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Decreased Expression of Long Non-Coding RNA GMDS Divergent Transcript (GMDS-DT) is a Potential Biomarker for Poor Prognosis of Hepatocellular Carcinoma

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Increasing evidence suggests that long non-coding RNA (lncRNA) is closely related to the development of cancer. The present study investigated the potential predictive value of lncRNA GMDS divergent transcript (GMDS-DT) in the prognosis of patients with hepatocellular carcinoma (HCC) after hepatectomy.

Material/Methods: GMDS-DT was acquired by microarray data in 3 pairs of M1 and M2 macrophage duplicate samples. Real-time polymerase chain reaction (PCR) was performed to evaluate expression levels of GMDS-DT in liver cancer relative to normal tissue of 198 patients. The significance of GMDS-DT in prognosis after hepatectomy was examined via Kaplan-Meier test and Cox regression analysis.

Results: The expression of GMDS-DT in liver cancer tissue was significantly lower than that in adjacent normal liver tissue ($P<0.001$), and was significantly associated with drinking history and metastasis (both $P<0.05$). The Kaplan-Meier test suggested that patients with lower expression levels of GMDS-DT in liver cancer tissue had significantly shorter disease-free survival and overall survival times after hepatectomy ($P=0.028$ and $P=0.003$, respectively). Cox regression analysis further indicated that GMDS-DT was an independent risk factor for disease-free survival and overall survival times of patients after hepatectomy ($P=0.015$ and $P=0.001$, respectively).

Conclusions: LncRNA GMDS-DT might be a potential biomarker for the prognosis of patients with liver cancer after hepatectomy.

MeSH Keywords: Carcinoma, Hepatocellular • Prognosis • RNA, Long Noncoding

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Background

Hepatocellular carcinoma (HCC) is the second leading cause of cancer death worldwide, ranking fifth and ninth in incidence for men and women, respectively, with nearly 800 000 newly diagnosed cases annually [1]. It is most prevalent in east and southeast Asia, and about half of new cases and deaths occur in China [2]. The diagnosis and treatment of liver cancer has advanced with modern medical technology, but the postoperative 5-year survival rate is still only 15% to 40% [3,4]. Early diagnosis and intervention, as well as postoperative monitoring, are crucial for improving the prognosis of patients with liver cancer [5].

Long non-coding RNAs (lncRNAs) are RNAs longer than 200 nucleotides that are incapable of encoding protein. Previously, lncRNAs were considered the transcriptional byproduct of RNA polymerase II, with no biological function [6]. Evidence now indicates that many abnormally expressed lncRNAs closely correlate with the recurrence, metastasis, and prognosis of liver cancer [7,8]. On the other hand, emerging studies also have shown that tumor-related macrophages are involved in the occurrence, growth, invasion, and metastasis of tumors [9]. Tumor-related macrophages are classified as M1 or M2 subtypes, based on cellular functions and cytokines that induce the differentiation of macrophages [10,11]; M1 macrophages have anti-tumor and anti-bacterial activities, while the M2 subtype can promote tumor development and has low or no antibacterial activity [12].

Multiple lncRNAs expressed by MI and M2 macrophages affect the diagnosis and treatment of various tumors. A recent study conducted by Cao et al. [12] found that lncRNA-MM2P (modulator of macrophage M2 polarization) affects M2 tumor formation and tumor angiogenesis through M2 polarization in *in vivo* mouse experiments. Previously, our group analyzed the expression profiles of lncRNAs in 3 pairs of duplicate samples of M1 and M2 cells, and found that the differentially expressed gene UC306 may be involved in the development of HCC [13]. In the present study, we further explored the prognostic value of the lncRNA GMDS divergent transcript (GMDS-DT) in HCC, which is also differentially expressed in M1 and M2 macrophages, but the role in HCC has not been reported up to now.

Material and Methods

LncRNA microarray

U937 cells were placed in 6-well plates, and fresh media of different concentrations was added. Different concentrations of PMA (phorbol 12-myristate 13-acetate) and IFN-γ (interferon gamma) were then added to the induced differentiation group. U937 cells were differentiated into M1 and M2 macrophages, and 3 pairs of duplicate samples of M1 and M2 cells were subjected to microarray analysis.

