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Research Article

lncRNA MALAT1, MEG3, and PANDAR Levels may be Potential Diagnostic Biomarkers in Multiple Myeloma

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Abstract

Aim: Long non-coding RNAs (lncRNAs) play a significant role in the development of various diseases, including cancer, and have been investigated as potential diagnostic and prognostic markers. The specific mechanisms underlying their involvement in the progression and development of multiple myeloma (MM), as well as their potential as diagnostic markers, remain to be fully elucidated. This study aimed to elucidate the involvement of lncRNAs in the pathogenesis of MM, explore their relationship with clinical parameters, and assess their potential as biomarkers for MM diagnosis.

Material and Methods: Patients above 18 years of age, diagnosed with MM and not yet receiving treatment, were included in the study. The expression levels of three lncRNAs (MALAT1, PANDAR, MEG3) regulated by the p53 gene were determined in a study involving 19 patients diagnosed with MM and 20 healthy volunteers. The expression levels were determined using RT-PCR.

Results: The levels of plasma lncRNAs were observed to be significantly down-regulated ($p<0.05$) in the patient group. No significant difference was observed between disease stages and the expression levels of the lncRNAs. There was a negative correlation between lncRNA expression levels and albumin levels ($p=0.019$; $p=0.048$; $p=0.033$, respectively), while no significant associations were found with other clinicopathological characteristics. ROC analysis demonstrated that the plasma expression levels of lncRNAs had diagnostic value in predicting MM (AUC=0.729, $p=0.015$; AUC=0.742, $p=0.010$; AUC=0.703, $p=0.031$, respectively).

Conclusion: In conclusion, MALAT1, PANDAR and MEG3 may serve as novel biomarkers for MM patients. Furthermore, these lncRNAs may be potential drug targets in MM.

Keywords: lncRNA, multiple myeloma, MALAT1, MEG3, PANDAR

INTRODUCTION

Multiple myeloma (MM) is a type of blood cancer where abnormal plasma cells in the bone marrow multiply uncontrollably (1). The pathogenesis of MM involves complex genetic and epigenetic processes (2). Advances in genetic and molecular research have shed light on the connection between the clinical manifestations of MM patients and the underlying biological properties of myeloma cells, enabling personalized treatment approaches (3).

The findings of the Human Genome Project have revealed that a minimum of 90% of the human genome undergoes active transcription into RNA molecules, whereas the contribution of RNA in encoding proteins is less than 2% (3). Non-coding RNAs (ncRNA) have been found to be unregulated in cancerous tissues and contribute to oncogenic or tumor-suppressive processes (4). Furthermore, lncRNAs are recognized for their ability to epigenetically modulate gene expression and participate in diverse biological functions (3). Additionally, their dysregulation has been implicated in numerous cancer types. Extensive research indicates their association with disease diagnosis, prognosis, tumor initiation, and metastasis (5).

MALAT1, located on chromosome 11q13.1, exhibits

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heightened expression in tumor tissues and is implicated in the processes of tumor invasion and metastasis (6). This lncRNA, approximately 800 nucleotides in length, demonstrates conservation among mammals (7). Existing literature highlights that reduced MALAT1 expression leads to the activation of p53 (8). However, MALAT1 has been observed to be indispensable for G1/S cell cycle progression and mitotic advancement (9, 10). MALAT1 expression has been identified in bone marrow, B lymphocytes, and lymphoid tissue (11).

PANDAR, located at chromosome 6p21.2, produces a non-coding RNA, which is thought to regulate the DNA damage response. This gene is induced by p53 and modulates its activity by interacting with a transcription factor. The deregulation of this gene has been associated with cancer progression (12-14). Emerging research indicates that PANDAR exerts oncogenic effects in the context of tumorigenesis, and its expression is dysregulated in numerous tumor tissues (15-20).

