Original Article

Clinicopathologic correlations of Golgi protein 73 and signal transducer and activator of transcription 3 expression in hepatocellular carcinoma

Huayu Yang[1], Haifeng Xu[1], Yanan Wang[2], Jinchun Zhang[1], Xinting Sang[1], Yilei Mao[1]

[1]Department of Liver Surgery, Peking Union Medical College (PUMC) Hospital, Beijing 100005, China; [2]National Key Laboratory of Basic Medical Sciences, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences and PUMC, Beijing 100005, China

Contributions: (I) Conception and design: All authors; (II) Perform the research: H Yang, H Xu, Y Wang, J Zhang; (III) Data analysis and interpretation: All authors; (IV) Manuscript writing: All authors; (V) Final approval of manuscript: All authors.

Correspondence to: Professor Haifeng Xu. Department of Liver Surgery, Peking Union Medical College Hospital, 1 Shuai-fu-yuan, Dongcheng District, Beijing 100730, China. Email: xuhf781120@sina.com.

Background: To study whether there is correlation between the expressions of Golgi protein 73 (GP73) as well as signal transducer and activator of transcription 3 (STAT3) and the prognosis in hepatocellular carcinoma (HCC) patients.

Methods: Expression levels of GP73 and STAT3 were assessed in HCC tumor tissues from those who underwent hepatectomy in Peking Union Medical College Hospital. Relationships between clinicopathologic features and GP73/STAT3 protein expression levels were analyzed by Chi-square test. Kaplan–Meier method was employed to evaluate survival, whereas the log-rank test was employed to compare the survival differences between several groups.

Results: In HCC tumors, the median level of Golgi Protein 73 protein was 4.0 (2.1–5.3) RU, while the median STAT3 protein level was 1.2 (0.4–2.1) RU; both of which were significantly elevated compare to those in normal liver (NL) tissue [1.6 (1.3–2.1) RU, P<0.001, 0.7 (0.5–1.3) RU, P<0.001, respectively]. Additionally, GP73 protein levels were significantly decreased in patients without vein invasion compare to those of patients with vein invasion [3.3 (1.7–4.9) *vs.* 4.7 (4.4–5.7) RU, P<0.05]. The expressions of STAT3 in patients with HCC were associated with the size of tumor, differentiation, and vein invasion. Survival analysis showed that the mean disease free survival (DFS) time was notably decreased in patients with high GP73 expression (857±141 days, P<0.05) compared with patients of low GP73 expression (1,019±148 days). STAT3 expression in HCC tissues was related with DFS and overall survival (OS), with a Pearson correlation of –0.374 (P<0.01) and –0.501 (P<0.05), respectively. High STAT3 expression in HCC tissues could be associated to a worse prognosis. In patients with different STAT3 expression, a high expression of GP73 protein was associated with a short DFS.

Conclusions: GP73 and STAT3 have different roles in different stages of tumor progression in HCC patients.

Keywords: GOLM1; liver cancer; prognosis; signal transducer and activator of transcription 3 (STAT3); survival analysis

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most commonly occurred as well as the third most deadly cancer (1,2) which caused a huge medical and social burden (3). With a 5-years survival rate less than 5%, HCC is one of the cancers that have the poorest prognosis (4,5). However, prognosis could be ameliorated obviously by early diagnosis and treatment (6). Surgical resection is the still first choice of treatment for HCC. Tumor recurrence and metastasis, however, results in poor prognosis. It will be of significance to explore new methods for prognosis prediction so as to provide more effective treatment options for HCC patients.