Patients and tissue sources

HCC tissues and corresponding adjacent normal liver tissues of 198 patients with HCC were collected during hepatectomy from January 2014 to December 2016 in the Hepatobiliary Surgery Department of Guangxi Medical University Affiliated Tumor Hospital. The study protocol was approved by the Hospital Ethics Committee. All patients signed the relevant informed consents. The corresponding adjacent normal liver tissues were collected more than 2 cm away from the boundary of tumor, and normality was confirmed by pathological examination. Tissues were stored at –80°C.

Patients were followed once every 3 months in the short term (within 1 year) mainly by outpatient reexamination and in the long-term by telephone. The follow-up deadline was May 2018. The median follow-up was 32 months (range, 2 to 52 months). The recorded clinical characteristics included the following: age, gender, drinking history, family history, body mass index, liver cirrhosis, size and number of tumors, serum alpha-fetoprotein, and carcinoembryonic antigen levels, Barcelona Clinic Liver Cancer stage, and metastasis.

RNA extraction, reverse transcription, and quantitative real-time polymerase chain reaction (qRT-PCR)

TRIzol reagent (Invitrogen, Carlsbad, CA, USA) was used to extract total RNA from the collected tissues. The concentration of RNA was measured by NanoDrop 8000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). RNA was reverse transcribed into cDNA using a M-MLV Reverse Transcriptase kit (Takara Biotechnology, Dalian, China). Quantitative real-time polymerase chain reaction (PCR) was employed to detect the expression of GMDS-DT using a SYBR Premix Dimmer Eraser kit (Takara Biotechnology, Dalian, China) and a StepOnePlus Real-time fluorescence quantitative PCR System (Applied Biosystems, Foster City, CA, USA). The Livak ($2^{-\Delta\Delta CT}$ method) was used to calculate the relative expression levels. The primer sequences are listed in Table 1.

LncRNA GMDS-DT target prediction

MicroRNAs (miRNAs) associated with GMDS-DT were predicted via the lncRNA single-nucleotide polymorphism (SNP; www.LncRNAblog.com) and DIANA-lncBase v2 databases (carolina.imis.athena-innovation.gr). The potential target genes of miRNAs were predicted using multiple databases including TargetScan (*http://www.targetscan.org/vert_72/*) and miRPathDB (*https://mpd.bioinf.uni-sb.de/*). The possibility of interaction between GMDS-DT and target genes was assessed via RPISeq (*http://pridb.gdcb.iastate.edu/RPISeq*).

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Table 1. Primers used for quantitative real-time polymerase chain reaction.

Gene	Primer sequence	Length (bp)	Tm (°C)
GMDS-DT	Forward 5'-TTGCTCCTCATTTCAGTGTC-3'	724	60
	Reverse 5'-TCAGGTGTCCAGGGTAAGA-3'		
β-actin	Forward 5'-GGGAAATCGTGCGTGACATTAAG-3'	275	60
	Reverse 5'- TGTGTTGGCGTACAGGTCTTTG-3'		

