Pathol. Oncol. Res. (2014) 20:805–811
DOI 10.1007/s12253-014-9757-y

RESEARCH

Overexpression of YAP1 is Correlated with Progression, Metastasis and Poor Prognosis in Patients with Gastric Carcinoma

Xiaobin Hu · Yan Xin · Yuping Xiao · Jing Zhao

Received: 11 June 2013 / Accepted: 25 February 2014 / Published online: 19 March 2014

Abstract YAP1 is overexpressed in numerous cancers, but its molecular mechanism in the carcinogenesis and clinic significance in tumor diagnosis and prognosis remains to be determined. We attempted to analyze the clinicopathologic significance of YAP1 expression and the correlation of the YAP1 levels with the progression, metastasis and prognosis of patients with gastric carcinoma. By immunohistochemistry, we determined YAP1 expression in 214 of primary gastric carcinoma (GC), 167 of matched normal gastric mucosa, 40 of chronic atrophic gastritis, 11 of dysplasia and 73 of intestinal metaplasia. The positive rate of YAP1 in gastric carcinoma was significantly higher than that in normal gastric mucosa, chronic atrophic gastritis and intestinal metaplasia. In the gastric cancers with lymph node metastasis, the positive rate of YAP1 was much higher than that in the group without lymph node metastasis. Moreover, gastric cancer patients with YAP1 overexpression demonstrated poorer prognosis than those with YAP1 negative staining. Finally, multivariate analysis of 191 patients with gastric carcinoma indicated that YAP1 overexpression, the invasion depth and lymph node metastasis were high hazard factors for gastric carcinoma. Our results demonstrated that YAP1 overexpression is correlated to the progression, lymph node metastasis and poor prognosis of gastric carcinoma, suggesting that overexpression of YAP1 might be an adjuvant factor for predicting lymph node metastasis, and a useful biomarker for the diagnosis and prediction of prognosis in patients with gastric cancers.

Keywords YAP1 · Gastric carcinoma · Metastasis · Prognosis

Abbreviations

CAG	Chronic atrophic gastritis
Dys	Dysplasia
ESCC	Esophageal squamous cell carcinoma
GC	Gastric carcinoma
HCC	Hepatocellular carcinoma
IM	Intestinal metaplasia
SRC	Signet ring cell carcinoma
YAP1	Yes-associated protein 1

Introduction

Gastric cancer (GC) is the second common cancer-related death across the globe. Most gastric cancer patients are diagnosed at advanced stages, with 90 % of lymphatic metastases and 35 % of blood-borne metastases [1]. The prognosis of gastric cancer is generally poor, with a 5-year survival rate below 30 % [2]. So, there is a great need in understanding the molecular mechanism of gastric carcinogenesis in order to find molecular targets for the development of new drugs, and diagnosis of GC patients.

The Hippo signaling pathway controls the intrinsic size of organs by coordinating cell proliferation and apoptosis. In tumors, mutation in Hippo signaling pathway leads to dephosphorylation and activation of YAP1. YAP1 is a candidate oncogene in human chromosome 11q22 amplicon [3–6]. Mutation of Yki, the Drosophila homolog of YAP1, results in dramatically reduced organ size, while Yki overexpression causes tissue overgrowth [7–10]. Similarly, transgenic

X. Hu
Gastrointestinal Tumor Pathology Laboratory of Cancer Institute and Department of Pediatrics, No. 1 Hospital of China Medical University, 155 North Nanjing Street, Heping District, Shenyang 110001, Liaoning Province, China
e-mail: huxiaobin0325@sina.com