Golgi protein 73 (GP73), also named as Golgi membrane protein 1 (GOLM 1) or Golgi phosphoprotein 2 (GOLPH2), is a 73 kD transmembrane glycoprotein which localized within the cis-Golgi complex, and has been reported to be a new serum biomarker of HCC (7). Our previous study, the largest global cohort study of GP73, demonstrated that GP73 had a sensitivity of 74.6% and a specificity of 97.4% for HCC diagnosis (8). Both sensitivity and specificity of GP73 are higher than those of AFP for HCC diagnosis. Using the combination of both GP73 and AFP levels for HCC would increase the sensitivity to 89.2%, and specificity to 85.2%. Further studies have indicated that the serum GP73 levels have no correlation to tumor clinicopathologic features; however, the GP73 levels in HCC tissues were associated with the size and differentiation of the tumor as well as its vein invasion status (8,9). Our most recent study showed that the increased GP73 could promote the proliferation and migration of HCC cell lines and tumor development in mice (10). Ye *et al*. reported that GOLM1 modulated EGFR/RTK cell-surface recycling to drive HCC metastasis (11). This confirmed that GP73 has a vital role in promoting primary liver cancer development. Our previous study on the relationship between GP73 and inflammatory pathways found that the expression of signal transducer and activator of transcription 3 (STAT3) was significantly decreased in cell lines that had increased GP73 expression. Meanwhile, the proliferation and migration of the cell lines were increased significantly. This was contradicted with the finding that STAT3 promotes tumorigenesis (10). In current study, therefore, we conducted an investigation for the relationship between GP73 and STAT3 in HCC tissues.

Methods

Patients and samples

Sixty-four HCC patients and 11 patients with hepatic hemangioma were involved in this study between March 2009 and May 2013. All the enrolled patients received hepatectomy in the Department of Liver Surgery of the Peking Union Medical College Hospital. HCC tissues and normal liver (NL) tissues were acquired in the operation room and reserved into liquid nitrogen directly. Then the tissues were transferred to –80 ℃ for further analysis.

Diagnoses were confirmed by histopathology. The patients' characteristics and clinicopathologic features such as gender, age, etiological factor, tumor size, tumor number, tumor differentiation, vein invasion, serum AFP, serum GP73, and recurrence status were collected. Vein invasion and recurrence were defined as previously described (9). The follow-up data were collected from patient themselves or their relatives. Disease-free survival (DFS, the time from hepatectomy to tumor recurrence) and overall survival (OS, the time from resection to death or the last follow-up point) were analyzed. The last follow-up date for this study was April 30, 2016. Three patients lost contact during follow-up.

GP73 and STAT3 protein expression analysis

Total protein was extracted from either HCC or NL tissues with lysis reagent (Dingduo, Beijing, China) using an SDT Tissumizer (Kimble, Vineland, NJ, USA). After extraction, the mixtures were centrifuged at 11,000 g at 5 ℃ for 4 minutes. Supernatants were then kept at –80 ℃, and next tested in batches. Protein concentrations were measured with bicinchoninic-acid (BCA) protein assay kit (Dingduo, Beijing, China).

Western blotting was conducted to measure the protein levels of GP73 and STAT3 as descripted in the previous report (9). Primary antibodies were either goat anti-GP73 polyclonal antibody (Santa Cruz Biotechnology, USA) with a dilution of 1:800 or mouse anti-STAT3 monoclonal antibody (Santa Cruz Biotechnology) with a dilution of 1:1,000. Anti-GAPDH (glyceraldehyde phosphate dehydrogenase) antibody with a dilution of 1:1,000 (Santa Cruz Biotechnology) was also used as internal control. The secondary antibodies, either anti-goat or anti-mouse (Santa Cruz Biotechnology), were diluted at 1:20,000. Quantification of the proteins was achieved by densitometric analysis of the bands using BandScan

Table 1 Clinicopathologic characteristics of HCC patients (n=64)

Parameter	No. (%)
Age (years)	50.1±9.0
Gender (male/female)	54/10
Etiological factor	
HBV	58 (90.6)
HCV	1 (1.6)
HBV + HCV	1 (1.6)
Unknown	4 (6.3)
Tumor size	
>3 cm	47 (73.4)
≤3 cm	17 (26.6)
Multiplicity	
Single	44 (68.8)
Multiple	20 (31.2)
Differentiation	
Well	28 (43.8)
Middle	10 (15.6)
Poor	26 (40.6)
Vein invasion	
Positive	14 (21.9)
Negative	50 (78.1)
AFP value (μg/mL)	
≥400	28 (43.8)
<400	36 (56.2)
Serum GP73 value (RU)	
≥5	48 (75.0)
<5	16 (25.0)
Recurrence status	
Yes	35 (54.7)
No	29 (45.3)

HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha fetoprotein; RU, relative units.

