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RESEARCH

Expression of miR-101-3p and its target ADAM15 gene in colorectal cancer patients

Kolon kanseri hastalarında miR-101-3p ve hedefi ADAM15 geninin ekspresyonu

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Abstract

Purpose: This study aims to evaluate the expression patterns of miR-101-3p and its target ADAM15 in colorectal cancer patients.
Materials and Methods: Thirty patients with colorectal cancer had their tumor and corresponding normal tissue samples taken. Following RNA extraction, real-time PCR (qRT-PCR) was used to determine the relative expression of miR-101-3p and its anticipated target gene, ADAM15, using β-actin as a housekeeping gene. The 2^–ΔΔCt technique was used to determine the relative gene expression levels
Results: Considering colorectal malignant tissues compared to their surrounding non-cancerous counterparts, miR-101-3p expression was significantly lower. On the other hand, tumor tissues showed noticeably higher levels of ADAM15 mRNA. The expression levels of miR-101-3p and ADAM15 were shown to be significantly inversely correlated ($r = -0.6719$, $p < 0.05$).
Conclusion: Our results suggest that miR-101-3p potentially regulates the expression of ADAM15, whose upregulation is associated with tumor tissues. The hypothesis that their interaction may play a significant role in the pathogenesis of CRC is supported by the inverse correlation between these two markers. More studies are required, particularly with bigger patient populations. These results highlight the potential of the miR-101-3p/ADAM15 pathway as a useful biomarker for the future diagnosis or treatment of colorectal cancer.
Keywords:. MicroRNA-101-3p, ADAM15, colorectal cancer, gene expression

Öz

Amaç: Bu çalışmanın amacı, kolorektal kanserli bireylerde miR-101-3p ve hedefi ADAM15'in ekspresyon paternlerini değerlendirmektir.
Gereç ve Yöntem: Kolorektal kanser tanısı almış 30 hastadan tümör ve komşu normal dokulardan örnekler elde edildi. RNA ekstraksiyonunun ardından, miR-101-3p ve hedef geni ADAM15'in ekspresyonu, beta-aktin referans gen olarak kullanılarak gerçek zamanlı PCR (qRT-PCR) yöntemi ile kantitatif olarak ölçüldü. Göreceli gen ekspresyonu ise 2^–ΔΔCt yöntemi kullanılarak belirlendi.
Bulgular: Kolorektal tümör dokularında miR-101-3p ekspresyonu, komşu kanser olmayan dokulara kıyasla anlamlı derecede azalmıştı. Buna karşın, ADAM15 mRNA seviyeleri tümör örneklerinde belirgin şekilde artmıştı. ADAM15 ve miR-101-3p ekspresyon seviyeleri arasında istatistiksel olarak anlamlı ters bir korelasyon gözlendi ($r = -0,6719$, $p < 0,05$).
Sonuç: Elde edilen bulgular, miR-101-3p'nin, ekspresyonu tümör dokularında artmış olan ADAM15'i düzenlemede rol oynayabileceğini düşündürmektedir. Bu iki belirteç arasındaki ters ilişki, etkileşimlerinin kolorektal kanserin gelişiminde önemli olabileceğini desteklemektedir. Özellikle daha büyük hasta gruplarında ek araştırmalara ihtiyaç vardır. Bu bulgular, miR-101-3p–ADAM15 ekseninin gelecekte kolorektal kanserin tanısında veya potansiyel tedavisinde faydalı bir biyobelirteç olabileceğini vurgulamaktadır.

Anahtar kelimeler: MicroRNA-101-3p, ADAM15, kolorektal kanser, gen ekspresyonu

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INTRODUCTION

Colorectal cancer (CRC) ranks as the third most prevalent malignancy and stands as the second leading cancer-associated mortality[1]. With over 881,000 deaths and 1.8 million new cases predicted globally, CRC shows differences across age, gender, and racial groupings, as well as between different parts of the world, with notable variation in its epidemiology[2]. The genetic and epigenetic modifications facilitate the development of CRC. Which impact the cell's normal regulatory processes, including the proliferation, differentiation, and death of colon epithelial cells. Most CRCs arise from premalignant lesions, such as adenomas, and progress to adenocarcinoma via three major pathways: chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype, accounting for approximately 85%, 15%, and 17% of cases, respectively[3].

