



## CORRESPONDENCE

# Comment on ‘MicroRNA-199b-5p attenuates TGF- $\beta$ 1-induced epithelial–mesenchymal transition in hepatocellular carcinoma’

British Journal of Cancer <https://doi.org/10.1038/s41416-018-0013-1>

We read with great interest the recent publication by Zhou and colleagues, which provides novel relevant data about the role of microRNA-199b-5p (miR-199b) and N-cadherin as regulators of epithelial–mesenchymal transition (EMT) in human hepatocellular carcinoma (HCC). In this work, the authors demonstrate that N-cadherin is a direct miR-199b target, and observed that miR-199b downregulation in HCC patients predicts poor outcome and inversely correlates with N-cadherin overexpression. At the functional level, they demonstrated that miR-199b inhibits both migratory and invasive abilities of HCC cells, and metastatic progression *in vivo*. In addition, they identified a positive regulatory loop between N-cadherin, TGF- $\beta$ 1, and Akt, and showed that miR-199b reduces TGF- $\beta$ 1-induced Akt phosphorylation, thereby affecting EMT in HCC. Despite that this is a very interesting piece of work that provides novel important findings, some considerations should be taken into account.

From our point of view, it would be very important to evaluate the potential relevance of alternative miR-199b targets and even more strongly in the work by Zhou et al. due to the following rationale. The authors showed in their work that the functional effects of miR-199b were only partially reversed by N-cadherin restoration, which highlights the involvement of additional molecular targets. Of note, miR-199b has been reported to target SET,<sup>1,2</sup> which has been recently confirmed by our group in colorectal cancer, showing that SET is of key relevance for miR-199b-induced effects.<sup>3</sup>

Interestingly, SET has been reported to have a relevant role in EMT in pancreatic cancer via N-cadherin regulation. SET overexpression was found to activate signaling through Rac1/JNK/c-Jun, thereby inducing the transcriptional activation of N-cadherin expression. In fact, SET overexpression positively correlated with N-cadherin levels.<sup>4</sup> These observations would indicate that the direct miR-199b-induced N-cadherin regulation would be indirectly reinforced by modulating SET.

Furthermore, the authors showed that miR-199b predicted poor outcome in their HCC cohort and reduced TGF- $\beta$ 1-induced Akt phosphorylation. In concordance, SET overexpression has been described to confer poor clinical outcome and correlate with p-Akt expression in HCC tumors.<sup>5</sup> SET is a potent endogenous inhibitor of the tumor suppressor protein phosphatase 2A (PP2A), and PP2A activation has been reported to suppress TGF- $\beta$ 1-induced EMT.<sup>6</sup> In addition, PP2A directly targets and dephosphorylates Akt, which has also been described in HCC.<sup>7</sup> In fact, SET targeting using an antagonist to this protein restored PP2A-mediated p-Akt downregulation and induced apoptosis of HCC cells.<sup>5</sup>

Finally, Zhou et al. found that miR-199b inhibits both migration and invasion in HCC cells, and some evidence highlights the potential involvement of SET in these effects. First, SET has a role inducing Rac1-mediated migration.<sup>8</sup> Second, a recent work has described that matrix metalloproteinase-9 (MMP-9) deregulation through PP2A inhibition is a relevant event in HCC that contributes to the tumor invasion,<sup>9</sup> and the PP2A inhibitor SET has been reported to induce MMP-9 expression activity in breast and non-small cell lung cancer.<sup>10,11</sup> Altogether, the work by Zhou et al.<sup>12</sup> suggest that miR-199b/N-cadherin deregulation is a relevant event that predicts poor outcome and contributes to EMT in HCC. However, forthcoming studies are warranted to confirm the wide range of evidence indicating that SET could also be having a key role in the miR-199b/N-cadherin interplay.

## ACKNOWLEDGEMENTS

This work was supported by PI15/00934 and PI16/01468 grants from “Instituto de Salud Carlos III FEDER”. B.T. is supported by Fundación Conchita Rábago de Jiménez Díaz.

