Int J Clin Exp Pathol 2020;13(9):2280-2288
www.ijcep.com /ISSN:1936-2625/IJCEP0112567

*Original Article*

# Low expression of NTF3 is associated with unfavorable prognosis in hepatocellular carcinoma

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Received April 14, 2020; Accepted May 20, 2020; Epub September 1, 2020; Published September 15, 2020

**Abstract:** Neurotrophin 3 (NTF3) is a member of the nerve growth factor (NGF) family involved in cancer progression, including medulloblastoma and breast cancer. However, the expression and prognostic value of NTF3 has not been reported in human hepatocellular carcinoma (HCC). Here, we first performed an mRNA expression analysis of the NTF family using the TCGA database and found that NTF3 was significantly downregulated in patients with HCC. Low expression of NTF3 in various HCC cohorts from the GEO database was frequently identified. Consistently, NTF3 protein level was also decreased in HCC tissues as compared with controls. Moreover, survival analysis showed that low NTF3 expression correlated with shorter overall survival (OS) and disease-free survival (DFS) in HCC patients. In addition, there was a positive correlation between the mRNA expression of NTF3 and TrkC in HCC specimens. Generally, these results revealed that low expression of NTF3 predicted an unfavorable clinical outcome. NTF3 may be a diagnostic and prognostic marker in HCC.

**Keywords:** HCC, neurotrophin 3, prognosis, diagnosis

## Introduction

Liver cancer is the fifth most common cancer and the fourth highest cause of cancer-related mortality in the world [1]. 75%-85% of primary liver cancer is hepatocellular carcinoma (HCC) [2], the incidence of which is increasing and may reach 1 million cases per year in the next decade [3]. The vast majority of HCC cases occur in East Asia and sub-Saharan Africa, where medical and social care resources are often limited [4, 5]. HCC is a highly heterogeneous disease with differing histomolecular features and clinical outcome [1]. Only 40% of HCC patients can be diagnosed at early stage, when the main treatments including radiofrequency ablation (RFA) or resection are applicable [6, 7]. Patients with metastasis at late stage have a poor prognosis. Hence, predictive and prognostic biomarkers need to be found to improve the diagnosis and therapeutic strategy.

Nerve growth factors (NGFs) consist of several proteins including a prototype member NGF, NTF3, NTF4/5 and NT-7, (reported in invertebrates only), brain-derived neurotrophic factor (BDNF), neurturin (NRTN), human cilliary neurotrophic factor (CNTF), and glia-derived neurotrophic factor (GDNF) [8]. These NGFs, which bind Trk receptors (high affinity) and receptor p75NTR (low affinity) [8], have stimulating effects on neuronal differentiation, survival, neurite growth, and neurotransmitter synthesis. Furthermore, it also has been demonstrated that NTFs contribute to tumor progression in several types of cancer, whereas BDNF functions as a tumor suppressor [9]. Similarly, NTF3/TrkC signaling exhibited a growth-inhibitory effect in medulloblastomas (MBL) [10, 11]. In primitive neuroectodermal tumors (PNETs), TrkC through its ligand NTF3 accelerates cell apoptosis and terminal neuronal differentiation [12, 13]. The Louie group reported that NTF3 facilitated the growth of breast cancer cells, which were metastatic [14]. Based on these