5.0 software, and was shown as integrated intensity units relative to that in NL tissues.

Statistical analysis

Statistical analysis was done with SPSS 20.0 software (SPSS Inc., Chicago, USA). Numerical values are shown as mean ± standard deviation (SD) or median (25^{th} and 75^{th} percentiles). GP73 and STAT3 protein expression between HCC and NL tissues was compared with Mann-Whitney U-test. Correlation between GP73/STAT3 expression and clinicopathologic parameters in patients with HCC was analyzed by Chi-square test and Fisher's exact test. The correlations between GP73/STAT3 expression and prognosis were analyzed by Bivariate Correlations. OS and DFS was estimated by Kaplan–Meier method and analyzed by log-rank test. All tests were two-tailed and was considered statistically significant when $P<0.05$.

Results

Patient characteristics

The mean age of the healthy controls was 48.3±10.5 years, 63.6% (7/11) were male. They were all patients with hepatic hemangioma, without hepatitis or cirrhosis. The HCC patient clinicopathologic features were summarized in *Table 1*. The mean age of patients with HCC was 50.1±9.0 years, and 84.4% (54/64) patients were male. Fifty-eight patients had hepatitis B virus (HBV, 90.6%) positive, one with hepatitis C virus (HCV, 1.6%), one with both (1.6%), and 4 had no history of viral hepatitis (6.3%). All HCC patients had various degrees of cirrhosis. Based on pathological classification, 28 HCC patients were well-differentiated, 10 were middle-differentiated, and 26 were poorly-differentiated. The mean tumor diameter was 5.3±2.6 cm. Forty-four patients had a single tumor (68.7%), whereas the other 20 patients had multiple tumors. Invasion to hepatic vein, portal vein, or major branch was detected in 14 patients (21.9%).

Forty-three patients died in follow-up. Median survival time was 738 days (59–2,167 days) and 5-year survival rate was 3.1%. In the cohort, 40.6% of patients had recurrence within 1 year and 54.7% of patients (35/64) had recurrence during follow-up.

GP73 and STAT3 protein expression in NL and HCC tissues

The median GP73 protein level in HCC tumor was 4.0 (2.1–5.3) RU. This was notably higher than that in NL tissues [1.6 (1.3–2.1) RU, $P<0.001$]. The median STAT3 level in HCC tissue was 1.2 (0.4–2.1) RU, which was also notably higher than that in NL tissues [0.7 (0.5–1.3) RU,

