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The Downregulation of miRNA-152 Gene Expression in Colorectal Cancer Patients: A Case-Control Study

Afrah N. Ali[1*], Ahmed Rushdi Abdullah[2] and Ahmed Zuhiar Alsammarraie[3]
[1]Bacteriology Analysis, Baghdad Educational Hospital, Ministry of Health, Bab al-Muazzam Region. Baghdad, 1001, Iraq
[2]Department of Medical Microbiology, College of Medicine, University of Al-Iraqia, Al-Adhamiya Region, Baghdad, 1001, Iraq
[3]Medical Oncology Specialist, Oncology Teaching Hospital, Ministry of Health, Bab Al-Muazzam Region. Baghdad, 1001, Iraq

Author Designation: [1]Msc Student, [2]Professor, [3]Medical Oncology Consultant

*Corresponding author: Afrah N. Ali (e-mail: afrahalkhafaji911@gmail.com).

Abstract **Background:** microRNA (miRNA) is a short, non-coding RNA molecule that regulates gene expression by binding to messenger RNA (mRNA) to prevent it from being translated into proteins or by causing its degradation. (Removed). miRNA-152 belongs to the miR-148/152 family . It is often downregulated in various cancers, including colorectal cancer, acting as a potential tumor suppressor by targeting genes involved in cancer cell growth, migration and invasion. **Objective:** to study the microRNA-152 gene expression in colorectal cancer compared to colorectal diseases. **Methods:** The Al-Iraqia University College of Medicine has given its approval to the study. Three groups of participants were formed: The first group included thirty patients with Colorectal Cancer (CRC), the second group included thirty patients with Colorectal benign Diseases (CRD) and the third group consisted of ten healthy people (control group). Five milliliters of blood were collected from all group participants who were gathered from the Medical City Directory (Baghdad Educational Hospital and Oncology Educational Hospital) Removed. The study plan ran for three months, from November 2024 to January 2025. MicroRNA-152 can be detected by using RT-qPCR. **Results:** A Significant decrease in gene expression ($p<0.05$) of MicroRNA-152 was identified among patients with colorectal cancer compared to patients with colorectal benign diseases (61.1% Vs 38.9%, respectively). **Conclusion:** The expression of microRNA-152 was significantly downregulated in colorectal cancer patients compared to the Colorectal Disease (CRD) group, which needs further study to evaluate its predictive value the findings suggest the potential of miRNA-152 as a non-invasive biomarker, which may be used alone or in combination with traditional tumor markers for improved diagnostic and prognostic applications in CRC.

Key Words Colorectal Cancer, Colorectal benign Disease, MicroRNA-152, RT-qPCR, Biomarker, Gene Expression

INTRODUCTION

MicroRNAs (miRNA or miRs) are Small, endogenous, non-coding RNAs that attach to the 3´-Untranslated Region (UTR of target messenger RNAs (mRNAs) to control gene expression after transcription. This binding either prevents the mRNA from being translated or causes it to degrade [1,2]. MiRNA-152, a member of the miR-148/152 family, is found in the first intron of the COP72 gene on chromosome 17q21.32. A CpG island usually surrounds its promoter region [3]. Aberrant expression of miRNA-152, which can behave as an oncogene or a tumor suppressor based on its activities and patterns of expression, is a frequent feature of many cancer types [3]. Additionally, by downregulating ZEB1/2, SNAI1 and KLF5, it inhibits the Epithelial-Mesenchymal Transition (EMT) [4,5]. By blocking CDC25B and E2F3, it controls the cell cycle [6,7]. Additionally, it improves anti-tumor immunity by inhibiting immunological evasion molecules such as B7-H1 [9] and HLA-G [8]. Furthermore, microRNA-152 targets tumor suppressors such as p27 [10] and PTEN [11] to produce oncogenic effects in prostate cancer and Chronic Myeloid Leukemia (CML). Targeting several oncogenic pathways and compounds, miRNA-152 has tumor-suppressive effects in colorectal cancer. Targeting DNA Methyltransferase (DNMT1) is a crucial strategy that reactivates dormant tumor suppressor genes and lowers global DNA methylation through a negative feedback loop [12]. The biological properties of Colorectal Cancer (CRC) cells are impacted by DNMT1's function in the methylation of microRNA (miR-152-3p); hence, increased DNMT1 may counteract the impact of miR-152-3p overexpression on CRC development and tumor growth [13]. However, in other colorectal diseases, like IBD, where miRNAs modulate inflammatory pathways and impact important biological processes like extracellular matrix