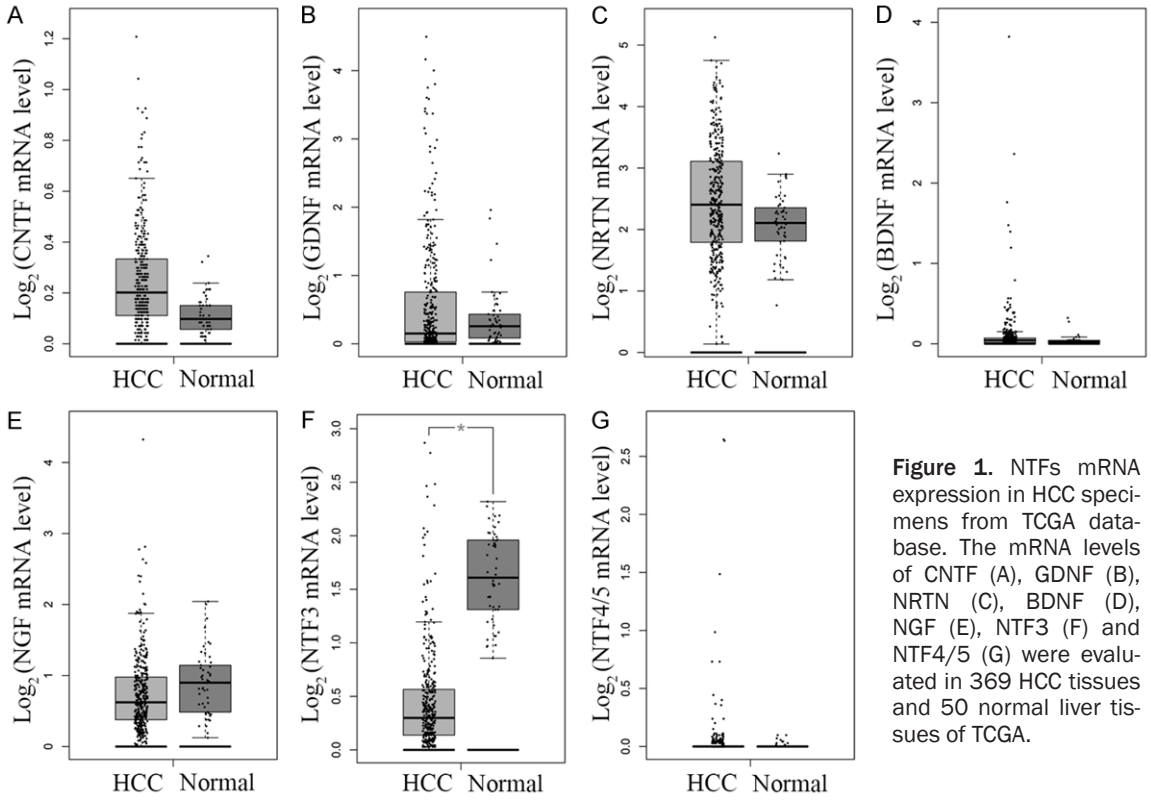


**Figure 1.** NTFs mRNA expression in HCC specimens from TCGA database. The mRNA levels of CNTF (A), GDNF (B), NRTN (C), BDNF (D), NGF (E), NTF3 (F) and NTF4/5 (G) were evaluated in 369 HCC tissues and 50 normal liver tissues of TCGA.

studies, we further explore the expression and clinical outcome of NTF3 in progression of HCC.

Here, we first report that NTF3 expression is down-regulated in HCC patients. Elevated NTF3 levels are closely correlated with favorable prognosis. Our study indicates that NTF3 has an important clinical diagnostic and prognostic value.

## Materials and methods

### *Public databases*

The mRNA levels of NGFs family in HCC samples and normal liver samples were evaluated by using the GEPIA website (http://gePia.cancer-Pku.cn/), which analyzes their mRNA expression on the basis of The Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) microarray data [15]. These data include 369 liver hepatocellular carcinoma (LIHC) samples from the TCGA project, 50 normal liver samples from TCGA project, and 110 normal liver samples from GTEx project. GEPIA also was used to perform OS and DFS analysis based on NTF3 mRNA expression in LIHC. The correlation analysis between NTF3 expression and TrkC expression was obtained by GEPIA. Then, GSE6764, GSE55092, GSE25097, GSE121248, GSE64041 and GSE14520 Cohort 2 from Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo) were brought into our study.

### *Patient samples*

Tissue microarray was obtained from Servicebio (Wuhan, China). There were 32 paired tumorous liver tissues and adjacent nontumoral liver tissues. Informed consent was received from each patient recruited, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of West China Second University Hospital of Sichuan University.

### *Immunohistochemistry*

Antigen retrieval of all liver samples was conducted with microwave heat in sodium citrate buffer (10 mmol/L, pH 6.0) and permeabilization with 0.5% Triton X-100 for 20 min.

