

Original Article

High expression of NME1 correlates with progression and poor prognosis in patients of hepatocellular carcinoma

Jie Yang¹, Zhihua Lv¹, Jingtao Huang², Yi Zhao³, Yan Li¹

¹Department of Clinical Laboratory, Rennin Hospital of Wuhan University, Wuhan, Hubei, China; ²Center for Gene Diagnosis, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China; ³The PLA Navy Anqing Hospital, Anqing, Anhui, China

Received May 22, 2017; Accepted July 14, 2017; Epub August 1, 2017; Published August 15, 2017

Abstract: Hepatocellular carcinoma (HCC) is one of the most common malignancies that results from genes regulation via different pathways. NME/NM23 nucleoside diphosphate kinase 1 (NME1) is generally regarded as a metastasis suppressor, but its function in HCC is largely unknown. In our study, we explored the role of NME1 in HCC. By analyzing the gene expression omnibus (GEO) database, we discovered that NME1 was more highly expressed in HCC tumor tissues than non-HCC liver tissues ($P < 0.001$), and NME1 was significantly up-regulated in HCC tumor tissues than in adjacent normal tissues ($P < 0.001$). Then, validated by the enrolled HCC patients and The Cancer Genome Atlas (TCGA) database, NME1 was upregulated in HCC tumor tissues compared with matched adjacent normal tissue ($P < 0.05$). Besides, NME1 was down-regulated in Stage III/IV HCC patients than Stage I/II HCC patients ($P = 0.009$). Moreover, Kaplan-Meier analysis showed that HCC patients with high NME1 expression had poor overall survival ($P = 0.004$) and higher recurrence rate ($P < 0.001$). Our data revealed that NME1 was a special oncogene, and its expression was significantly associated with the progression and prognosis of HCC. NME1 may be a novel molecular biomarker for the targeted therapy and prognosis of HCC.

Keywords: NME1, hepatocellular carcinoma, prognosis

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and the ninth in women [1, 2]. In 2012, there was more than 780000 incident cases diagnosed, and half of new cases were occurred in China. There was nearly 740000 deaths caused by liver cancer and HCC had become the second mortal cause in all cancers worldwide [3]. HCC occurrence depends on a complex interplay of genetic predisposition factors, environmental factors, exposure to carcinogens and virus [4]. Recent studies considered that several single nucleotide polymorphisms (SNPs) were associated with HCC [5]. These SNPs regulated many biologic pathways of carcinogenesis, including inflammation through TNFA and IL1B [6, 7]; oxidative stress via SOD2 [8]; cell cycle via MDM2 and TP53 [9, 10] and growth factor with EGF [11]. Genes modulate HCC developing via many

pathways, for example, high levels VEGFA and CCND1 are observed in HCC patients [12], EGFR and Ras signaling is activated in more than 50% HCC [12]; meanwhile, tumor suppressor PTEN is inactivated and disrupted mTOR pathway in disease developing [13]. Besides, Wnt signaling was active in a third of hepatocellular carcinomas with transcription factor β catenin or inactivation of E-cadherin [14].

NME1, also known as NM23-H1 and NDPK-A, is generally regarded as a metastasis suppressor, and its expression is found associated with the metastatic potential of various neoplasms. Previous studies demonstrated that NME1 had significant metastasis suppressing function, and the expression of NME1 inversely related to metastatic behavior in experimental animals [15]. Besides, mice lacking NME1 protein were twice as prone to develop lung metastases compared with wild-type controls [16]. Toku-

NME1 associated with HCC progression and prognosis

naga discovered that reduced expression of NME1 protein was concordant with the frequency of lymph-node metastasis in human breast cancer [17]. Whereas, in neuroblastoma the elevated NME1 protein expression is correlated to poor survival [18], which is different from its metastasis suppressing function in other cancers. In colorectal cancer, Lindmark demonstrated that *NME1* is not useful as predictor of metastatic potential of colorectal cancer [19]; reversely, Martinez and his colleagues regard *NME1* as a prognostic factor in human colorectal carcinoma, and *NME1* was overexpressed in tumors compared with adjacent mucosa and *NME1* overexpression lost in advanced tumor stages [20]. Previous studies demonstrated that elevated *NME1* expression group had a higher incidence of distant metastasis and a lower 2-year disease-free survival rate than the non-elevated group in gastric cancer [21, 22]. The result was not consistent with the previous assumption that *NME1* is an anti-metastatic gene for gastric cancer [23]. Above all, *NME1* function in different cancers did not draw a consistent conclusion and rarely study concentrated on *NME1* function in HCC patients. In HCC, *NME1* acts as a tumor promoter or a tumor suppressor is still obscure, which need to be further study. Here, we explored the correlation between *NME1* expression, tumor pathology, and tumor prognosis to better understand the *NME1* function in HCC progress.

