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MicroRNAs miR-1 and miR-206 Regulate Monocarboxylate Transporter-4 and Vascular Endothelial Growth Factor Gene Expression in Colorectal Cancer

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Authors' contributions

This work was carried out in collaboration among all authors. Author AK designed the study. Author RAE performed the statistical analysis author CIB wrote the protocol. Author WAR wrote the first draft of the manuscript. Authors AAE, AT and AM managed the analyses of the study. Author YSB managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Colorectal cancer (CRC) is currently the third most common cancer type in males and the second most occurring in females. The role of microRNA (miRNA) in the development of colorectal cancer is not fully elucidated. Therefore, understanding the mechanistic interaction between miRNA and their target oncogenes may hold great importance as a possible target for interventional anticancer therapy.

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Aims: To identify miRNAs that are part of the regulating pathway of Monocarboxylate Transporter-4 *(MCT4)* and Vascular Endothelial Growth Factor (*VEGF*) oncogenes.
Study Design: We used publicly available prediction tools (e.g. TargetScan, MicroCosm, PicTar, and DIANA-microT-CDS) to identify the possible miRNA that target the two oncogenes.
Methodology: We used the GeneMania database to visualize the network and verify gene names and remove ambiguity and duplications. Furthermore, we used miRTarBase database to identify experimentally validated targets which we used to further confirm miRNA-oncogene relationships. Finally, we utilized miR-Mfold web-tool to further visualize the circular structures and the simulated miR-1 and miR-206 targeting arrangements.
Results: We found two putative miRNA (miR-1 and miR-206) that may downregulate MCT4 coded by *SLC16A3* gene and VEGF which is coded by *VEGF gene*. We found relationships between the validated target genes of miR-1 and miR-206 through GeneMania which we extracted from the literature. And we elucidated the proposed structure of these two miRNAs through miR-Mfold web-tool.
Conclusion: Our results elucidated a novel regulation pathway in CRC cells and may suggest a potential therapeutic approach for CRC therapy. MiR-1 and miR-206 may help cells go to apoptosis and inhibit the angiogenesis of colorectal cancer cells by down-regulation of MCT4 and VEGF proteins in tumor tissues.

Keywords: MCT4; colorectal cancer; VEGF; microRNA; miR-1; miR-206.

1. INTRODUCTION

Monocarboxylate transporters (MCTs) are expressed in normal colonic epithelium and facilitate the transport of butyrate, the primary energy source for these cells [1]. However, in colorectal tumor cells, lactate is produced and transported via cell membranes during glycolysis and utilized for energy. The intracellular pH is regulated as the influx and efflux of lactate is controlled by MCTs. MCTs, hence have a vital role in the regulation of pH homeostasis [2]. If this balance is disrupted, the cells normally go through apoptosis. For carcinoma cells to survive by avoiding apoptosis, the control of lactate in glycolysis is considered necessary, and MCTs play an important role in this process [3]. In carcinogenesis, monocarboxylate transporter MCT-4 has a role in the efflux of lactate from tumor cells, which results in escaped apoptosis [4]. Moreover, MCT4 has been reported to be induced by the hypoxic conditions which are usually present in the tumor microenvironment [5].

VEGF is a well-known growth factor and numerous scientific evidences proved the indisputable role of Vascular Endothelial Growth Factor (VEGF) in angiogenesis as well as carcinogenesis [6]. Both MCT4 and VEGF were recently found to be overexpressed in colorectal cancer (CRC) [7].

Micro RNAs, which are usually shortened to miRNAs or miRs, are single-stranded RNAs capable of posttranscriptional gene regulation via either degrading or suppressing target mRNA [8]. Moreover, in CRC, miRNAs have dual effect possibility; serving either as tumor suppressors or oncogenes depending on their target gene [9,10,11,12]. VEGF has been studied thoroughly and found to be targeted by several miRNAs such as miR-150 [13], miR-195 [14], miR-503[15] miR-195 and miR-378 [16]. However fewer studies focused on miRNAs targeting VEGF in CRC [17,18,19].

To our knowledge MCT4 regulating miRNAs have not been described previously. In the current study, we aim to identify miRNAs that regulate MCT4 and VEGF using the miRNA target prediction web tools because these two genes are over expressed in CRC.