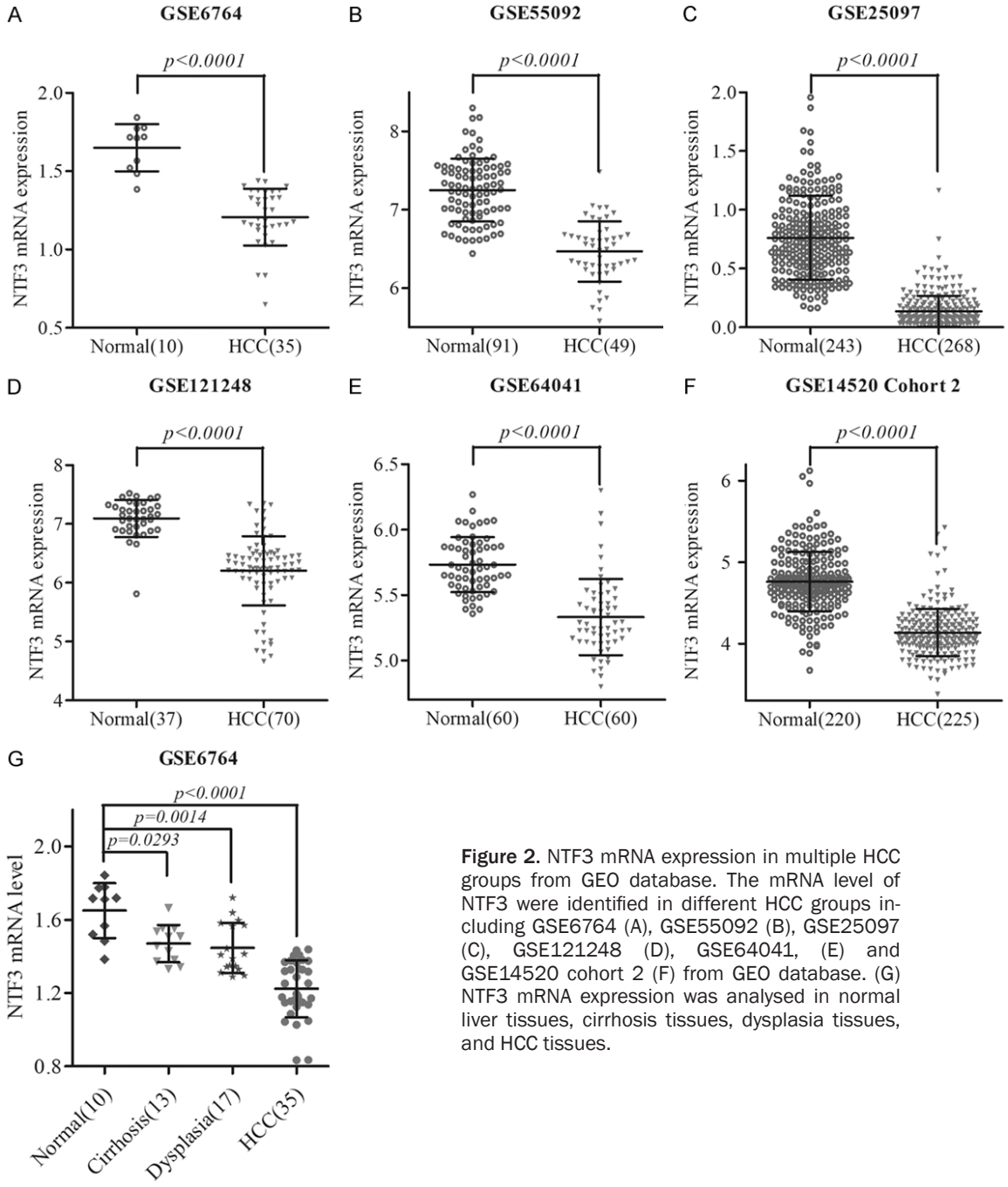


**Figure 2.** NTF3 mRNA expression in multiple HCC groups from GEO database. The mRNA level of NTF3 were identified in different HCC groups including GSE6764 (A), GSE55092 (B), GSE25097 (C), GSE121248 (D), GSE64041, (E) and GSE14520 cohort 2 (F) from GEO database. (G) NTF3 mRNA expression was analysed in normal liver tissues, cirrhosis tissues, dysplasia tissues, and HCC tissues.

Endogenous peroxidase activity of the tissues was blocked in 3% $H_2O_2$. Then, the slide was successively incubated with primary antibody (anti-NTF3, 1:200) overnight at 4°C and with secondary antibodies purchased from Molecular Probes and Vector Laboratories for 1 h. Immunoreactivity detection was performed using diaminobenzidine (DAB) staining (Dako) according to manufacturer's instructions. Hematoxylin was used for nuclear counterstaining. Two independent pathologists conducted the analysis, as previously described [16]. The proportion of cells with positive staining is scored as: 0 (<10%); 1 (10%-30%); 2 (30%-50%); 3 (>50%). HScore takes into consideration the intensity of the staining and the percentage of positive cells per the formula: HScore = 1× (% light staining) +2× (% moderate