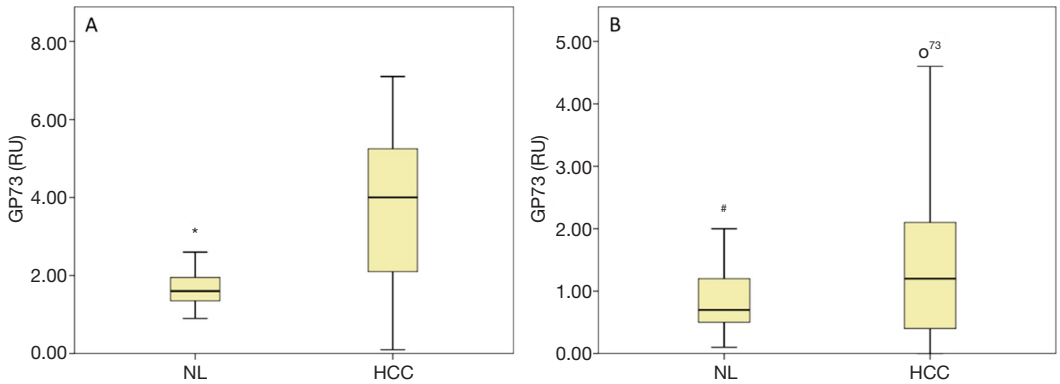

Figure 1 GP73 and STAT3 protein expression in normal liver (NL) and hepatocellular carcinoma (HCC) tissues. (A) GP73 protein expression in NL and HCC tissues; (B) STAT3 protein expression in NL and HCC tissues. *, P<0.001 *vs.* HCC; #, P<0.001. ° is the outlier. GP73, Golgi protein 73; STAT3, signal transducer and activator of transcription 3; NL, normal liver; HCC, hepatocellular carcinoma.

P<0.001] (As shown in *Figure 1*).

Correlation between GP73 and STAT3 expression and clinicopathologic features

On account of the expression levels of GP73 in HCC tissue, patients were separated into two groups: 15 belonged to the low expression group whereas the GP73 protein levels were lower than those in NL tissues; 49 belonged to the high expression group whereas the GP73 protein levels were higher than those in NL tissue.

There was significantly higher percentage of patients with positive vein invasion in the GP73 high expression group comparing with that in GP73 low expression group (P=0.047). At the same time, GP73 protein levels were found significantly higher in HCC patients with vein invasion than those without [4.7 (4.4–5.7) *vs.* 3.3 (1.7–4.9) RU, P<0.05].

The correlation of STAT3 protein expression levels and clinicopathologic features was also analyzed. Similarly, patients with HCC were separated into two groups according their HCC tissue STAT3 protein levels: 33 belonged to the high expression group whereas the STAT3 protein levels were higher than those in NL tissues, 31 belonged to the low expression group whereas the STAT3 protein levels were lower than those in NL tissue. As shown in *Table 2*, significant differences were observed in tumor size, differentiation, and vein invasion between these two groups.

HCC patients with a tumor size >3 cm had notably higher STAT3 expression levels than those with a tumor size ≤3 cm [1.7 (0.7–2.9) *vs.* 0.3 (0.1–0.7) RU, P<0.01]. Similarly, HCC patients with vein invasion expressed notably greater levels of STAT3 than those without [2.1 (0.9–3.0) *vs.* 0.9 (0.4–1.8) RU, P<0.01]. STAT3 expression in poorly-differentiated HCC tissues was notably greater than that in well-differentiated tissues [2.3 (1.7–3.4) *vs.* 0.4 (0.2–1.0) RU, P<0.001].

Association of GP73 and STAT3 expression with HCC prognosis

Analysis of whether a correlation between survival time and GP73 or STAT3 expression levels exists was performed using Bivariate Correlation. Expression levels of GP73 in HCC tissues were related to both DFS and OS, with Pearson correlations of –0.327 (P<0.01) and –0.302 (P<0.05) respectively. Survival analysis revealed that the mean DFS time of the GP73 high expression group was significantly shorter (857±141 days, P<0.05) than that of the GP73 low group (1,019±148 days). Similarly, the mean OS time of GP73 high expression group was 895±113 days, that was smaller than that of GP73 low group (1,050±149 days). However, there has no statistical difference between these groups (P=0.076).

Bivariate Correlations indicated that STAT3 protein expression in HCC tissues was correlated with DFS and OS, with a Pearson correlation of –0.374 (P<0.01) and –0.501 (P<0.05), respectively. Kaplan–Meier survival analysis and log-rank tests revealed that high level of STAT3 protein expression in HCC tissues correlated with a poor prognosis. As shown in *Figure 2*, the mean DFS of the STAT3 high expression group was significantly shorter (728±171 days, P<0.05) compared with STAT3 low

Table 2 Relationship between GP73/STAT3 protein expression and clinicopathological features in 64 cases of HCC