2. METHODS

2.1 Prediction Web Tools used to Identify miRs

We queried four target prediction web tools; (TargetScan7.2) [20], PicTar [21], MicroCosm previously called miRBase [22] and DIANA-microT-CDS [23]). using the gene name *SLC16A3* for MCT4 and *VEGF* to find putative miRs.

2.1.1 miRNA selection based on web tools prediction

We selected two miRNAs as candidates from the results of step 1 for our study. These miRNAs

(miR-1 and miR-206) have never been investigated in CRC but have been reported to be involved in carcinomas.

PubMed search for experimentally validated targets of miR-1 and miR-206.

We did a PubMed database search of the literature looking for experimentally validated targets of miR-1 and miR-206. This search yielded 24 oncogenes that are targeted by miR-1 and miR-206.

2.1.2 Experimentally validated24 oncogenes targets uploaded to GeneMania

We uploaded the 24 oncogenes that we found in step 3 to the GeneMania databases [24] in order to visualize the network and verify gene names and remove ambiguity and duplications.

2.1.3 miRTarBase for miR-1 and miR-206 miRNA-target interactions (MTIs)

We utilized miRTarBase database to download miR-1 and miR-206 MTIs [25].

2.1.4 mfold web-tool to visualize miR-1 and miR-206 structures

We utilized mfold web-tool [26], (http://mfold.rna.albany.edu/), to visualize miR-1 and miR-206 circular structures and show the virtual miR targeting arrangement.

2.1.5 Pathway analysis and identifying overlapping target genes

To discover the 24 genes pathways and overlapping relationships/diseases. We utilized Gene set enrichment analysis (GSEA) [27] web tool. Furthermore, to identify overlapping target genes we used DIANA-microT-CDS web tool [23].

3. RESULTS AND DISCUSSION

Putative miRs from the four web tools algorithm yielded two candidates; miR-1 and miR-206. Consequently, the PubMed search showed 24 validated gene targets for miR-1 and miR-206. The result of the PubMed database search of the literature for experimentally validated targets of miR-1 and miR-206 are summarized in Table 1.

In the next step we uploaded those target genes to GeneMania which resulted in several gene-gene interactions including; co-expression (57.54%), physical interactions (19.62%), genetic pathway (18.92%), C-localization (3.63%), genetic interactions (0.15%), shared protein domains (0.13%). In addition, GeneMania yielded a genetic network presented in Fig. 1, where genes in black represent our 24 query genes targeted by miR-1 and miR-206.