MEG3 is located on 14q9 and is defined as a tumor suppressor gene in various malignant tumors (21). MEG3 is expressed in many tissues and is known to regulate the p53 gene expression and induce p53-dependent transcription (22). It has been demonstrated in the literature that the expression of MEG3 is significantly downregulated in the brain, bladder, cervix, colon, bone marrow, lung, liver, and prostate cancer cells (23-25).

The current study focuses on the role and diagnostic power of cell-free lncRNAs in the bloodstream in the pathogenesis of MM. When we analyzed the expression levels in different cells and tissues in databases to select the most appropriate lncRNA molecules involved in the MM pathogenesis, we planned to analyze the expression of 3 lncRNAs in MM patients according to their tumor suppressor (MEG3) and oncogenic (MALAT1, PANDAR) functions that regulate the p53 gene and p53 targets (9,22).

The aim of this study was to determine the expression levels of lncRNAs that are regulated by the p53 gene in the plasma of patients diagnosed with multiple myeloma (MM). Additionally, the study aimed to explore the association between these expression levels and clinical parameters. Furthermore, the diagnostic potential of these lncRNAs was assessed by comparing the MM patients with a control group.

MATERIAL AND METHOD

Selection of Samples and Clinical Data

This study received local ethics committee approval (dated 27.05.2019 with decision number 77420). All patients provided written informed consent. Nineteen patients with untreated MM (mean age 69±8.8 years, 10 males, 9 females) and 20 controls (mean age 43.9±3.7 years, 12 males, 8 females) were included in the study. Patients older than 18 years of age who were diagnosed with MM and who had not yet received any treatment were included in the study. The study excluded patients with diseases other than multiple myeloma (MM). The control group consisted of individuals without chronic illnesses or medication usage. The patients' medical histories were obtained and recorded. Cases were evaluated in terms of cytogenetic evaluation with parameters such as age, gender, complete blood count, sedimentation rate, CRP, leukocytes, ferritin, iron, IgG, IgA, IgM, globulin, albumin, total protein, creatinine, and calcium. In addition, patients were classified by stage and subclassification according to the Durie-Salmon classification. 4 ml of venous blood from the patients was drawn into EDTA tubes.

cDNA Synthesis

RNA extraction from plasma cells of the patients was conducted following the protocol recommended by the manufacturer (Gene All Biotechnology, Korea). Briefly, homogenization was performed by adding 1mL of RiboEx reagent to a 200 µl plasma sample. The homogenate was centrifuged at 10,000 g for 13 minutes. The resulting supernatant was carefully transferred into a tube, and 200 µl of chloroform was added. After incubating at room temperature for 2 minutes, the mixture was subjected to centrifugation at 9000 g for 14 minutes. The supernatant was transferred to a clean tube and centrifuged with the addition of RB1 buffer, SW1 buffer, and RNW buffer respectively, and the collection tube was changed.

Subsequently, 50 µL of RNase-free water was gently added to the column, and the mixture was maintained at room temperature for 1 minute. mRNA samples were obtained by centrifuging at 10,000xg for 1 minute. The quantification of isolated total RNAs was performed using a Thermo Fisher NanoDropTM spectrophotometer instrument. Total RNA isolated from plasma samples was used for cDNA synthesis using the Hyper ScriptTM First-Strand Synthesis Kit. The obtained cDNA samples were stored at -80 °C until RT-PCR was conducted.

Quantification of lncRNAs

Real-time amplification of lncRNAs was performed using the Step One Plus RT-PCR Detection System (ThermoFisher Scientific, USA) according to the manufacturer's recommended protocol. The expression levels of lncRNAs were examined using the SYBR Green method with the Actin Beta gene (ACTB) serving as the internal control (housekeeping gene). The cycle threshold (CT) values of the target primers (Table 1) were determined, and the reference gene ACTB was used for normalization. The fold change in expression for each lncRNA was calculated using the 2-ΔΔCt equation.

