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miR-21, miR-221, and miR-222 upregulation in lung cancer promotes metastasis by reducing oxidative stress and apoptosis

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SUMMARY

OBJECTIVE: The purpose of our research was to observe the effects of miR-21, miR-221, and miR-222, as well as their target genes on oxidative stress, lung cancer formation, and metastasis.

METHODS: Positron emission tomography/computed tomography, fiberoptic bronchoscopy, and/or endobronchial ultrasonography were performed on a total of 69 lung cancer patients to detect the presence or absence of metastasis, and the patients were classified based on the types of cancer. Total RNA and miRNA were isolated from the obtained biopsy samples. The quantitative analysis of hsa-miR-21-5p, hsa-miR-222-3p, and hsa-miR-221-3p and their target genes was performed by the RT-qPCR method. In determining oxidative stress, total antioxidant status and total oxidant status in tissue and total thiol and native thiol in blood were determined spectrophotometrically. OSI and disulfide were calculated.

RESULTS: We discovered that the metastasis group had higher levels of hsa-miR-21-5p, hsa-miR-221-3p, and hsa-miR-222-3p ($p<0.05$). While TIMP3, PTEN, and apoptotic genes decreased in metastasis, anti-apoptotic genes increased ($p<0.05$). In addition, while oxidative stress decreased in the metastasis group, no change was found in the serum ($p>0.05$).

CONCLUSION: Our findings show that upregulation of hsa-miR-21-5p, hsa-miR-221-3p, and hsa-miR-222-3p effectively contributes to both proliferation and invasion by influencing oxidative stress and mitochondrial apoptosis.

KEYWORDS: Lung cancer. Metastasis. miRNA. Oxidative stress. Apoptosis.

INTRODUCTION

Cancer is defined as a disease that causes death as a result of uncontrolled cell growth, tumors, and developing metastases[1]. Tumor cells specifically have abilities such as insensitivity to growth and inhibition signals, unlimited replication potential, avoidance of apoptosis, angiogenesis, and eventually invasion and metastasis. Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are the two types of lung cancer, with NSCLC being the most common. With an increased incidence of new cases and a survival rate of less than 18%, lung cancer is the most common cause of cancer-related death in both sexes[2,3]. The most important factor affecting treatment, prognosis, and survival time in lung cancer is the early detection of the disease[4]. For this reason, it is important to identify metastases in lung cancer at an early stage, to reveal their mechanisms, and to develop diagnostic markers that will prolong life.

In studies on the human genome, it has been determined that miRNAs are effective on genes related to cell growth, differentiation, cell migration, aging, and apoptosis. Previous studies have shown that miRNAs are useful biomarkers in diagnosing cancer, including NSCLC. According to the research, an increase in the expression of miR-21, miR-221, and miR-222 acts by downregulating the PTEN and TIMP3 genes, which play a role in tumor development and survival, as well as invasion and metastasis. Previous studies have shown that an increase in miR-21 promotes poor prognosis and tumor metastasis, especially in NSCLC patients[5]. It has also been reported that miR-221 and miR-222 have tumor suppressive effects on lung cancer and that the increase in miR-222 level worsens the course of the disease[6,7]. Apoptosis, which is defined as programmed cell death, is genetically and biochemically regulated by pro-apoptotic and anti-apoptotic mechanisms in cells. Apoptosis is activated or inhibited by extrinsic and intrinsic pathways. In the intrinsic pathway, factors such as cell stress and DNA damage increase Bax, Bid, Bak, and Bcl-xs, while inhibiting Bcl-2, Bcl-xl, and Bcl-w, thereby increasing apoptosis[8]. These pro-apoptotic and anti-apoptotic genes are located in the PTEN and TIMP 3 gene pathways[9].

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An increase in reactive oxygen species (ROS) and a disruption in the balance between oxidants and antioxidants lead to oxidative stress. ROS are produced during events such as mitochondrial electron transport, phagocytic activation against natural stimuli, biosynthesis, and destruction, and they play an important role in the formation of cancer by mediating intracellular survival signaling pathways[10]. In determining oxidative stress in tissues, total oxidant status (TOS), total antioxidant status (TAS), and the oxidative stress index can be measured, as well as non-enzymatic thiol-disulfide balance in determining oxidative stress in serum[11].

In our study, we aimed to investigate the effects of miR-21, miR-221, and miR-222 on lung cancer metastasis with oxidative stress and apoptosis mechanisms.

