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.

Article Information

DOI: 10.9734/JPRI/2020/v32i1330594

Editor(s):
(1) Dr. Dharmesh Chandra Sharma, G. R. Medical College & J. A. Hospital, India.
(2) Anshul Tiwari, Harvard Medical School, USA.

Reviewers:
(1) Anshul Tiwari, Harvard Medical School, USA.
(2) Dayo Rotimi Omotoso, Redeemer’s University, Nigeria.

Complete Peer review History: http://www.sdiarticle4.com/review-history/59474

Received 22 May 2020
Accepted 28 July 2020
Published 06 August 2020

Original Research Article

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 validated 24 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-1 and 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        | Rhabdomyosarcoma                                 | [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/lqRT-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-1 and 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-1 and 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_TRANSDUCTION_BY_GROWTH_FACTOR_RECEPTORS_AND_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_TRANSCRIPTION [1375]                                             | RNA Polymerase II Transcription                                            | 8                     | 5.4 e⁻⁷       | 3.02 e⁻⁴    |
| REACTOME_INTRACELLULAR_SIGNALING_BY_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_SIGNALING [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.

ACKNOWLEDGEMENT

The authors would like to acknowledge the Deanship of Scientific Research and Graduate Studies role for their tremendous support. This work was supported by the Deanship of Scientific Research and Graduate Studies; support fund number 30/4/2020

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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