Table 1. The primer sequences of the detected lncRNA		
Gene	Primer sequence	GenBank accession number
MALAT1	F 5′-CGCCATTTTAGCAACGCAGA	NR_144567.1
	R 5′- CCCAAGGACTCTGGGAAACC	NR_144567.1
PANDAR	F 5′- GCTTGTTCCAGAGCCAGGAT	NR_109836.1
	R 5′- CATCCTCAATGCCACCACCT	NR_109836.1
MEG3	F 5′- CCCTAGCGCAGACGGC	NR_046467.1
	R 5′- GAAGACAAGGAGGTGGACGG	NR_046467.1
ACTB	F 5′- CATGTACGTTGCTATCCAGGC	NM_001101
	R 5′- CTCCTTAATGTCACGCACGAT	NM_001101

Statistical Analysis

Independent samples t-test was used for normally distributed data, while the Mann-Whitney U test was utilized for non-normally distributed data. The chi-square test was employed to compare categorical variables. Pearson correlation analysis was conducted to determine the relationship between continuous variables. Additionally, ROC analysis was performed to calculate the AUC, specificity, and sensitivity values.

RESULTS

Patient Characteristics

The characteristics of the study groups are presented in Table 2. Hemoglobin, leukocyte, neutrophil, lymphocyte, thrombocyte, total protein, creatinine, calcium, LDH, and albumin levels were studied from the serum samples of the patient and control groups. IgG, IgA, IgM, cytogenetic, and FISH analyses were also performed in the patient group. Ten (52.6%) of the multiple myeloma patients included in the study were male, 9 (47.4%) of them were female; whereas 12 (60%) patients in the control group were male, 8 (40%) of them were female. hemoglobin (SD, 11.1±2.7), leukocyte (SD, 5±1.6), and albumin levels (SD, 8.7±1.8) of the MM group were significantly lower (Table 2). Total protein (SD, 8.7±1.8) was significantly higher in the MM group (Table 2).

Table 2. Demographic and clinical data of groups			
	Multiple miyeloma (n=19)	Control (n=20)	p*
Male/female, n	10/9	12/8	0.444
Age (years)	69±8.8	43.9±3.7	0.000
Haemoglobin	11.1±2.7	14.2±1.3	0.000
Leukocyte	5±1.6	7.5±1.8	0.000
Neutrophil	55.8±12.4	59.4±9.4	0.314
Lymphocyte	32.7±12.2	27.6±11.6	0.191
Platelet	192.5±104.7	270.2±65.4	0.08
Calcium	9.5±1.1	9.4±0.5	0.934
Total protein	8.7±1.8	7.2±0.7	0.03
Albumin	3.4±0.6	4.3±0.5	0.000
Creatinine	0.9±0.3	0.8±0.3	0.328
LDH	211.6±83.5	239.8±140.3	0.453
IgA	1090.6±2059.9	-	
IgM	39.4±45.1	-	
IgG	1701±1479.1	-	
Cytogenetics		-	
Normal (46,XX/XY)	13 (68.4%)		
No metaphase	6 (31.6%)		
FISH			
Del17p	0 (0%)		
Del13q	4 (21.1%)		
Monozomy	4 (21.1%)		
Trizomy	1 (5.3%)		
t(4;14)	2 (10.5%)		
t(11;14)	1 (5.3%)		

Data are expressed as mean±SD. *p<0.05 was considered to be significant. LDH: lactatedehydrogenase, IgA: immunoglobulin A, IgM: immunoglobulin M, IgG: immunoglobulin G, FISH: flouresan in situ hybridization

There was no difference in neutrophil (SD, 55.8±12.4), lymphocyte (SD, 32.7±12.2), platelet (SD, 192.5±104.7), calcium (SD, 9.5±1.1), creatinine (SD, 0.9±0.3), lactate dehydrogenase (LDH) (SD, 211.6±83.5) levels between the groups (Table 2). In cytogenetic analysis, 13 (68.4%) of the patients had a normal karyotype, whereas metaphase could not be obtained from 6 (31.6%) of them. In FISH analysis, although no 17p deletion was found in the patients, it was found that 4 of them (21.1%) had del13q, 4 of them (21.1%) had monosomy (monosomy 13, monosomy 14, monosomy 7), 1 of them (5.3%) had trisomy 8, 2 of them (10.5%) had t (4; 14), 1 of them (5.3%) had t (11; 14) (Table 2).

