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Diabetes Mellitus-Mediated MALAT1 Expression Induces Glioblastoma Aggressiveness

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ABSTRACT

AIM: Hyperglycemia and hyperinsulinemia increase the risk of glioblastoma (GB) by affecting the regulation of insulin-like growth factor (IGF). Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is involved in regulating IGF-1/PI3K/Akt signaling. This study was designed to describe the role of MALAT1 in GB progression in patients concurrently diagnosed with diabetes mellitus (DM).

MATERIAL and METHODS: Formalin-fixed paraffin-embedded (FFPE) tumor samples of 47 patients diagnosed with GB only and 13 patients diagnosed with GB and DM (GB-DM) were enrolled in this study. Data for P53 and Ki67 immunohistochemical staining of the tumors and blood HbA1c levels of patients with DM were retrospectively collected. MALAT1 expression was assessed using quantitative real-time polymerase chain reaction.

RESULTS: The coexistence of GB and DM induced the nuclear expression of P53 and Ki67 compared with GB only. MALAT1 expression was higher in GB-DM tumors than in GB only tumors. The expression of MALAT1 and HbA1c levels were positively correlated. Additionally, MALAT1 was positively correlated with tumoral P53 and Ki67. The disease-free survival of patients with GB-DM with high MALAT1 expression was shorter than that of those diagnosed with GB only and with a lower MALAT1 expression.

CONCLUSION: Our findings suggest that one of the mechanisms of the facilitating effect of DM on GB tumor aggressiveness is via MALAT1 expression.

KEYWORDS: Diabetes mellitus, Glioblastoma, MALAT1, HbA1c

INTRODUCTION

Glioblastoma (GB), classified as a grade IV glioma, is the most malignant and common primary tumor group, according to the World Health Organization (WHO) (16). The survival of patients with GB is heterogeneous; after diagnosis, it becomes shorter for some patients (21). The survival potential of most patients with GB is unpredictable because of the effect of comorbid diseases, such as diabetes mellitus (DM) (25). DM-mediated hyperglycemia and hyperinsulinemia have been recognized to accelerate

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the oncogenic process (25). The changes in the regulation of the axis of insulin-like growth factors (IGFs), their receptors, and binding proteins, which play a subtle role in building the diabetic environment, have been shown to stimulate tumor development (25). Therefore, DM could trigger increased tumor growth and relapse in patients with GB (27).

Long non-coding RNAs (lncRNAs) are a class of ncRNAs with a size of more than 200 nucleotides that play multiple roles in different cellular processes, including regulating many biological processes, such as proliferation, invasion, and apoptosis by suppressing protein-coding target genes (26). Therefore, lncRNAs have been envisioned as novel biomarkers and therapeutic targets in various diseases, including cancer (26). LncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) has been shown to regulate IGF-1/PI3K/Akt signaling (28) and has been linked to the malignant transformation of various cancer types (3). Previously, we showed the importance of elevated MALAT1 expression as an unfavorable prognostic factor for overall survival in IDH1/2 wild-type primary GBs (3). Besides, high expression of MALAT1 was observed in DM and led to insulin resistance (7). However, the potential role of MALAT1 in GB development in patients with DM still needs to be fully explained. Therefore, in this study, we aimed to describe the regulation of MALAT1 in GB co-existing with DM and its potential effect on disease progression.

MATERIAL and METHODS

Patients

Formalin-fixed paraffin-embedded (FFPE) tumor tissue samples from 60 patients (34 males and 26 females) who applied to the Neurosurgery Department of XXX Hospital and were diagnosed with GB by a pathologist between 2005 and 2016 and these patients were retrospectively enrolled in this study. Thirteen of these patients were also diagnosed with DM type 2 (GB-DM) (7 males and 6 females) according to the standards of medical care in diabetes proposed by the American Diabetes Association (2). Tumor phenotypic characteristics were assessed by collecting the retrospective data of nuclear P53 and Ki67 immunohistochemical staining from the pathology reports of each patient. Tissue samples of patients with GB who received radiation and chemotherapy before the surgical operation, those who had only stereotactic biopsies, and those with a family history of cancer were excluded from this study. Post-treatment health status of the patients was followed up until death or for a maximum of 85 months. This study was approved by the Ethics Committee of Bursa Uludag University (approval number 2017-13/98).