METHODS

Patient selection

In Süleyman Demirel University, Department of Chest Diseases, 69 patients were diagnosed with lung cancer using fiberoptic bronchoscopy (FOB) and/or endobronchial ultrasonography (EBUS), and metastasis was detected according to the positron emission tomography/computed tomography (PET/CT) results. Lung tissue samples were placed in Eppendorf tubes after a biopsy was performed by a pulmonologist and stored at -80°C for later use to perform genetic analysis. The blood obtained from the patients was centrifuged, and the serum obtained was stored at -80°C.

Quantitative real-time PCR

The samples were homogenized with the GeneAll RiboEx™ RNA Isolation Kit. miRNA and total RNA were isolated by the manufacturer's kit protocol. The amount and purity of RNA samples to be used in cDNA synthesis were measured with a nanodrop device (Thermo Scientific, USA). Quantitative determinations of RNA samples with purity levels between 1.7 and 2.0 were recorded for use in cDNA synthesis. In the translation of miRNAs to cDNA, a stem-loop primer and miR cDNA synthesis kit were used for each miRNA and converted to cDNA according to the manufacturer's protocol (A.B.T.™ miRcDNA synthesis kit, Turkey). For PTEN, TIMP3, caspase 9, BAD, Bcl-XL, MDM2, and p53 gene cDNA synthesis, cDNAs were synthesized with a cDNA synthesis kit using a random hexamer primer (Atlas Biotechnology, Turkey). Sequences of the U6 gene region were used to normalize miR-21, miR-221, and miR-222. The primer design of the PTEN, TIMP3, caspase-9, BAD, Bcl-XL, MDM2, and p53 genes used in the study was determined using NCBI primer-BLAST, and the actin B (AKTB) gene was used as a reference gene. The obtained cDNAs were studied with the Biorad CFX96 (California, USA) instrument using the A.B.T.™ 2X qPCR SYBR-Green MasterMix (Atlas Biotechnology, Turkey) and the primers mentioned above. The obtained Cq values were normalized and calculated using the formula $2^{-\Delta\Delta Cq}$.

Biochemical analyses

After homogenization, the samples were centrifuged at 10,000 rpm for 10 min to determine the oxidative stress in the lung tissue. The TAS and TOS levels were determined using Erel's colorimetric method on supernatants collected after homogenization using an automated analyzer (Beckman Coulter, USA). Then, the OSI value was determined by calculating OSI=[(TOS, µmol/L)/(TAS, mmol Trolox eq/L)x100][12].

According to the procedure described by Erel et al., thiol and native thiol levels were assessed spectrophotometrically using the Real Assay Diagnostics Commercial Kit and the Beckman Coulter AU5800 autoanalyzer. (Total Thiol-Native Thiol/2) was used to calculate the levels of disulfide (-S-S-).

Statistical analysis

G-Power analysis was performed for all tests, and the effect power was determined to be >90 with the number of patients studied. The results of the expression levels of the normalized miRNAs and genes were analyzed with the Kolmogorov-Smirnov test. A t-test was performed on the values that had a normal distribution. The Mann-Whitney U test was used to analyze those that did not exhibit a normal distribution. AUC values were determined by performing a receiver operating characteristic (ROC) analysis. The IBM SPSS (version 20) program was used to conduct all statistical analyses. Statistics were considered significant at $p<0.05$.

RESULTS

As a result of the evaluations made of the 69 lung cancer patients in the study, it was determined that 32 patients had non-metastasis and 37 patients had metastasis. In addition, in the evaluation made according to the type of lung cancer, it was determined that 42 patients were NSCLC and 27 patients were SSLC. While the mean age was 68.75 and 65.03 years in the non-metastasis and metastasis groups, it was 65.81 and 68.22 years in the NSCLC and SSLC groups, and there was no statistically significant difference ($p>0.05$). In our study, there was no statistical difference in terms of gender in the non-metastasis and metastasis groups ($p>0.05$).

When we compared the expression levels of miRNAs in non-metastasis and metastasis groups, we found that

hsa-miR-21-5p, hsa-miR-221-3p, and hsa-miR-222-3p were significantly increased in the metastasis group (p<0.001, p=0.001, and p=0.003, respectively). There was a significant decrease in the expression levels of TIMP 3 and PTEN genes in the metastasis group (p=0.002 and p<0.001). While a significant decrease was observed in the expression levels of the pro-apoptotic genes Caspase 9, BAD, and P53 in the metastasis group, a significant increase was observed in the anti-apoptotic BCL XL and MDM2 gene expression levels (p<0.001, p=0.037, p=0.001, p<0.001, and p<0.001, respectively) (Table 1).