Y. Xin (✉) · Y. Xiao · J. Zhao
Gastrointestinal Tumor Pathology Laboratory of Cancer Institute and General Surgery Institute, No.1 Hospital of China Medical University, 155 North Nanjing Street, Heping District, Shenyang 110001, Liaoning Province, China
e-mail: yxin@mail.cmu.edu.cn

overexpression of YAP1 in mice liver results in enlarged liver and causes liver tumor [4, 11]. In MCF-10A mammary epithelial cells, overexpression of YAP1 leads to oncogenic transformation [12]. YAP1 protein levels were shown to be frequently elevated in multiple types of human cancers including hepatocellular carcinoma (HCC), prostate cancer, colon cancer, ovary cancer, esophageal squamous cell carcinoma (ESCC) and breast cancer [13–17]. Recently, it was found that knockdown YAP1 in gastric cancer cell lines led to a dramatic decrease in proliferation and colony formation, whereas YAP1 overexpression significantly increased cell growth both in vitro and in vivo [18], supporting the proposal that YAP1 is an oncogene [12, 19]. These findings led us to hypothesize that the oncogenic function of YAP1 may promote the multistep processes of gastric carcinogenesis and YAP1 is a potential biomarker for the GC.

In this study, we detected YAP1 expression in human gastric carcinoma and its precancerous lesions, and analyzed the correlations of YAP1 level with gastric tumorigenesis, lymph node metastasis, organic metastasis and prognosis. Our results demonstrated that upregulation of YAP1 is associated with the process of gastric carcinogensis, metastasis and poor prognosis of GC patients.

Materials and Methods

Clinicopathological Data Two hundreds and 14 patients with primary gastric carcinoma (GC) who underwent curative resection without radiotherapy or chemotherapy at the first Affiliated Hospital of China Medical University and Tumor Hospital of Liaoning Province between December 2003 and April 2007 were involved in the present study. The patients were comprised of 150 males and 64 females with a median age of 58.9 years (range from 30 to 81 years). Surgically resected tissue specimens collected for the investigation were comprised of 214 cases of primary gastric carcinoma, 167 cases of matched normal gastric mucosa (obtained at greater than 5 cm apart from the edge of primary tumor focus), 40 chronic atrophic gastritis (CAG), 11 dysplasia (Dys) and 73 intestinal metaplasia (IM). According to Borrmann's classification, gross typings of advanced GC were classified as nine cases of Borrmann I, 34 cases of Borrmann II, 155 cases of Borrmann III, and 16 cases of Borrmann IV. According to WHO's histological classification of GC, 214 cases were classified as four with papillary adenocarcinoma, nine well and 70 moderately as well as 116 poorly differentiated adenocarcinoma, one undifferentiated carcinoma, eight mucinous adenocarcinoma and six signet ring cell carcinoma (SRC). There were 87 cases of intestinal, 127 diffuse typing tumors according to Lauren's classification. There were 161 cases without and 53 cases with the penetrated serosa, 56 cases without and 158 cases with lymph node metastasis, 203 cases without and 11 cases with distant organ metastasis (Table 2).

Tissue Microarray Construction and Immunohistochemical Staining Samples were fixed in 10 % formalin, embedded in paraffin and cut into 4 μm thick sections. All the samples were evaluated by two experienced pathologists to confirm the diagnoses, and marked various target lesions. Seven blocks of tissue microarray containing gastric cancers and their corresponding precancerous lesions, normal gastric mucosa were constructed by using Microarrayer (USA). Sections were cut in 4 μm size for conventional H&E staining and the others for further immunohistochemistry. YAP1 protein was detected by using PV-9000 two-step immuno- histochemical method. Mouse monoclonal antibody against human YAP1 was purchased from Abcam Company (working dilution 1:50) and DAB kit was from Fuzhou Maixin Company (Fuzhou, China). PV-9000 kit was from Beijing Zhongshan Goldenbridge Biotechnology Company (Beijing, China). Tissue microarray slides were deparaffinized in xylene and hydrated with alcohol before being placed in 3 % H_2O_2 methanol blocking solution, which was followed by heat-induced antigen retrieval. The slides were incubated with primary antibodies overnight at 4 °C, stained using the PV-9000 detection system and counterstained with hematoxylin. All procedures were implemented according to the manufacturer's instructions. For negative controls, sections were treated with 0.01 M phosphate-buffered saline instead of primary antibodies.