CIN involves the gain or loss of whole chromosomes or large chromosomal regions, which leads to the inactivation of tumor suppressor genes and the disruption of key signaling pathways. Key genes affected including: TP53, APC, KRAS, PI3KCA, and others[4]. MSI results from an aberrant DNA mismatch repair (MMR) system, causing frameshift mutations in the microsatellites and generating a mutator phenotype[5]. CIMP is an epigenetic instability defined by widespread promoter hypermethylation, a mechanism that silences various tumor suppressor genes, which is frequently associated with BRAF mutations, female sex, age, and right-sided location[6].

Additionally, to these mechanisms, post-transcriptional regulation by microRNAs (miRNAs) plays an important role in CRC development[7]. MiRNAs are short, approximately 21-nucleotide non-coding RNAs that bind to complementary sequences within the 3' untranslated region (UTR) of target mRNAs through the RNA-induced silencing complex (RISC), facilitating mRNA cleavage, translational repression, or degradation[8]. Because perfect complementarity is not required, a single miRNA can regulate hundreds of mRNAs, thereby altering multiple cancer-related pathways. Among these miRNAs, miR-101-3p, a well-known tumor suppressor miRNA, is reduced in several cancers, including colorectal adenocarcinoma, hepatocellular carcinoma, osteosarcoma, glioblastoma, and prostate cancer[9,10].

The progression of CRC is also associated with the aberrant expression of proteolytic enzymes, which regulate cell adhesion, motility, and signaling. A key example is a disintegrin and metalloprotease 15 (ADAM15), which is a type I transmembrane metalloproteinase that is encoded on chromosome 1q21.33[11,12]. Structurally, the ADAM15 protein has multiple domains: the metalloprotease, disintegrin, cysteine-rich, and cytoplasmic domains. These domains contribute to its diverse cellular functions and allow it to cleave numerous substrates, including EGFR ligands, transforming growth factor beta (TGFβ), E-cadherin, N-cadherin, and other key regulatory factors, which are crucial in controlling cellular motility and adhesion. Among the 21 ADAM proteins, 13 are found to be catalytically active, while 8 are inactive. Catalytically active ADAMs typically mediate ectodomain shedding, a process in which the extracellular domains of membrane-associated proteins are cleaved and released into the extracellular space[13].

The ADAM15 gene consists of 23 exons (63-316 bp) and 22 introns (79-1283 bp). Among malignancies, ADAM15 is overexpressed in the lung, breast, prostate, and CRC[14]. Although miR-101-3p downregulation and ADAM15 overexpression have been reported separately in CRC, the regulatory relationship between them remains unclear. Bioinformatic predictions suggest that miR-101-3p directly binds to the ADAM15 mRNA, indicating a potential regulatory axis that may influence tumor invasion and metastasis.

While our understanding of CRC continues to expand, the exact regulatory function of miR-101-3p and ADAM15 remains unclear. This study represents the first description of their interaction in CRC. We assume that the downregulation of miR-101-3p represents a key factor driving metastatic progression and modulates ADAM15 expression. Our study aims to define this mechanism for the development of novel biomarkers of advanced CRC and potential therapeutic targets in the future.

MATERIALS AND METHODS

Sample collection

The samples were collected at the Zheen International Hospital in Erbil, Iraq. The study examined 60 formalin-fixed paraffin-embedded (FFPE) tissues. 30 pairs of matching normal and malignant tissue samples were included in our study

based on patient age, clinical characteristics, and CRC type. The Salahaddin University Research Ethics Committee gave its approval for this study (Reference No. 45/63; April 29, 2025). Every procedure involving human tissue samples was carried out in accordance with the Declaration of Helsinki and the ethical requirements of the Salahaddin University Ethics Committee.

The genetic analysis and molecular techniques were performed at Zheen International Hospital's specialized genetic laboratory (Exogen Genetics). All the experiments conducted in the laboratory (RNA extraction, cDNA synthesis, and qRT-PCR analysis) were performed by experienced laboratory technicians under the direct supervision of the researcher and her supervisor.