dynamics, tight junctions, cellular hemostasis and the microbiota, miR-152 plays a crucial role in the differentiation, maturation and functional control of immune cells. As a result, altered miR-152 expression can influence intestinal barrier integrity, tight junctions and the extracellular matrix and accelerate the course of disease [14]. For the following reasons, this study was created to examine the expression of the microRNA-152 gene in colorectal cancer as opposed to other colorectal diseases: (1) The majority of miRNAs are tumor suppressors (common findings) in CRC tissue and cell lines, miR-152 (particularly miR-152-3p) is downregulated, according to the majority of recent reviews and experimental research; restoring miR-152 inhibits colony formation, causes apoptosis and decreases proliferation. (2) DNA methylation and DNMT1 are important molecular targets. One important and frequently mentioned mechanism is miR-152's direct targeting of DNMT1. Tumor growth is aided by lower miR-152 → increased DNMT1 → hypermethylation and silencing of tumor-suppressor genes (e.g., PTEN/RASSF1A). Restoring miR-152 can reduce DNMT1 activity and demethylate tumour suppressor promoters. (3) Suppresses pathways driving invasion/EMT (Wnt, PI3K/AKT, etc.). miR-152 negatively regulates EMT and metastasis-related signalling (Wnt/β-catenin, PI3K/AKT/mTOR and downstream effectors), lowering migration and invasion in CRC models. (4) Biomarker and therapeutic potential. The objective of this study is to study the microRNA-152 gene expression in colorectal cancer patients compared to colorectal benign disease patients by achieving a molecular study using RT-qPCR.

METHODS

Patients and Sampling

The Al-Iraqia University Medical College Council has given its approval to the study. The target population comprised 90 samples and was divided into three groups: 30 patients with a confirmed diagnosis of Colorectal Cancer (CRC group) and 30 patients with other Colorectal Diseases (CRD group), including polyps, ulcers, IBD and Hirschsprung disease. The active inflammation and congestion group and the third group was the control group (n = 10), who were healthy individuals. The age of the samples ranged from 16 to 81 years, with a mean of 47.60±14.980 and most of them fell within the age group of 30-60 years old (68.9%). Blood samples were collected from various hospitals (GIT Centre, Oncology Teaching Hospital, Baghdad Teaching Hospital), regardless of gender or age, with an emphasis on elderly patients, from 1st November 2024 to 31 January 2025. During this time, a series of data was collected. These data include: obtaining information from the patients by using the questionnaire (patient data sheet), reviewing patients´ reports (histopathology reports) to know the stage, grade and type of cancer. As well as to know the type of other non-cancerous colorectal disease.

Genetic Analysis

The concentration of miRNAs in blood plasma is in the picomolar range and they make up only 0.01% of total RNA. For miRNA analysis, quantitative PCR (qPCR) techniques are the most often utilized methodologies. Two hundred fifty (250) µL from a blood sample (EDTA tube) was added to a 1.5 ml Eppendorf tube, which contains five hundred (500) µL TRIzol for each patient of two groups (CRC) and (CRD), besides healthy individuals (control groups), then the tube was inverted many times for mixing. For the detection of microRNA-152 in these groups, firstly, the total RNA was isolated from the blood of these groups by using TRIzol and then using RT-qPCR, which was conducted through two phases: in the first phase, we synthesized cDNA from the isolated RNA by using a specific reverse transcriptase enzyme.

The second one involves choosing the cDNA sample from each patient, then using quantitative PCR (qPCR) to amplify and measure the amount of specific cDNA in real time using a fluorescent dye, SYBR® Green. For each sample, there are two PCR tubes, one for miRNA-152 and the other for the (RNA U6) gene, which is considered a housekeeping gene in this study.

RT-qPCR Protocol:

- Five microliters from each extracted total RNA sample were added to a new PCR tube
- Easy-Script reaction mix that contains dNTPs, buffer and other essential components was added as 10 µL for each sample
- MUL-V Enzyme (reverse transcriptase) was then added to the reaction as 1µl per sample
- One microliter of random primer for the U6 gene, also 1µL specific RT primer for (miR-152) and the volume was completed up to 20 µL by adding nuclease-free water
- This mixture was incubated as shown in the Table 1-3 and Figure 1

Table 1: The Mixture (Temperature, time and Purpose) of RT-qPCR

Temperature	Time	Purpose
65°C	5 min	Complex RNA relaxation
25°C	10 min	Random primer and specific oligos binding
42°C	15 min	Enzyme activation
85°C	1 min	Enzyme inactivation