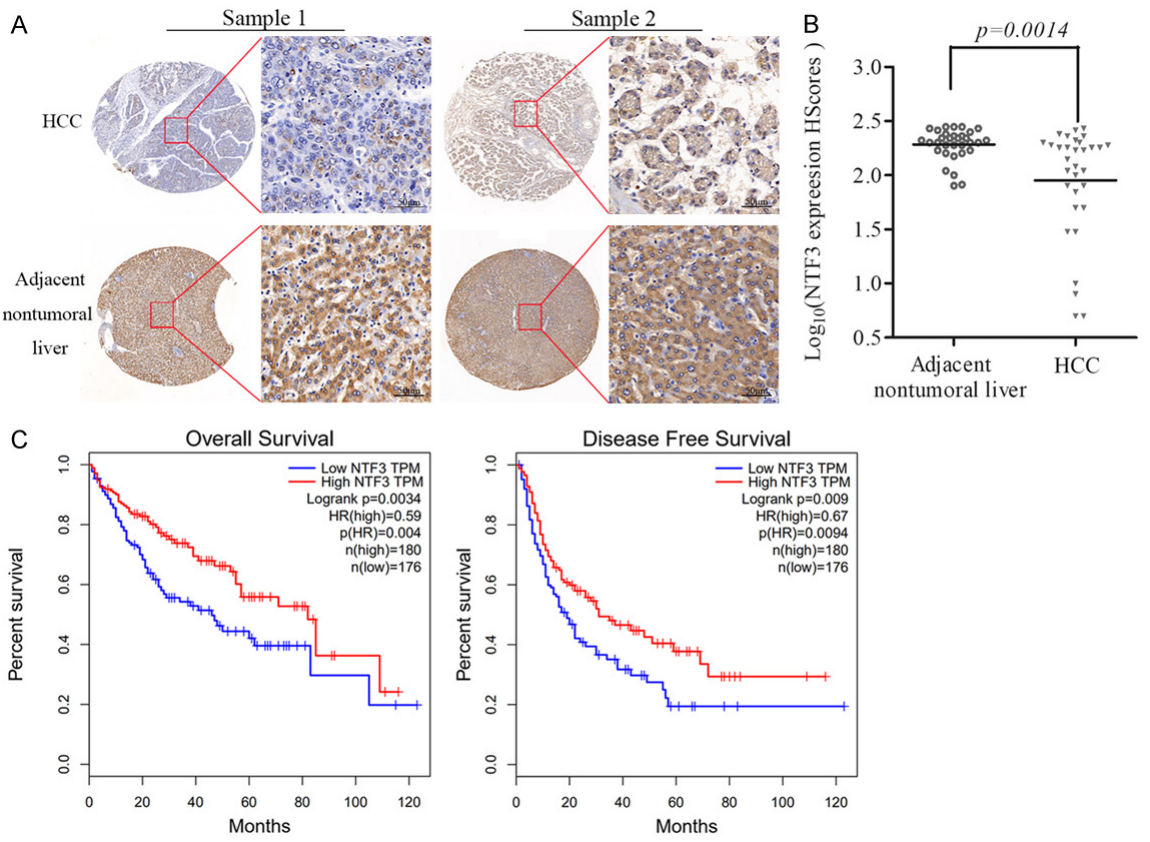


**Figure 3.** NTF3 protein levels in HCC tissues and their adjacent normal tissues. A. Representative immunohistochemical images of NTF3 in HCC tissues and their corresponding liver tissues are shown. Magnification, ×400. Scale bar: 50 μm. B. Tissue sections from HCC had higher IHC scores for NTF3 compared with normal adjacent liver tissue. C. Association between NTF3 expression and survival (OS and DFS) in HCC cohort from TCGA.

staining)+ 3× (% strong staining). HScores range from 0 to 300 [17].

*Statistical analysis*

The data were evaluated by using GraphPad Prsim 7.0 and SPSS software 19.0. The quantitative values were displayed as mean ± SD. Student's t-test was used to assess the difference between two groups. The relevance of NTF3 protein level to clinicopathologic characteristics was evaluated by chi-square test or Fisher's exact test. Survival analysis for NTF3 expression and other measures was conducted by using the Kaplan-Meier method and the log-rank test. Correlation analysis between NTF3 and TrkC mRNA from GEPIA was analyzed by Spearman's rank test. Moreover, to identify NTF3 prognostic significance, measures that were significant by univariate analysis were selected for Cox multivariate analysis. P<0.05 was considered significant.

## Results

*Transcription level of NGFs in patients with HCC*

Abnormal expression and function of NGF family members was found in several tumors [9]. To investigate the effect of NGF members in patients with HCC, we first downloaded the results regarding to NGF gene expression from 369 HCC specimens and 50 normal liver specimens in TCGA database. The result showed NTF3 mRNA levels were markedly downregulated in HCC compared to normal tissues (**Figure 1A**). However, the mRNA levels of CNTF, GDNF, NRTN, BDNF, NGF, and NTF4/5 had no significant change in HCC and normal tissues (**Figure 1B-G**).