Materials and methods

Patients

A total of 72 HCC patients [56 males and 16 females, mean (SD) age 55.3 (11.6) years] were enrolled in this study between December 2014 and August 2016 at the Renmin Hospital of Wuhan University. Informed consent was obtained from each participant, and the ethics committee of Renmin Hospital of Wuhan University, approved the study. All patients were confirmed as HCC by operation and pathology.

438 liver hepatocellular carcinoma (HCC) patients with clinical data in the Cancer Genome Atlas (TCGA, <http://cancergenome.nih.gov/>) was download from the NCI Cancer Genomics Hub [24]. The gene expression, tumor pathology, overall survival, recurrence and other demographic characteristics of patients were obtained from database.

RNA extraction and real-time PCR

Total RNA of specimens was extracted using TRIzol reagent (Invitrogen) according to the manufacturer's protocol. Quantification of isolated RNA was performed by NanoDrop ND-2000 spectrophotometer (NanoDrop Technologies, USA). Then, the cDNA was synthesized from total RNA by ReverTra Ace qPCR RT Master Mix with gDNA Remover kit (Toyobo, Japan). The primer sequences used in this study was showed in follow: *NME1* forward primer: 5'-AAGGAGATCGGCTTGTGGTTT-3', reverse primer: 5'-CTGAGCACAGCTCGTGTAAATC-3'; β -Actin forward primer: 5'-CCTGGCACCCAGCACAAT-3', reverse primer: 5'-GGGCCGGACTCGT CATACT-3'; *GAPDH* forward primer: 5'-ATGACATCAAGAAGGTGGTG-3', reverse primer: 5'-CATACCAGGAATGA GCTTG-3'. β -Actin and *GAPDH* were used as internal controls.

Bioinformatics analysis

Gene expression profiling datasets were obtained from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) database (accession numbers: GSE10143, GSE62232, GSE36376 and GSE45436).

Gene expression data and clinical data of 438 HCC patients in TCGA database was download from the NCI Cancer Genomics Hub (CGHub).

Statistical analysis

All data were analyzed by SPSS version 19.0. Normally distributed data were presented as mean (SE) and analyzed by Student's *t* test; abnormally distributed data were presented as median (interquartile range) and was analyzed by Mann-Whiney U test. Kaplan-Meier survival analysis was performed. All statistical tests were 2-sided, and the level of statistical significance was set at $P < 0.05$.

Results

Patients' characteristics

Among the enrolled HCC patients in this study, the mean age of 72 HCC patients was 55.3 years, and the male: female ratio was 56:16. In enrolled HCC patients, 37 cases had stage I disease, 14 cases had stage II disease, 20 cases had stage III disease and 1 case had stage IV disease based on the tumor-nodes-

NME1 associated with HCC progression and prognosis

Table 1. Baseline characteristics of studied HCC patients

Baseline variables	Enrolled HCC patients (n = 72)	HCC patients in TCGA database (n = 438)
Age, years (mean; SD)	55.3±11.6	60.3±13.7**
Males/females, n (%)	56 (77.8)/16 (22.2)	292 (66.7)/146 (33.3)
Sample type, n (%)		
Adjacent normal tissues	72 (50)	59 (13.5)***
Primary tumor tissues	72 (50)	377 (86.1)***
Recurrent tumor tissues	0 (0)	2 (0.04)
TNM staging, n (%)		
I	37 (51.4)	198 (45.2)
II	14 (19.4)	100 (22.8)
III	20 (27.8)	100 (22.8)
IV	1 (1.4%)	6 (1.4)
NA	0 (0%)	34 (7.8)*
Child-Pugh classification, n (%)		
A	65 (90.3)	253 (57.8)***
B	7 (9.7)	30 (6.8)
C	0 (0)	2 (0.5)
NA	0 (0)	153 (34.9)***

p values of normally distributed data were derived from unpaired Student's *t* test. Difference between two groups were tested using the Chi-Square test for proportions and unpaired Student's *t* test for continuous variables. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

metastasis (TNM) staging system. Of 72 HCC patients, 65 patients had Child-Pugh A liver function, 7 patients had Child-Pugh B liver function and no patients had Child-Pugh C liver function.