Quantitative Real-Time Polymerase Chain Reaction (RT-qPCR)

According to the manufacturer's instructions, total RNA was extracted using the Zymo Research RNA Isolation Kit (Thermo-Fisher Scientific, Glasgow, UK). RNA concentrations were measured using a spectrophotometer (260 nm; Gene Quant, Pharmacia Biotech, USA). Then, 500 ng of total RNA was used for cDNA synthesis. cDNA synthesis was performed using the ProtoScript M-MuLV First Strand cDNA Synthesis Kit. The expression level of lncRNA MALAT1 was determined using TaqMan™ Gene Expression Assays (Hs00273907_s1) using the ABI StepOnePlus™ Real-Time PCR System (Applied Biosystems). The expression level of MALAT1 was normalized to a housekeeping gene, glyceraldehyde 3-phosphate dehydrogenase (Hs02786624_g1). The relative expression level of MALAT1 was calculated using the $2^{-\Delta\Delta Ct}$ method.

Statistical Analysis

The difference in the tumor protein expression of P53 and Ki67, and the RNA expression of MALAT1 between patients with GB who were concurrently diagnosed with DM and those who were diagnosed with GB only was defined using an independent sample t-test. The correlations between the tumor expression of MALAT1 and blood hemoglobin A1C (HbA1c) levels and between the tumor expression of P53 and Ki67 protein levels were assessed using Pearson's correlation analyses. A Kaplan–Meier analysis plotted the survival of patients with GB with and without DM and the effect of MALAT1 expression on the survival duration of those patients. A p-value was calculated using a log-rank test for Kaplan–Meier analysis. All statistical analyses were performed using Statistical Package for the Social Sciences, version 23.0 (IBM Corp., Armonk, NY). GraphPad Prism 9.3.1 (San Diego, CA) was used to create scatter plots and correlation graphs. Statistical significance was two-tailed, and p-values of less than 0.05 were considered significant for all statistical analyses.

RESULTS

Patients' Clinicopathological Characteristics

The median ages of patients diagnosed with GB only and those diagnosed with GB-DM were similar at the time of diagnosis ($t=-1.199$; $p=0.236$) (the median age of patients diagnosed with GB only was 60 years (range, 28–77 years), whereas it was 62 years (range, 52–79 years) in patients diagnosed with GB-DM). All tumor samples were expressed in terms of glial fibrillary acidic protein and IDH1/2 wild-type. In patients with GB only, primary tumors were localized in the brain's parietal region in seven cases, the frontal region in 14 cases, the temporal region in 15 cases, and the occipital region in 11 cases. Meanwhile, in patients with GB-DM, primary tumors were localized in the brain's parietal region in four cases, the frontal region in three cases, the temporal region in one case, the occipital region in one case, the insular region in three cases, and the cerebellum in one case. The clinicopathological features of individuals with GB-DM are shown in Table I. Among these patients with DM-GB, five (case nos. 3, 4, 5, 6, and 13) were on intensive insulin therapy, six (case nos. 1, 2, 9, 10, 11, and 12) were on oral antidiabetic medication, and two (case nos. 7 and 8) were newly diagnosed with DM at the time of the diagnosis of GB and had not received any antidiabetic therapy previously. In cases 1, 2, and 6, strict glucose control was achieved (HbA1c < 7.5). Diabetic polyneuropathy and peripheral vascular disease were detected as the micro–macrovascular complications in cases 3, 5, 6, 7, 10, 12, and 13 with poor blood sugar control. In patients with uncontrolled