Parameter	GP73		P	STAT3		P
	High (n=49)	Low (n=15)		High (n=33)	Low (n=31)	
Age (years)	48.8±9.1	53.9±7.2	0.053	48.0±8.0	52.0±9.5	0.064
Gender			0.899			0.651
Male	41	13		29	25	
Female	8	2		4	6	
Etiological factor			0.520			0.976
HBV	45	13		28	28	
HCV	1	0		0	1	
HBV + HCV	1	0		1	0	
Unknown	2	2		2	2	
Tumor size			0.854			0.001*
>3 cm	36	10		30	17	
≤3 cm	13	5		3	14	
Multiplicity			0.160			0.363
Single	31	13		21	23	
Multiple	18	2		12	8	
Differentiation			0.105			0.001*
Well	20	8		5	23	
Middle	5	5		3	7	
Poor	24	2		25	1	
Vein invasion			0.047*			0.022*
Positive	14	0		11	3	
Negative	35	15		22	28	
AFP value (μg/mL)			0.738			0.072
≥400	22	6		18	10	
<400	27	9		15	21	
Serum GP73 value (RU)			0.865			0.194
≥5	36	12		27	21	
<5	13	3		6	10	
Recurrence status			0.058			0.083
Yes	30	5		22	14	
No	19	10		11	17	

Values are presented as a number (%) unless otherwise indicated. HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha fetoprotein; RU, relative units.

expression group (1,120±144 days). The mean OS of the STAT3 high expression group was also significantly shorter (738±129 days, P<0.01) than that of STAT3 low group (1,143±124 days).

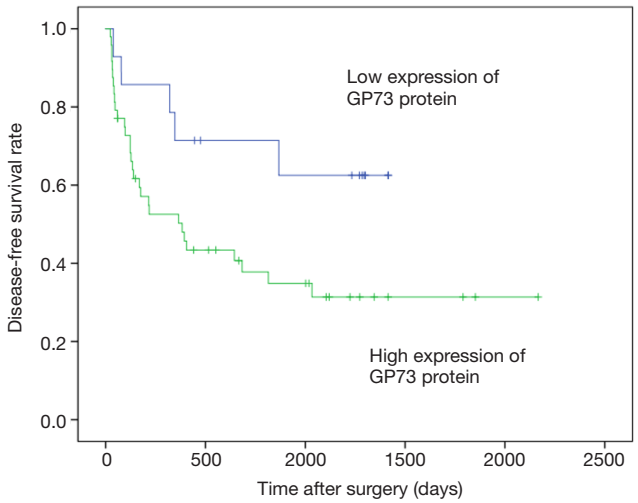

Figure 2 Survival curves for disease-free survival in hepatocellular carcinoma (HCC) according to Golgi protein 73 (GP73) expression. Kaplan-Meier method showed that the mean disease free survival time of the GP73 high expression group (857±141 days) was significantly lower, compared with the GP73 low expression group was (1,019±148 days, P<0.05).

When expression levels of both proteins were considered, the patients with HCC were separated into four groups: group A has low expression levels in both GP73 and STAT3; group B has high expression levels in both proteins; group C has low GP73 but high STAT3; and group D has high GP73 and low STAT3. Shown in *Figure 3* were the Kaplan–Meier survival curves. As shown in *Figure 4*, the DFS of four Groups were significantly different (P<0.01), at 1,085±176 days, 545±162 days, 1,149±240 days, and 960±182 days, respectively. The OS of four Groups were also significantly different (P<0.05), at 1,177±173 days, 684±132 days, 781±238 days, and 1,089±149 days, respectively.

Discussion

In normal human liver tissues, GP73 is mainly expressed in epithelial cells of the bile duct, with little or no expression in hepatocytes. Marked increased expression of GP73 could be the result of viral (HBV and HCV) infection in liver cells (7), or non-viral causes (alcoholic liver disease and autoimmune hepatitis) (12,13). Therefore, the expression of GP73 may respond to different mechanisms, such as acute hepatocyte injury, or chronic liver disease.