In TCGA database, the mean age of 438 HCC patients was 60.3 years, and the male: female ratio was 292:146. Of 438 HCC samples, 59 samples were derived from adjacent normal tissues, 377 samples were derived from primary tumor tissues and 2 samples were derived from recurrence tumor tissues. Among them, 198 cases were TNM I disease, 100 cases were TNM II disease, 100 cases were TNM III disease, 6 cases were TNM IV disease and TNM stage of rest 34 cases were not given. Of 438 HCC samples, 253 patients had Child-Pugh A liver function, 30 patients had Child-Pugh B liver function, 2 patients had Child-Pugh C liver function and the rest 153 patients were unknown. Patients demographic and clinicopathological information is presented in **Table 1**.

NME1 expression in human expression profiling array

To explore the *NME1* function in liver cancer, we downloaded four human expression profil-

ing databases (GSE10143, GSE62232, GSE36376 and GSE45436) and analyzed *NME1* function in HCC patients. For GSE10143 database, *NME1* expression of HCC patients tissues (n = 80) was 2.36 fold higher than *NME1* expression of hepatitis/cirrhotic patients tissues (n = 307) (*P* < 0.001, **Figure 1A**). Besides, the similar phenomenon was observed in GSE62232, *NME1* expression of HCC patients tissues (n = 81) was 2.65 fold higher than *NME1* expression of normal liver tissues (n = 10) (*P* < 0.001, **Figure 1B**). What is more, we discovered that *NME1* was up-regulated in HCC tumor tissues (n = 240) compared with adjacent normal tissues (n = 193) in GSE36376 database (*P* < 0.001, **Figure 1C**). Meanwhile, GSE45436 showed that *NME1* was evaluated in HCC tumor tissues (n = 95) compared with adjacent normal tissue (n = 39) as well (*P* < 0.001, **Figure 1D**). These databases demonstrated that *NME1* was up-regulated in tumor tissues compared with adjacent normal tissues or normal/hepatitis/cirrhotic liver tissues.

NME1 involved in HCC tumors progression

To verify the results of GEO databases, we detected *NME1* expression in enrolled HCC tissues by qPCR and compared *NME1* expression in tumor tissues and paired adjacent normal tissues. As expected, compared with matching adjacent normal tissues, *NME1* was up-regulated in tumor tissues. As shown in **Figure 2A**, the *NME1* was evaluated in tumor than adjacent normal tissues (*P* = 0.021, **Figure 2A**), which is in accordance with the results of GSE36376 and GSE45436, showed that *NME1* was evaluated in tumor tissues. Then, we evaluated *NME1* expression in HCC progression, and discovered that *NME1* expression in Stage III/IV HCC patients was significantly lower than in Stage I/II HCC patients (*P* = 0.009, **Figure 2B**). However, no significant association was found between *NME1* expression in HCC and other