Immunohistochemistry Assessment The YAP1 positive was defined as that there was clearly brown granules located in cytoplasm or nuclei. The expression of YAP1 was assessed by assigning a proportion score and an intensity score in tumor cells and gastric mucosa epithelial cells. The proportion score was made according to the proportion of positive cells (0, none; 1, <=10 %; 2, 11 %–25 %; 3, 26 %–50 %; 4, >50 %). The intensity score was assigned for the average intensity of positive cells (0, none; 1, weak; 2, intermediate; 3, strong). The score of YAP1 was the product of proportion and intensity scores, ranging from 0 to 12. The expression was categorized into negative (0), (−); low (score 1 to 3), (+); intermediate (score 4–6), (++); and high (score 7–12), (+++). According to above assessing criterion, the immunostaining results were classified into: negative (score 0), (−); low (score 1–4), (+); intermediate (score 5–8), (++) and high (score 9–12), (+++). The scoring was independently assessed by two experienced pathologists.

Statistical analysis Categorical data are described using frequencies and percentages. Continuous data are described as means with standard deviations for normally distributed data. Statistical analysis was performed using SPSS 16.0 Package and χ^2 test, or Fisher's exact test was used to differentiate the rates of different groups. Time-to-event data was

estimated by the Kaplan-Meier method and analyzed with the log-rank test. The cumulative overall survival rates were calculated using life table techniques, illustrated by Kaplan-Meier plots. Multivariable analysis model was fit using a Cox proportional hazards regression model using SPSS16.0. The enter method was used to determine a final Cox model. All statistical analysis were two-sided, and significance was assigned at α=0.05.

Results

YAP1 Expression is Correlated with the Progression of Gastric Carcinogenesis Averagely, a solid tumor has accumulated around 100 genetic alterations during the multistep process of tumorigenesis. It has been shown that YAP1 is upregulated in gastric cancers (18), but whether YAP1 is a driver or passenger for the tumorigenesis of GC that remains to be determined. For this, we checked YAP1 levels of normal gastric mucosa, chronic atrophic gastritis, intestinal metaplasia, dysplasia and gastric cancer (Table 1). The positive rate of YAP1 protein expression in gastric carcinoma (68.7 %, 147/214) was significantly higher than that in normal gastric mucosa (19.2 %, 32/167), chronic atrophic gastritis (25.0 %, 10/40) and intestinal metaplasia (39.7 %, 29/73) (P<0.05). The positive rate of YAP1 in intestinal metaplasia (39.7 %, 29/73) was significantly higher than that in normal gastric mucosa (19.2 %, 32/167) (P<0.05). In addition, the positive rate of YAP1 in dysplasia (45.5 %) is apparently higher than those in normal gastric mucosa, chronic atrophic gastritis. These data demonstrated that the positive rate of YAP1 protein expression was gradually increased from normal gastric mucosa, chronic atrophic gastritis and intestinal metaplasia, dysplasia to gastric cancer (Fig. 1a–d). Further analysis showed that the positive rate of YAP1 was positively related to the severity of gastric diseases (r_k=0.411, P<0.05) (Table 1), indicating that YAP1 might be required for the progression of GC tumorigenesis.

Elevated Expression of YAP1 in Gastric Cancer with Lymph Node Metastasis Most cancer patients die from metastasis and the majority of GC patients are diagnosed at metastasis stages. It is still unknown whether overexpression of YAP1 is related to or plays a role in GC metastasis. There was no significant difference between the YAP1 expression in gastric cancer and patients' gender, age, Bormann's typing, invasion depth or distant organ metastasis. In Lauren's typings of gastric cancer, the positive rate of YAP1 protein in gastric cancer of intestinal typing (77.0 %, 67/87) was significantly higher than that in diffuse typing (63.0 %, 80/127), (P<0.05). The overexpression of YAP1 was positively related to the histological differentiation of tumors (r_k=0.135, P<0.05). In gastric cancer with lymph node metastasis, the positive rate of YAP1 protein (72.8 %, 115/158) was significantly higher than that in the group without lymph node metastasis (57.1 %, 32/56) (P<0.05) (Table 2). Thus, lymph node metastasis is accompanied with increased expression of YAP1.