STATs are proteins involved in the control of signal transduction and transcription. Among the members of the STAT protein family, STAT3 is a key factor in the Janus

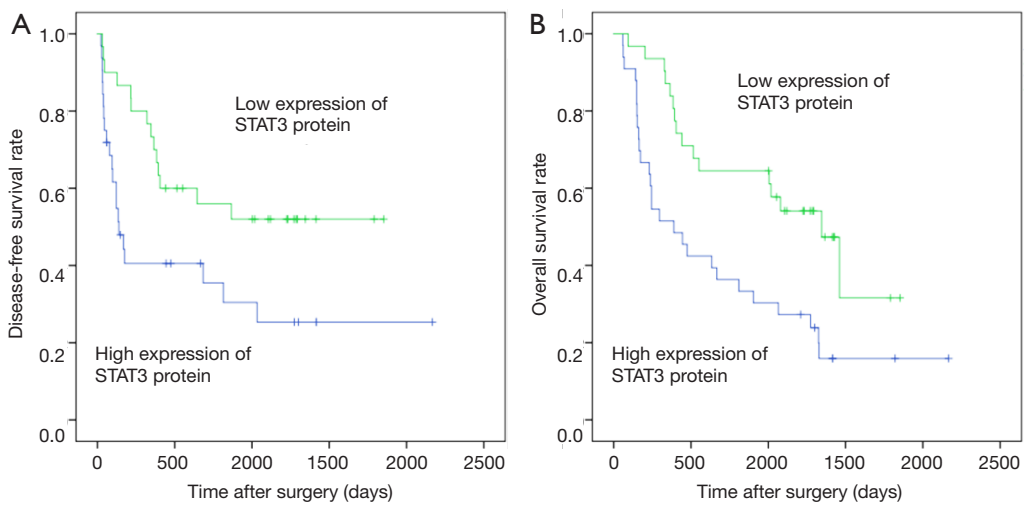

Figure 3 Kaplan–Meier curves for disease free survival (DFS) and overall survival (OS) in hepatocellular carcinoma (HCC) according to signal transducer and activator of transcription 3 (STAT3) expression. (A) The mean DFS of the STAT3 high expression group was significantly lower 728±171 days, compared with the STAT3 low expression group (1,120±144 days, P<0.05); (B) the mean OS of the STAT3 high expression group (738±129 days) was also significantly lower, compared with STAT3 low expression group (1,143±124 days, P<0.01)