Table 2: The RT-qPCR Thermocycling Protocol

Cycle Steps	Temperature	Time	Cycles
Initial Denaturation	95°C	60 seconds	1
Denaturation	95°C	15 seconds	
Annealing/Extension	60°C	30 seconds (+plate read)	45
Melt Curve	60-95°C	40 minutes	1

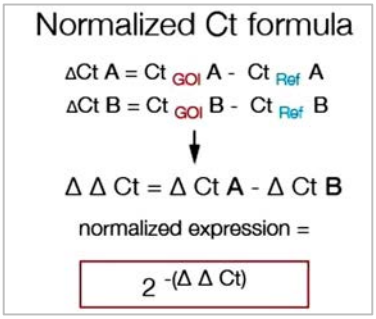

Figure 1: The Results were Collected and Analyzed by the Livak Formula

Table 3: The Name, the Sequence and the Reference of the Primers that have been used in this Study

The name of the primer	The sequence	The reference
miRNA-152 RT	5′-CTCAACTGGTGTCGTGGAGTCGGCAATTCAGTTGAGCCAAGTTC-3′	Korea
miR-152 F	5′-ACACTCCAGCTGGGTCAGTGCATGACAGAACT-3′	Korea
miR-152 R	5′-CT CAACTGGTGTCGTGGA-3′	Korea
U6-FP	5-CTCGCTTCGGCAGCACA-3	Korea
U6-RP	5-AACGCTTCACGAATTTGCGT-3	Korea

Statistical Analysis

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 26 and STATISTICA version 9. The present analysis utilised analysis of variance (ANOVA) to compare the continuous variables among more than two groups, while a Chi-square test was used to assess association within categorical variables in independent groups.

RESULTS

Demographic Data

With an average age of 47.60±14.980, the samples' ages ranged from 16 to 81 years, with the majority (68.9%) falling into the 30- to 60-year-old age range. The mean age of the subgroup of cases with colorectal cancer was 56.50±14.562 years old, with 60% of them falling into the 30- to 60-year-old age range. The subgroup of cases with colorectal diseases was 38.57±13.268 years old, with 66.7% of them falling into the 30- to 60-year-old age range. In contrast, the controls group's mean age was 47.73±11.585 years old, with the majority of them falling into the 30- to 60-year-old age group (80%). The mean differences between the groups were significant (F= 13.857, df: (2, 87), (p<0.05).

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The cause for non-carcinogenic mass among colorectal diseases subgroup revealed that, about one quarter of Colorectal Disease subgroup (CRD) reported to have Acute Inflammatory Disease (AID) (23.3%), followed ulcerative colitis (20%), chronic inflammation and congestion (each 13.3%), polyps and adenoma (10%), diverticula, lipoma and Crohn's disease (each 3.3%) respectively (Figure 2,3).

Furthermore, adenocarcinoma was the most common cancer type among the patients in the colorectal cancer subgroup of cases (86.7%), followed by mucinous adenocarcinoma (6.7%), metastatic adenocarcinoma and non-mucinous adenocarcinoma (3.3% each), in that order.

Similarly, the majority of patients (83.3%) in the case subgroup of colorectal cancer patients had moderately-differentiated tumors, followed by 13.3% with poorly-differentiated tumors and only 3.3% with well-differentiated tumors (Figure 4).

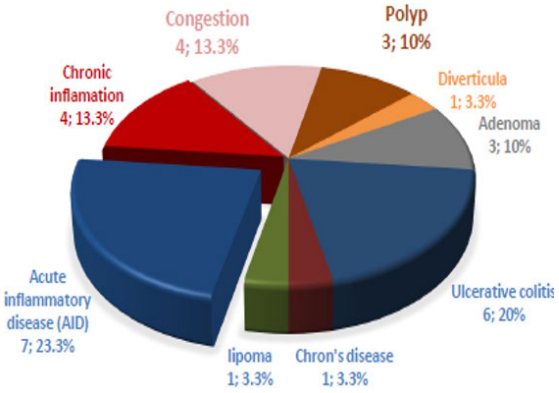

Figure 2: Distribution of Tumour-Related Causes among Colorectal Diseases in the Case Sample (n = 30)