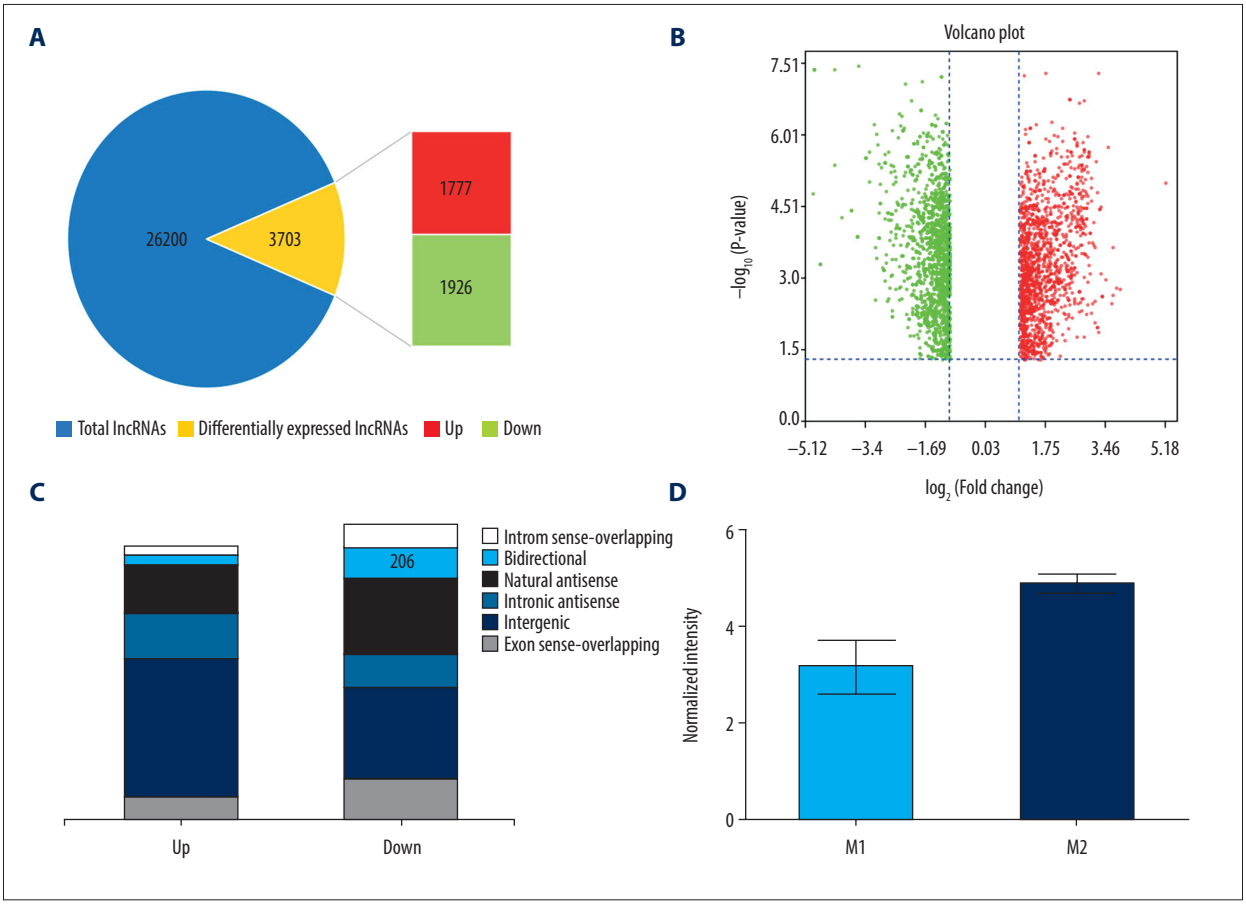

Figure 1. Acquisition of differentially expressed long non-coding RNAs (lncRNAs) from M1 and M2 macrophages. (**A**) Differentially expressed lncRNAs in total lncRNAs. (**B**) Volcanic map of differentially expressed lncRNAs (fold change >2 q value <0.05). (**C**) Different types in differentially expressed lncRNAs. (**D**) Relative expression of GMDS-DT in M1 and M2 macrophages

Statistical analysis

Statistical analyses were performed using SPSS version 24.0 software (SPSS, Chicago, IL, USA). The graphs presented in this study were created with GraphPad Prism 5 software (GraphPad Software, La Jolla, CA, USA). Differences in the expressions of GMDS-DT in HCC tissue and adjacent normal liver tissues were evaluated by paired Student's *t*-test. The association between GMDS-DT expression and clinicopathologic features was analyzed by the chi-squared test. The survival curves were drawn from Kaplan-Meier survival analyses. The prognosis of patients with primary liver cancer was evaluated by multivariable Cox regression analysis. $P<0.05$ was considered statistically significant.

Results

LncRNA microarray analysis

Overall, 26 200 lncRNAs were obtained in M1 and M2 cells, of which 3703 lncRNAs were differentially expressed between M1 and M2 ($P<0.05$; fold change >2). Among them, 1777 lncRNAs