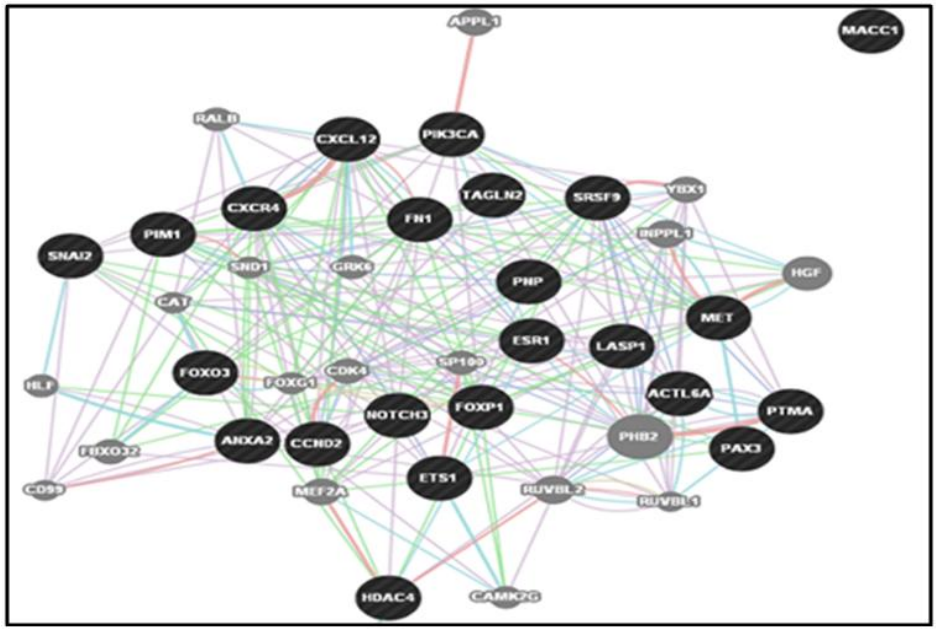


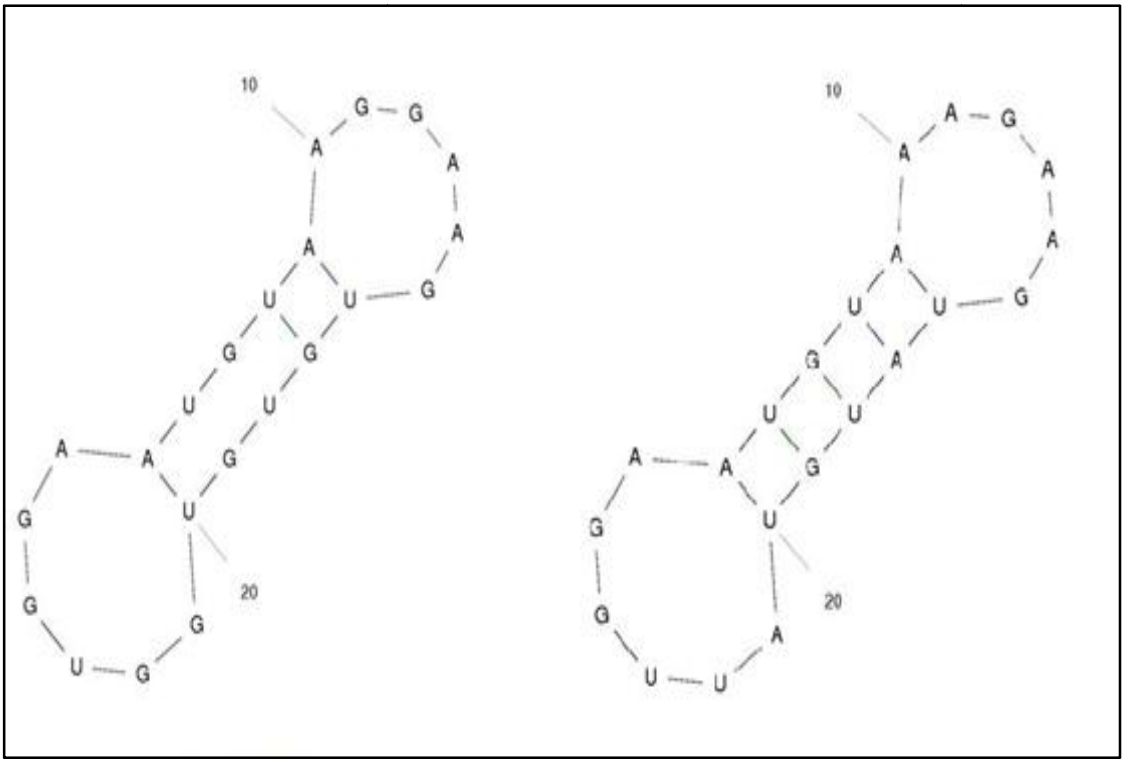
Fig. 1. GeneMania network for the 24 genes targeted by miR-1 and miR-206

Table 1. Experimentally validated genetargets of miR-1and miR-206 in various cancers