*Verification of NTF3 mRNA and protein down-expression in HCC patients*

To further validate this observation, the mRNA expression of NTF3 was presented by using dif-

**Table 1.** Correlative analysis of NTF3 protein level with clinicopathologic features

| Clinicopathologic Features | No. of Specimens | NTF3 Expression | | *P* value |
|---|---|---|---|---|
| | | Low | High | |
| Gender | | | | 0.374 |
| Female | 7 | 6 | 1 | |
| Male | 25 | 15 | 10 | |
| Age (mean ± SD) | | 51.90±2.06 | 52.36±3.36 | 0.903 |
| Tumor size | | | | 0.088 |
| ≤3 cm | 8 | 3 | 5 | |
| >3 cm | 24 | 18 | 6 | |
| Cell differentiation | | | | 0.322 |
| Low | 8 | 7 | 1 | |
| Middle | 17 | 10 | 7 | |
| High | 7 | 4 | 3 | |
| Intrahepatic satellite | | | | 0.534 |
| No | 30 | 19 | 11 | |
| Yes | 2 | 2 | 0 | |
| Lymph node metastasis | | | | 1.000 |
| No | 31 | 20 | 11 | |
| Yes | 1 | 1 | 0 | |
| Extrahepatic metastasis | | | | 0.637 |
| No | 26 | 16 | 10 | |
| Yes | 6 | 5 | 1 | |
| Cirrhosis | | | | 0.283 |
| No | 19 | 14 | 5 | |
| Yes | 13 | 7 | 6 | |
| HBV | | | | 1.000 |
| No | 9 | 6 | 3 | |
| Yes | 23 | 15 | 8 | |

ferent HCC cohorts from Gene Expression Omnibus (GEO) database. Consistently, lower NTF3 mRNA levels in HCC samples were identified compared with normal samples in GSE6764, GSE55092, GSE25097, GSE121248, GSE64041 and GSE14520 Cohort 2 (**Figure 2A-F**). Furthermore, we analyzed the mRNA expression of NTF3 in different subgroup of GSE6764 and discovered that NTF3 expression was gradually decreased in normal liver tissues, cirrhosis tissues, dysplasia tissues, and HCC tissues (**Figure 2G**).

Next, to determine whether the protein level of NTF3 was altered in HCC and normal tissues, we tested NTF3 protein expression level in HCC samples and matched neighboring normal tissues from 32 human cases by immunohistochemistry (IHC). IHC analysis showed decreased expression of NTF3 in most HCC samples (65.63%, 21/32), generally localized in cytoplasm of cells (**Figure 3A**). Further, the average IHC HScore of NTF3 protein in HCC was significantly lower compared with corresponding normal tissues (**Figure 3B**). In summary, these data indicated that NTF3 was frequently downregulated in HCC specimens.

*Relationship between of NTF3 protein levels and clinicopathologic features of HCC patients*

To better understand the association of NTF3 with HCC, we next divided 32 HCC specimens into groups according to the clinicopathologic factors and estimated the differences in NTF3 expression level among these groups (**Table 1**). There was no significant relation between NTF3 protein level and clinicopathologic features including gender, age, tumor size, cell differentiation, intrahepatic satellite, lymph node metastasis, extrahepatic metastasis, cirrhosis, and HBV.

*The prognostic merit of NTF3 in HCC patients*

The prognostic merit of NTF3 mRNA levels from the TCGA database was analyzed by using the Kaplan-Meier method and log-rank test. The result showed that HCC patients with decreased levels of NTF3 mRNA had a notably worse OS and DFS (**Figure 3C**). In addition, the relationship of clinicopathologic features with OS was further investigated in HCC patients. AFP level and stage were markedly related to OS of HCC patients. Furthermore, multivariate analysis revealed that low NTF3 expression was one of the independent prognostic factors for OS of HCC patients (**Table 2**). These results indicated that NTF3 is a clinical prognostic marker in patients with HCC.

*Potential mechanism of NTF3 in HCC*

NTF3 signals mainly through receptor tyrosine kinases TrkC [18]. To assess the underlying

**Table 2.** Prognostic role of expression of NTF3 in HCC patients assessed by univariate analysis and multivariate analysis

| Variables | Median survival time (months) | *P* value | HR | 95% CI | *P* value |
|---|---|---|---|---|---|
| NTF3 expression | | | | | |
| Low | 40.37 | 0.003 | 1 | | |
| High | 70.01 | | 0.646 | 0.419-0.996 | 0.048 |
| Gender | | | | | |
| Female | 48.95 | 0.232 | | | |
| Male | 81.67 | | | | |
| Age (years) | | | | | |
| ≤60 | 83.18 | 0.227 | | | |
| >60 | 53.29 | | | | |
| α-fetoprotein (AFP) | | | | | |
| ≤20 ng/mL | 80.68 | 0.021 | 1 | | |
| >20 ng/mL | 55.35 | | 1.550 | 0.998-2.408 | 0.051 |
| Stage | | | | | |
| 1-2 | 80.68 | 0.000 | 1 | | |
| 3-4 | 23.36 | | 1.941 | 1.223-3.082 | 0.005 |
| Cirrhosis | | | | | |
| No | 80.68 | 0.523 | | | |
| Yes | 90.64 | | | | |
| Grade | | | | | |
| 1 | 69.51 | 0.519 | | | |
| 2-4 | 55.65 | | | | |
| Vascular invasion | | | | | |
| No | 80.68 | 0.208 | | | |
| Yes | 81.67 | | | | |
| Alcohol | | | | | |
| No | 60.84 | 0.771 | | | |
| Yes | 53.35 | | | | |