When the oxidative stress parameters TOS, TAS, and OSI were evaluated in tissues in the non-metastasis and metastasis groups, we determined that TOS and OSI increased in lung cancers but decreased in the metastasis group (p<0.001). There was no significant difference between the groups in TAS levels (p=0.694). There was no significant difference between the groups in serum oxidative stress parameters such as total thiol, native thiol, and disulfide (p>0.05) (Table 2).

In the ROC analysis we performed on non-metastasis and metastasis groups, we found that hsa-miR-21-5p, hsa-miR-221-3p, and hsa-miR-222-3p also had a statistically significant discriminating power with varying sensitivity and specificity values (p<0.001, p=0.001, and p=0.003, respectively) (Table 3).

Table 1. Statistical analysis of hsa-miR-21-5p, hsa-miR-221-3p, hsa-miR-222-3p, and genes in non-metastasis and metastasis groups.

	Non-metastasis (n=32) Mean±SD [CI]	Metastasis (n=37) Mean±SD [CI]	p-value
hsa-miR-21-5p	1.17±0.65 [0.94–1.41]	3.80±1.57 [3.27–4.32]	<0.001**
hsa-miR-221-3p	1.37±1.36 [0.88–1.85]	2.83±2.47 [2.00–3.65]	0.001**
hsa-miR-222-3p	1.28±1.04 [0.90–1.65]	2.34±1.64 [1.81–2.90]	0.003*
TIMP3	1.43±1.11 [1.03–1.83]	0.66±0.50 [0.50–0.83]	0.002*
PTEN	1.24±0.81 [0.96–1.54]	0.49±0.28 [0.39–0.58]	<0.001**
Caspase 9	1.40±1.15 [0.98–1.81]	0.34±0.29 [0.24–0.44]	<0.001**
BAD	1.68±1.22 [1.24–2.12]	0.89±0.69 [0.66–1.12]	0.001*
BCL XL	1.52±1.31 [1.04–2.0]	4.49±2.44 [3.67–5.30]	<0.001**
P53	1.62±1.36 [1.13–2.11]	0.90±0.76 [0.64–1.15]	0.015*
MDM2	1.26±1.03 [0.89–1.63]	3.75±3.08 [2.73–4.78]	<0.001**

SD: standard deviation; CI: confidence interval; TIMP3: metalloproteinase inhibitor 3; PTEN: phosphatase and tensin homolog; Caspase 9: cysteine-aspartic acid protease 9; BAD: BCL2 associated agonist of cell death; BCL XL: B-cell lymphoma-extra large; MDM2: Mouse double minute 2 homolog. **p<0.001, *p<0.05.

Table 2. Statistical analysis table of oxidative stress markers in tissue and blood.

		Non-metastasis (n=32) Mean±SD [CI]	Metastasis (n=37) Mean±SD [CI]	p-value
TOS	Tissue	12.59±3.47 [11.34–13.84]	6.89±3.25 [5.8–7.9]	<0.001**
TAS		1.63±1.67 [1.45–1.81]	1.67±0.36 [1.55–1.79]	0.694
OSI		0.84±0.36 [0.72–0.97]	0.42±0.21 [0.35–0.49]	<0.001**
Total thiol	Serum	256.3±26.5 [247–266]	264.4±28.9 [258–278]	0.08
Native thiol		216.8±21.7 [209–225]	227.5±26.1 [219–236]	0.07
Disulfide		19.8±10.7 [15.9–23.6]	17.7±6.74 [15.4–19.9]	0.32

TOS: total oxidant stress; TAS: total antioxidant stress; OSI: oxidative stress index; SD: standard deviation; CI: confidence interval. **p<0.001.

Table 3. ROC analysis of miRNAs in non-metastasis and metastasis groups.

Non-metastasis and metastasis groups						
	AUC	Cutoff	95%CI	Sensitivity %	Specificity %	p-value
hsa-miR-21-5p	0.979	>2.05	0.95–1.00	94.59	90.63	<0.001
hsa-miR-221-3p	0.733	>1.271	0.611–0.856	70.27	71.88	<0.001
hsa-miR-222-3p	0.707	>1.533	0.584–0.830	56.76	81.25	0.003

DISCUSSION

Previous studies have revealed that worsening prognosis in lung cancer is closely related to tumor formation and metastasis and that early diagnosis affects survival[13]. Therefore, we tried to determine the relationships of miR-21-5p, miR-221-3p, and miR-222-3p, which are known to be effective in tumor formation and metastasis in both NSCLC and SSLC types of lung cancer. We also aimed to reveal the mechanisms of action of these miRNAs and their target genes in oxidative stress and mitochondrial apoptotic processes.