Survival Curves and Multivariate cox Proportional Hazards Regression of Patients with Gastric Carcinoma of Different YAP1 Expression To determine the clinic significance of YAP1 in GC patient prognosis, we did Kaplan-Meier analysis of disease-free survival (DFS) rates for 191 cases of gastric cancer patients (23 out of the 214 patients were lost from follow-up) categorized with positive and negative expression for YAP1 expression. DFS was calculated from the date of primary surgery to the date of last follow-up or to the date of death due to cancer relapse or metastasis. With a total follow-up of 65 months, 85 of the 191 assessable patients were still alive and 106 patients died. The DFS for all patients was 44.5 %. The DFS for patients with negative and positive YAP1 expression was 59.6 % and 38.1 %, respectively (P=0.004) (Fig. 2). Our data demonstrated that patients with

Table 1 Expression and correlation of YAP1 in normal gastric mucosa, CAG, IM, Dys and GC

Groups	*n*	YAP1 expression				+~+++ (%)	χ^2	*P*
		−	+	++	+++			
								<0.001[w*]
Normal	167	135	17	14	1	19.2	0.68[a]/11.332[b]	0.41[a]/0.001[b]
CAG	40	30	10	0	0	25	2.479[c]	0.115[c]/0.264[d]
IM	73	44	15	7	7	39.7	1.593[e]/19.255[f]	0.751[e]/<0.001[f]
Dys	11	6	5	0	0	45.5		0.053[g]/0.182[h]
GC	214	67	51	62	34	68.7	92.382[i]/27.254[j]	<0.001[i]/<0.001[j]
r_k=0.411, P<0.001								

[w] Overall compared; [a] Normal mucosa vs CAG; [b] Normal mucosa vs IM; [c] CAG vs IM; [d] CAG vs Dys; [e] IM vs Dys; [f] IM vs GC; [g] Normal mucosa vs Dys; [h] Dys vs GC; [i] Normal mucosa vs GC; [j] CAG vs GC

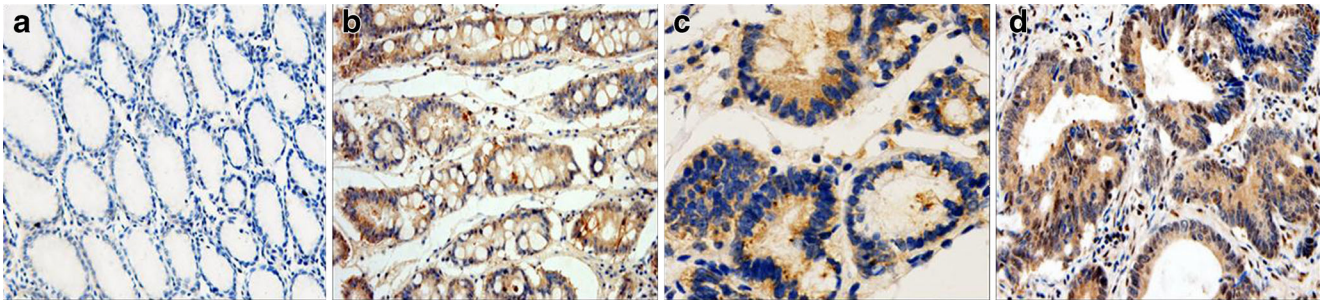

Fig. 1 Expression of YAP1 is correlated with the progression of the tumorigenesis of gastric cancers. The negative staining of YAP1 in normal gastric mucosa epithelial cells (**a**), positive staining of YAP1 in intestinal metaplasia (**b**), strongly positive staining of YAP1 in dysplasia (**c**) gastric carcinoma with both cytoplasm and nucleus present (**d**). Original magnification, A, B=×200; C, D=×400