HR: hazard; CI: confidence interval.

mechanism of NTF3 in the progression of HCC, we next assessed the correlation between NTF3 mRNA and TrkC mRNA. The data showed that there was not only a positive correlation between NTF3 mRNA and TrkC mRNA in HCC specimens, but also in two normal liver specimen cohorts (**Figure 4A-C**). We speculate that NTF3 and TrkC may be a regulatory axis in vivo.

## Discussion

Nerve growth factors (NGFs) have long been known for the functions of neurogenesis and neurocognitive regulation, but they have been demonstrated to induce tumor progression, suggesting that NGFs play the important roles in cancer cell growth, apoptosis, metastasis, and differentiation. Furthermore, researchers found that NGFs act by combining with Trk receptors including TrkA, TrkB, TrkC, and p75NT receptor [19, 20]. In particular, BDNF is the one of NGFs members studied widely, whereas its expression and role in tumor progression remain debatable. BDNF overexpression is found in breast cancer and stimulates cancer cell growth and metastasis through TrkB and p75NTR [21]. Similarly, studies have demonstrated that BDNF/TrkB pathway promotes gastric [22] and colorectal [23] cancer progression. In contrast, the serum concentration of BDNF is significantly decreased in colorectal cancer patients [24] and a positive association between high expression of BDNF and a better survival [25]. These results might indicate BDNF plays a role as a tumor suppressor or promoter. HCC expresses NGFs that regulate HCC cell development [26, 27]. Low-expression of TrkC, which is the main receptor for NTF3, inhibits HCC cell proliferation, migration, and invasion [28]. Nevertheless, the expression and function of NTF3 in HCC have been poorly investigated. In our study, we observed that NTF3 mRNA levels were dramatically reduced in HCC samples compared with normal liver samples from the TCGA database, which was validated in multiple HCC cohorts from GEO database. Consistently, immunohistochemistry analysis indicated that NTF3 protein level in HCC tissues was also lower than corresponding normal tissues. Together these results emphasize NTF3 as a marker to improve the diagnosis of HCC.

Previous studies have uncovered that increased TrkC mRNA levels correlates with favorable tumor clinical outcomes [10, 12, 13]. Our analysis showed that decreased NTF3 mRNA expression was related more with lower 5-year survival rate for both OS or DFS. When compared

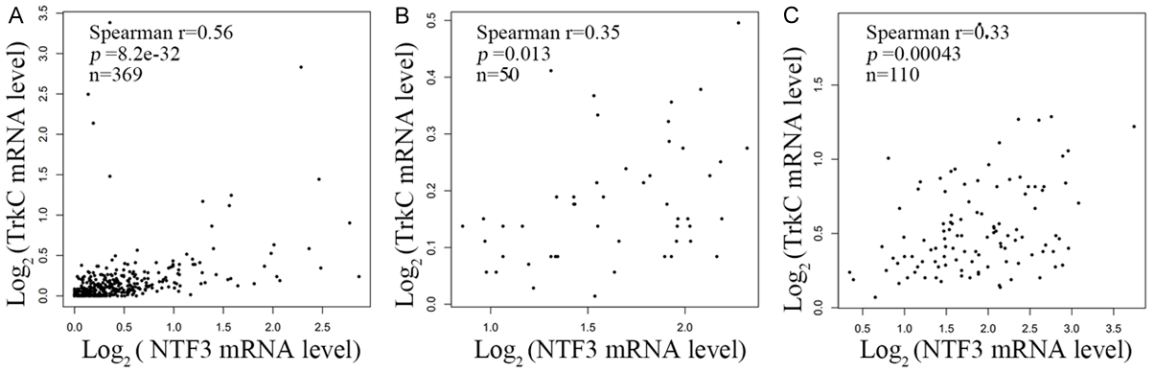


**Figure 4.** Relationship between NTF3 and TrkC mRNA from TCGA database. Correlation between NTF3 and TrkC mRNA in 369 HCC specimens (A), 50 normal liver specimens (B) and 110 GTEx normal liver specimens (C). Correlation analysis was done by Spearman rank test.

with clinicopathologic characteristics, through univariate analysis, NTF3 mRNA levels were one of the powerful predictors for HCC prognosis, even exceeding the clinical prognostic factor AFP. The hazard ratio still had significance by multivariate analysis. These data suggest NTF3 may be a prognostic marker of HCC.