RNA extraction and complementary DNA (cDNA) synthesis

Total RNA was extracted from FFPE sections in Eppendorf tubes using the Qiagen RNeasy Mini Kit (Qiagen, Germany). The purity and concentration were determined using a One Drop Touch Nanodrop spectrophotometer (Biometrics, USA). Samples for which the (A260 – A320)/ (A280 – A320) value was less than 1.8 or whose total yield was below 0.5 μg were excluded. All RNA samples were stored at –80 °C until further use.

Following the manufacturer's instructions, the cDNA was synthesized from approximately 1 μg of total RNA using the High-Capacity cDNA Reverse Transcription Kit (PCR Biosystems, UK). The following components were added to the reaction mixture for a total volume of 20 μL: 4 μL of 5× cDNA synthesis mix, 1 μL of 20× Ultra Script enzyme mix, 10 μL of PCR-grade water (dH_2O), and 5 μL of total RNA. Reverse transcription was performed in a thermocycler at 42 °C for 30 min for cDNA synthesis, followed by 85 °C for 10 min for enzyme inactivation. The synthesized cDNA was then preserved at –20 °C until subsequent qPCR analysis.

RNA expression and quantitative real-time polymerase chain reaction (qRT-PCR)

Quantitative real-time PCR (qRT-PCR) was performed in a CFX96 real-time PCR Detection System with a C1000 Touch Thermal Cycler (Bio-Rad Laboratories, USA), using the qPCRBIO SyGreen Blue Mix with Separate ROX Kit (PCR Biosystems, UK). The 20 μL reaction volume contained 10 μL of 2× SyGreen mix, 1 μL of each forward and reverse primer, 2 μL of cDNA template, and 6 μL of nuclease-free water. Expression levels of miR-101-3p and ADAM15 were quantified using β-ACTIN as the endogenous control. The thermal cycling conditions were: 95 °C for 2 min, 40 cycles of 95 °C for 5s, primer-specific annealing temperature (55–60 °C) for 30 s, and 72 °C for 30 s, with a final extension at 72 °C for 2 min. Fluorescence signals were measured during each amplification cycle, and melting curve evaluation was performed to confirm reaction specificity.

Primer design

Specific primers for miR-101-3p and ADAM15 were designed using sequences from the miRbase and NCBI databases. To prevent non-specific amplification, primer sequences were examined for specificity using BLAST analysis, as indicated in Table 1.

Table 1. List of primers used in gene expression study

Primer Name	Primer Sequence 5'-3'	Nucleotide	Tm
miRNA101 F	CGGCGGTACAGTACT GTGATAA	22nt	59.9°C
miRNA101 R	CTGGTGTCGTGGAGTCGGCAATTC	24nt	65.92°C
ADAM15 F	GCCTCAAAAAAGGTGCTTCAGAC	23nt	60.8°C
ADAM15 R	GTTCTCCAAAGTGTGTCCCTCA	22nt	60.16°C
B ACTIN F	CCTTCCTTCCTGGGCATGGAG	21nt	62.48°C
B ACTIN R	GGAGTACTTGCGCTCAGGAGGAG	23nt	64.44 °C

F:forward primer; R: reverse primer; 5'-3': sequence orientation; Tm: melting temperature; nt: nucleotides

Statistical analysis

Data analysis was performed using the relative gene expression method (Livak method). First, for each sample, after the cycle threshold (Ct) was collected from qRT-PCR of both miR-101-3p and ADAM15, values were normalized to the housekeeping gene (β-actin) Ct values. The following formula was then

used: ($\boldsymbol{\Delta Ct = Ct_{target\ gene} - Ct_{reference\ gene}}$). Then, the ΔΔCt method was employed to calculate the relative gene expression levels between the tumor and nearby normal tissues ($\boldsymbol{\Delta\Delta Ct = \Delta Ct_{tumor} - \Delta Ct_{normal}}$). Finally, fold changes were calculated using the 2^−ΔΔCt formula. A fold change less than <1 indicates downregulation, whereas a value >1 indicates upregulation.

After data analysis, statistical analysis was performed using GraphPad Prism 8.0.2 and Microsoft Excel. The normality of the data distribution was examined using the Anderson-Darling, D'Agostino-Pearson, Shapiro-Wilk, and Kolmogorov-Smirnov tests. For normally distributed data, the paired Student's t-test was applied using the ΔCt values from matched normal and tumor samples for miR-101-3p and ADAM15. For non-normally distributed data, the Wilcoxon signed-rank test was used. To demonstrate the correlation between the two molecules, Spearman's rank correlation coefficient was employed. A P-values less than <0.05 were considered statistically significant.