Plasma lncRNA Expression Levels

The relative expression levels of cell-free lncRNA PANDAR, MALAT1, and MEG3 in the plasma from patients with multiple myeloma were 2.28±2.06, 1.49±1.55, and 0.19±1.76, respectively, and were significantly downregulated in the MM group (p=0.006; p=0.006; p=0.009, respectively). In the MM group, the changes compared with the control group were 0.23, 0.14, and 0.28, respectively. The relative expression levels of lncRNA of the groups are shown in Figure 1, and the scatter plot of these expression values is shown in Figure 2.

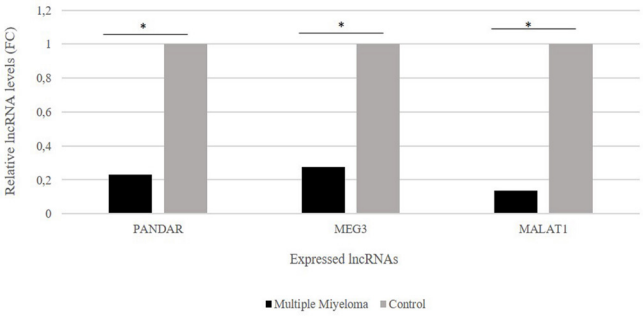

Figure 1. Relative lncRNA expression of MM according to healthy controls. *p<0.01, statistically significant. FC; fold change. The relative expression value of the control group was accepted as 1. Expression levels of specific lncRNAs PANDAR, MEG3, MALAT1 (FC=0.23, p=.006; FC=0.28, p=.009; FC=0.14, p=.006, respectively) in 19 MM patients, and 20 HC were analyzed using parametric Independent Samples Test. Data are presented as a median of normalized lncRNA expression in log2(2−ΔΔCT)

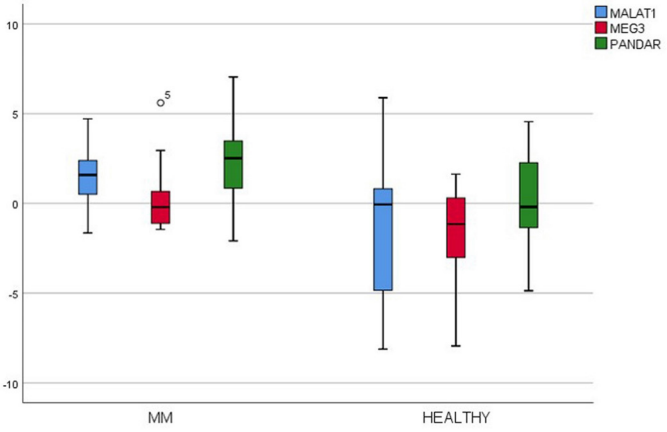

Figure 2. Distribution of the lncRNA expression levels in the disease groups

Expression Levels and Clinicopathological Characteristics

The correlation between clinicopathological parameters such as hemoglobin, leukocyte, neutrophil, lymphocyte, thrombocyte, calcium, total protein, albumin, creatinine, LDH, IgA, IgM, IgG levels, and Durie-Salmon staging was investigated to determine the clinical relationship of lncRNA expressions in MM. While there was a negative correlation between serum albumin levels and plasma lncRNAs of MALAT1, MEG3, and PANDAR in MM patients (r=-0.373, p=0.019; r=-0.342, p=0.033; r =-0.318, p=0.048; respectively), no significant correlation was found for the other clinicopathological parameters (p>0.05). According to the Durie-Salmon staging system; 6 (31.58%) patients were classified as stage 1A and 13 (68.42%) as stage 2A. No significant difference (p>0.05) was found in the expression levels of lncRNAs when compared across different stages of the disease.

