Non-coding RNA Research 8 (2023) 187–191

Contents lists available at ScienceDirect

Non-coding RNA Research

journal homepage: www.keaipublishing.com/en/journals/non-coding-rna-research

Original Research Article

Signature of micro RNA 146a/215 and IL-6/TGF-β levels in a cross-link axis between obesity and colorectal cancer

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ARTICLE INFO

Keywords:
Obesity
Colorectal cancer
BMI
TGF-β
IL-6
miR-215
miR-146a

ABSTRACT

Numerous malignancies, including colorectal and liver cancers, are ultimately more likely to occur in obese people, and chronic inflammatory conditions have been linked to this association. We are attempting to determine the clinical relevance of the mechanisms controlling the microRNA (miR-215 and miR-146a) expression and transforming growth factor-β (TGF-β)/interleukin-6 (IL-6) in a cross-link axis between obesity and colorectal cancer (CRC). Study participants were divided into four groups: healthy controls; obese without colorectal cancer; non-obese colorectal cancer; and obese with colorectal cancer. Obese and CRC patients had markedly higher expression of IL-6 and TGF-β, as well as tumor biomarkers, such as carcinoembryonic antigen (CEA), carbohydrate antigen 19.9 (CA19.9), and alpha-fetoprotein (AFP) levels. The relative expression of microRNAs (miR-215 and miR-146a) was significantly lower in obese patients with colorectal cancer. BMI and the microRNAs(miR-215 and miR-146a) showed a substantial negative correlation. TGF-β was favorably linked with IL-6, cholesterol, triglyceride levels, and BMI. High levels of TGF-β and IL-6 in the blood indicate how intensely inflammation develops in obesity, which could increase the risk of colorectal cancer.

1. Introduction

A high-energy, low-nutrient diet and a lack of physical activity are two factors that can contribute to obesity and overweight, which are now public health problems and nutritional disorders [1,2]. Obesity is a key hallmark of metabolic syndrome, and the relationship has been linked to a chronic inflammatory state [3,4]. Obesity promotes CRC carcinogenesis through complicated pathways, and it is regarded as an independent risk factor for cancer in general and CRC in particular, contributing to a higher mortality rate for these diseases [5]. Excess macronutrients in adipose tissues increases the release of inflammatory adipokines and transforming growth factor-β (TGF-β), resulting in chronic inflammation in obese individuals [6,7]. Pro-inflammatory IL-6 cytokine promotes inflammation and controls inflammatory responses [8]. Obese patients such as those with chronic inflammatory diseases and aberrant blood lipid concentrations had higher IL-6 serum levels, which may raise their risk of cardiovascular diseases and cancer [3,9,10].

TGF-β is a cytokine that regulates tissue growth and homeostasis, and present in high concentrations at the site of an ongoing inflammatory response [11]. Elevated levels of TGF-β in the initial colorectal tumor are connected to advanced CRC stages, which promote tumor growth in the late stages of colorectal carcinogenesis [12]. The prognosis of individuals with distant metastases beginning with metastasis is still poor despite significant improvements in diagnostic and therapeutic approaches to CRC. Thus, the need for novel biomarkers for the detection of CRC cancer growth and metastasis is imperative [13,14].

MiR-146a and miR-215 have emerged as significant immune response regulators among the numerous miRNAs that may contribute to regulating the immune system. miR-146a/215 are multifunctional miRNAs, their deficiency results in excessive production of inflammatory adipokines and inflammatory diseases [15,16]. This study investigates the significance of micro RNA 146a/215 and IL-6/TGF-β levels and their association with obesity and colorectal cancer. Moreover, the study investigates whether the gene expression of miR-146a and miR-215 in the serum of obese and CRC patients suggests their diagnostic utility in the early detection of CRC in obese patients.