## ADDITIONAL INFORMATION

**Competing interests:** The authors declare no competing financial interest.

**Note:** This work is published under the standard licence to publish agreement. After 12 months the work will become freely available.

Ion Cristóbal<sup>1</sup>, Andrea Santos<sup>1</sup>, Silvia González<sup>1</sup>, Melania Luque<sup>2</sup>, Blanca Torrejón<sup>1</sup>, Federico Rojo<sup>2</sup> and Jesús García-Foncillas<sup>1</sup>  
<sup>1</sup>*Translational Oncology Division, Oncohealth Institute, IIS-Fundacion Jimenez Diaz-UAM, University Hospital “Fundacion Jimenez Diaz”, Madrid, Spain and* <sup>2</sup>*Pathology Department, IIS-Fundacion Jimenez Diaz-UAM, University Hospital “Fundacion Jimenez Diaz”, Madrid, Spain*

Correspondence: Ion Cristóbal ([ion.cristobal@fjd.es](mailto:ion.cristobal@fjd.es)) or Jesús. García-Foncillas ([jgfoncillas@gmail.com](mailto:jgfoncillas@gmail.com))

## REFERENCES

- Chao, A. et al. Decreased expression of microRNA-199b increases protein levels of SET (protein phosphatase 2A inhibitor) in human choriocarcinoma. *Cancer Lett.* **291**, 99–107 (2010).
- Cristóbal, I. et al. Overexpression of SET is a recurrent event associated with poor outcome and contributes to protein phosphatase 2A inhibition in acute myeloid leukemia. *Haematologica* **97**, 543–550 (2012).
- Cristóbal, I. et al. Downregulation of microRNA-199b predicts unfavorable prognosis and emerges as a novel therapeutic target which contributes to PP2A inhibition in metastatic colorectal cancer. *Oncotarget* **8**, 40169–40180 (2017).
- Mody, H. R. et al. SET contributes to the epithelial–mesenchymal transition of pancreatic cancer. *Oncotarget* **8**, 67966–67979 (2017).

Received: 28 November 2017 Revised: 13 December 2017 Accepted: 8 January 2018  
Published online: 19 March 2018

5. Hung, M. H. et al. Upregulation of the oncoprotein SET determines poor clinical outcomes in hepatocellular carcinoma and shows therapeutic potential. *Oncogene* **35**, 4891–4902 (2016).
6. Kim, E. J. et al. Cardamonin suppresses TGF- $\beta$ 1-induced epithelial–mesenchymal transition via restoring protein phosphatase 2A expression. *Biomol. Ther.* **23**, 141–148 (2015).
7. Chen, K. F. et al. Synergistic interactions between sorafenib and bortezomib in hepatocellular carcinoma involve PP2A-dependent Akt inactivation. *J. Hepatol.* **52**, 88–95 (2010).
8. ten Klooster, J. P., Leeuwen, I., Scheres, N., Anthony, E. C. & Hordijk, P. L. Rac1-induced cell migration requires membrane recruitment of the nuclear oncogene SET. *EMBO J.* **26**, 336–345 (2007).
9. Ward, M. P. & Spiers, J. P. Protein phosphatase 2A regulation of markers of extracellular matrix remodelling in hepatocellular carcinoma cells: functional consequences for tumour invasion. *Br. J. Pharmacol.* **174**, 1116–1130 (2017).
10. Li, J. et al. Stable SET knockdown in breast cell carcinoma inhibits cell migration and invasion. *Biochem. Biophys. Res. Commun.* **453**, 7–12 (2014).
11. Liu, H. et al. Overexpression of PP2A inhibitor SET oncoprotein is associated with tumor progression and poor prognosis in human non-small cell lung cancer. *Oncotarget* **6**, 14913–14925 (2015).
12. Zhou, S. J. et al. MicroRNA-199b-5p attenuates TGF- $\beta$ 1-induced epithelial–mesenchymal transition in hepatocellular carcinoma. *Br. J. Cancer* **117**, 233–244 (2017).