ROC Analysis

ROC curves were plotted to evaluate the potential diagnostic power of plasma MALAT1, PANDAR, and MEG3 in MM patients (Figure 3). For MALAT1, the area under the curve (AUC) was 0.729 (95% CI, 0.560-0.898, p=0.015). For PANDAR, the AUC was 0.742 (95% CI, 0.582-0.902, p=0.010). For MEG3, the AUC was 0.703 (95% CI, 0.536-0.869, p=0.031).

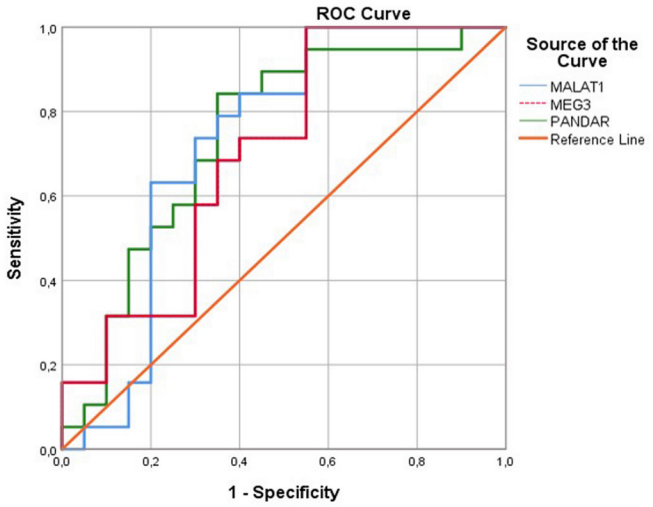

Figure 3. Receiver operating characteristic (ROC) curves based on RT-qPCR data. ROC; receiver operating characteristic. Sensitivity, specificity (both with 95% CI), AUC, and cutoff values of normalized lncRNA expression in log2(2−ΔΔCT) for MM obtained by ROC analysis

DISCUSSION

Multiple myeloma is considered to be multifactorial, and both genetic and epigenetic changes have been reported in its pathogenesis. Recent studies have shown that altered lncRNA levels in MM can lead to abnormal expression of genes related to oncogenesis (3). LncRNAs play a crucial role in tumor biology and possess the potential to serve as diagnostic biomarkers for specific types of cancers (26).

In this study, we investigated the expression levels of 3 candidate lncRNAs from plasma samples of patients with MM. To the best of our knowledge, this study is the first

to reveal the expression levels of MALAT1, PANDAR and MEG3 in the plasma of MM patients. Our findings revealed down-regulation of all lncRNAs evaluated in the patient group. This finding suggests that MALAT1, PANDAR, and MEG3 may play a role in the pathogenesis of MM.

Studies have shown that lncRNAs can regulate the p53 gene or p53 targets and are overexpressed in various human cancers (8). In a study conducted in AML patients, it was revealed that MALAT1 was upregulated and caused poor prognosis by affecting proliferation and apoptosis pathways (27). It was also associated with poor prognosis and carcinogenesis in non-small cell lung cancer (28). In another study, MALAT1 was shown to be upregulated in mononuclear cells of treated MM patients (2). Işın et al. (29) demonstrated increased MALAT1 expression in CLL patients and suggested that this increase was compatible with cell proliferation. In our study, we observed a significant downregulation of MALAT1 expression in MM patients (FC=0.14; p=0.006). We hypothesize that this downregulation of MALAT1, which is involved in the splicing mechanism and mitotic progression of the cell cycle, may lead to abnormal splicing formation and cell proliferation.

Recent studies have provided evidence of deregulation and oncogenic effects of PANDAR in various tumor tissues (15-20). Peng et al. (19) and Li et al. (16) reported upregulation of PANDAR in their respective study groups, which correlated with poor prognosis. Another study suggested that PANDAR predicts poor prognosis in non-small cell lung cancer and influences apoptosis through Bcl-2 (15). In contrast, Zhan et al. (21) found significant upregulation of PANDAR in bladder cancer tissues. Yang et al. (30) demonstrated upregulation of PANDAR in patients with acute myeloid leukemia (AML) and its association with poor prognosis. These studies collectively indicate the prognostic value of PANDAR in cancer patients. In our study, we observed downregulation of lncRNA PANDAR in the patient group, which is consistent with the findings of Han et al. (15) (FC=0.23; p=0.006). We believe that the expression and function of PANDAR, which is a type of lncRNA, may vary in different cell types and different diseases, depending on the various interaction mechanisms and the elements involved in these mechanisms.

