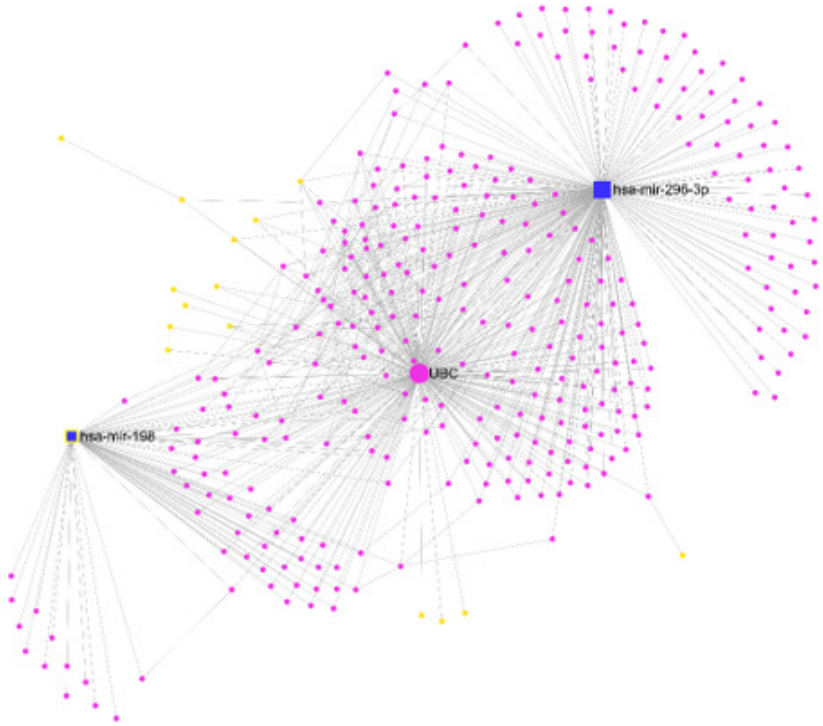

Figure 8 : Interaction gene networks and target predictions for uniquely expressed hsa-mir-198 and hsa-mir-296-3p. Multiple gene targets were common between the two miRNAs, however, UBC target gene was the strongest gene target amongst the two miRNAs.

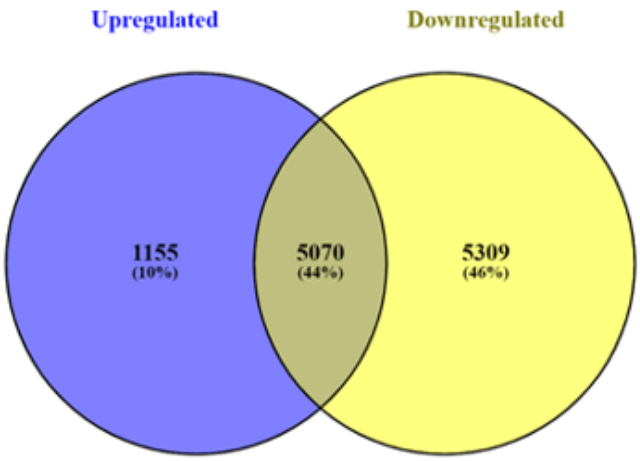

Figure 9: Venn diagram analysis of genes from upregulated and downregulated miRNAs. Of these, 1155 genes were found to be unique to upregulated miRNAs, 5309 were found to be unique to downregulated miRNAs, and 5070 were found to be unique to both.

Similar to upregulated miRNAs, we explored the regulatory information networks (RIN) associated CRC for uniquely identified downregulated miRNAs using publicly available data warehouses to predict the potential targets using CyTargetLinker plugin in Cytoscape. The RIN for hsa-miR-198-3p and has-miR-296b-3p showed multiple gene targets as demonstrated in Figure 8 however also showed a strong interaction with target gene UBC.

Discussion

In this study, we aimed to critically review the current literature on miRNA involvement in CRC. A total of 94 unique miRNAs were identified, of which 35 were found to be upregulated and 59 were found to be downregulated. We also identified unique biological pathways from the predicted target genes of the up and downregulated miRNAs. The miRNAs 135b-3p and mir-191-3p were unique identifiers for the upregulated miRNAs and the miRNAs 296b-3p and mir-198-3p were unique identifiers for the downregulated miRNAs.