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https://doi.org/10.1016/j.ncrna.2023.01.001
Received 27 November 2022; Received in revised form 5 January 2023; Accepted 6 January 2023
Available online 6 January 2023

2. Materials and methods

2.1. Study population

A total of 190 Egyptians with a history of obesity and positive colonoscopy results for cancer were enrolled in this study from the Tropical Medicine Department, the Faculty of Medicine, Cairo University, during the period between October 2020 through March 2021. Tumor grading and staging were done in accordance with the tumor-node-metastasis (TNM) classification after the histopathological investigation verified the presence of colorectal cancer. In accordance with the standards established by the World Health Organization (WHO) in 1997 and the National Institutes of Health (NIH) in 1998, a BMI of 30 kg/m^2 or more was considered obese for study participants. Healthy study participants, age and sex-matched with the recruited patients, were considered as controls. Members of the control group had no recognizable diseases and were clinically free from any abnormality. Individuals who consumed alcohol were excluded from the study to avoid the confounding effect of alcohol intake on the blood γ-GT level.

Study participants were classified into four groups: 40 subjects in the healthy control group (G1), 50 subjects who were obese (G.2), and 100 patients diagnosed with CRC who were distributed into two groups (each containing 50 patients), namely, G.3: non-obese CRC, and G.4: obese CRC patients.

Exclusion criteria of this group included autoimmune disorders as well as respiratory, kidney, liver, cerebrovascular, and heart diseases and other medical conditions. Furthermore, pregnant and lactating women were not enrolled in this study.

The institutional ethical committee of the Faculty of Medicine at Cairo University gave its approval to the study protocol. Written consents were obtained from participants following the ethical standards of the institutional ethical committee and the rules of the amended version of the Helsinki declaration for human studies.

2.2. Samples collection

Six ml blood was withdrawn and collected in 2 tubes, then centrifuged at 4000 rpm for ten minutes after being allowed to clot for fifteen minutes. Separate serum samples were kept at −80 °C until usage. These sera were used for biochemical analysis of cholesterol, triglycerides, HbA1c, liver function profile (albumin, total bilirubin, ALT, and γ-GT), and tumor biomarkers (CEA, CA19.9, and AFP), IL-6, and TGF-β evaluation.

The IL-6 and TGF-β in the serum per the manufacturer's protocol were evaluated using an ELISA kit (Cat#SEA079Hu, and Cat# BEK_2093_1P; respectively).

The miScript SYBR Green PCR Kit was used to assess the relative expression levels of miR-146a and miR-215 (Qiagen, Valencia, CA, USA). Primers for miR-146a, miR-215, and internal control were received from Qiagen in Valencia, California, USA. As an internal control, SNORD 68 (Cat No. MS00033712) was used utilizing the Rotor-gene Q System, real-time PCR (Qiagen, Valencia, CA, USA) was carried out and then, the relative expression of miR-146a and miR-215 were calculated by the $2^{-\Delta\Delta Ct}$ method for relative quantification [17].

2.3. Statistical analysis

The Statistical Package for Social Sciences version (IBM, New York, NY, USA) was employed for the statistical data analysis and Tukey's test multiple post-hoc comparison test was used for pairwise comparison. Data were accessed as means ± standard error means (SEM) or percentages when appropriate. Pearson's correlation analysis assessed the relations between the variables studied. $p < 0.05$ was considered to indicate a statistically significant difference.

3. Results

Table 1 provides data of the study participants' biochemical and demographic characteristics. Age and sex were matched between the case and control groups ($P > 0.05$). Our results revealed that obese patients (G2) and obese CRC patients (G4) had significantly higher values for BMI ($P < 0.05$), lipid profile (total cholesterol and triglycerides), and HbA1c ($P < 0.05$) compared to the healthy participants. Furthermore, we did not observe significant differences between non-obese CRC patients and healthy controls for BMI($P > 0.05$) and triglycerides ($P > 0.05$) level. Our analysis revealed a non-significant difference in the level of albumin and ALT activity ($P > 0.05$) among participants groups (Table 1). Total bilirubin levels and γ-GT activities were significantly ($P < 0.05$) elevated in all CRC groups (G3 and G4) compared to those of healthy controls. Furthermore, a remarkable elevated level of tumor biomarkers (CEA, CA19.9, and AFP) ($p < 0.001$) was recorded in all CRC groups (G3 and G4) compared with that of healthy controls (Table 1). Obese CRC patients (G4) had higher tumor biomarker levels than normal controls. Additionally, compared with the non-obese CRC group (G3), the obese CRC subjects (G4) had significantly ($p < 0.05$) higher CEA levels, and non-significant ($p > 0.05$) elevation in CA19.9 and AFP levels. In addition compared with obese patients (G2), the obese CRC patients had significantly ($p < 0.001$) higher CEA and CA19.9 levels, and significant ($p = 0.05$) elevation in AFP levels (Table 1).