RESULTS

The experiment involved a group of 30 patients, with a gender distribution of 17 males and 13 females. The overall mean age was 58.9±11.0 (range:36-76years). The mean age for female patients was 56.85±11.95 years, while the mean age was 60.53±10.32 years for males. The distribution of tumor stages showed that the majority of patients were in stage 2 (36.7%). Regarding tumor location, the majority, 24(80.0%), were found in the colon, and 6 (20.0%) in the rectum. In terms of histological differentiation, 3(10%) were reported as well differentiated, 5(16.7%) were moderately differentiated, 1(3.3%) was poorly differentiated, and 21 (70%) were not specified. Regarding histological type, 24 cases (80.0%) were non-mucinous adenocarcinoma, and 6(20%) were mucinous adenocarcinoma, as shown in Table 2.

Table 2. The biological and clinical-pathological characteristics of the patients

Characteristics	Categories	Frequency %
1-Age	<50	6 (20%)
	≥50	24 (80%)
2-Gender	Male	17 (53.33%)
	Female	13 (46.7%)
3-Stage /Grade	I	6 (20%)
	II	11 (36.7%)
	III	8 (26.7%)
	IV	5 (16.7%)
4-Tumorlocation	Colon	24 (80.0%)
	Rectum	6 (20%)
5-Differentiation	Well	3 (10.0%)
	Moderately	5 (16.7%)
	Poorly	1 (3.3%)
	Not specified	21 (70.0%)
6-Histological type	No-mucinous adenocarcinoma	24 (80.0%)
	Adenocarcinoma	6 (20.0%)

The average ΔCt for miR-101-3p in normal tissues was 7.053±2.612, while in tumor tissues, it was 8.976±2.949. The observed increase in ΔCt values for miR-101-3p in tumor tissues relative to adjacent normal tissues indicates a significant reduction in its expression. Among all samples analyzed, miR-101-3p was significantly decreased in tumor tissues compared to neighboring normal tissues, with a final fold change of 0.26. This represents an expression level in tumor tissue, approximately 74% lower than in the control, which equates to a 3.8-fold decrease in expression. This downregulation is consistent with the suggested role of miR-101-3p as a tumor suppressor. The result of downregulation is shown in Figures 1 & 2.

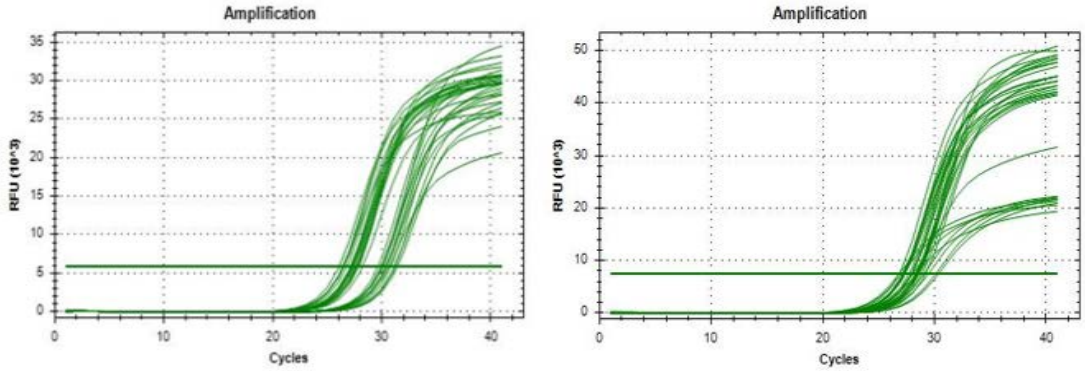

Figure 1. Amplification plots of: miR-101-3p (control, tumor).