Colorectal cancer represents the third most common cancer diagnosis and the second most lethal malignancy for both men and women [2]. There has been a steady decline in the incidence of new cases and mortality over the past few years, except for individuals under the age of 50, which is perhaps due to an increase in the frequency of cancer screenings and better treatment options [118]. Colon cancer development is explained by clonal mutations that give cells a survival advantage and allow for the development of mutations that can lead to other characteristics associated with cancer, such as proliferation, invasion, and metastasis [119]. To treat CRC, it is essential to identify the molecular mechanisms involved in the progression of the disease. MicroRNAs (miRNAs) are a class of small noncoding RNAs that bind to target mRNA and inhibit translation, cleave, or degrade mRNA, ultimately downregulating the level of a target protein [120]. A miRNA can function as either a tumor suppressor or tumor promoter, depending on the cell environment in which it is expressed, and plays an important role in several biological functions [120]. There is evidence that miRNAs play a role in proliferation, metastasis, angiogenesis, autophagy, apoptosis, and chemoradiotherapy in colorectal cancer [121].

Biological pathways of upregulated miRNAs

As previously mentioned, pathways of interesting clinical relevance identified from predicted target genes of upregulated miRNAs were TGF-B signaling pathway, fatty acid metabolism pathway, FOX-O signaling and HIPPO signaling pathway. Here, we will explore the clinical relevance of each pathway in CRC including same major biological pathways such as TGF-B, Fatty acid metabolism, FOX-O signaling, and HIPPO signaling pathway. First, TGF-B, several biological processes are regulated by the TGF-B signaling pathway, including cell proliferation, differentiation, migration, and apoptosis [122]. In the setting of CRC, the signaling effects of TGF-B on colon epithelial cells are reported to reduce proliferation and promote apoptosis and differentiation [123]. The TGF-B signaling pathway targets several key cell-cycle checkpoint genes, including CDKN1A (p21), CDKN1B (p27) and CDKN2B (p15) [124]. Hence, TGF-β acts as a tumor suppressor in the normal intestinal epithelium. Furthermore, many CRCs lose tumor suppressor proteins during the initial and subsequent stages of cancer. Interestingly, evidence has suggested TGF-β as a multifunctional cytokine that acts as a tumor promoter or tumor suppressor in a cell- and context-dependent manner [125]. As a consequence of TGF-B signaling' s pleiotropic nature, it contributes to drug resistance, tumor escape, and diminished response to therapy [125].

Second, Fatty acid metabolism, there is growing evidence that dysregulation of fatty acid (FA) metabolism plays an important role in cancer development and progression [126–128]. In the cell, FAs

are used for numerous purposes, including signaling molecules, membrane synthesis components, and, perhaps most importantly, as sources of direct energy [127]. There has been previous evidence that fatty acid synthase upregulation contributes to the growth and progression of primary CRCs [127]. Through the chemical inhibition of fatty acid synthase through a novel fatty acid synthase inhibitor TVB-3664, there has been significant progress in the treatment of CRC in vitro by reducing CRC proliferation through a decrease in cellular respiration [129]. A previous study demonstrated that CD36, a transporter of fatty acids, promotes the growth of colorectal cancer tumors [129]. When studying the role of CD36 in colorectal cancer, it was found that it promotes invasion of colorectal cancer in vitro and metastasis in vivo, as well as upregulating expression of the matrix metalloproteinase 28 [129].

Third, FOX-O signaling, the FOXO gene subfamily controls genetic pathways such as tumor suppression in cancer. In CRC, the EGFR signaling pathway, which is mediated by activated AKT, induces proliferation in the normal and transformed colonic epithelium via the suppression of FOXO3 [130, 131]. FOXO4, on the other hand, has a tumor-suppressive role which inhibits EMT, migration, and in vivo metastases in colorectal cancer by regulating the APC2/B-catenin axis, which illustrates the function and mechanism of FOXO4 in CRC and provides a potential therapeutic strategy for patients with the disease [132].

Fourth, HIPPO signaling pathway, The Hippo signaling pathway is involved in stem cell proliferation, morphology, survival, migration, self-renewal, migration, tissue homeostasis, as well as the regulation of organ size [133]. It has been reported that Hippo signaling is one of the most significant signaling pathways in tumor development, as it inhibits the development of tumors through multiple components of this pathway, including fat storage-inducing transmembrane protein, large tumor suppressor kinase (LATS), macrophage stimulating factors (MST), taffazin (TAZ), Yes-associated protein 1 (YAP1), and transcriptional enhancer associated domain (TEAD) [134]. One recent study found that cucurbitacin B, a natural herb with anticancer properties, inhibits the Hippo-YAP Signaling pathway and exerts anticancer activity in colorectal cancer cells [135]. Given this interesting paradigm, it is imperative to focus on the study of upregulated miRNAs which we identified which may play a role in HIPPO signaling.