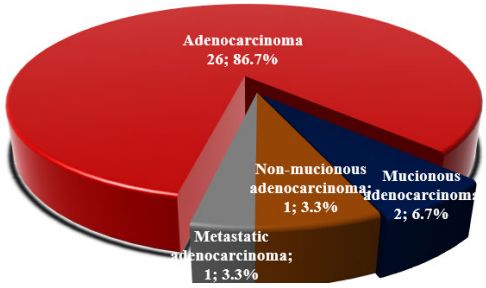

Figure 3: The Cancer Type among Cases of Colorectal Cancer Patients, n = 30

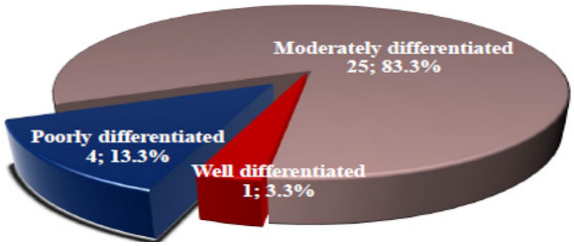

Figure 4: The Cancer Grade among Cases of Colorectal Cancer Patients (n = 30)

Comparison of microRNA Genetic Expression among the Study's Case Subgroups

Comparison of the genetic expression of microRNA in the case subgroups of the study.

Significant differences were found when comparing the microRNA genetic expression of the study case groups. Patients with colorectal cancer in the cases group had a significantly downregulated genetic expression compared to patients with colorectal diseases in the study cases group (61.1 Vs 38.9%, respectively).

Table 4: The Expression of MicroRNA-152 among the Cases' Study Groups, n = 60

Expression of Micro-RNA	Study's cases subgroups				Total	p value
	CRC (30)		CRD (30)			
	n	%	n	%		
<1(downregulation)	22	61.1	14	38.9	36	0.035
≥1(upregulation)	8	33.3	16	66.7	24	

However, patients with colorectal disorders had significantly upregulated genetic expression compared to patients with colorectal cancer (66.7% Vs 33.3%), respectively ($x2$: 4.444, df: 1, p = 0.035) (Table 4).

DISCUSSION

MicroRNA-152 (miR-152) is increasingly recognised as a key tumour-suppressive microRNA in Colorectal Cancer (CRC). Abnormal expression patterns of miRNAs have been linked to CRC. Moreover, they are clinically applicable as early diagnostic biomarkers [15]. The current study indicates that there is a downregulation of miRNA-152 in the Colorectal Cancer (CRC) group, compared to the other Colorectal Disease (CRD) group. This finding was supported by multiple studies, which demonstrated that miR-152 is significantly downregulated in CRC tissues, serum and cell lines. The low expression may be attributed to multiple mechanisms, one of them suggested that the downregulation of miRNA-152 in CRC was correlated with advanced TNM stage, lymph-node metastasis and poorer survival outcomes, Additionally, identified that phosphoinositide-3-Kinase Regulatory Subunit 3 (PIK3R3) as a direct and functional downstream target of miR-152 and the PIK3R3 expression was found to be upregulated in clinical CRC tissues so, inhibit and downregulate miR-152 expression [16,17]. Another mechanism is the role of epigenetic modifications in tumor progression, such as the hypermethylation of the miR-152 gene promoter, which has been identified as a significant factor leading to its downregulation in CRC. This epigenetic alteration silences the expression of miR-152, thereby contributing to tumor progression [18,19,20]. The best-characterized mechanism involved in the downregulation of miRNA-152 in CRC was DNA Methyltransferase 1 (DNMT1), a direct targeting of miRNA-152. CRC tissues show low miR-152 and high DNMT1 levels, correlating with poor prognosis. This finding was reported by Dougherty *et al.* [21]. Similarly, this result was conducted by Liu *et al.* [3], who suggested that the miR-152 gene promoter contains a CpG island that undergoes hypermethylation during cancer progression, leading to transcriptional silencing. This process is often driven by overexpression of DNA methyltransferase 1 (*DNMT1*), which creates a reciprocal regulatory loop: DNMT1 methylates and silences miR-152, while miR-152 targets and suppresses DNMT1 expression. Restoration of miR-152 decreases DNMT1 levels, reverses promoter methylation and reactivates silenced tumor-suppressor pathways [22], primarily by targeting oncoproteins (ADAM17, ERK, AKT, Rictor, TMSB10) that drive CRC proliferation and invasion [13]. Another mechanism correlated with the downregulation of miRNA-152 in CRC suggested that the miR-152 expression is regulated by various noncoding RNAs acting as competing endogenous RNAs (ceRNAs), long noncoding RNAs (lncRNAs) such as H19, which function as molecular sponges that sequester miR-152 across different cancer types, including colorectal cancer [17].