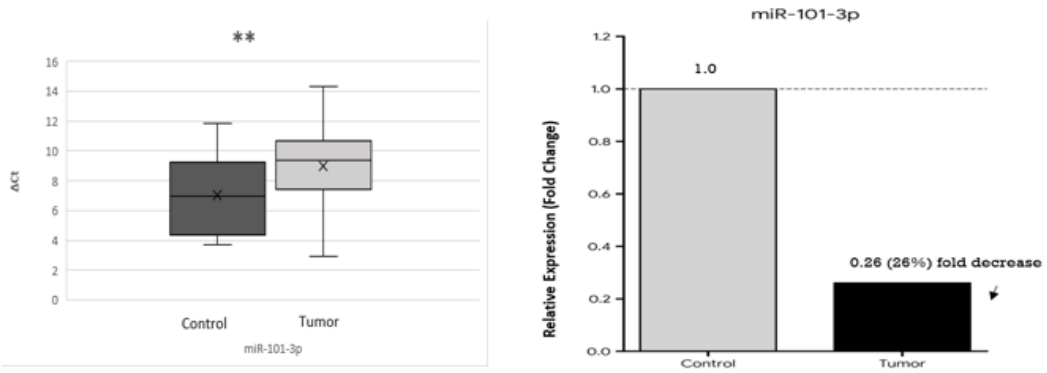

Figure 2. miR-101-3p downregulation in tumor tissues. Relative expression analysis shows that the expression amount of miR-101-3p is reduced by 0.26-fold (p = 0.0081).

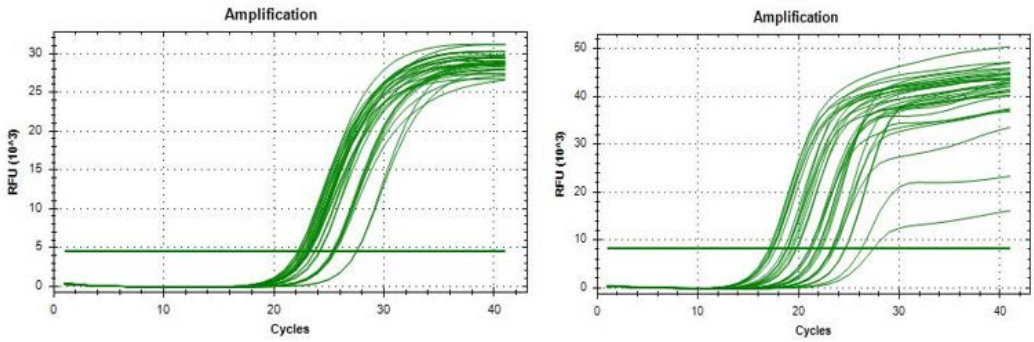

Figure 3. Amplification plots of ADAM15 (control, tumor)

The average ΔCt of ADAM15 in normal tissues was 2.758 ± 2.67, while in tumor tissues it was 1.265 ± 4.213. The observed decrease in ΔCt values for ADAM15 in tumor tissues relative to adjacent normal tissues indicates a significant increase in its expression. This result shows a 2.83-fold change, indicating a 183% increase in the expression in tumor tissues compared to controls. This reveals that ADAM15 mRNA levels are substantially higher in tumor samples than in healthy tissues. This elevated expression may contribute to tumor growth, possibly by involvement in cell adhesion, migration, and invasion mechanisms. The result of upregulation is shown in Figures 3 & 4.

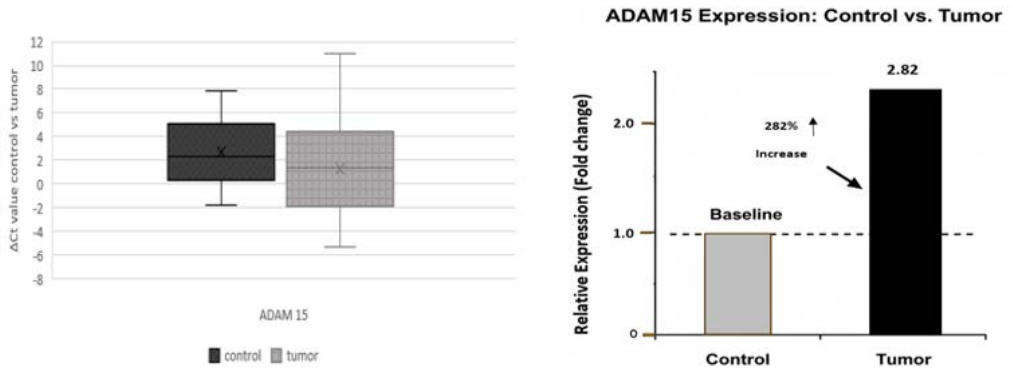

Figure 4. ADAM15 upregulation in tumor tissues. Relative expression analysis shows that the expression amount of ADAM15 is increased by 2.28-fold (p = 0.0002).