Table 2 Correlation between YAP1 expression and clinicopathological features of GC

Groups	*n*	YAP1 expression				+~+++ (%)	χ^2	*P*
		–	+	++	+++			
Gender							0.096	0.757
Male	64	21	13	14	16	67.2		
Female	150	46	38	48	18	69.3		
Age (years old)							0.005	0.1
≤61	111	35	28	37	11	68.5		
>61	103	32	23	25	23	68.9		
Borrmann's typing								0.175
Bor.I	9	1	0	2	6	88.9		
Bor.II	34	13	14	4	3	61.8		
Bor.III	155	51	34	45	25	67.1		
Bor.IV	16	2	3	11	0	87.5		
WHO's hist. typing								0.206*
Papillary. ade.	4	1	0	2	1	75		
Tubular ade.								
Well-diff.	9	0	3	4	2	100	r_k=0.135	0.040
Moderately-diff.	70	19	15	21	15	72.9		
Poorly-diff.	116	41	28	31	16	64.7		
Undiff.	1	0	0	1	0	100		
Mucinous ade.	8	4	2	2	0	50		
SRC	6	2	3	1	0	66.7		
Lauren's typing							4.718	0.030
Intestinal	87	20	20	29	18	77.0		
Diffuse	127	47	31	33	16	63.0		
Invasion depth							0.296	0.286
Serosanon-penetrated	161	52	33	49	27	67.7		
Serosa penetrated	53	15	18	13	7	71.7		
Lymphnode metastasis							4.704	0.030
No	56	24	11	15	6	57.1		
Yes	158	43	40	47	28	72.8		
Distant metastasis								0.58*
Ovary	2	0	1	0	1	100		
Liver	4	0	2	1	1	100		
Peritoneum	5	1	3	0	1	80		
None	203	66	45	61	31	67.5		

*Fisher's exact test; *ade.* Adenocarcinomas; *diff.* Differentiated; *hist.* histological

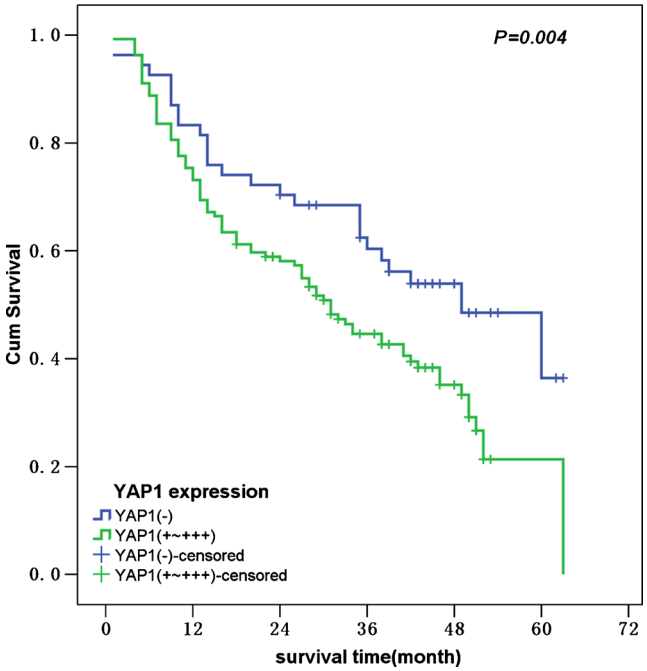

Fig. 2 Kaplan–Meier analysis of overall survival rates for 191 gastric cancer patients categorized with positive and negative expression for YAP1 expression in gastric cancers. Patients with YAP1 positive tumors showed significantly worse outcome than that with YAP1 negative ones, P=0.004

YAP1 positive tumors tend to have worse prognosis than those with negative tumors.