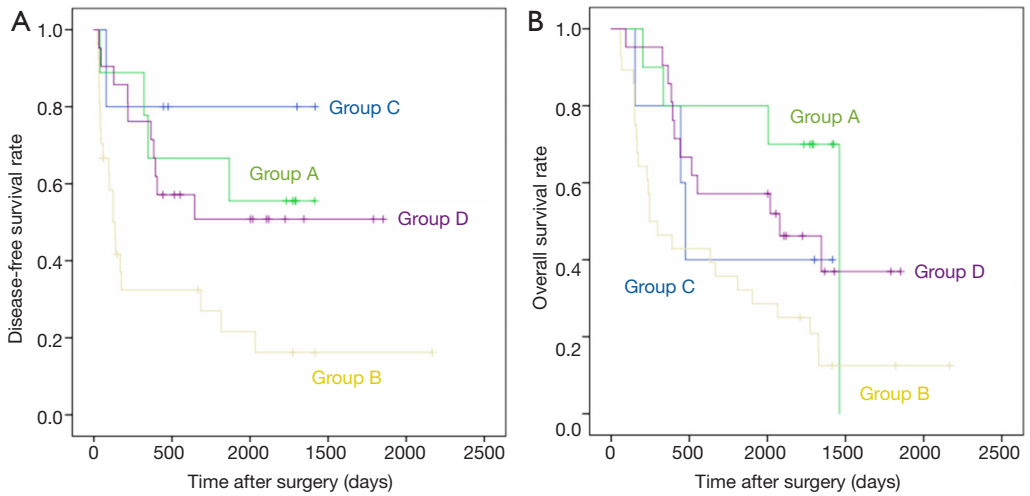

Figure 4 Kaplan–Meier curves for disease free survival (DFS) and overall survival (OS) in hepatocellular carcinoma (HCC) according to Golgi protein 73 (GP73) and signal transducer and activator of transcription 3 (STAT3) expression. (A) The DFS of Groups A, B, C, and D have significantly different (P<0.01); (B) the OS of Groups A, B, C, and D have significantly different (P<0.05). Group A with GP73 low expression and STAT3 low expression; group B with GP73 high expression and STAT3 high expression; group C with GP73 low expression and STAT3 high expression; and group D with GP73 high expression and STAT3 low expression.

kinase/STAT signaling pathway. It can be phosphorylated as the result of the stimulation by several cytokines and growth factors, and played a vital role in cell proliferation, apoptosis, cell cycle regulation, and differentiation (14-18). The improved STAT3 expression is because of the molecular mechanisms on HCC evolution and progression (19-21). Therefore, STAT3 has become an attractive target for the study of tumor therapy (22).

In the current study, the protein expression levels of GP73 and STAT3 in HCC tissues were assessed and we investigated whether there is a relationship between these two key proteins and clinical outcome. The median protein levels of GP73 and STAT3 in HCC tumors were both notably greater than those in NL tissues. The vein invasion status of the GP73 high expression group and GP73 low expression group was significantly different, indicating that GP73 protein could be associated with tumor invasion. Furthermore, the survival analysis exhibited that the mean DFS of the GP73 low expression group was 18.9% longer than that of the GP73 high expression group. Of note, this finding is not consistent with our previous reports (9).

STAT3 protein expression in HCC tissues and its correlation with tumor characteristics and outcomes was also analyzed. The results indicated that STAT3 expression was correlated with differentiation, tumor size, and vein invasion. Kaplan–Meier analysis demonstrated that high expression of STAT3 protein in HCC tissues was related to a poor prognosis. The DFS of the STAT3 low expression group was 53.8% longer than that of STAT3 high group, while the OS of the STAT3 low expression group was 54.9% longer than that of STAT3 high group.

Multivariable analysis with GP73 TAT3 protein expression levels for their correlation with the HCC patients survival, it was noted that the DFS and OS of the four groups were significantly different. We found that the OS of group A (low GP73 and low STAT3) was longer than that of the other three groups. Group B (high GP73 and high STAT3) had the shortest OS. The OS of group D (high GP73 and low STAT3) was longer than that of group C (low GP73 and high STAT3). This could suggest that the effect of STAT3 on the OS was greater than that of GP73.

It was worth noting that the effect of GP73 and STAT3 on OS and DFS were not consistent in the four groups. The DFS of group C was longer than that of other three groups. In patients with both low expressions of GP73, patients with low STAT3 expression had an average shorter DFS than those with higher STAT3 expression (comparing group A and C). In contrast, low STAT3 expression led to an average longer DFS in patients with high GP73 expression than those with low GP73 expression (comparing group D and A). However, high expression of GP73 always correlated with shorter DFS regardless the expression levels of STAT3 (comparing group A and D, or B and C). Taken together, this study demonstrated that GP73 has a greater

influence on the DFS rather than the OS. However, once HCC recurs, STAT3 might be a more reliable indicator for patient prognosis.

In conclusion, this is the first study of both GP73 and STAT3 protein expressions from the same HCC tissues and their correlations with clinicopathologic features and prognosis of HCC. Our study suggested that GP73 and STAT3 may have different roles in different stages of disease progression in HCC patients. GP73 has a greater impact on disease recurrence, whereas STAT3 has a greater impact on OS. The mechanisms involved require further study.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.01.03). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethical committee, and written informed consent was obtained from each patient.

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