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The importance of MicroRNA 106b as a biomarker in gastric cancer

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Abstract

Objective: Gastric cancer (GC) is the fourth most common malignant disease worldwide, and it is observed 2-3 times more frequently in men than in women. It is important to make an early diagnosis in GC, by using screening methods such as serological markers and histological precursor. MiRNAs circulating in the blood have come to the fore in the early diagnosis of GC. In this study, our aim was to detect the most specific and sensitive microRNA by studying the microRNAs in the patient and control groups.

Material and methods: Fourteen patients diagnosed with gastric cancer and fourteen healthy individuals of the same age and gender were selected as the control group. Three miRNAs (miR-34a, miR-106b, miR-223 and miR 181 and miR 192 used as the endogenous control group in line with their binding potentials and gene expression levels.

Results: Only miR106b was upregulated and statiscally important compared with the endogenous control miR181 for patients and healthy individuals (p:0.022).

Conclusion: MiR-106b may have an important role in both the early diagnosis. Further extensive studies are needed

Introduction

Gastric cancer (GC) is the fourth most common malignant disease worldwide, and it is observed 2-3 times more frequently in men than in women. Gastric cancer is a multifactorial disease, both environmental and genetic factors play a role [1].

As in other cancers, it is important to make an early diagnosis by using screening methods in GC. Although there are serological markers used for the early detection of GC, they are not very specific and sensitive [2].

MicroRNAs (miRNA) circulating in the blood have come to the fore in the early diagnosis of GC. MicroRNAs are non-coding 18-25 nucleotide-containing molecules that are involved in epigenetic mechanisms in many cellular processes such as differ-

entiation, proliferation and apoptosis [3]. MiRNAs are generally deregulated in the gastric mucosa during Helicobacter pylori infection [4].

In this study, our aim was to detect the most specific and sensitive microRNA by studying the microRNAs in the patient and control groups.

Materials & methods

Fourteen patients diagnosed with gastric cancer and fourteen healthy individuals of the same age and gender were selected as the control group. After each individual included in the study was informed and signed a written consent form, 5cc EDTA blood samples were taken from the patients and the control group.

Approval was obtained from Faculty of Medicine Clinical Research Ethics Committee of Akdeniz University. Ethics committee approval number and date 471 and 17.08.2016.

Three miRNAs (miR-34a, miR-106b, miR-223) selected and MiR 181 and miR 192 used as the endogenous control group in line with their binding potentials and gene expression levels.

MiRNA extraction and measurement from blood samples, the measurement methods of the four available miRNAs in patients and healthy individuals were performed as indicated in our previous study [5]. Blood samples were centrifuged for 15 minutes and plasma was separated. MiRNA isolation (Invitrogen by Thermo Fisher Scientific-mirVana™ miRNA Isolation Kit) was performed from plasma. The obtained miRNA was measured in ng / µl on the QUBIT 3 FLUOROMETER device (Invitrogen by Thermo Fisher Scientific-Qubit ™ microRNA Assay Kit). The miRNA samples, whose concentration was found to be suitable, were obtained by using Thermal Cycler (Applied Biosystems by Life Technologies-TaqMan Advanced miRNA c DNA Synthesis Kit). cDNAs were kept at -20°C until the sufficient number was reached in two formats, 30 and 50. Gene expression levels of the component and cDNA prepared with a total volume of 20 µl in each well were measured with StepOne ™ Real-Time PCR (Catalog No: 4376357 Thermo Fisher) device. Cт values automatically taken from the system are reported in the excel file. The average C_T values of the duplicated samples were compared with the control group miR 181 and miR 192, and the ΔCт values were calculated. At the end of the study, the ΔCт values of individuals with colon cancer were compared with the ΔCтs of the healthy control group like other our studies [5,6].

Statistical methods

The data were evaluated using the SPSS (Statistical Package for the Social Sciences) version 23.0 (SPSS Inc., Chicago, IL, USA) program. Descriptive findings are presented with number, percentage, mean ± standard deviation and median. Shapiro-Wilk test and skewness/kurtosis values were used to evaluate whether the data represented normal distribution. Independent samples "t" test was used if the data conformed to the normal distribution and Mann-Whitney U test was used if the data was not normally distributed. Comparisons were made between colon cancer group and healthy control group. A p value $p<0.05$ was considered statistically significant. Receiver Operating Characteristic (ROC) curve analysis was performed to determine the sensitivity and specificity and diagnostic efficacy of miRNAs among the investigated groups [7].