We next used Multivariate Cox proportional hazards regression of 191 patients with gastric carcinoma to adjust the survival for the effect of independent predictors of prognosis. We have defined the parameters according to Table 1. These included the presence of YAP1 positive expression (P=0.043, hazard ratio [HR] 1.676), invasion depth (P=0.003 HR 1.543), and lymph node metastasis of gastric cancer (P<0.001, HR 3.080). Table 3 indicated that YAP1 overexpression, invasion depth and lymph node metastasis were high hazard factors for gastric carcinoma.

Discussion

Several reports have showed that high-expression or nuclear accumulation of YAP1 was correlated with poor survival in patients with gastric carcinoma, but the majority of these studies were carried out in small cohorts of patients [18–23]. To our knowledge, only one study was performed in a large cohort with 223 patients with gastric cancer, however, normal gastric mucosa was not included as control [20]. Here, we used a relative large cohort including 214 of primary gastric carcinoma, 167 of matched normal gastric mucosa, 40 of chronic atrophic gastritis, 11 of dysplasia and 73 of intestinal metaplasia to clarify the role and clinical significance of YAP in gastric carcinoma. Our results demonstrated that YAP1 was correlated with the progression of gastric carcinogenesis and its high-expression was associated with lymph node metastasis and poor prognosis.

The positive rate of YAP1 protein expression in gastric carcinoma was about 68.7 %, which was significantly higher than that in normal gastric mucosa, chronic atrophic gastritis and intestinal metaplasia. The positive rate of YAP1 in gastric carcinoma in this study is similar to that reported by zhang et al. [21] but higher than that showed by Da et al. and Song et al. [19, 20]. These reports supported the oncogenic role of YAP1 in gastric cancer [18]. More importantly, by correlation analysis, we found that the positive rate of YAP1 protein expression was gradually increased from normal gastric mucosa, chronic atrophic gastritis, intestinal metaplasia, dysplasia to gastric cancer, indicating that YAP1 was associated with the degree of malignancy and might be involved in the whole process of gastric tumorigenesis. Similarly, it was showed that there was a significant increase of cytoplasmic and nuclear localization of YAP1 in high-grade dysplastic epithelium, esophagus adenocarcinoma, gastric carcinoma and metastatic gastric disease compared to nonneoplastic related epithelium tissue, suggesting a role for YAP1 in esophageal and gastric epithelial tumorigenesis [17]. These results suggest that overexpression of YAP1 might not only contribute to the development of gastric carcinoma, but also be involved in the initiation process of gastric carcinoma.

Table 3 Multivariate Cox regression analysis of survival of 191 GC patients

Variable	Regression Coefficient (± SE)	P	Hazard Ratio (95.0 % CI)
YAP1 expression	0.517±0.255	0.043	1.167 (1.017–2.762)
Gender	0.107±0. 215	0.618	1.113 (0.731–1.694)
Age	0.422±0. 220	0.056	1.525 (0.990–2.348)
Borrmann's typing	0.291±0. 168	0.083	1.338 (0.962–1.860)
WHO's Hist.typing	−0.266±0. 145	0.066	0.766(0.577–1.018)
Lauren's typings	0.505±0.272	0.063	1.657 (0.973–2.822)
Invasion depth	0.434±0.145	0.003	1.543 (1.162–2.050)
Lymph node metastasis	1.125±0.293	0.000	3.080(1.736–5.465)
Organic metastasis	0.119±0.370	0.747	1.126 (0.546–2.324)