miRNA	Symbol	Gene name	Cancer type	Reference
miRNA-1	*MET*	met proto-oncogene	Osteocarcinoma/CRC/ rhabdomyosarcoma/ thyroid carcinoma	[28,29,30,31,32]
miRNA-1	*ETS1*	v-ets avian erythroblastosis virus E26 oncogene homolog 1	hepatocellular carcinoma	[33]
miRNA-1	*MACC1*	metastasis-associated in colon cancer 1	colon cancer	[30]
miRNA-1	*PIM1*	pim-1 oncogene	lung cancer	[34]
miRNA-1	*PIK3CA*	phosphoinositide-3-kinase catalytic subunit alpha	non-small cell lung cancer	[35]
miRNA-1	*ANXA2*	Annexin A2	Glioblastoma	[36]
miRNA-1	*SNAI2*	snail family zinc finger 2	lung cancer	[37]
miRNA-1	*PTMA*	prothymosin-α	bladder cancer	[38]
miRNA-1	*PNP*	purine nucleoside phosphorylase	maxillary sinus squamous cell carcinoma	[39]
miRNA-1	*PAX3*	paired box 3	Rhabdomyosarcoma	[29]
miRNA-1	*CCND2*	cyclin D2	Rhabdomyosarcoma	[29,40]
miRNA-1	*SRSF9*	serine/arginine-rich 9	bladder cancer	[41]
miRNA-1	*PNP*	purine nucleoside phosphorylase	prostate cancer	[42]
miRNA-1	*PTMA*	prothymosin-α	nasopharyngeal carcinoma cells	[43]
miRNA-1	*PTMA*	prothymosin alpha	bladder cancer	[38]
miRNA-1	*FN1*	fibronectin1	laryngeal squamous carcinoma	[44]
miRNA-1	*TAGLN2*	transgelin-2	renal cell carcinoma	[45]
miRNA-1	*TAGLN2*	transgelin-2	head and neck squamous cell carcinoma	[46]
miRNA-1	*TAGLN2*	transgelin-2	bladder cancer	[47]
miRNA-1	*LASP1*	LIM and SH3 protein 1	bladder cancer	[45]
miRNA-1	*CXCR4*	CXC chemokine receptor 4	thyroid carcinoma	[40]
miRNA-1	*FOXP1*	forkhead box P1	hepatocellular carcinoma	[48,49]
miRNA-1	*HDAC4*	histone deacetylase 4	hepatocellular carcinoma	[48,50]
miRNA-206	*ESR1*	estrogen receptor 1	breast cancer	[51]
miRNA-206	*MET*	met proto-oncogene	papillary thyroid carcinoma	[52]
miRNA-206	*MET*	met proto-oncogene	Rhabdomyosarcom	[31]
miRNA-206	*NOTCH3*	notch 3	HeLa cancer cells	[53]
miRNA-206	*BAF53A*	BAF complex 53 kDa subunit	Rhabdomyosarcoma	[54]
miRNA-206	*FOXO3*	forkhead box O3	breast cancer	[55]

Table 2. MiR-1 and miR-206 validated targets that were extracted from miRTarBase web tool

miRNA	Species (miRNA)	Target gene	Target gene (Entrez ID)	Experiments
hsa-miR-1	Homo sapiens	*MYEF2*	50804	PAR-CLIP
hsa-miR-1	Homo sapiens	*CDK9*	1025	Proteomics
hsa-miR-1	Homo sapiens	*CEBPA*	1050	Luciferase reporter assay
hsa-miR-1	Homo sapiens	*MEF2A*	4205	Luciferase reporter assay
hsa-miR-1	Homo sapiens	*MEF2A*	4205	qRT-PCR
hsa-miR-1	Homo sapiens	*GATA4*	2626	Luciferase reporter assay
hsa-miR-206	Homo sapiens	*NOTCH3*	4854	Luciferase reporter assay//qRT-PCR//Western blot// Reporter assay
hsa-miR-206	Homo sapiens	*NOTCH3*	4854	qRT-PCR//Immunohistochemistry//Western blot



MiR-1: UGGAAUGUAAAGAAGUAUGUAU
MiR-206: UGGAAUGUAAGGAAGUGUGUGG

Fig. 2. The structure arrangement of miR-1 and miR-206 as constructed by the Mfold program (http://mfold.rna.albany.edu/) [25]

The miRNA-target interactions (MTIs) that were extracted from miRTarBase database are shown in Table 2.

To further visualize the circular structures and the simulated miR1 and miR2 targeting arrangements, we utilized miR-Mfold web-tool, the resulting structure is shown in Fig. 2.

MCT-4 is frequently deregulated in various cancer cells, it promotes their migration and proliferation and is associated with the level of malignancy and recurrence [56,57,58]. On the other hand, the expression of *VEGF* was reported more frequently in early compared to advanced-stage cancer types. Recent research suggests that *VEGF* is a negative prognostic factor for CRC [59,60]. Gotanda et al. have shown recently that increased *MCT4/VEGF* expression is associated with tumor growth, infiltration, and angiogenesis in their CRC cohort [7].

MiRNAs are small RNAs that have a regulatory effect on their target mRNAs post-transcriptionally. The effect of these microRNAs is the inhibition of gene expression via either degradation or suppression of target mRNAs (Fig. 3).