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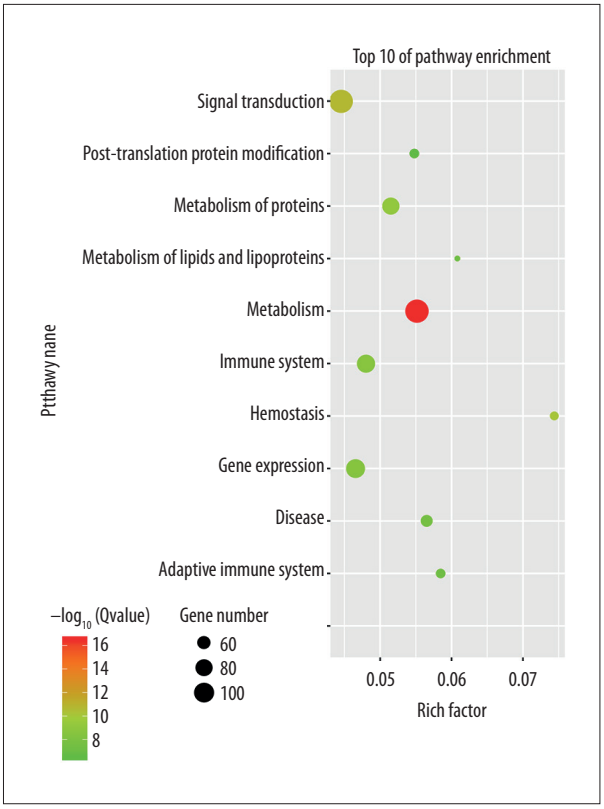

Figure 2. Bubble maps for all differentially expressed long non-coding RNA (lncRNA) functions. The abscissa is the percentage of differentially expressed lncRNAs in all genes of the corresponding pathway

were significantly more abundant in M1 relative to M2, and 1926 lncRNAs were significantly less abundant (Figure 1A, 1B). There were 6 types of lncRNAs: bidirectional, exon sense-overlapping, intergenic, intron sense-overlapping, intronic antisense, and natural antisense. GMDS-DT is a bidirectional lncRNA (fold change >3; $P<0.01$), and was highly expressed in M2 types, and little in M1 types (Figure 1C, 1D). The functions of all 3703 differential genes associated with GMDS-DT were analyzed, and determined to be primarily involved in various metabolic processes (Figure 2).

Downregulation of GMDS-DT in HCC tissues associated with worse prognosis

The grouping was based on the median GMDS-DT levels in HCC tissues; less or greater than 99 (Figure 3A). The results of qRT-PCR analyzed by paired *t*-test indicated that the expression of GMDS-DT in HCC tissue was significantly lower than that of the corresponding adjacent normal liver tissue ($P<0.001$; Figure 3B). Kaplan-Meier curves of the low and high expression groups were drawn, and the log-rank test was performed. The results showed that patients in the low expression group had significantly poorer prognosis after hepatectomy, manifested as significantly shorter postoperative disease-free survival ($P=0.028$) and overall survival ($P=0.003$; Figure 4A, 4B).

Association between GMDS-DT level and clinicopathological parameters

The results of the chi-squared analysis showed that GMDS-DT expression was significantly associated with drinking history and metastasis, but not with gender, age, family history, liver cirrhosis, number of tumors, Barcelona Clinic Liver Cancer stage, or the other clinicopathologic indexes (Table 2).

All indexes were included in the multivariate COX regression analysis (Table 3). The results showed that the following were independent risk factors affecting the disease-free survival of HCC patients: low expression of GMDS-DT, male gender, number of tumors (≥3) and alpha-fetoprotein ≥400 ng/mL. Significant