Several groups have reported that NTF3/TrkC signaling has a growth-inhibitory effect on medulloblastomas. Kim et al. first found that NTF3-stimulated TrkC activation inhibited tumor growth by promoting cell apoptosis [10]. Subsequently, Grotzer et al. speculated that TrkC activation by binding its ligand NTF3 in Primitive Neuroectodermal Brain Tumor (PNET) patients may initiate programmed cell death or terminal neuron differentiation [12, 13]. A subsequent trial revealed the mechanism by which NTF3 suppressed MBL cell growth was through apoptosis and neuron differentiation of tumor cells [11]. On the other hand, Louie's group presented that NTF3 facilitated the growth of metastatic breast cancer cells in the brain by reversing MET of metastatic breast cancer cells and downregulating microglial toxicity [14]. In this investigation, it was interesting that NTF3 expression was progressively reduced in normal liver tissues, cirrhosis tissues, dysplasia tissues, and HCC tissues. This observation indicates that NTF3 expression may affect the transformation of normal liver to HCC. However, when further analyzing the association between NTF3 expression level and clinicopathologic features of 32 HCC patients, we found no significant relevance between NTF3 expression and clinicopathologic features. This result may be affected by limitations including the number of clinical cases and discontinuous cases and we hope to reduce this drawback in future work. Furthermore, the relationship between NTF3 and TrkC was found to be positive not only in HCC, but also in two normal liver cohorts. This might indicate that NTF3 affects HCC progression by modulating TrkC, whereas the accurate mechanism will be further explored to verify these links.

The present study is the first research to suggest NTF3'svalue as a clinical diagnostic and prognostic marker in HCC. In addition, NTF3/TrkC signaling may induce the progression of HCC and deserves study as a therapeutic target in HCC.

## Acknowledgements

This work was supported by National Natural Science Foundation of China (Grant No. 81801628 to TL), the Key Research and Development Projects of Sichuan Science and Technology Department (Grant No. 2019YFS0315 to TL) and Xinya Research Foundation from West China Second University Hospital, Sichuan University (Grant No. KX200 to QXY).

## Disclosure of conflict of interest

None.

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## References


[1] Calderaro J, Ziol M, Paradis V and Zucman-Rossi J. Molecular and histological correlations in liver cancer. J Hepatol 2019; 71: 616-30.

[2] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.

[3] Llovet JM, Montal R, Sia D and Finn RS. Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol 2018; 15: 599-616.

[4] Tang A, Hallouch O, Chernyak V, Kamaya A and Sirlin CB. Epidemiology of hepatocellular carcinoma: target population for surveillance and diagnosis. Abdom Radiol (NY) 2018; 43: 13-25.

[5] El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012; 142: 1264-73, e1.

[6] European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol 2018; 69: 182-236.

[7] Kulik L and El-Serag HB. Epidemiology and management of hepatocellular carcinoma. Gastroenterology 2019; 156: 477-91, e1.

[8] Kumar A, Pareek V, Faiq MA, Kumar P, Raza K, Prasoon P, Dantham S and Mochan S. Regulatory role of NGFs in neurocognitive functions. Rev Neurosci 2017; 28: 649-73.

[9] Griffin N, Faulkner S, Jobling P and Hondermarck H. Targeting neurotrophin signaling in cancer: the renaissance. Pharmacol Res 2018; 135: 12-7.

[10] Kim JY, Sutton ME, Lu DJ, Cho TA, Goumnerova LC, Goritchenko L, Kaufman JR, Lam KK, Billet AL, Tarbell NJ, Wu J, Allen JC, Stiles CD, Segal RA and Pomeroy SL. Activation of neurotrophin-3 receptor TrkC induces apoptosis in medulloblastomas. Cancer Res 1999; 59: 711-9.

[11] Kim YH, Cho SH, Lee SJ, Choi SA, Phi JH, Kim SK, Wang KC, Cho BK and Kim CY. Growth-inhibitory effect of neurotrophin-3-secreting adipose tissue-derived mesenchymal stem cells on the D283-MED human medulloblastoma cell line. J Neurooncol 2012; 106: 89-98.