Results

Fourteen patients with gastric cancer included in the study, eleven female and three male of them, the mean age and range of them was 51.80 ± 16.4 and 49-62 years: In the control group, there was eleven female and three male, their mean age 52.7± 15.6 and range 47-63 years. Only miR106b was upregulated and statiscally important compared with the endogenous control 181 for patients and healthy individuals (p:0.022) (Table 1). None of the miRNAs were significant when compared with the endogenous control 192 for patients and healthy individuals (Table 2). MiR106 was found sensitivity and specificity in ROC curve analysis

Table 1: MiRNA comparison of gastric cancer and healthy subjects according endogen control Delta181CT .

miRNA	Mean±SD†	Median	p
Mir34a			
Gastric ca (n=9)	56421979256 ± 3584079417565	188,274,383,500	0,354†
Healthy control (n=9)	-43198828633 ± 3010141470798	-40,878,105,200	
Mir106b			
Gastric ca (n=9)	-110296694456 ± 2572690888372	-93,476,867,700	0,022*
Healthy control (n= l3)	-444681102346 ± 3395215271844	-509,927,177,400	
mir223			
Gastric ca (n= l3)	59930185162 ± 3953948183765	-01,079,940,800	0,758*
Healthy control (n= 12)	13448075358 ± 3469701113679	86,535,835,250	

* Independent samples t test, † Mann-Whitney U testi

Table 2: MiRNA comparison of gastric cancer and healthy subjects according endogen control Delta181CT .

miRNA	Mean ± SD[t]	Median	p
Mir34a			
Gastric ca (n=9)	3,70042928056 ± 3,275487541380	308,452,796,900	0,922*
Healthy control (n=9)	3,91304071711 ± 5,536476822871	447,024,536,100	
Mir106b			
Gastric ca (n=9)	1,07763926189 ± 3,630580526578	136,598,205,600	0,367[t]
Healthy control (n=9)	-40961976492 ± 3,294329019983	02,373,123,200	
mir223			
Gastric ca (n=14)	3,86729894357 ± 2,504831952574	437,507,438,700	0,382*
Healthy control (n= l2)	4,78384651183 ± 2,737275883769	486,307,048,800	

* Independent samples t test, [t] Mann-Whitney U testi

Discussion

Serum tumor markers such as CEA and CA 19-9, which are used in the early detection of gastric cancer, do not have sufficient sensitivity and specificity. In recent studies, there have been advances in the application of miRNAs as gastric cancer biomarkers and therapeutic targets [8].

Wei et al. investigated a total of 77 studies in a meta-analysis study. They published a sensitivity of 0.76 and a specificity of 0.81 in the diagnosis of gastric cancer with circulating miRNAs [9].

Tsujiura et. al. compared the plasma miRNAs of 10 GC patients before and after surgery with healthy controls. They published that four microRNAs (miR-17-5p, miR-21, miR-106a, miR106b) including miR 106b, which we found unique in our study, were significantly higher in GC patients than in controls [10].

Arias Sosa et al. showed that miR21 and miR106b, which were unique in our study, were significantly up-regulated in patients with GC and may have a pro-oncogenic effect [11].

Larki et Al. compared the expression levels of miR-21, miR-25, miR-93, miR-106b, and miR-375 during the sequential model of GC development in plasma samples from normal subjects, subjects with gastric dysplasia, and subjects with GC. They revealed increased expression levels of miR-21 (p = 0.034), miR-25 (p = 0.0003), miR-93 (p = 0.0406) and miR106b (p = 0.023) in GC samples [12].

We found miR106b to be significantly upregulated of the three miRNAs (miR-34a, miR106b, miR-223), in patients and healthy individuals when compared with the endogenous control miR181 (p:0.022)

The miR-106b~25 cluster has been investigated in preoperative plasma samples and tumor tissues in 40 patients with GC for tumor invasion depth, lymph node metastases, and distant metastases (TNM), and a significant correlation has been found (P<0.05). MiR-106b~25 may be a potential tumor biomarker in the prognosis as well as in the prognosis of patients with GC [13].

Limitations: The small number of cases in our study was the most important limitation. It is planned to increase the number of patients and to evaluate the pathological diagnoses in detail in future validation studies.

Conclusion

As conlusion; MiR-106b may have an important role in both the early diagnosis of GC. Further extensive studies are needed.

Main points

MicroRNAs have attracted attention as promising biomarkers in gastric cancer for early diagnosis and prognosis. In this study, our aim was to detect the most specific and sensitive microRNA by studying the microRNAs in the patient and control groups.MiR-106b may have an important role in both the early diagnosis of GC.

Declarations

Author Contrıbutions:

1. Conception: DC,
2. Design: DC,OY,YS
3. Supervision: YS, MRA
4. Fundings: DC
5. Material: HSC, SSG, SU, BY
6. Data collection and Processing: HSC, SSG, BY
7. Analysis and Interparation: DC, OY, YS
8. Literature Review: DC,YS
9. Writing: DC, YS
10. Critical Review: MRA

Conflict of interest: There is no conflict of interest among the authors.

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