Table I: Clinicopathological Characteristics of GB-DM Patients

Case no	Gender	Age	Tumor localization	Tumor size (cm)	Ki67/‰	P53 %	HbA1c	MALAT1 (fold)
1	M	57	right frontal	2x2x1	80	0	7.5	3.21
2	F	62	right parietooccipital	6x5x1.6	250	0	7.5	3.71
3	F	79	right frontoparietal	1.5x1x0.2	80	0	9.5	3.06
4	F	57	right frontal	2.5x1.5x0.4	300	60	8	9.56
5	M	63	left temporoparietal	1.5x1.5x1	175	5	10	7.91
6	F	52	left temporal	4.5x4x1	250	0	10.5	5.82
7	M	66	right insular	5x3x2	250	20	9.3	8.04
8	F	57	right cerebellum	2.5x0.5x1	200	5	6.8	3.07
9	F	68	left parietal	0.5x0.4x0.1	250	0	7.8	5.90
10	M	61	right frontal	3.5x3x1.5	350	5	8.2	6.54
11	M	67	left insular	0.3x0.3x0.3	300	0	7.1	4.47
12	M	68	right parietal	0.9x0.7x0.3	400	70	8.1	8.56
13	M	57	left insular	0.6x0.2x0.2	500	0	11.5	12.31

DM (case nos. 3, 5, 6,7, and 13) (HbA1c > 9), the duration of DM was long, and the age at diagnosis was early. According to the blood sugar follow-ups, the Endocrinology Department started appropriate oral antidiabetic treatment for patients newly diagnosed with DM (cases 7 and 8).

DM Increases the Severity of Glioblastoma

The protein expression of P53 in the tumors of patients with GB-DM was 18.17 ± 8.51-fold lower than those in the tumors of patients with GB only (the mean protein expression of P53 in the tumors of patients with GB only was 30.87 ± 4.11, whereas, in the tumors of patients with GB-DM, it was 26.86 ± 3.63; t = 2.135; p=0.037) (Figure 1A). Additionally, the expression of nuclear protein Ki67 in the tumors of patients with GB-DM tended to be more induced (3.57 ± 35.87-fold; t = –0.100; p=0.921) than that in the tumors of patients with GB only (Figure 1B). Furthermore, the median disease-free survival was shorter in patients with GB-DM than in those with GB only. The median survival of patients with GB-DM was 8 months, whereas that of patients with GB only was 14 months. The Kaplan–Meier plots comparing the median survival rates of patients with GB-DM and those of patients with GB only are presented in Figure 1C. These findings suggest a potential promoting effect of DM on GB tumor aggressive characteristics.

MALAT1 Expression is Induced in the Tumors of Patients with GB-DM

The RNA expression of MALAT1 was 4.602 ± 2.018-fold higher in the tumors of patients with GB-DM than that in the tumors of patients with GB only (p=0.026) (Figure 2A). Besides, induced MALAT1 expression was positively correlated with elevated HbA1c levels in patients with GB-DM (p=0.0145) (Figure 2B). These findings indicated an increasing effect of DM on MALAT1 expression level in GB tumors.

DM-Mediated High MALAT1 Expression Aggravates GM Prognosis

The elevated expression of MALAT1 was correlated with the protein expression of Ki67 (p=0.0001) (Figure 3A) in GB tumors. Additionally, the median disease-free survival was shortened depending on DM-mediated MALAT1 expression levels (the median survival of patients was as follows: GB only-MALAT1^{high}: 10 months; GB only-MALAT1^{low}:14.5 months; GB-DM-MALAT1^{high}: 8 months; GB-DM-MALAT1^{low}:10 months) (Figure 3B). Besides, the median disease-free survival of patients with GB-DM with high MALAT1 expression was shorter than that of patients with GB only with high MALAT1 expression (Figure 3C), suggesting that DM MALAT1 expression worsens GB tumor characteristics and disease progression.