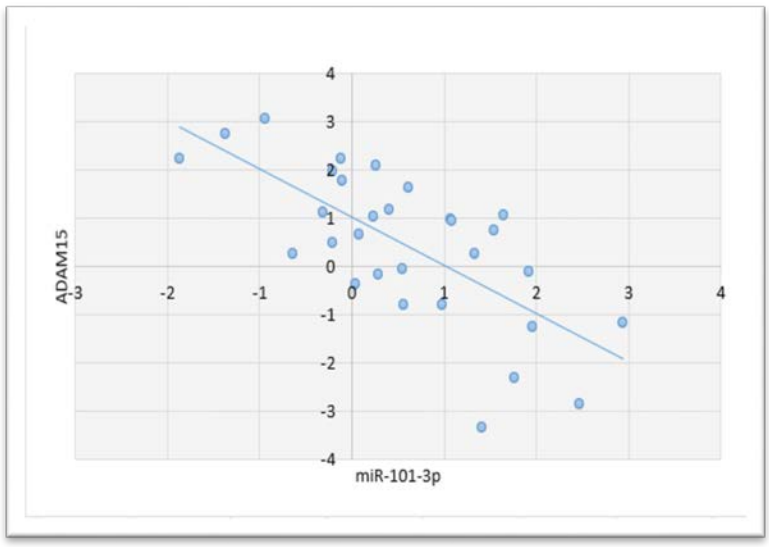

Figure 5. Correlation analysis between miR-101-3p and ADAM15 expression in CRC tissues. Show an inverse expression profile of miR-101-3p and ADAM15 in CRC.

After Spearman's rank correlation analysis was used, based on the values obtained using log10 (2^-ΔΔCt) for both molecules, across 30 paired colorectal tumor and neighboring normal tissue samples. The result shows a substantial negative connection between miR-101-3p and ADAM 15 expression ($r = -0.6719$, $p < 0.0001$). This adverse connection lends support to our idea that miR-101-3p may operate as a post-transcriptional ADAM15 inhibitor in CRC by binding to its 3' UTR mRNA and promoting translation inhibition or destruction. As presented in Table 3 and Figure 5.

Table 3. Spearman correlation analysis of miR-101-3p and ADAM 15 expression in paired colorectal tumor and adjacent normal tissues.

Correlation Test	Spearman r	95% confidence interval	P value	Conclusion
Spearman rank correlation	-0.6719	-0.8344 to -0.4019	<0.0001	Significant negative correlation

DISCUSSION

Colorectal cancer (CRC) is associated with high mortality rates and is a major worldwide health issue. In addition to numerous available screening approaches for CRC detection, such as colonoscopy, and both blood and fecal-based biomarkers, current diagnostic procedures are not ideal and need to be improved to enable early diagnosis and boost survival rates. Researchers have investigated the potential use of miRNAs as early detection biomarkers across many cancer types, including CRC, taking into account their roles in the onset and progression of cancer[15].

based on the patients' clinical details in our study, including age, gender, tumor location, and stage of illness. Only 20% of the patients in this study were 50 years of age or younger, while the vast majority, 80%, were older. This age distribution is consistent with worldwide epidemiological data that demonstrate a marked increase in prevalence with age, especially after the fifth decade of life. Age is a known risk factor for CRC, primarily due to the result of declining immunosurveillance, the accumulation of genetic abnormalities, and extended exposure to environmental pollutants[16].

With 53.3% of the study's participants being male and 46.7% being female, males are the most commonly affected demographic by CRC. This results from an interaction of behavioral, hormonal, and biological factors linked to this gender disparity. Adenocarcinoma, a form of CRC that arises in the glandular epithelium of the colon lining, accounted for the majority of cases among histological types. There were 6 (20%) mucinous adenocarcinomas and twenty-four (80%) non-mucinous adenocarcinomas in this study. The synthesis of a large amount of extracellular mucin is a characteristic of mucinous adenocarcinomas. They frequently show microsatellite instability, chemoresistance, and worse clinical outcomes[17].