NME1 associated with HCC progression and prognosis

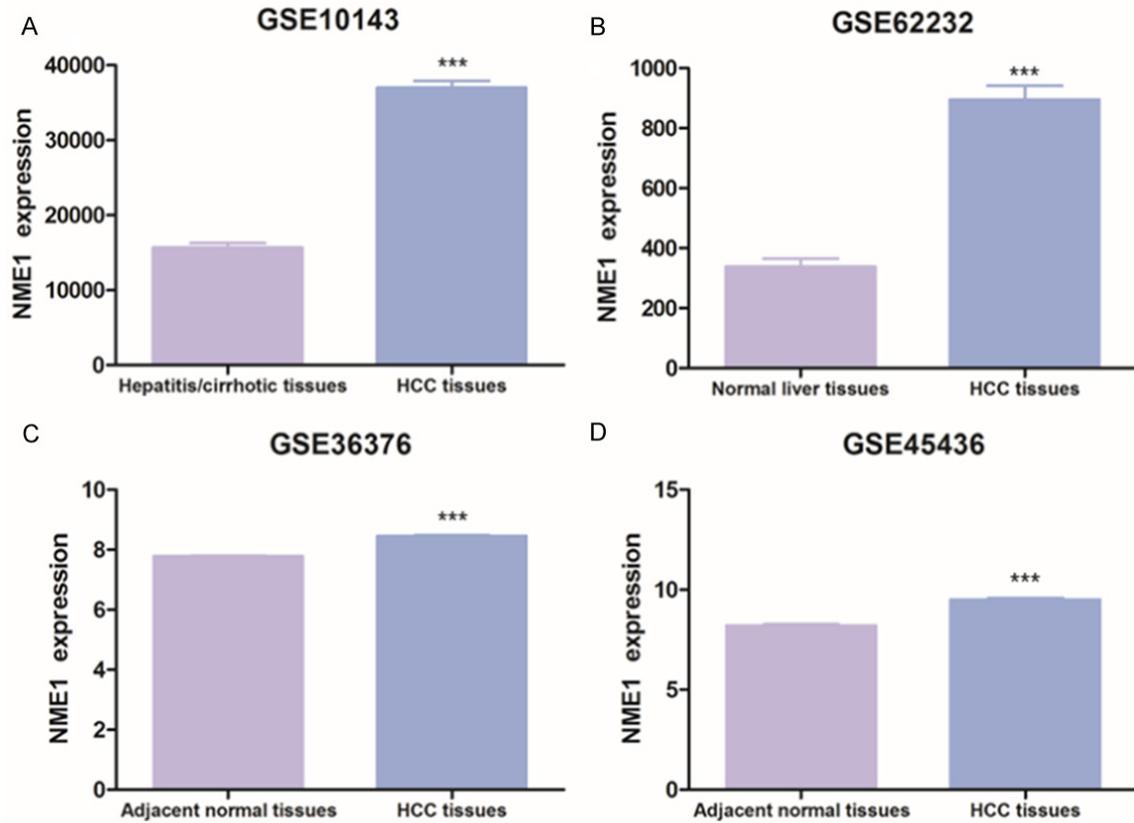


Figure 1. The NME1 expression in human expression profiling array. A. GSE10143, hepatitis/cirrhotic liver tissues (n = 307) vs HCC tumor tissues (n = 80). B. GSE62232, normal liver tissues (n = 10) vs HCC tumor tissues (n = 81). C. GSE36376, adjacent normal tissues (n = 193) vs HCC tumor tissues (n = 240). D. GSE45436, adjacent normal tissues (n = 39) vs HCC tumor tissues (n = 95). Data are shown as mean (SE). *** $P < 0.001$.

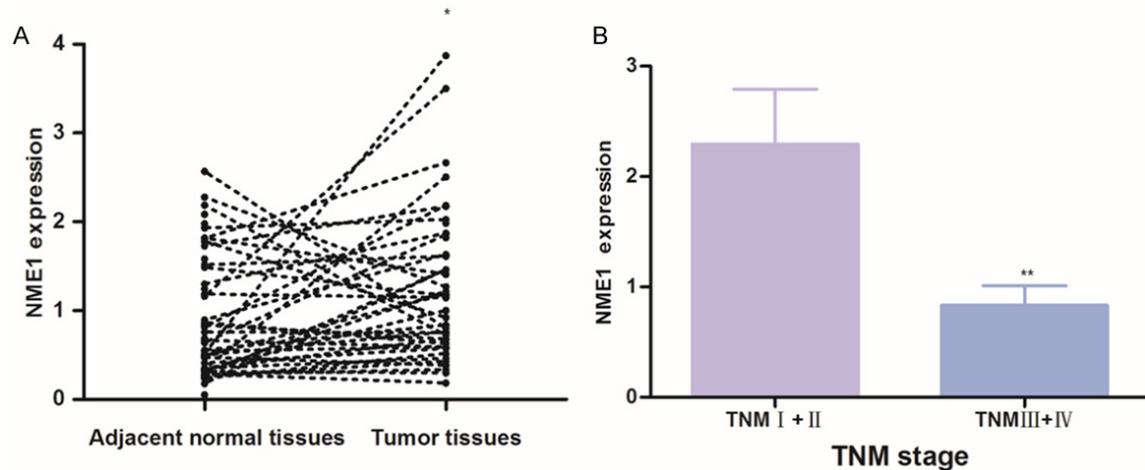


Figure 2. Expression of *NME1* were verified by real-time qPCR in enrolled HCC patients. A. Paired adjacent normal tissues (n = 72) vs HCC tumor tissues (n = 72); B. *NME1* expression in HCC tissues at I/II (n = 51) and III/IV (n = 21) clinical stages. Results are shown as mean (SE). * $P < 0.05$, ** $P < 0.01$.

parameters, such as liver cirrhosis, size of tumor and Child-Pugh classification. Overall,

our result demonstrated *NME1* involve in HCC tumor oncogenesis progression.