DISCUSSION

DM characterized by hyperglycemia increases cancer risk, including liver, pancreas, endometrium, colon and rectum, breast, and bladder cancers (9). Additionally, elevated blood glucose concentrations have been linked to an increased rate of GB recurrence (6). Glucose metabolism contributes to the development of GB (6), whereas the absence of glucose forces GB cells to undergo apoptosis (12). Supporting previous findings, in this study, we observed lower nuclear P53 and higher Ki67 expression in patients with concurrent DM and GB than in patients diagnosed with GB only. P53, encoded by the tumor suppressor TP53 gene, contributes to repairing damaged DNA by inducing cell cycle arrest to avoid abnormal cell division or forcing cells to die via programmed cell death (23). P53 plays a regulatory role in glucose hemostasis, which makes P53 important for both the inhibition of tumor maintenance and insulin resistance (17). Increased glucose uptake and the fermentation of tumor cells accelerate tumor

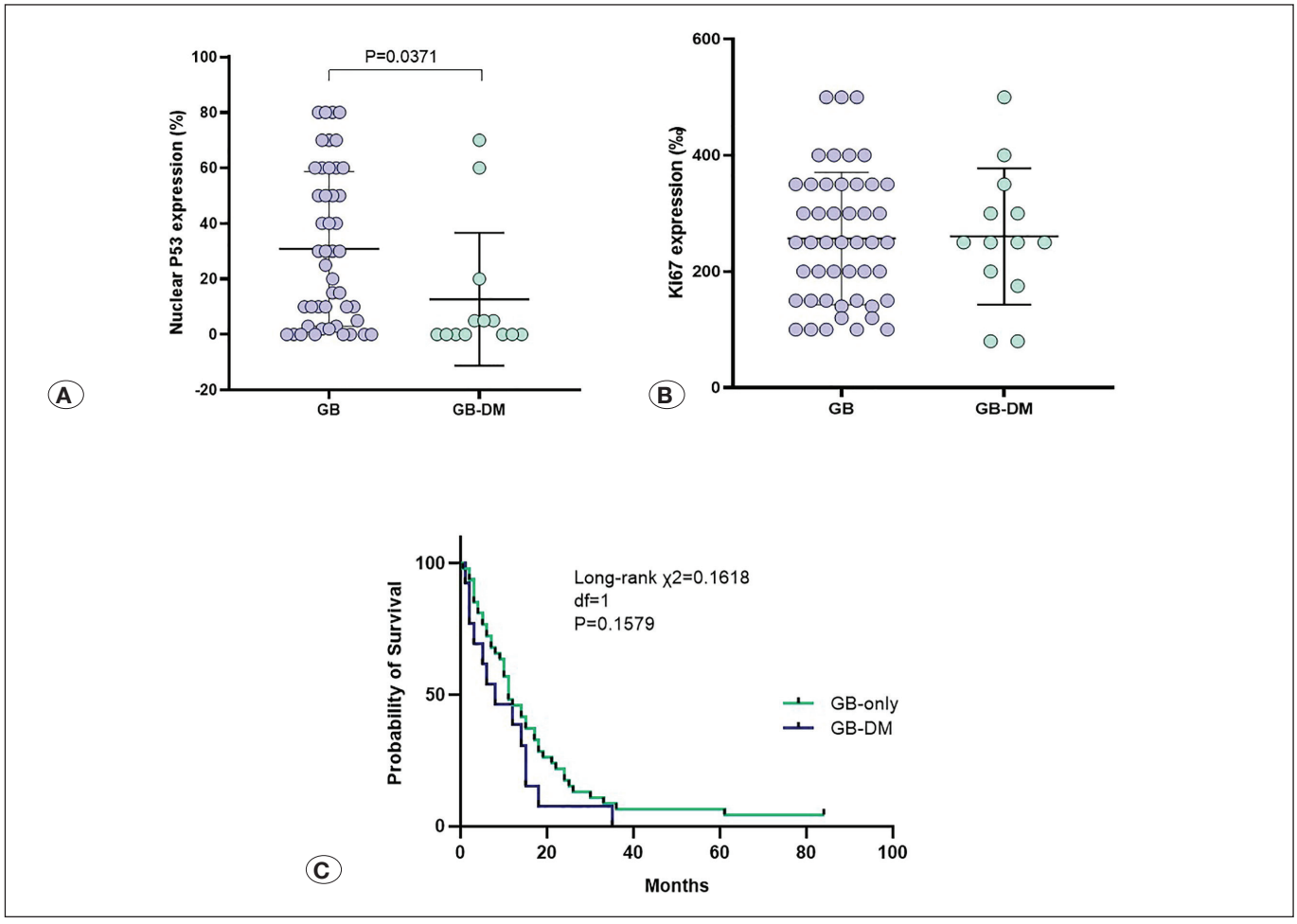

Figure 1. The effect of DM on GB prognosis. **A)** Nuclear P53 expression; **B)** Ki67 expression **C)** Disease-free survival of patients with GB only and those with GB-DM. **GB:** glioblastoma; **GB-DM:** glioblastoma together with diabetes mellitus. Statistical significance was calculated using an independent sample t-test for A and B and the Kaplan–Meier log-rank test for C. P-values less than 0.05 were considered statistically significant.

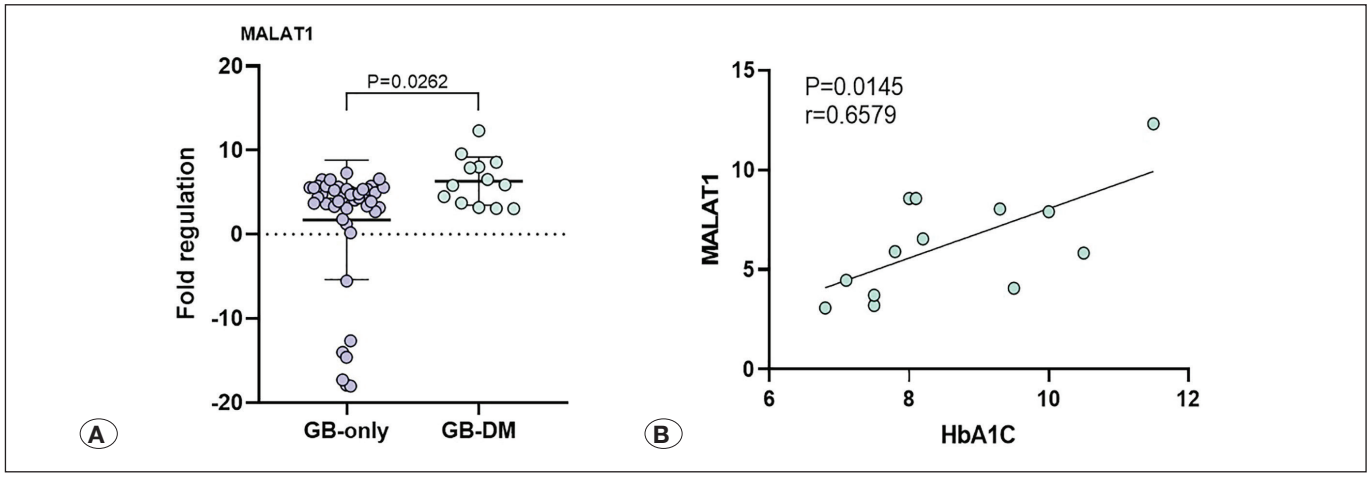

Figure 2: MALAT1 expression in GB-DM tumors. **A)** The effect of DM on MALAT1 expression in GB tumors. The p-value was calculated using an independent sample t-test. **B)** The correlation between MALAT1 expression and blood HbA1C levels in patients with GB-DM. The p-value was calculated using Pearson's correlation analyses. **GB:** glioblastoma; **GB-DM:** glioblastoma and diabetes mellitus; **HbA1c:** hemoglobin A1c. P-values less than 0.05 were considered statistically significant.