Previous research showed that miRNAs could serve as tumor suppressors or oncogenes [9]. Thus miR-1and miR-206 might help in targeting and regulating cancer cell proliferation, migration, and angiogenesis by downregulating the expression of these two genes: *MCT4 and VEGF*. Fig. 4 illustrates this theory.

In this study, we found two plausible miRNAs which were computationally validated to show that the mRNA of *MCT4* and *VEGF* is a putative target of miR-1 and miR-206, by using publicly available miRNA target prediction web-tools.

Pathway analysis by GSEA [27] revealed that most genes overlap were in PI3K/AKT cancer signaling pathway, and diseases of signal transduction by growth factor receptors and second messengers. As shown in Table 3.

DIANA-microT-CDS web tool showed overlapping target genes between the two miRNAs with miTG scores of 0.99 (Supplementary Table 1).

These two miRNAs, miR-1 and miR-206, may help in restoring apoptosis pathways by suppressing MCT4 along with inhibiting angiogenesis by targeting *VEGF* [61,62].

Previous study has reported that miR-1 and miR-206 can regulate angiogenesis by targeting and reducing the levels of *Vegf* gene in zebrafish and the knocking down of miR-1and miR-206 increased angiogenesis in the same setting [63]. Recent reports have also shown that both miR-1 and miR-206 were down-regulated in many human cancer types including CRC [64,34,30,65]. Previous reports showed inhibitory roles of miRNAs of MCTs which could reduce tumor cell proliferation [66]. And some studies showed other potential roles of these small RNAs as negative regulators that may lead eventually to growth suppression in some malignancies [67].

In the future, our computational approach needs to be validated by in-vitro and in-vivo expression studies of both miRNAs and target genes in CRC cell-lines i.e. miR-1 and miR-206 and *MCT4/VEGF*.

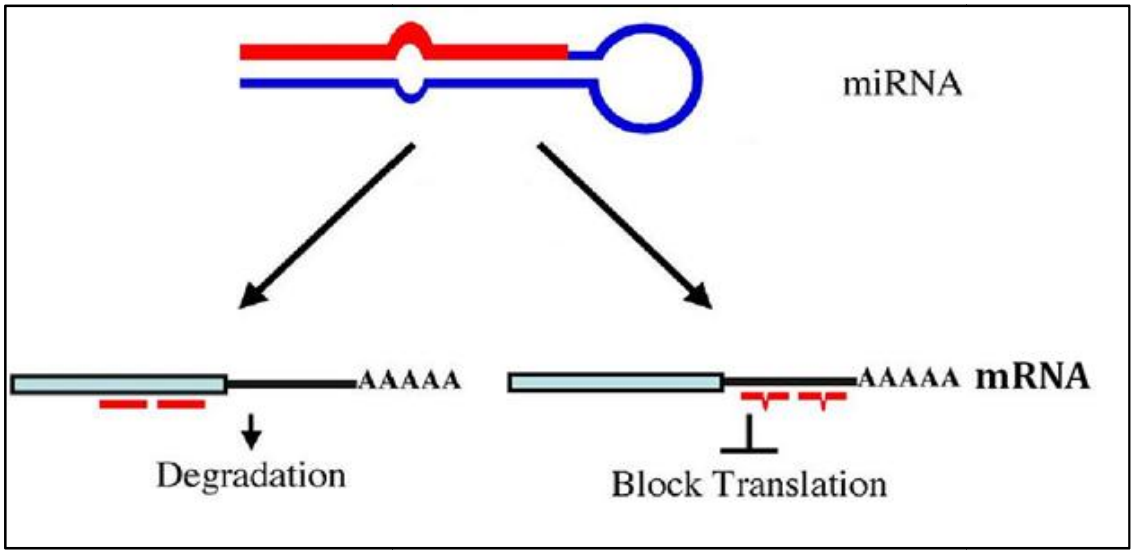


Fig. 3. schematic organization of microRNA blocking machinery towards target mRNA