NME1 associated with HCC progression and prognosis

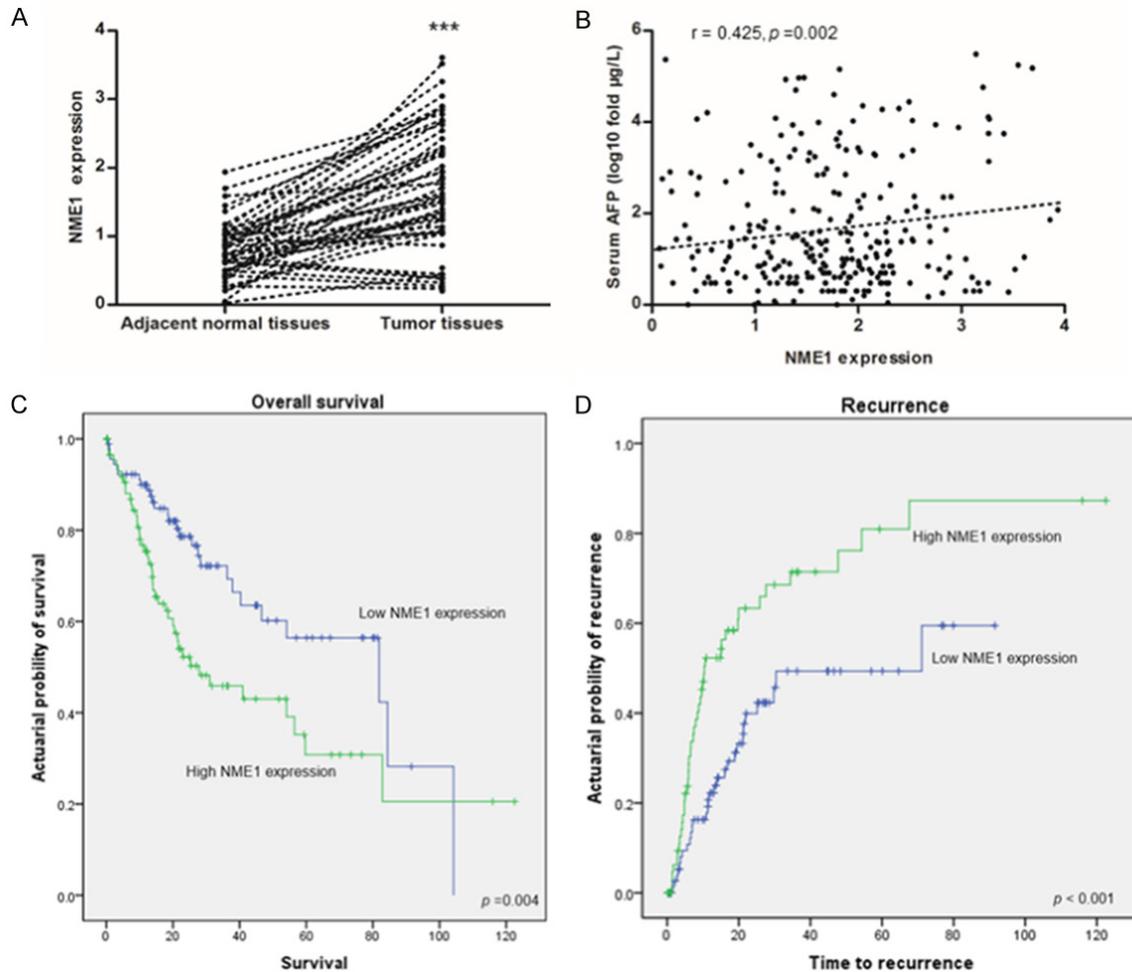


Figure 3. The expression and prognostic value of *NME1* were explored by RNA-seq in TCGA database. A. Matched adjacent normal tissues ($n = 59$) vs HCC tumor tissues ($n = 59$); B. The correlation between *NME1* expression and serum AFP level ($n = 377$); C and D. Kaplan-Meier curves and estimates of overall survival and recurrence in patients with high or low *NME1* expression, p values are calculated based on the log-rank test, *** $P < 0.001$.

High NME1 expression was associated with poor prognosis in HCC patients

To confirm *NME1* function in HCC, we download gene expression data and clinical data of 438 HCC patients from TCGA database. We explored mRNA expression of *NME1* in 377 primary tumor tissues and 59 adjacent normal tissues, and discovered that *NME1* was significant up-regulated in HCC compared with paired adjacent normal tissues ($P < 0.001$, **Figure 3A**), which is in consistent with previous results. Besides, Spearman's correlation test also showed that *NME1* expression was positively associated with serum AFP level ($r = 0.425$, $P = 0.002$) (**Figure 3B**). What is more, the Kaplan-Meier survival analysis was performed to estimate the prognosis function of

NME1. The median *NME1* concentration in HCC patients was 1.64, with the 25th and the 75th percentile values at 1.03 and 2.21, respectively. The top quartile of *NME1* concentrations (> 2.21) was defined as high *NME1* expression patients, and the lowest quartile of *NME1* concentrations (< 1.03) was defined as low *NME1* expression patients. Notably, the low *NME1* expression patients showed a higher overall survival than the high *NME1* expression patients ($P = 0.004$, **Figure 3C**). Besides, the recurrence rate of HCC patients with high *NME1* expression group was significantly higher than that of patients with low *NME1* expression group ($P < 0.001$, **Figure 3D**), which demonstrated high *NME1* expression predicted worse outcome.