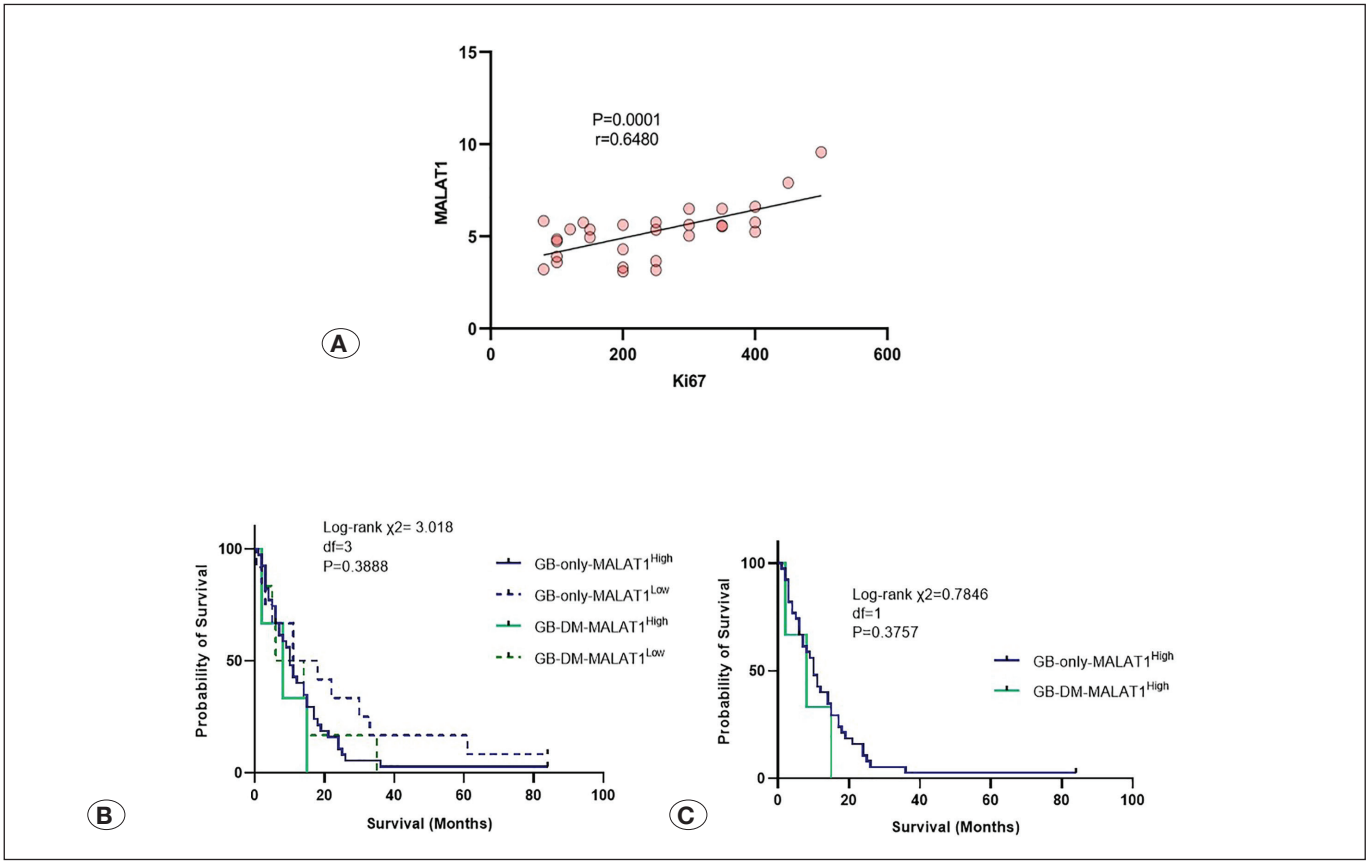

Figure 3: DM-mediated MALAT1 expression affects GB severity. **A)** The correlation of MALAT1 expression with Ki67 expression. **B** and **C)** The effect of MALAT1 on the disease-free survival of patients with GB only and those with GB-DM. **GB:** Glioblastoma; **GB-DM:** Glioblastoma together with diabetes mellitus. P-values were calculated using Pearson's correlation analyses for A and B and the Kaplan–Meier log-rank test for C. P-values less than 0.05 were considered statistically significant.

growth and plasticity (15). Therefore, the dysregulation of P53 in patients with GB-DM could contribute to tumorigenesis faster than that in patients with GB only. Ki67 is expressed in all active cell cycle phases, whereas it is suppressed in resting cells (14). Thereby, the expression level of Ki67 refers to the proliferative capability of cells and is a reliable tool for predicting the growth potential of a malignant tumor (14). Therefore, our findings suggest that the simultaneous presence of DB with GB could increase the aggressive characteristics of GB tumors.

