



## Reply to: “YAP in tumorigenesis: Friend or foe?”

### To the Editor:

We read with interest the letter by Liu *et al.*, commenting on our study about the activation of YAP in early stages of hepatocellular carcinoma (HCC) development and its potential role as a therapeutic target in liver cancer development, recently published in *Journal of Hepatology* [1]. In their letter, Liu *et al.* cite some papers and reviews proposing an oncosuppressive role of YAP.

Although these studies suggest a role for YAP as a tumor suppressor in certain contexts, the literature demonstrating an oncogenic role of YAP in solid experimental and human tumors is undoubtedly overwhelming. This is particularly true in the case of HCC. Indeed, many transgenic mice with liver-specific YAP overexpression or knockout for Mst1/Mst2 develop primary liver tumors, morphologically resembling human HCC or cholangiocarcinomas (CCs) [2–5]. Moreover, increased YAP expression and its nuclear translocation in neoplastic cells were observed in chemically-induced HCCs in non-transgenic mice [6]. In relation to human HCC, many studies have shown a clear association between YAP expression and tumor development [7–9], with poor prognosis associated with YAP expression. Notably, a recent study showed that overall survival rate was lower in HCCs and combined HCC-CCs (cHC-CCs) that were overexpressing YAP, compared to those that were not [10]. The latter study also provided clinicopathological evidence that YAP is overexpressed more frequently in HCCs displaying stemness-related markers (EpCAM and CK-19) and in cHC-CCs, compared to HCCs lacking such expression. Finally, YAP expression is associated to poor prognosis in several other human malignancies, including non-small cell lung cancer, gastric cancer and colorectal cancer [11–13].

Interestingly, some studies provided evidence for the therapeutic benefits of YAP inhibition in cancer. Indeed, verteporfin (that inhibits the transcriptional activity of YAP) blocked YAP-induced liver tumorigenesis in mice and rats [1,14]; VGLL4-mimicking peptide (a natural inhibitor of the YAP-TEAD interaction) prevented YAP-induced liver tumorigenesis in mouse models [15] and in human primary gastric cancer models [16]; cyclic YAP-like peptides (preventing YAP-TEAD interaction) inhibited tumor growth in a HCC xenograft model [17].

In conclusion, while YAP might exert a dual role on tumorigenesis, depending on the specific tissues or cancer types, the results of our work, together with a vast existing literature, support the notion that YAP acts as an oncogene in HCC. Moreover, based on our novel finding that YAP is overexpressed at very early stages of the carcinogenic process, YAP can be considered critical for the development of HCCs and, thus, as a potential therapeutic target.

### Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

### References

- [1] Perra A, Kowalik MA, Ghiso E, Ledda-Columbano GM, Di Tommaso L, Angioni MM, et al. YAP. Activation is an early event and a potential therapeutic target in liver cancer development. *J Hepatol* 2014;61:1088–1096.
- [2] Dong J, Feldmann G, Huang J, Wu S, Zhang N, Comerford SA, et al. Elucidation of a universal size-control mechanism in *Drosophila* and mammals. *Cell* 2007;130:1120–1133.
- [3] Zhou D, Conrad C, Xia F, Park JS, Payer B, Yin Y, et al. Mst1 and Mst2 maintain hepatocyte quiescence and suppress hepatocellular carcinoma development through inactivation of the Yap1 oncogene. *Cancer Cell* 2009;16:425–438.
- [4] Song H, Mak KK, Topol L, Yun K, Hu J, Garrett L, et al. Mammalian Mst1 and Mst2 kinases play essential roles in organ size control and tumor suppression. *Proc Natl Acad Sci U S A* 2010;107:1431–1436.
- [5] Lu L, Li Y, Kim SM, Bossuyt W, Liu P, Qiu Q, et al. Hippo signaling is a potent in vivo growth and tumor suppressor pathway in the mammalian liver. *Proc Natl Acad Sci U S A* 2010;107:1437–1442.
- [6] Kowalik MA, Saliba C, Pibiri M, Perra A, Ledda-Columbano GM, Sarotto I, et al. Yes-associated protein regulation of adaptive liver enlargement and hepatocellular carcinoma development in mice. *Hepatology* 2011;53:2086–2096.
- [7] Zender L, Spector MS, Xue W, Flemming P, Cordon-Cardo C, Silke J, et al. Identification and validation of oncogenes in liver cancer using an integrative oncogenomic approach. *Cell* 2006;125:1253–1267.
- [8] Xu MZ, Yao TJ, Lee NP, Ng IO, Chan YT, Zender L, et al. Yes-associated protein is an independent prognostic marker in hepatocellular carcinoma. *Cancer* 2009;115:4576–4585.
- [9] Tschaharganeh DF, Chen X, Latzko P, Malz M, Gaida MM, Felix K, et al. Yes-associated protein up-regulates Jagged-1 and activates the Notch pathway in human hepatocellular carcinoma. *Gastroenterology* 2013;144:1530–1542.
- [10] Kim GJ, Kim H, Park YN. Increased expression of Yes-associated protein 1 in hepatocellular carcinoma with stemness and combined hepatocellular-cholangiocarcinoma. *PLoS One* 2013;8:e75449.
- [11] Wang Y, Dong Q, Zhang Q, Li Z, Wang E, Qiu X. Overexpression of yes associated protein contributes to progression and poor prognosis of non-small cell lung cancer. *Cancer Sci* 2010;101:1279–1285.
- [12] Kang W, Tong JH, Chan AW, Lee TL, Lung RW, Leung PP, et al. Yes-associated protein 1 exhibits oncogenic property in gastric cancer and its nuclear accumulation associates with poor prognosis. *Clin Cancer Res* 2011;17: 2130–2139.
- [13] Wang L, Shi S, Guo Z, Zhang X, Han S, et al. Overexpression of YAP and TAZ is an independent predictor of prognosis in colorectal cancer and related to the proliferation and metastasis of colon cancer cells. *PLoS One* 2013;8:e65539.
- [14] Liu-Chittenden Y, Huang B, Shim JS, Chen Q, Lee SJ, Anders RA, et al. Genetic and pharmacological disruption of the TEAD-YAP complex suppresses the oncogenic activity of YAP. *Genes Dev* 2012;26:1300–1305.
- [15] Koontz LM, Liu-Chittenden Y, Yin F, Zheng Y, Yu J, Huang B, et al. The Hippo effector Yorkie controls normal tissue growth by antagonizing scalloped-mediated default repression. *Dev Cell* 2013;25:388–401.
- [16] Jiao S, Wang H, Shi Z, Dong A, Zhang W, Song X, et al. A peptide mimicking VGLL4 function acts as a YAP antagonist therapy against gastric cancer. *Cancer Cell* 2014;25:166–180.
- [17] Zhou Z, Hu T, Xu Z, Lin Z, Zhang Z, Feng T, et al. Targeting Hippo pathway by specific interruption of YAP-TEAD interaction using cyclic YAP-like peptides. *FASEB J* 2014, [Epub ahead of print].

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