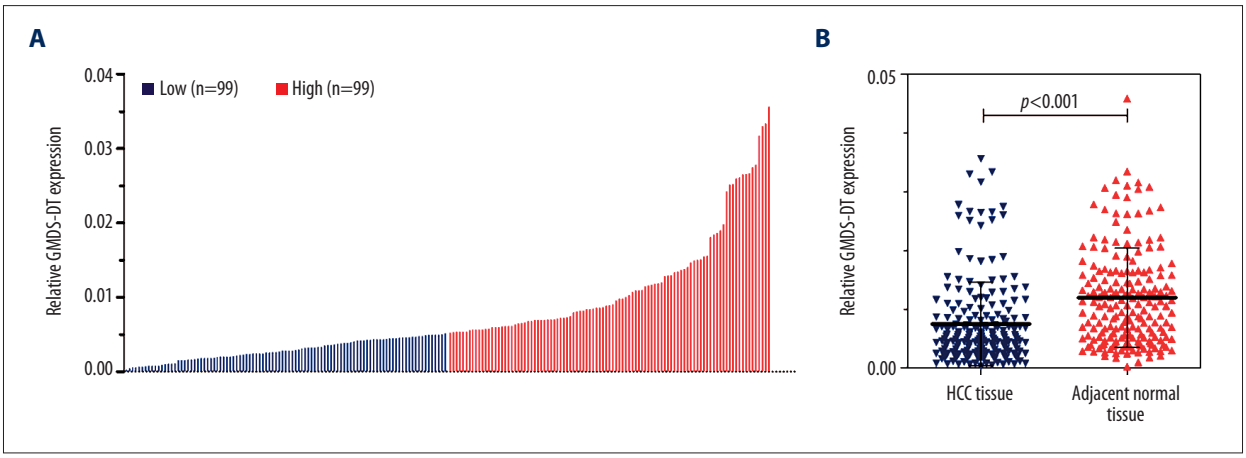

Figure 3. Relative expression levels of GMDS-DT. (**A**) Patients were divided into groups based on levels higher or lower than the median value in hepatocellular cancer (HCC) tissues. (**B**) GMDS-DT expression in 198 paired HCC tissues and adjacent normal tissues.

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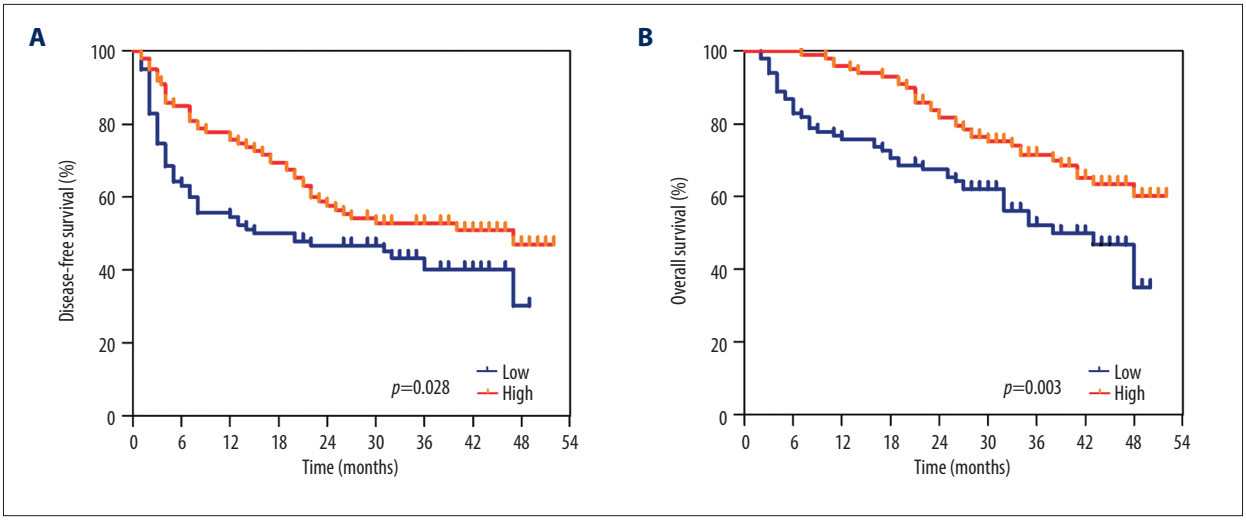

Figure 4. Kaplan-Meier analysis was used to evaluate the role of GMDS-DT in the prognosis of hepatocellular cancer patients. (**A**) Disease-free survival. (**B**) Overall survival.

Table 2. Association between GMDS-DT expression and clinicopathological features.

Variable	N	Low (n=99)	High (n=99)	χ^2	*P* value
Sex					
Female	27	9	18	3.474	0.062
Male	171	90	81		
Age, years					
≤55	138	68	70	0.096	0.757
>55	60	31	29		
Family history					
No	167	84	83	0.038	0.845
Yes	31	15	16		
Drinking history					
No	150	67	83	7.040	0.008*
Yes	47	32	16		
BMI					
≤25	159	82	77	0.798	0.372
>25	39	17	22		
Liver cirrhosis					
No	21	9	12	0.479	0.489
Yes	177	90	87		
AFP					
<400	98	53	45	1.293	0.255
≥400	100	46	54		
CEA					
≤5	179	88	91	0.524	0.469
>5	19	11	8		

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Table 2 continued. Association between GMDS-DT expression and clinicopathological features.