LncRNA MALAT1 regulates alternative pre-mRNA splicing and gene expression and is expressed abundantly in normal and malignant tissues (30). The overexpression of MALAT1 has been shown to promote tumor cell proliferation, migration, metastasis, and chemoresistance in lung cancer, hepatocellular carcinoma, breast cancer, and colorectal carcinoma (30). Additionally, our recent studies provided evidence of the increased expression of MALAT1 in GB (1,3). Besides, studies have indicated that expression of MALAT1 could be promoted by various mitochondria-damaging factors, such as ionizing radiation and mitochondrial damage associated with concurrent diseases (13). The adenosine triphosphate generated from mitochondria is crucial in regulating blood glucose levels with insulin secretion. Therefore, mitochondrial dysfunction is a common predisposition observed in DM (13). An upregulated expression of MALAT1 in diabetic retinopathy has been shown to contribute to oxidative damage and mitochondrial dysfunction (18). Similar to diabetic retinopathy, recent studies have provided evidence of the aberrant expression of MALAT1 in other symptoms of DM, including diabetic nephropathy, through interaction with the miR-15b-5p/TLR4 (29) and Nox4/AMPK/mTOR signaling pathways (24) and neuropathies through interaction with miR-19b-3p (19) and the miR-1-3p/CXCR4 axis (4). Collectively, these findings suggest the increased expression of MALAT1 in patients with DM.

DM-mediated mitochondrial dysfunction could lead to a change from oxidative phosphorylation to glycolysis by triggering energy metabolism, which could contribute to cancer progression (11). Our findings showed an increased expression of MALAT1 in GB tumors of patients who were concurrently diagnosed with DM compared with that in the tumors of patients who were diagnosed with GB only. Additionally, tumoral MALAT1 expression in patients with GB-DM increased in correlation with their blood HbA1c levels, indicating that serum glucose levels can be used as a marker

of the severity of DM complications (22). Studies have shown that an *in vitro* administration of glucose increases the level of MALAT1 in endothelial cells (5). Besides, MALAT1 expression in hyperglycemic conditions has been reported to promote inflammatory cytokine production, leading to cellular insult, tissue injury, and functional impairments (10). These findings suggest that glucose uptake of cells may directly induce MALAT1 expression (5,10). The two main triggering signals for GB development are the signaling pathways interacting with MALAT1: mTOR (8) and CXCR4 (20). mTOR is crucial in regulating GB cell growth and proliferation (8), whereas CXCR4 signaling maintains the phenotype of GB stem-like cells (20). Therefore, our findings suggest that the presence of DM increases MALAT1 expression in GB tumors. Moreover, considering the reduced P53 and increased Ki67 levels in patients with GB-DM compared with those in patients with GB only, the interaction of elevated MALAT1 expression with mTOR and CXCR4 may exaggerate the aggressiveness of GB tumor phenotypes. In support of this, based on the follow-up findings of this study, patients with GB-DM with high MALAT1 expression tended to survive for a shorter period than those with GM only who presented a lower level of MALAT1 expression.

CONCLUSION

Our findings provide unique evidence that one of the mechanisms of the facilitating effect of DM-related hyperglycemia on tumor development and aggressiveness could be via MALAT1 expression. Further studies with *in vivo* GB-DM models will provide more information on the therapeutic targeting potential of MALAT1 to treat DM-induced GB tumors.

Ethics statements: All procedures performed in this study followed the ethical standards of the Ethics Committee of Bursa Uludag University (approval number: 2017-13/98) and complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

AUTHORSHIP CONTRIBUTION

Study conception and design: BT, AB, HK, MÖT
Data collection: AAK, SAA, ME, CT
Analysis and interpretation of results: AAK, GT, ST
Draft manuscript preparation: AAK
Critical revision of the article: GT, BT
All authors (AAK, SAA, ME, GT, CT, HK, AB, MOT, ST, BT) reviewed the results and approved the final version of the manuscript.

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