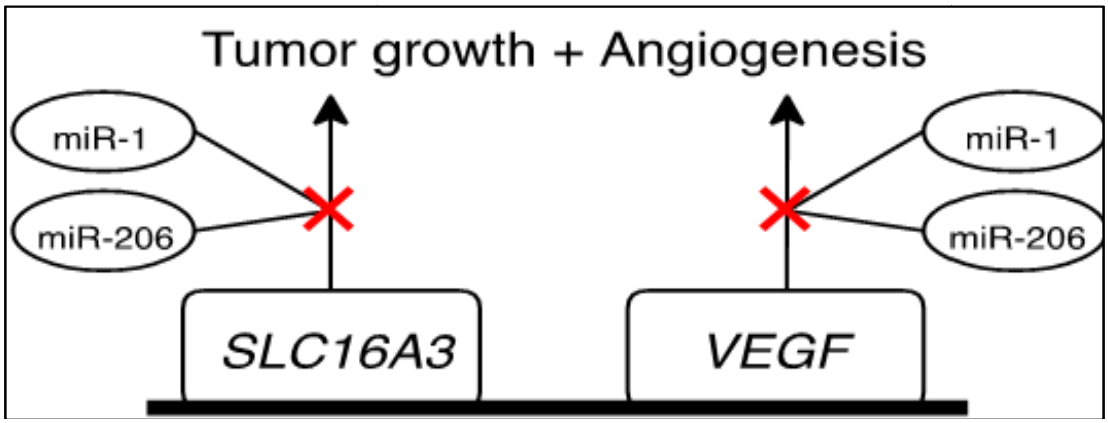


Fig. 4. miR-1 and miR-206 act to downregulate the expression of SLC16A3 and VEGF genes, in turn leading to a reduction in tumor growth and angiogenesis

Table 3. GSEA showing PI3K/AKT cancer signaling pathway, and diseases of signal transduction by growth factor receptors and second messengers

Gene set name [# Genes (K)]	Description	# Genes in Overlap(k)	p-value	FDR q-value
REACTOME_DISEASES_OF_SIGNAL_TRANSDUCTI CTION_BY_GROWTH_FACTOR_RECEPTORS_AND_S D_SECOND_MESSENGERS [374]	Diseases of signal transduction by growth factor receptors and second messengers	6	$5.36\ e^{-8}$	$1.2\ e^{-4}$
PID_MYC_ACTIV_PATHWAY [79]	Validated targets of C-MYC transcriptional activation	4	$1.18\ e^{-7}$	$1.32\ e^{-4}$
REACTOME_PI3K_AKT_SIGNALING_IN_CANCER [102]	PI3K/AKT Signaling in Cancer	4	$3.31\ e^{-7}$	$2.46\ e^{-4}$
REACTOME_RNA_POLYMERASE_II_TRANSCRIPTI PTION [1375]	RNA Polymerase II Transcription	8	$5.4\ e^{-7}$	$3.02\ e^{-4}$
REACTOME_INTRACELLULAR_SIGNALING_BY_SE _SECOND_MESSENGERS [304]	Intracellular signaling by second messengers	5	$7.09\ e^{-7}$	$3.17\ e^{-4}$
REACTOME_DISEASE [1470]	Disease	8	$8.95\ e^{-7}$	$3.33\ e^{-4}$
PID_ANGIOPOIETIN_RECEPTOR_PATHWAY [49]	Angiopoietin receptor Tie2-mediated signaling	3	$2.95\ e^{-6}$	$9.42\ e^{-4}$
PID_KIT_PATHWAY [52]	Signaling events mediated by Stem cell factor receptor (c-Kit)	3	$3.54\ e^{-6}$	$9.88\ e^{-4}$
REACTOME_MET_ACTIVATES_PI3K_AKT_SIGNAL NALING [6]	MET activates PI3K/AKT signaling	2	$4.69\ e^{-6}$	$1.06\ e^{-3}$
KEGG_FOCAL_ADHESION [199]	Focal adhesion	4	$4.76\ e^{-6}$	$1.06\ e^{-3}$

4. CONCLUSION

MiRNAs are pivotal regulators of gene expression, as they contribute to multiple critical biological processes, including cell proliferation, angiogenesis, and apoptosis. This study could help in deciphering the potential mechanism of acquired regulation of tumor growth and angiogenesis in CRC. In addition, this work sheds light on the involvement of miR-1 and miR-206 in the tumor inhibitory effect by targeting the two oncogenes *VEGF/MCT4.* Our results elucidated a novel regulatory pathway in CRC cells and could suggest a potential therapeutic approach for CRC. The possibility of metabolic modification of the tumor microenvironment via regulation or manipulation of *MCT4* and *VEGF* may prove to be a promising target for future studies.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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