The analysis of IL-6 and TGF-β gene expression showed a significant ($p < 0.001$) elevation in obesity (G2) and CRC patients (G3, G4) compared with the expression levels in healthy controls (G1), and this elevation was higher in the obese CRC group (G4). In addition,

Table 1
The demographic data age, gender, body mass index, lipid profile, liver function profile (Albumin, TB, ALT, γ-GT), and tumor biomarkers profile (CEA, CA19.9, and AFP) HbA1c among study participants.

Variables	G1(40)	G2(50)	G3(50)	G4(50)
Age (range, year) (mean ± SD)	48.64 ± 10.07^a	49 ± 5.28^a	51.88 ± 12.61^a	46.96 ± 9.93^a
Gender				
Male (n,%)	23(57.5%)	22(44%)	29(58%)	26(52%)
Female (n, %)	17(42.5%)	28(56%)	21(42%)	24(48%)
BMI (kg/m^2)	23.08 ± 2.83^a	33.93 ± 3.01^b	23.20 ± 2.32^a	33.34 ± 2.34^b
Cholesterol(mg/dL)	175.52 ± 11.89^a	345.33 ± 11.43^d	232.88 ± 4.82^b	313.92 ± 4.67^c
Triglycerides (mg/dL)	109.12 ± 4.30^a	172.60 ± 6.68^b	105.85 ± 2.35^a	166.06 ± 2.60^b
HbA1c (%)	4.88 ± 0.05^a	5.79 ± 0.14^b	5.92 ± 0.12^b	5.96 ± 013^b
Albumin (g/dL)	4.49 ± 0.06^a	4.52 ± 0.09^a	4.91 ± 0.11^a	4.74 ± 0.11^a
TB (mg/dl)	0.55 ± 0.02^a	0.50 ± 0.03^a	0.93 ± 0.04^b	0.93 ± 0.03^b
ALT(U/L)	21.15 ± 1.39^a	20.43 ± 1.34^a	23.35 ± 1.01^a	24.02 ± 1.16^a
γGT(U/L)	13.77 ± 1.17^a	14.29 ± 1.94^a	92.93 ± 4.40^b	98.20 ± 3.78^b
CEA (ng/mL)	2.38 ± 0.17^a	2.72 ± 0.33^a	20.25 ± 1.23^b	26.16 ± 1.48^c
CA19.9 (U/ml)	7.67 ± 0.57^a	15.44 ± 5.55^a	36.75 ± 3.21^b	46.04 ± 3.31^b
AFP (ng/mL)	1.14 ± 0.11^a	1.20 ± 0.12^a	10.93 ± 0.78^b	12.90 ± 0.90^b

Cholesterol, triglycerides, and HbA1c levels are represented as Mean ± SEM. G.1 (Healthy control group); G.2 (Obese participants): G.3 (Non-obese CRC patients); and G.4 (Obese CRC patients). Values which share the same superscript symbol are not significantly different. BMI: body mass index, HbA1c%: glycated hemoglobin. ALT: Alanine transaminase; TB: total bilirubin; γ-GT: Gamma glutamyl transferase. CEA: Carcinoembryonic antigen; CA19.9: Carbohydrate antigen19.9; AFP: alpha-fetoprotein.