In addition, HLA-G (an immunosuppressive molecule) expression is associated with low expression levels of miRNA-148a and miR-152 in colon cancer, by binding of these miRNAs to the 3′UTR terminal of the HLA-G molecule [23].

miR-152 plays a significant role in regulating the expression of the MAGEA3 gene in Colorectal Cancer (CRC) cells, primarily functioning as a tumour suppressor. Research indicates that miR-152 is frequently downregulated in CRC and its restoration can inhibit cell proliferation, migration and survival, while promoting apoptosis [24].

Although the predominant tumour-suppressive role of miRNA-152 has been highlighted, recent findings highlight context-dependent effects. Notably, miR-152-3p has been shown to enhance liver metastasis in CRC through downregulation of AQP11 (Aquaporin Protein 11). *In vitro* cellular assays revealed that miR-152–3p, by targeting AQP11, facilitated CRC cell proliferation, migration, invasion and adhesion. An in vivo assay suggested that AQP11 could notably repress CRC growth and metastasis. [25]. Additionally, miR-152-3p facilitates cancer progression as revealed by colon cancer articles. To take examples, Zhu *et al.* [26] revealed that KLF4 (Kruppel-like factor 4), a zinc finger transcription factor, is involved in the regulation of thymocyte as well as the colonic goblet cell proliferation, differentiation, apoptosis and metabolism. Its level is reduced by miR-152–3p, thereby facilitating CRC cell proliferation and repressing cell apoptosis.

This study found that there is an upregulation of miRNA-152 in other colorectal diseases, such as Inflammatory Bowel Disease (IBD). These findings were supported by other studies that showed inflammatory mediators, such as cytokines and reactive species, can modulate the biosynthesis of miRNAs, including microRNA-152 in non-cancerous colorectal diseases. These mediators may enhance the expression of microRNA-152 [27].

Moreover, inflammatory cytokines, such as interleukin-13 (IL-13), are known to influence the expression of miRNAs (including miRNA-152) in the colonic mucosa and have been linked to the pathophysiology of ulcerative colitis, a form of IBD [28].

In addition, miRNAs (including miR-152) identified as overexpressed in CD associated with epigenetic mechanisms are involved in the regulation of several biological processes closely related to immunological and tumorigenic processes [29].

Nguyen *et al.* [30] found that some pathogenic bacteria, such as adherent-invasive *Escherichia coli* (AIEC), alter the expression of miRNAs in CD patients. They found that AIEC infection increases the expression of miRNA (including microRNA-152), which reduces the expression of autophagy proteins (ATG5 and ATG16L1) and inhibits autophagy [30].

Furthermore, the inflamed mucosa of IBD patients has reduced expression of DNMT genes; therefore, overexpression of microRNA-152 in IBD patients can be attributed to reduced levels of the DNMT1 enzyme in the inflamed colonic mucosa of these patients, as reported by Fazio *et al.* [31]. Similarly, a study identified a missense variant affecting the catalytic domain of DNMT1 that showed reduced activity in vivo assays using zebrafish in the inflamed intestinal mucosa of IBD. This suggests elevated levels of miRNA-152 in IBD patients [32].

Although the current study indicates the upregulation of miRNA-152 in IBD and other non-cancerous colorectal diseases. Some studies have demonstrated that miRNA-152 levels decrease in models of intestinal inflammation, suggesting a potential role in disease progression [33].

In colonic polyps, there are differences in miRNA expression (including miRNA-152) by type, with adenomatous polyps being upregulated compared to normal colonic mucosa, while their expression in Sessile Serrated Polyps (SSP) and Hyperplastic Polyps (HP) is usually downregulated [34,35].

CONCLUSION

The expression of microRNA-152 was significantly downregulated in the colorectal cancer patients compared to the Colorectal Disease (CRD) group, which needs further study to evaluate its predictive value.

Availability Data

The data in the current study may be requested from the corresponding author.

Authors' Contributions

Afrah N. Ali, Ahmed Rushdi Abdulla and Ahmed Zuhair: Conceptualisation, Data curation, Investigation, Methodology, Project administration, Resources, Software, Writing-original draft, Writing-review and editing.

Conflicts of Interest

There is no conflict of interest related to this article.

Ethical Statement

The present study, which was conducted by Afrah N. Ali, Ahmed Rushdi Abdulla and Ahmed Zuhair, was approved by the local department of Al-Iraqia University, College of Medicine (No. FM.SA.130, Date14/10/2024) and the Medical City Committee. Also, it was approved by the patients.

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