Biological pathways downregulated miRNAs

Similar to the predicted target genes of upregulated miRNAs, we identified clinically significant pathways regarding predicted target genes of downregulated miRNA which included: MAPK signaling pathway, ErbB signaling pathway, and PI3K-Akt signaling pathway. First, MAPK signaling pathway, the mitogen-activated protein kinases (MAPKs), which function as a major cell proliferation signaling pathway from the cell surface to the nucleus, belong to a large family of serine-threonine kinases [136]. It is becoming increasingly apparent that activation of the ERK MAPK pathway is involved in the pathogenesis, progression, and oncogenic behavior of human colorectal cancer [136]. Ras, Raf, MEK, and ERK are thought to play a role in the induction of vascular endothelial growth factor (which is involved in the regulation of angiogenesis) when human colorectal cancer is present [137]. These pathways may provide opportunities for the development of new anticancer drugs to target specific targets and to be less toxic than traditional chemotherapeutic agents [137]. Interestingly, some evidence has suggested a direct role of miRNA regulation on MAPK signaling pathway in CRC, however, further studies are necessary to elucidate their role as potential biomarkers [138].

Second, ErbB signaling pathway, the ErbB family of receptors comprises four subtypes, namely ErbB1 (EGFR), ErbB2 (HER2), ErbB3 (HER3) and ErbB4 (HER4)[139]. The EGFR receptor triggers a molecular cascade that activates MAPK and PI3K pathways, promoting proliferation, apoptosis inhibition, dedifferentiation, and angiogenesis in CRC [140]. ErbB2 activation has been shown to play an important role in the differentiation, proliferation, and apoptosis of CRC cells. Among patients with CRC, one study reported a 69.7% ErBb3 response rate and lymph vascular invasion [139]. Moreover, ErbB4 has been shown to activate the PI3K and Shc pathways to promote cell proliferation and metastasis but inhibit differentiation. The ErbB signaling pathway has also been recently shown to be modulated by miR-323a in CRC, specifically by blocking gefitinib resistance acquisition [141].

Third, PI3K-Akt signaling pathway, PI3K is a receptor tyrosine kinase activated by several receptors such as EGFR, human EGFR 2 (HER2), insulin growth factor (IGF-1R), and platelet derived growth factor (PDGF) [142]. It is involved in the regulation of many different cellular functions, such as proliferation, survival, apoptosis, migration, and metabolism. The presence of PIK3CA, a subunit of PI3K, has been reported in 10-20% of CRC cases, with over 80% of mutations found in two hot spots in exon 9 and exon 20 [143]. PIK3CA mutations have been associated with poorer clinical outcomes and with a negative prediction of clinical response to anti-EGFR monoclonal antibodies in RAS wild-type mice with CRC [144]. One study reported an improved survival of CRC patients using regular aspirin in tumors harboring a PIK3CA mutation [145]. Given the intricate involvement of PI3K-AKT on CRC development and its potential role in therapy it is thus paramount to better understand the biological roles of the identified miRNAs which affect this pathway.

We believe this review entails an updated review of total, upregulated and downregulated miRNAs in CRC with an analysis (Gene Ontology, KEGG, gene network, target gene prediction) which provides insight into the molecular pathways and genes involved with these miRNAs. The work identified biological processes and gene targets related to miRNAs in CRC that could be studied in more detail in the future. Furthermore, the highly significant up-regulated miRNAs can be used as screening tools for CRC and the down-regulated can also be used as a negative for CRC. The limitations of this study, include not able to distinguish which miRNAs can be used for early detection, however, as global these miRNAs can be used as negative and positive markers for CRC. The role of miRNAs in colorectal cancer has been reported [9,146,147], however, larger patient cohorts are warranted to confirm their potential to be used as CRC diagnostic biomarkers [148–151] . Large-scale validation studies in asymptomatic screening participants should be conducted to validate those miRNAs. Future research will have to specifically address the potential role for miRNA-based

classifiers and therapeutics in medicine. While there is still much to be done, we remain optimistic that microRNA related diagnostics and therapeutics have substantial potential for the prevention and treatment of CRC.

Conclusion

CRC is a very devastating disease which requires identification of biological biomarkers for diagnostic and prognostic function. Our study identified a total of 94 miRNAs from over 100 studies in the literature. Thus, we are e able to narrow down uniquely upregulated and downregulated miRNAs as well as their respective biological functions in cancer pathways. We believe those miRNAs identified may potentially serve a role as candidates for screening and therapeutic targets for CRC in the future.4.

Author Contributions

Conceptualization, and data analyses, A.A.K and A.K.; writing-original draft preparation A. A.A.K drafted the manuscript, N.R reviewing, editing the manuscript. A.K finalized the manuscript and data analyses. All authors have read and agreed to the published version of the manuscript.

Funding

The work was partially funded by research start-up funds to A.K. from the Department of Child Health at the University of Missouri, Columbia. The work received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Data will be available up request.

Conflicts of Interest

The authors declare no conflict of interest.

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