Variable	N	Low (n=99)	High (n=99)	χ^2	*P* value
Number of tumor					
<3	161	82	79	0.299	0.584
≥3	37	17	22		
Size of tumor, cm					
<5	57	21	26	0.697	0.404
≥5	151	78	73		
Metastasis					
No	165	74	91	10.509	0.001*
Yes	33	25	8		
BCLC stage					
0/A	106	57	49	1.299	0.254
B/C	92	42	50		

Table 3. Cox regression analyses of factors predicting disease-free survival and overall survival of HCC.

Variable	DFS			OS		
	HR	95% CI	P	HR	95% CI	P
Sex (Female/Male)	2.692	1.155–6.270	0.022*	1.303	0.573–2.963	0.528
Age, years (≤55/>55)	0.772	0.490–1.214	0.262	0.538	0.304–0.951	0.033*
Family history (No/Yes)	0.594	0.321–1.101	0.098	0.741	0.362–1.517	0.412
Drinking history (No/Yes)	1.540	0.959–2.474	0.074	1.290	0.729–2.282	0.381
BMI (≤25/>25)	0.942	0.541–1.641	0.834	1.218	0.649–2.288	0.539
Liver cirrhosis (No/Yes)	1.037	0.509–2.110	0.921	1.672	0.654–4.275	0.283
AFP, ng/ml (<400/≥400)	1.578	1.024–2.433	0.039*	1.277	0.774–2.106	0.339
CEA (≤5/>5)	0.771	0.391–1.521	0.454	1.223	0.583–2.565	0.594
Number of tumor (<3/≥3)	1.703	1.016–2.855	0.043*	2.158	1.163–4.002	0.015*
Size of tumor, cm (<5/≥5)	1.097	0.662–1.819	0.720	2.215	1.101–4.455	0.026*
Metastasis (No/Yes)	0.625	0.340–1.150	0.131	0.812	0.425–1.551	0.528
BCLC stage (0, A/B, C)	1.180	0.749–1.858	0.476	1.216	0.703–2.101	0.484
GMDS-DT expression (Low/High)	0.586	0.381–0.903	0.015*	0.427	0.254–0.715	0.001*

independent risk factors affecting overall survival time were: low expression of GMDS-DT, age (≤55 years), number of tumors (≥3), and size of tumor (≥5 cm).

LncRNA GMDS-DT target prediction

The top 10 miRNAs potentially associated with GMDS-DT were identified (Figure 5A). Among them, the target genes of miR-514-5p were predicted using TargetScan and MIRpathDB, and the rate of coincidence of the 2 databases reached 85.2% (Figure 5B). Among these target genes, GMDS, which partly overlaps with the GMDS-DT gene, was highly likely to interact with GMDS-DT as predicted using RPISeq (*http://pridb.gdcb.iastate.edu/RPISeq*). Therefore, a KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analysis was further performed and GMDS was found mainly involved in glucose metabolism (Figure 6).