Discussion

NME1 was a metastatic suppressor because of its down-regulated expression in highly metastatic murine melanoma cell lines [25]. Previous studies demonstrated that over-expression of *NME1* could reduce cell motility in various tumors cell lines, such as melanoma, breast carcinoma, and prostate cell lines [26-28]. Meanwhile, researchers discovered that the *NME1* function was coincident in different cancers, and rarely study concentrated on *NME1* function in HCC. Our study focused on the expression of *NME1* in HCC patients and *NME1* function in tumor progress and prognosis.

Our results showed that *NME1* was up-regulated in HCC tissues compared to hepatitis/cirrhotic tissues or normal livers tissues in GEO database (**Figure 1A, 1B**). Besides, *NME1* was up-regulated in HCC tissues than adjacent normal tissues in GEO database as well (**Figure 1C, 1D**), and this phenomenon was also observed in our study (**Figures 2A, 3A**). The correlation of *NME1* expression with metastasis of HCC is still inconclusive, because it is mentioned in a few studies [16, 29]. Boissan et al [16] found that *NME1* were overexpressed in the primary liver tumors compared with non-tumor liver tissues and more ASV/*NME1*(-/-) mice than ASV/*NME1*(+/+) mice developed lung metastases in mouse models; whereas, Shimada et al [29] demonstrated that *NME1* expression did not decrease in metastatic HCC but instead tended to increase at both intrahepatic and extrahepatic metastatic sites. In our study, *NME1* was down-regulated in Stage III/IV HCC patients HCC patients than that in Stage I/II HCC patients (**Figure 2B**), which was similar to Boissan' study, *NME1* was a metastasis suppressor in HCC progression.

A parallel correlation of *NME1* expression with the overall survival was observed in various human malignancies, such as laryngeal squamous cell carcinomas, head and neck squamous cell carcinoma and breast cancer [30-32]. However, an inverse relationship was reported in other tumors, such as peripheral T-cell lymphoma, gastric cancer, neuroblastoma and acute myeloid leukemia [18, 21, 22, 33-35]. Our data showed a negative effect of *NME1* on survival, that patients with tumors high expressing *NME1* had worse prognoses

than those with low *NME1* tumors ($P = 0.004$, **Figure 3C**). Besides, the high *NME1* expression tumors showed significant higher recurrence rates than the low *NME1* expression tumors ($P < 0.001$, **Figure 3D**).

In summary, our results for GEO database, enrolled HCC patients and TCGA database showed that expression of *NME1*, as its function as a metastasis suppressor gene, is correlated with poorer prognosis and higher recurrence. *NME1* is a reliable indicator of prognosis and recurrence in HCC and may be a novel molecular biomarker for the targeted therapy and prognosis of HCC.

Acknowledgements

This work was supported by a Grant from The National Natural Science Foundation of China (NSFC No. 81572069).

Disclosure of conflict of interest

None.

Address correspondence to: Yan Li, Department of Clinical Laboratory, Rennin Hospital of Wuhan University, Wuhan 430060, Hubei, China. E-mail: liyan@whu.edu.cn

References

- [1] Forner A, Llovet JM and Bruix J. Hepatocellular carcinoma. *Lancet* 2012; 379: 1245-1255.
- [2] El-Serag HB. Hepatocellular carcinoma. *N Engl J Med* 2011; 365: 1118-1127.
- [3] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D and Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; 136: E359-386.
- [4] Zucman-Rossi J, Villanueva A, Nault JC and Llovet JM. Genetic landscape and biomarkers of hepatocellular carcinoma. *Gastroenterology* 2015; 149: 1226-1239, e1224.
- [5] Nahon P and Zucman-Rossi J. Single nucleotide polymorphisms and risk of hepatocellular carcinoma in cirrhosis. *J Hepatol* 2012; 57: 663-674.
- [6] Wang Y, Kato N, Hoshida Y, Yoshida H, Taniguchi H, Goto T, Moriyama M, Otsuka M, Shiina S, Shiratori Y, Ito Y and Omata M. Interleukin-1beta gene polymorphisms associated with hepatocellular carcinoma in hepatitis C virus infection. *Hepatology* 2003; 37: 65-71.