Based on disease stage, the majority of cases were diagnosed at intermediate (stages II and III). This indicates that they are not diagnosed early in their illnesses, as symptoms typically do not present until the disease has progressed significantly. This can be understood by considering that CRC remains asymptomatic during its early stages; hence, patients usually seek medical intervention when the disease has reached an advanced stage. The transformation of cancer medications toward the management of advanced-stage cancer itself emphasizes an indispensable need for enhanced screening in an effort to facilitate an early-stage diagnostic process.

Based on the site from which the tumor originates, the most common location found is the colon, compared to the rectum. This coincides with the fact that the incidence of colon cancer is greater than that of rectal cancer. This can be attributed to the fact that the colon has a greater surface area, which causes increased exposure to carcinogens. Additionally, the influence of some risk factors, such as high body mass index and the fact that one is physically inactive, is more closely related to the incidence of colonic cancer than that of the rectum[18].

When compared to adjacent normal tissues, miR-101-3p levels in CRC samples appear markedly suppressed. Such a finding is hardly an outlier; indeed, both Zhang et al. (2019) and Li et al. (2021) have previously suggested that this miRNA inhibits CRC proliferation by targeting the EZH2 and MCL-1 pathways. Interestingly, this downregulation is frequently reported across various malignancies, including gastric carcinoma, which points toward a broader function for the molecule as a tumor suppressor. It stands to reason, then, that the loss of this regulatory 'brake' effectively paves the way for the uncontrolled activation of carcinogenic pathways[19]. The loss may result from several mechanisms, including transcriptional repression, epigenetic silencing, or malfunctions in the miRNA biogenesis machinery[20].

On the other hand, ADAM15 expression was noticeably higher in CRC tissues. This has been linked to angiogenesis, cell signaling, and tumor invasiveness. It is frequently overexpressed in solid tumors[21]. Mochizuki et al. (2018) and Lendeckel et al. (2017) showed similar upregulation in gastrointestinal malignancies, suggesting that ADAM15 plays a crucial role in enhancing invasion and metastases, as well as changes in the tumor microenvironment[22].

A significant inverse relationship was found between the two markers. This suggests that the decreased expression of miR-101-3p is linked to the increased expression of ADAM15. The idea that miR-101-3p may function as a negative regulator of ADAM15 is supported by the increase of ADAM15 in the context of miR-101-3p suppression. These results are consistent with the larger knowledge of miRNA–mRNA interactions in cancer, which shows that oncogenes can become derepressed when tumor-suppressive miRNAs are lost[23].The dysregulation of other miRNAs, such as miR-21, miR-143, and miR-145, has also been implicated in CRC pathogenesises[24].

The limitations of this study are that although the findings indicate a strong correlation between miR-101-3p and ADAM15, they are based on 30 sample pairings. To ensure that these results hold for all demographics and cancer subtypes, a larger, more diverse patient sample would be required. However, because of limited time, we only evaluated the expression levels of both molecules; to confirm the regulatory relationship, protein evaluation, such as western blotting, and functional tests like luciferase assay, are required to validate the direct regulatory interaction.

Our results lead us to the conclusion that, compared to nearby normal tissues, miR-101-3p is downregulated, which correlates inversely with ADAM15 overexpression. Moreover, the dysregulation identified suggests that these molecules may serve as potential biomarkers for disease. Further studies are needed to determine the role of miR-101-3p and ADAM15 in the process of cancer growth and metastasis, specifically with the aid of in vivo approaches such as the xenograft model and genetically modified mice, to obtain concrete findings. Although this research has generated interesting outcomes, further studies must specifically focus on developing a safe and efficient system for miRNA therapy, such as a viral vector and a nanoparticle, to evaluate their therapeutic potential.

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Ethical Approval: Ethical approval was obtained from the Human Research Ethics Committee (HREC) of the Salahaddin University - Erbil Science College, Ministry of Higher Education and Scientific Research, with decision number 45/63 dated 29.04.2024.
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Conflict of Interest: The authors declare no conflict of interest.
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