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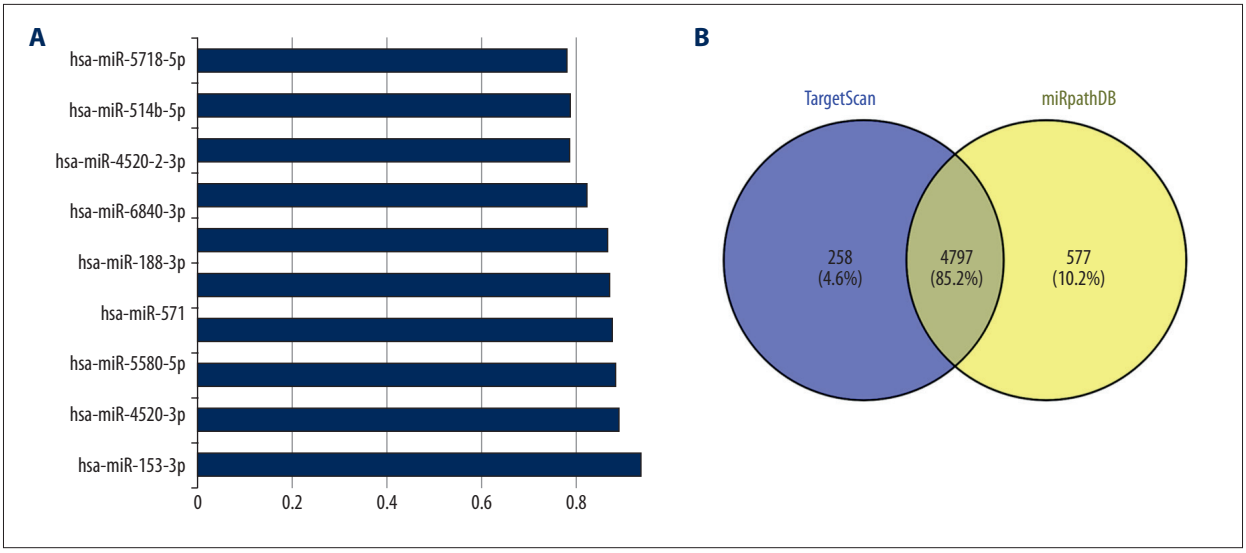

Figure 5. Target gene prediction of GMDS-DT. (**A**) Top 10 microRNAs (miRNAs) associated with GMDS-DT. The abscissa is the correlation score. (**B**) MiR-514-5p predicted target genes on TARGETSCAN and MIRpathDB, and the coincidence rate of the 2 databases reached 85.2%.