MEG3 has been shown to induce p53-dependent transcription by regulating the expression of the tumor suppressor gene p53. Down-regulated lncRNA levels are common in various types of cancer and are recognized as a cancer biomarker and therapeutic target (22). In the literature, Sun et al. (31) demonstrated that upregulation of MEG3 inhibits the proliferation and metastasis of endometrial cancer cells. Yao et al. (32) reported downregulation of MEG3 in acute myeloid leukemia cell lines. Consistent with the existing literature, our study revealed a significant downregulation of MEG3 in the patient group (FC=0.28; p=0.009). The downregulation of MEG3 suggests its potential contribution to tumor cell proliferation by influencing the binding of the tumor suppressor gene p53 to its target.

In recent years, there has been a growing interest among researchers in exploring novel tumor biomarkers and investigating the molecular mechanisms that are associated with tumor screening, diagnosis, prognosis, and the assessment of treatment effectiveness (33). To date, many studies have been conducted on how lncRNAs can be prognostic biomarkers in cancer. Kong et al. (34) reported that MEG3 may be a prognostic biomarker (AUC=0.73, p=0.0003) for lung metastasis in early-stage colorectal cancer. Wan et al. (35) showed that MEG3 has a diagnostic value in predicting cervical cancer (AUC=0.858, p=0.03). Jiang et al. (36) showed that the expression of MEG3 in acute promyelocytic leukemia (APL) has an important diagnostic value (AUC=0.840, p<0.0001) in the diagnosis of APL. Li et al. (37) reported that the expression of MALAT1 can predict the poor prognosis of cervical cancer (AUC=0.788, p<0.05). Another study showed that MALAT1 can function as an oncogene in gastric cancer and serve as a marker for distant metastasis (38). Yang et al. (39) reported that the expression of PANDAR can be used as a biomarker (AUC=0.800, p<0.001) in the diagnosis of acute myeloid leukemia. Yang et al. (39) also suggested that the expression of PANDAR may be a diagnostic biomarker (AUC=0.767, p<0.05) for predicting gastric cancer. In our study, the sensitivity of MALAT1, PANDAR, and MEG3 in plasma was 95%, while the specificity was 70%, which demonstrated that these lncRNAs have high sensitivity and specificity. Our results suggest that these lncRNAs may be a potential diagnostic target in MM patients.

The findings from our study indicate that the relative expression of the studied lncRNAs could potentially serve as a valuable adjunctive test in the diagnosis of MM. However, there are some limitations in generalizing our results in this study. These limitations include a small sample size, assessment of a small number of lncRNAs, sample collection from a single institution, underreporting of personal data, and studying only plasma samples.

CONCLUSION

In conclusion, our study demonstrates that the expression levels of the cell-free lncRNAs investigated were significantly downregulated in the plasma samples of patients with MM. Our results suggest that MALAT1, PANDAR, and MEG3 may play a role in MM pathogenesis and could be potential diagnostic targets in MM patients. While these findings provide valuable insights for future research, additional molecular studies are required to elucidate the potential involvement of these lncRNAs in disease prognosis and their potential contribution to targeted therapeutic approaches. In addition, long-term follow-up and further examination are required to evaluate the predictability of these plasma lncRNAs.

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Conflict of Interest: *The authors have no conflicts of interest to declare.*

Ethical approval: *The study protocol complies with the Helsinki Declaration principles and was approved by the Süleyman Demirel University Clinical Research Ethics Committee (dated 27.05.2019 and with 77420 decision number).*

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