NME1 associated with HCC progression and prognosis

- [7] Tarhuni A, Guyot E, Rufat P, Sutton A, Bourcier V, Grando V, Ganne-Carrie N, Zioli M, Charnaux N, Beaugrand M, Moreau R, Trinchet JC, Mansouri A and Nahon P. Impact of cytokine gene variants on the prediction and prognosis of hepatocellular carcinoma in patients with cirrhosis. *J Hepatol* 2014; 61: 342-350.
- [8] Nahon P, Sutton A, Rufat P, Zioli M, Akouche H, Laguillier C, Charnaux N, Ganne-Carrie N, Grando-Lemaire V, N'Kontchou G, Trinchet JC, Gattegno L, Pessayre D and Beaugrand M. Myeloperoxidase and superoxide dismutase 2 polymorphisms modulate the risk of hepatocellular carcinoma and death in alcoholic cirrhosis. *Hepatology* 2009; 50: 1484-1493.
- [9] Yoon YJ, Chang HY, Ahn SH, Kim JK, Park YK, Kang DR, Park JY, Myoung SM, Kim DY, Chon CY and Han KH. MDM2 and p53 polymorphisms are associated with the development of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. *Carcinogenesis* 2008; 29: 1192-1196.
- [10] Dharel N, Kato N, Muroyama R, Moriyama M, Shao RX, Kawabe T and Omata M. MDM2 promoter SNP309 is associated with the risk of hepatocellular carcinoma in patients with chronic hepatitis C. *Clin Cancer Res* 2006; 12: 4867-4871.
- [11] Abu Dayyeh BK, Yang M, Fuchs BC, Karl DL, Yamada S, Sninsky JJ, O'Brien TR, Dienstag JL, Tanabe KK, Chung RT; HALT-C Trial Group. A functional polymorphism in the epidermal growth factor gene is associated with risk for hepatocellular carcinoma. *Gastroenterology* 2011; 141: 141-149.
- [12] Villanueva A, Newell P, Chiang DY, Friedman SL and Llovet JM. Genomics and signaling pathways in hepatocellular carcinoma. *Semin Liver Dis* 2007; 27: 55-76.
- [13] Villanueva A, Chiang DY, Newell P, Peix J, Thung S, Alsinet C, Tovar V, Roayaie S, Minguez B, Sole M, Battiston C, Van Laarhoven S, Fiel MI, Di Feo A, Hoshida Y, Yea S, Toffanin S, Ramos A, Martignetti JA, Mazzaferro V, Bruix J, Waxman S, Schwartz M, Meyerson M, Friedman SL and Llovet JM. Pivotal role of mTOR signaling in hepatocellular carcinoma. *Gastroenterology* 2008; 135: 1972-1983, 1983, e1971-1911.
- [14] Farazi PA and DePinho RA. Hepatocellular carcinoma pathogenesis: from genes to environment. *Nat Rev Cancer* 2006; 6: 674-687.
- [15] Gao QL, Ma D, Meng L, Wang SX, Wang CY, Lu YP, Zhang AL and Li J. Association between Nm23-H1 gene expression and metastasis of ovarian carcinoma. *Ai Zheng* 2004; 23: 650-654.
- [16] Boissan M, Wendum D, Arnaud-Dabernat S, Munier A, Debray M, Lasco I, Daniel JY and Lacombe ML. Increased lung metastasis in transgenic NM23-Null/SV40 mice with hepatocellular carcinoma. *J Natl Cancer Inst* 2005; 97: 836-845.
- [17] Tokunaga Y, Urano T, Furukawa K, Kondo H, Kanematsu T and Shiku H. Reduced expression of nm23-H1, but not of nm23-H2, is concordant with the frequency of lymph-node metastasis of human breast cancer. *Int J Cancer* 1993; 55: 66-71.
- [18] Carotenuto M, Pedone E, Diana D, de Antonellis P, Dzeroski S, Marino N, Navas L, Di Dato V, Scoppettuolo MN, Cimmino F, Correale S, Pirone L, Monti SM, Bruder E, Zenko B, Slavkov I, Pastorino F, Ponzoni M, Schulte JH, Schramm A, Eggert A, Westermann F, Arrigoni G, Accordi B, Basso G, Saviano M, Fattorusso R and Zollo M. Neuroblastoma tumorigenesis is regulated through the Nm23-H1/h-Prune C-terminal interaction. *Sci Rep* 2013; 3: 1351.
- [19] Lindmark G. NM-23 H1 immunohistochemistry is not useful as predictor of metastatic potential of colorectal cancer. *Br J Cancer* 1996; 74: 1413-1418.
- [20] Martinez JA, Prevot S, Nordlinger B, Nguyen TM, Lacarriere Y, Munier A, Lasco I, Vaillant JC, Capeau J and Lacombe ML. Overexpression of nm23-H1 and nm23-H2 genes in colorectal carcinomas and loss of nm23-H1 expression in advanced tumour stages. *Gut* 1995; 37: 712-720.
- [21] Wang CS, Lin KH, Hsu YC and Hsueh S. Distant metastasis of gastric cancer is associated with elevated expression of the antimetastatic nm23 gene. *Cancer Lett* 1998; 128: 23-29.
- [22] Muller W, Schneiders A, Hommel G and Gabbert HE. Expression of nm23 in gastric carcinoma: association with tumor progression and poor prognosis. *Cancer* 1998; 83: 2481-2487.
- [23] Terada R, Yasutake T, Nakamura S, Hisamatsu T, Sawai T, Yamaguchi H, Nakagoe T, Ayabe H and Tagawa Y. Clinical significance of nm23 expression and chromosome 17 numerical aberrations in primary gastric cancer. *Med Oncol* 2002; 19: 239-248.
- [24] Wilks C, Cline MS, Weiler E, Diehkans M, Craft B, Martin C, Murphy D, Pierce H, Black J, Nelson D, Litzinger B, Hatton T, Maltbie L, Ainsworth M, Allen P, Rosewood L, Mitchell E, Smith B, Warner J, Groboske J, Telc H, Wilson D, Sanford B, Schmidt H, Haussler D and Maltbie D. The cancer genomics hub (CGHub): overcoming cancer through the power of torrential data. *Database (Oxford)* 2014; 2014.
- [25] Steeg PS, Bevilacqua G, Kopper L, Thorgeirsson UP, Talmadge JE, Liotta LA and Sobel ME. Evidence for a novel gene associated with low tumor metastatic potential. *J Natl Cancer Inst* 1988; 80: 200-204.
- [26] Steeg PS, Horak CE and Miller KD. Clinical-translational approaches to the Nm23-H1 me-