compared with obese patients, the obese CRC patients had significantly ($p < 0.001$) higher in the expression levels of IL-6 and TGF-β (Table 2). In contrast, miR-215 and miR-146a relative gene expression was significantly ($p < 0.001$) decreased in obese (G2) and CRC patients (G3, G4) compared with that in healthy controls. Additionally, compared with the obese group (G2), the obese CRC subjects (G4) had a significant ($p < 0.001$) elevation in the expression of TGF-β and IL-6 levels, besides, a significant ($p < 0.001$) decline in the expression of miR-215 and miR-146a levels (Table 2). Furthermore, compared with the non-obese CRC group (G3), the obese CRC subjects (G4) had a non-significant ($p > 0.05$) elevation in the expression of TGF-β and IL-6 levels, besides, a significant ($p < 0.05$) decline in the levels of miR-215 and non-significant decline in miR-146a expression levels (Table 2).

According to Pearson's correlation analysis, there is a strong positive association between changes in BMI and cholesterol ($r = 0.739$, $P < 0.001$) (Table 3). The results also revealed a drastically positive link ($P < 0.001$) between BMI and triglycerides ($r = 0.814$), as well as a positive correlation between BMI with TGF-β ($r = 0.258$, $P = 0.003$) and IL-6 ($r = 0.226$, $P = 0.01$). The relative expression of miR-215 and miR-146a, on the other hand, showed a substantial ($P < 0.001$) negative connection with BMI ($r = 0.478$, $P < 0.001$) and miR-146a ($r = 0.381$, $P < 0.001$). Additionally, remarkable positive correlation between TGF-β, IL-6, triglycerides, and cholesterol were observed, as shown in Table 3. The relative expression of miRNA (miR-146a and miR-215) with TGF-β expression, however, was found to be significantly inversely correlated. Likewise, IL-6 had a negative correlation with the relative expression of miRNA (miR-146a and miR-215) (Table 3).

We were anxious to know whether miR-215 and miR-146a could be used as distinctive markers for obese CRC patients. As illustrated in Fig. 1(a) and (b), ROC curve analysis significantly showed that miR-215 and miR-146a down-regulation has specificity and sensitivity in obese CRC patients [area under the curve (AUC) = 0.994, and 0.971 respectively, p-value <0.001], suggesting that miR-215 and miR-146a can help identify CRC obese patients. For example, the ROC curve analysis demonstrated that miR-215 could significantly discriminate obese CRC with cutoff value of 0.504, sensitivity 98%, and specificity 100% (Fig. 1 a, b).

4. Discussion

Obesity is considered a worldwide health issue with obese individuals presenting a driven inflammation in particular steps of colorectal cancer incidence and progression [18–20]. It is significant to note that understanding the pathophysiology of obesity is necessary for the development of efficient preventative measures and intervention tools that can help to lower the disease's rising incidence and co-morbidities. Herein, we aimed to investigate the relationship between miR-146a/miR-215 biomarkers and IL-6/TGF-β levels in a cross-link axis between obesity and colorectal cancer.

The results of our study showed a significant elevation in the expression of IL-6 and TGF-β in obese and CRC patients compared with the healthy group, and the highest rise was seen in the CRC group of obese patients. BMI, cholesterol, and triglycerides levels were all strongly associated with IL-6 and TGF-β levels. Previous studies have also reported remarkable elevation in the expression levels of IL-6 in obese and CRC patients [21–23]. Increased IL-6 expression level may be related to release from adipose tissue and chronic inflammation [22]. Plasma IL6 and TGF-1 levels were shown to be considerably higher in ovarian cancer patients, according to Almolakab et al. [24]. In addition, our results were in agreement with those of Fabregat and Caballero-Díaz [25], who states that TGF-β is a fundamental regulator of all stages of disease progression, from early liver injury through cirrhosis and hepatocellular carcinoma via inflammation and fibrosis. Recent studies have pointed out that the sustained TGF-β expression in obesity is mainly associated with the advanced stages of inflammation and considered as risk for significant disorders [26,27]. Moreover, the role of elevated IL-6 protein levels in CRC was confirmed by the high expression of tumor markers (CEA and CA19.9) of CRC patients, IL-6 serum levels that are high also significantly enhance the chance of developing CRC [21]. Furthermore, it has been demonstrated that IL-6 supports chronic inflammation and, as a result, promotes the development of many malignancies, including CRC. Obese people may ultimately be more likely to develop and advance CRC due to elevated levels of circulating proinflammatory cytokines such IL-6 [3]. A significant expression of IL-6 and TGF-β was also noted in hepatocellular cancer, according to Srivastava et al. [28], and IL-6 and TGF-β are adaptable substances that can be used to fine-tune processes for epigenetic regulation of transcription. These inflammation-associated cytokines were found to interact strongly, and they positively connected with cellular invasion, EMT, and resistance [29].