Our data showed that the positive rate of YAP1 protein in Lauren's type and intestinal type was significantly higher than that in diffuse type. The positive rate of YAP1 was positively related to histocytic differentiation degree of gastric cancer cells. The correlation was quite weak, although the correlative trend has reached statistical significance. Meanwhile, in gastric cancer with lymph node metastasis, the positive rate of YAP1 protein was significantly higher than that in the group without lymph node metastasis. These results indicated that YAP1 may promote lymph node metastasis and suggested that YAP1 can be used as an adjuvant factor to predict lymph node metastasis of gastric cancer. The ability of cancer cells to disseminate from the primary tumor to lymph nodes and to the nearest and distant tissues and organs is a fundamental feature of malignancies and it is the major cause of therapeutic failures. Consistently, YAP1 overexpression was negatively related to patient's prognosis. Therefore, detection of YAP1, one of tumor-specific biomarkers in gastric carcinomas, can provide additional efficacy in predicting patients' outcomes. However, the molecular mechanisms by which YAP1 promotes metastasis and helps cancer cells to escape from therapy remains to be elucidated.

In summary, by using a relatively large cohort, we demonstrated that YAP1 expression is correlated with the progression and metastasis of GC, and it is a potential diagnostic and prognostic biomarker for GC patients. To date, the functions and mechanisms of YAP1 and its related Hippo pathway in the tumorigenesis and cancer cell metastasis are largely unknown. Therefore, it is essential to elucidate the molecular biology of YAP1 in the future.

Authors' Contributions XY and HXB conceived the study and drafted the manuscript. HXB, XYP and ZJ collected and analyzed the data. XY secured funding. XY, HXB and XYP contributed to the quality control of study inclusion and discussion. All authors read and approved the final manuscript.

Grant Support This work was supported by the National Natural Science Foundation of China (NO.81071650; 30973503); Special foundation for Science and Technology Program in Liaoning Province, China (2013225303-103); the Supporting Project for Climbing Scholars in Liaoning Provincial Universities, China (2009-2012).

Conflict of Interest None to declare.