NME1 associated with HCC progression and prognosis

- tastasis suppressor. *Clin Cancer Res* 2008; 14: 5006-5012.
- [27] Li Y, Zhou Q, Sun Z, Sun Z, Wang Y, Qin Y, Zhu W and Chen X. [Experimental study on molecular mechanism of nm23-H1 gene transfection reversing the malignant phenotype of human high-metastatic large cell lung cancer cell line]. *Zhongguo Fei Ai Za Zhi* 2006; 9: 307-311.
- [28] Miyazaki H, Fukuda M, Ishijima Y, Takagi Y, Iimura T, Negishi A, Hirayama R, Ishikawa N, Amagasa T and Kimura N. Overexpression of nm23-H2/NDP kinase B in a human oral squamous cell carcinoma cell line results in reduced metastasis, differentiated phenotype in the metastatic site, and growth factor-independent proliferative activity in culture. *Clin Cancer Res* 1999; 5: 4301-4307.
- [29] Shimada M, Taguchi K, Hasegawa H, Gion T, Shirabe K, Tsuneyoshi M and Sugimachi K. Nm23-H1 expression in intrahepatic or extrahepatic metastases of hepatocellular carcinoma. *Liver* 1998; 18: 337-342.
- [30] Marioni G, Ottaviano G, Lionello M, Lora L, Lovato A, Staffieri C, Favaretto N, Giacomelli L, Stellini E, Staffieri A and Blandamura S. Nm23-H1 nuclear expression is associated with a more favourable prognosis in laryngeal carcinoma: univariate and multivariate analysis. *Histopathology* 2012; 61: 1057-1064.
- [31] Hirayama R, Sawai S, Takagi Y, Mishima Y, Kimura N, Shimada N, Esaki Y, Kurashima C, Utsuyama M and Hirokawa K. Positive relationship between expression of anti-metastatic factor (nm23 gene product or nucleoside diphosphate kinase) and good prognosis in human breast cancer. *J Natl Cancer Inst* 1991; 83: 1249-1250.
- [32] Wang YF, Chang CJ, Chiu JH, Lin CP, Li WY, Chang SY, Chu PY, Tai SK and Chen YJ. NM23-H1 expression of head and neck squamous cell carcinoma in association with the response to cisplatin treatment. *Oncotarget* 2014; 5: 7392-7405.
- [33] Niitsu N, Nakamine H and Okamoto M. Expression of nm23-H1 is associated with poor prognosis in peripheral T-cell lymphoma, not otherwise specified. *Clin Cancer Res* 2011; 17: 2893-2899.
- [34] Niitsu N. The association of nm23-H1 expression with a poor prognosis in patients with peripheral T-cell lymphoma, not otherwise specified. *J Clin Exp Hematop* 2014; 54: 171-177.
- [35] Lilly AJ, Khanim FL, Hayden RE, Luong QT, Drayson MT and Bunce CM. Nm23-h1 indirectly promotes the survival of acute myeloid leukemia blast cells by binding to more mature components of the leukemic clone. *Cancer Res* 2011; 71: 1177-1186.