The miR-146a/miR-215 differential expression fold was assessed in patients with obesity and CRC compared with that in healthy participants. All participants with obesity and CRC showed decreased miR-146a and miR-215 expression with a significant difference. Although the differential expression fold of miR-146a/miR-215 was very low in obese participants with CRC compared to that in non-obese patients with CRC, it was significant. The expression fold of miR-146a/miR-215 and BMI were found to be negatively correlated using Pearson's correlations.

These results were in concordance with the studies by Yan et al. [30] and Ullmann et al. [31], which revealed a significant depletion in the relative expression of miR-215 in CRC patients compared to healthy participants. Likewise, El Mahdy et al. [32] and Ashmawy et al. [33] found that relative expression of miR-215 was significantly lower in the HCC group. Along with renal cell carcinoma [34], glioma [35] and, acute myeloid leukemia [36], the tumor suppressor function of miR-215 has also been shown in gastric [37] and, lung cancer patients [38].

Ali et al. [39] found an up-regulation in the relative miR-215 expression levels in hepatocellular carcinoma (HCC) patients, which is in contrast to our findings. Moreover, Liu et al. [40] reported that the up-regulation of miR-215 leads to an elevation of HBV X (HBx) protein levels and hence the development of HCC.

Regarding relative expression of miR-146a, recent studies revealed a crucial role of miR-146a in the prognosis of cancer (prostate, colorectal, lung, hepatocellular carcinoma, and breast cancer) by contributing to the development and deterioration of breast cancer, supposing that miR-146a is a therapeutic target and potential biomarker [41–43].

Our findings that there was a significant down-regulation of miR-146a in CRC sera samples are consistent with those of Hofsli et al. [44], who also found that miR-146a was down-regulated in the sera of CRC patients. The dual role of miR-146a in carcinogenesis and metastasis (oncogenic and suppressive) has also been demonstrated [45]. In disagreement with our results, Chen et al. [46] and Lu et al. [47], reported an up-regulation of relative miR-146a expression in colorectal

Table 2
Changes in the levels of TGF-β, IL-6, and relative expression of miR-215 and miR-146a among study participants.

Group Characteristics	TGF-β (ng/ml)	IL-6 (*pg*/ml)	miR-215	miR-146a
G1	12.73 ± 0.53^{a}	2.36 ± 0.13^{a}	0.96 ± 0.03^{d}	0.92 ± 0.03^{c}
G2	22.51 ± 1.10^{b}	6.87 ± 0.50^{a}	0.72 ± 0.05^{c}	0.69 ± 0.03^{b}
G3	51.64 ± 2.10^{c}	49.25 ± 3.12^{b}	0.39 ± 0.02^{b}	0.42 ± 0.02^{a}
G4	57.85 ± 2.15^{c}	59.99 ± 3.20^{b}	0.18 ± 0.02^{a}	0.27 ± 0.04^{a}

Levels of TGF-β, IL-6, and relative expression of miR-215 and miR-146a are represented as Mean ± SEM. G.1 (Healthy control group); G.2 (Obese participants): G.3 (Non-obese CRC patients); and G.4 (Obese CRC patients). Values which share the same superscript symbol are not significantly different. TGF-β: Transforming growth factor-β; IL-6: Interleukin-6.

Table 3
The correlation between body mass index(BMI); cholesterol, triglycerides; transforming growth factor-beta (TGF-β); interleukin-6 (IL-6); microRNA-215(miR-215) and microRNA-146a (miR-146a) in study participants.