[12] Grotzer MA, Janss AJ, Fung K, Biegel JA, Sutton LN, Rorke LB, Zhao H, Cnaan A, Phillips PC, Lee VM and Trojanowski JQ. TrkC expression predicts good clinical outcome in primitive neuroectodermal brain tumors. J Clin Oncol 2000; 18: 1027-35.

[13] Grotzer MA, Janss AJ, Phillips PC and Trojanowski JQ. Neurotrophin receptor TrkC predicts good clinical outcome in medulloblastoma and other primitive neuroectodermal brain tumors. Klin Padiatr 2000; 212: 196-9.

[14] Louie E, Chen XF, Coomes A, Ji K, Tsirka S and Chen EI. Neurotrophin-3 modulates breast cancer cells and the microenvironment to promote the growth of breast cancer brain metastasis. Oncogene 2013; 32: 4064-77.

[15] Tang Z, Li C, Kang B, Gao G, Li C and Zhang Z. GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses. Nucleic Acids Res 2017; 45: W98-W102.

[16] Yang QX, Zhong S, He L, Jia XJ, Tang H, Cheng ST, Ren JH, Yu HB, Zhou L, Zhou HZ, Ren F, Hu ZW, Gong R, Huang AL and Chen J. PBK overexpression promotes metastasis of hepatocellular carcinoma via activating ETV4-uPAR signaling pathway. Cancer Lett 2019; 452: 90-102.

[17] Lavorato-Rocha AM, Anjos LG, Cunha IW, Vassallo J, Soares FA and Rocha RM. Immunohistochemical assessment of PTEN in vulvar cancer: best practices for tissue staining, evaluation, and clinical association. Methods 2015; 77-78: 20-4.

[18] Garrido MP, Torres I, Vega M and Romero C. Angiogenesis in gynecological cancers: role of neurotrophins. Front Oncol 2019; 9: 913.

[19] Ebendal T. Function and evolution in the NGF family and its receptors. J Neurosci Res 1992; 32: 461-70.

[20] Meakin SO and Shooter EM. The nerve growth factor family of receptors. Trends Neurosci 1992; 15: 323-31.

[21] Tajbakhsh A, Mokhtari-Zaer A, Rezaee M, Afzaljavan F, Rivandi M, Hassanian SM, Ferns GA, Pasdar A and Avan A. Therapeutic potentials of BDNF/TrkB in breast cancer; current status and perspectives. J Cell Biochem 2017; 118: 2502-15.

[22] Okugawa Y, Tanaka K, Inoue Y, Kawamura M, Kawamoto A, Hiro J, Saigusa S, Toiyama Y, Ohi M, Uchida K, Mohri Y and Kusunoki M. Brain-derived neurotrophic factor/tropomyosin-related kinase B pathway in gastric cancer. Br J Cancer 2013; 108: 121-30.

[23] Tanaka K, Okugawa Y, Toiyama Y, Inoue Y, Saigusa S, Kawamura M, Araki T, Uchida K, Mohri Y and Kusunoki M. Brain-derived neurotrophic factor (BDNF)-induced tropomyosin-related kinase B (Trk B) signaling is a potential therapeutic target for peritoneal carcinomatosis arising from colorectal cancer. PLoS One 2014; 9: e96410.

[24] Brierley GV, Priebe IK, Purins L, Fung KY, Tabor B, Lockett T, Nice E, Gibbs P, Tie J, McMurrick P, Moore J, Ruszkiewicz A, Burgess A and

Cosgrove LJ. Serum concentrations of brain-derived neurotrophic factor (BDNF) are decreased in colorectal cancer patients. Cancer Biomark 2013; 13: 67-73.

[25] Sarabi M, Perraud A, Mazouffre C, Nouaille M, Jauberteau MO and Mathonnet M. Psychoactive drugs influence brain-derived neurotrophic factor and neurotrophin 4/5 levels in the serum of colorectal cancer patients. Biomed Rep 2017; 6: 89-94.

[26] Lam CT, Yang ZF, Lau CK, Tam KH, Fan ST and Poon RT. Brain-derived neurotrophic factor promotes tumorigenesis via induction of neovascularization: implication in hepatocellular carcinoma. Clin Cancer Res 2011; 17: 3123-33.

[27] Kishibe K, Yamada Y and Ogawa K. Production of nerve growth factor by mouse hepatocellular carcinoma cells and expression of TrkA in tumor-associated arteries in mice. Gastroenterology 2002; 122: 1978-86.

[28] Xiong D, Sheng Y, Ding S, Chen J, Tan X, Zeng T, Qin D, Zhu L, Huang A and Tang H. LINC00052 regulates the expression of NTRK3 by miR-128 and miR-485-3p to strengthen HCC cells invasion and migration. Oncotarget 2016; 7: 47593-608.