References

1. Jackson C, Cunningham D, Oliveira J (2009) Gastric cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 20:34–36
2. Thun MJ, DeLancey JO, Center MM, Jemal A, Ward EM (2010) The global burden of cancer: priorities for prevention. Carcinogenesis 31: 100–110
3. Zhao B, Wei X, Li W, Udan RS, Yang Q, Kim J, Xie J, Ikenoue T, Yu J, Li L, Zheng P, Ye K, Chinnaiyan A, Halder G, Lai ZC, Guan KL (2007) Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. Genes Dev 21:2747–2761
4. Dong J, Feldmann G, Huang J, Wu S, Zhang N, Comerford SA, Gayyed MF, Anders RA, Maitra A, Pan D (2007) Elucidation of a universal size-control mechanism in drosophila and mammals. Cell 130:1120–1133
5. Zender L, Spector MS, Xue W, Flemming P, Cordon-Cardo C, Silke J, Fan ST, Luk JM, Wigler M, Hannon GJ, Mu D, Lucito R, Powers S, Lowe SW (2006) Identification and validation of oncogenesin liver cancer using an integrative oncogenomic approach. Cell 125: 1253–1267
6. Zhang X, George J, Deb S, Degoutin JL, Takano EA, Fox SB, AOCS Study group, Bowtell DD, Harvey KF (2011) The Hippo pathway transcriptional co-activator, YAP, is an ovarian cancer oncogene. Oncogene 30:2810–2822
7. Goulev Y, Fauny JD, Gonzalez-Marti B, Flagiello D, Silber J, Zider A (2008) SCALLOPED interacts with YORKIE, the nuclear effector of the Hippo tumor-suppressor pathway in Drosophila. Curr Biol 18: 435–441
8. Zhang L, Ren F, Zhang Q, Chen Y, Wang B, Jiang J (2008) The TEAD/TEF family of transcription factor Scal-loped mediates Hippo signaling in organ size control. Dev Cell 14:377–387
9. Wu S, Liu Y, Zheng Y, Dong J, Pan D (2008) TheTEAD/TEF family protein Scalloped mediates transcrip-tional output of the Hippo growth-regulatory pathway. Dev Cell 14:388–398
10. Huang J, Wu S, Barrera J, Matthews K, Pan D (2005) The Hipposignaling pathway coordinately regulates cell proliferation and apoptosis by inactivating Yorkie, the Dro sophila homolog of YAP. Cell 122:421–434
11. Camargo FD, Gokhale S, Johnnidis JB, Fu D, Bell GW, Jaenisch R, Brummelkamp TR (2007) YAP1 increases organ size and expands undifferentiated progenitor cells. Curr Biol 17:2054–2060
12. Overholtzer M, Zhang J, Smolen GA, Muir B, Li W, Sgroi DC, Deng CX, Brugge JS, Haber DA (2006) Transforming properties of YAP, a candidate oncogene on the chromosome 11q22 amplicon. Proc Natl Acad Sci U S A 103:12405–12410
13. Tufail R, Jorda M, Zhao W, Reis I, Nawaz Z (2011) Loss of Yes-associated protein (YAP) expression is associated with estrogen and progesterone receptors negativity in invasive breast carcinomas. Breast Cancer Res Treat 131:743–750
14. Steinhardt AA, Gayyed MF, Klein AP, Dong J, Maitra A, Pan D, Montgomery EA, Anders RA (2008) Expression of Yes-associated protein in common solid tumors. Hum Pathol 39:1582–1589
15. Zhang J, Ji JY, Yu M, Overholtzer M, Smolen GA, Wang R, Brugge JS, Dyson NJ, Haber DA (2009) YAP-dependent induction of amphiregulin identifies a non-cell-autonomous component of the Hippo pathway. Nat Cell Biol 11:1444–1450
16. Xu MZ, Yao TJ, Lee NP, Ng IO, Chan YT, Zender L, Lowe SW, Poon RT, Luk JM (2009) Yes-associated protein is an independent prognostic marker in hepatocellular carcinoma. Cancer 115:4576–4585
17. Lam-Himlin DM, Daniels JA, Gayyed MF, Dong J, Maitra A, Pan D, Montgomery EA, Anders RA (2006) The hippo pathway in human upper gastrointestinal dysplasia and carcinoma: a novel oncogenic pathway. Int J Gastrointest Cancer 37:103–109

18. Kang W, Tong JH, Chan AW, Lee TL, Lung RW, Leung PP, So KK, Wu K, Fan D, Yu J, Sung JJ, To KF (2011) Yes-associated protein 1 exhibits oncogenic property in gastric cancer and its nuclear accumulation associates with poor prognosis. Clin Cancer Res 17:2130–2139
19. Da CL, Xin Y, Zhao J, Luo XD (2009) Significance and relationship between Yes-associated protein and survivin expression in gastric carcinoma and precancerous lesions. World J Gastroenterol 15:4055–4061
20. Song M, Cheong JH, Kim H, Noh SH, Kim H (2012) Nuclear expression of Yes-associated protein 1 correlates with poor prognosis in intestinal type gastric cancer. Anticancer Res 32:3827–3834
21. Zhang J, Xu ZP, Yang YC, Zhu JS, Zhou Z, Chen WX (2012) Expression of Yes-associated protein in gastric adenocarcinoma and inhibitory effects of its knockdown on gastric cancer cell proliferation and metastasis. Int J Immunopathol Pharmacol 25:583–590
22. Zhang J, Yang YC, Zhu JS, Zhou Z, Chen WX (2012) Clinicopathologic characteristics of YES-associated protein 1 overexpression and its relationship to tumor biomarkers in gastric cancer. Int J Immunopathol Pharmacol 25:977–987
23. Zhou GX, Li XY, Zhang Q, Zhao K, Zhang CP, Xue CH, Yang K, Tian ZB (2013) Effects of the hippo signaling pathway in human gastric cancer. Asian Pac J Cancer Prev 14:5199–5205