Parameter	BMI		TGF-β		IL-6	
	R	*p*	R	*P*	R	*P*
Cholesterol	0.739***	<0.001	0.310***	<0.001	0.218*	0.013
Triglycerides	0.814***	<0.001	0.192*	0.03	0.141	0.11
TGF-β	0.258**	0.003	–	–	0.762***	<0.001
IL-6	0.226**	0.01	0.762***	<0.001	–	–
miR-215	−0.478***	<0.001	−0.663***	<0.001	−0.658***	<0.001
miR-146a	−0.381***	<0.001	−0.553***	<0.001	−0.477***	<0.001

*** Significant linear correlation at $p < 0.001$ (2-tailed). ** Significant linear correlation at $p < 0.01$ (2-tailed).* Significant linear correlation at $p < 0.05$ (2-tailed).

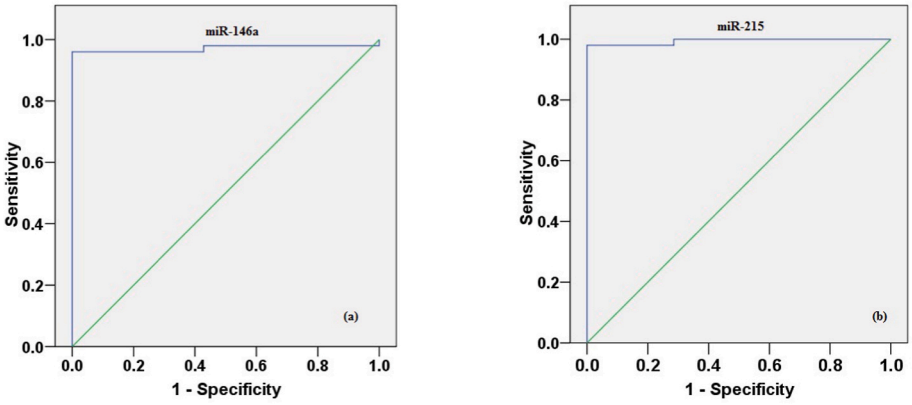

Fig. 1. Receiver operating characteristic curves (ROC) for miR-146a and miR-215 in obese CRC patients vs obese patients.

patients, associated with poor clinical outcomes.

An ROC curve was designed to evaluate the possible contribution of miR-146a/miR-215 to the diagnosis of CRC. According to our findings, to distinguish obese participants with CRC from obese participants, the AUC was 0.971 and 0.994, respectively ($P < 0.001$). This implies the impact of the differential expression of miR-146a/miR-215 as suitable diagnostic biomarkers for the progress of CRC. As far as we know, this is the first investigation pointing to the differential expression of TGF-β/IL-6 and their correlation with the miR-146a/miR-215 expression levels in a cross-link axis between obesity and colorectal cancer. The main limitation of this study, however, might be the limited sample size. To further understand how miR-146a, miR-215, and TGF-β/IL-6 might interact to provide a therapeutic impact in clinical trials, more extensive investigations and clinical trials are required.

5. Conclusion

According to our current investigation study, miR-146a and miR-215 can be employed as potential diagnostic biomarkers. The study also highlighted the significant correlation of TGF-β/IL-6 with miR146a/miR215 expression in obesity and CRC.

Ethics approval and consent to participate

"Our study was conducted in compliance with the Declaration of Helsinki, and the Research Ethical Committee, Faculty of Medicine, Cairo University, Egypt provided its approval". All study participants provided their informed consent permission for participation in this study.

Funding

The authors declares that they had received no funding for the research reported.

Patient consent for publication

Patient consent for publication was covered by the informed consent document.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

CRediT authorship contribution statement

Ghada Ayeldeen: Conceptualization, Data curation, Formal analysis, Material preparation. **Olfat G. Shaker:** Conceptualization, Writing – original draft, Material preparation. **Ahmed M. Khairy:** Data curation, Formal analysis. **Asharef Y. Elfert:** Data curation, Formal analysis, Writing – original draft. **Nabil A. Hasona:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Material preparation.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgements

Not applicable.

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