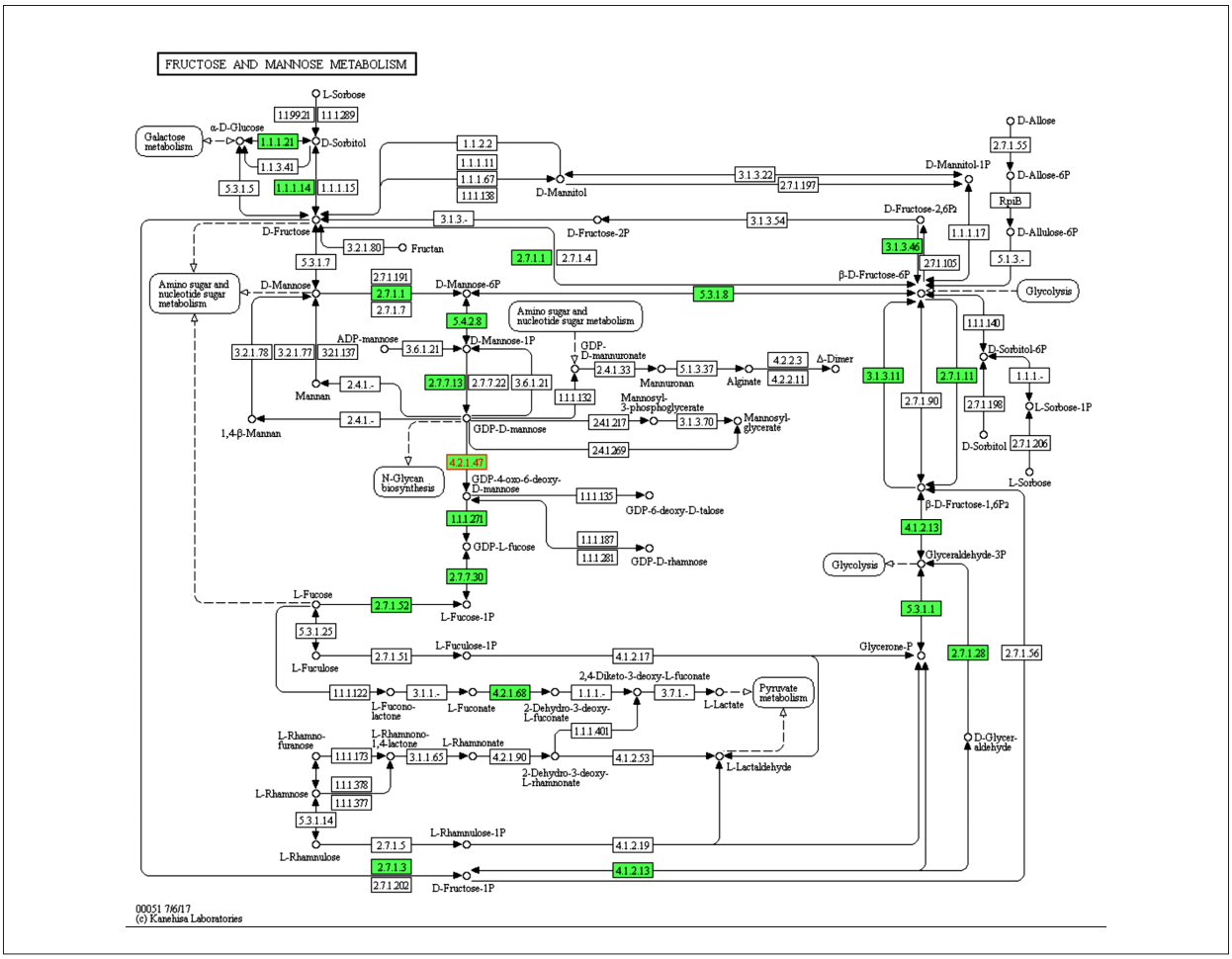

Figure 6. One of the most important pathways mediated by the GMDS-DT associated gene is shown (GMDS). The red star refers to the GMDS gene.

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Discussion

In this study, the lncRNA GMDS-DT was found downregulated in human HCC tissues relative to normal adjacent tissues and was significantly associated with disease-free survival and overall survival after hepatectomy. To the best of our knowledge, this is the first study to explore the role of GMDS-DT in human cancers.

LncRNA was once considered transcriptional noise incapable of encoding proteins, but has recently attracted considerable research interest. It has now been determined that lncRNAs are widely involved in regulating X chromosome silencing, gene imprinting and chromosome modification, transcriptional activation, transcriptional interference, intranuclear transport, and other important biological processes [14,15]. LncRNAs are closely related to the development, prevention and treatment of many kinds of diseases, especially tumors [16]. For example, Yang et al. [17] examined the expression profiles of lncRNA in liver cancer and found that lncRNA-HEIH was significantly upregulated in liver cancer tissues. The inhibition of lncRNA-HEIH using shRNA significantly suppressed the growth cycle of liver cancer cells.

With advances in surgical technique, the survival rate of patients with liver cancer after hepatectomy has improved. However, the 5-year survival rate is still low, perhaps due to invasion and metastasis of liver cancer [18]. Loss of epithelial polarity and reduced intercellular adhesion is characteristic of cancer metastasis [19]. Many studies have reported that the malignant phenotype of tumor cells can be inhibited by altering the expressions of lncRNA [16,20]. We found that GMDS-DT mostly overlaps with its adjacent gene GMDS, and that its similar positional association with lncRNA-ZEB1-AS1 regulates the adjacent gene ZEB1 and ultimately regulates cancer progression [21]. Therefore, we speculate that GMDS-DT is highly likely to interact with the GMDS gene.

LncRNA is mostly used to regulate target genes by adsorbing certain miRNAs [22]. Through database analysis, GMDS-DT might regulate the progress of liver cancer by adsorbing miR-514-5p, which affects its target gene GMDS. In addition, miR-514-5p has been reported to regulate epithelial to mesenchymal transition (EMT) in human cancers [23]. GMDS is also a key enzyme for *de novo* synthesis of GDP fucose. GMDS can be used to initiate abnormal glucose metabolism to participate in tumor proto-oncogene activation, tumor suppressor gene inactivation, and abnormal activation of downstream signaling pathways [24]. Similarly, lncRNA is able to regulate metabolic processes, mainly through the abnormal fucosylation, promoting the occurrence and development of lung, liver, breast, and other cancers [24–26]. Mehta et al. [27] pointed out that core fucosylation is directly related to the dedifferentiation of primary hepatocytes and the appearance of cellular EMT markers.

Conclusions

The results of the current study indicate that low expression of GMDS-DT is closely associated with poor prognosis in patients with HCC. This implies that GMDS-DT might be a novel biomarker for HCC. Further studies are warranted to clarify the biological role of GMDS-DT and its underling mechanisms in human cancers.

Conflict of interest

None.

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