Previous studies have also indicated that miR-21 upregulation contributes to tumor growth and invasion by downregulating the tumor suppressor PTEN gene[14,15]. Li et al. reported that miR-21 inhibited apoptosis and caused invasion through the AKT/cleaved caspase 3/MMP-2/MMP-9 pathway in NSCLC cell lines[16]. Chen et al. reported that miR-21 plays a role in the apoptotic process by downregulating the PTEN and TIMP3 genes[17]. In our study, we found that hsa-miR21-5p was upregulated in the metastasizing group in lung cancer, causing inhibition of the PTEN gene and a decrease in the expression of caspase-9, BAD, and P53 genes. In addition, we determined that anti-apoptotic genes also contribute to cell proliferation and invasion by causing an increase in BCL-XL and MDM2.

In a study conducted on NSCLC cancer cells and published in 2015, Yamashita et al. stated that the effects of miR221 and miR222 occur in the cell cycle or through apoptosis[18]. Zhang C et al. reported that the downregulation of miR-221/222 affects cell proliferation and mitochondrial-mediated apoptosis in human epithelial cancer cells through PUMA, a member of the BCL2 family[19]. Garofalo et al. reported that miR-221 and 222 increased tumor formation in NSCLC by causing downregulation in the PTEN and TIMP3 genes[20]. Guo Y et al. reported that miR-221/222 has an increasing effect on tumor formation and proliferation in lung cancer cells[21]. In our study, we found that while hsa-miR-221-3p and hsa-miR-222-3p were upregulated in patients with metastasis, there was downregulation in the PTEN and TIMP3 genes, as well as a decrease in pro-apoptotic genes (caspase 9, BAD, and P53) and a significant increase in anti-apoptotic genes (BCL-XL and MDM2).

The resulting cellular stress activates the intrinsic apoptotic pathways, which causes pro-apoptotic Bax, Bid, Bak, and Bcl-xs activation and a decrease in anti-apoptotic Bcl-2, Bcl-xl, and Bcl-w[8]. Yuan et al. reported that the upregulation of miR-21-5p prevents oxidative stress-induced apoptosis[22]. Jiang et al., in their study investigating the TGF-β1-miR-21-ROS pathway in non-small-cell lung cancer cells, determined that increased TGFB1 expression caused an increase in ROS, miR-21, and DNA damage. However, there is no information about its effects on the metastatic process[23]. Stephanie et al. reported that the regulation of miR 221 inhibits apoptosis against oxidative stress[24]. Şener et al. evaluated the balance of thiol/disulfide in lung cancer and reported that they could not find a significant difference between the metastasis and non-metastasis groups[25]. In our study, when we compared the oxidative stress parameters in the tissue metastasis and non-metastasis groups, we determined that TOS and OSI were decreased in the metastasized group, but there was no significant difference in terms of TAS levels. When we evaluated oxidative stress in serum, we could not find any difference in terms of thiol-disulfide balance.

Our study showed that it reduced apoptosis with the effect of gene pathways related to the upregulation of hsa-miR-21-5p, hsa-miR-221-3p, and hsa-miR-222-3p in patients with lung cancer metastasis. In addition to our findings, our study has some limitations. Our study is a single-center study, and the use of glutathione peroxidase (GPx) and superoxide dismutase (SOD) in the evaluation of oxidative stress in tissues and the TUNEL test in the evaluation of apoptosis will support the results of the study.

CONCLUSIONS

In this study, we determined that decreased oxidative stress and apoptosis in the tissue contributed to the development of metastasis as a result of upregulation of hsa-miR-21-5p, hsa-miR-221-3p, and hsa-miR-222-3p in patients with lung cancer. However, we suggest that more studies are needed on this subject.

CONSENT TO PARTICIPATE

Consent form was obtained from all patients participating in the study.

ETHICS APPROVAL

This study was approved by Isparta Süleyman Demirel University Medical Faculty Ethics Committee (dated: 01.04.2022, No. 110).

AUTHORS' CONTRIBUTIONS

MT: Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft. **ÖÖ:** Data curation, Supervision, Validation, Writing – review & editing.

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