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Comment on 'TAp63 suppress metastasis via miR-133b in colon cancer cells'

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We have read with great interest the recently published work by Lin *et al* (2014), which provides novel relevant findings about the tumour suppressor role of TAp63 via miR-133b downregulation in colorectal cancer (CRC). Of importance, the authors identified miR-133b as a transcriptional target of TAp63, and showed that the modulation of miR-133b expression is essential for the inhibitory effects of TAp63 in CRC cell migration and invasion. Moreover, they showed that TAp63 is expressed at low levels in CRC and proposed this alteration as a potential cause of miR-133b downregulation, which was previously described by our group in CRC cell lines and patient samples (Bandrés *et al*, 2006). Furthermore, it has been reported that miR-133b has a tumour suppressor role inhibiting cell growth through modulation of the MET signalling pathway (Hu *et al*, 2010), and it has also been described that low expression level of miR-133b correlates with poor clinical outcome in CRC (Akçakaya *et al*, 2011).

Notably, although the findings provided by Lin *et al* (2014) highlight the potential relevance of miR-133b deregulation in CRC progression and metastasis, this issue needs to be fully clarified. A recent publication pointed out that miR-133b contributes to increased CRC cell migration and invasion, and identified CXCR4 as a direct miR-133b target. In that work, Duan *et al* (2014) analysed 31 CRC patients observing miR-133b downregulation in 29 out of 31 tumour samples, and much lower expression in metastatic tumours. The authors proposed that miR-133b could be having a relevant role in CRC invasion and metastasis. However, only 13 out of the 31 CRC patients had metastatic disease (9 with lymph node metastasis and 4 with liver metastasis). Therefore, further studies confirming the role of miR-133b in the metastatic cohort are warranted.

In this line of thinking, we analysed the potential role of miR-133b in CRC progression and metastasis. We quantified the expression pattern of 377 mature microRNAs using Taqman Low Density Arrays (TLDAs) panel A (Applied Biosystems, Grand Island, NY, USA) in primary and paired metastatic tissues from 17 CRC patients, 12 with liver metastasis and 5 with lung metastasis previously reviewed by a pathologist (FR) to further confirm the diagnosis. All samples were taken anonymously and the ethical committee and institutional review board approved the project. Analysis of relative gene expression data was performed using the $2^{-\Delta Ct}$ method and U6B was used as internal control. Downregulation was considered when expression in the metastatic tissue showed at least three-fold decrease compared with its paired primary CRC tissue.

Interestingly, we found miR-133b significantly downregulated in liver metastatic tissues compared with their paired primary CRC tissues ($P<0.001$). We observed that miR-133b was markedly downregulated in all the 12 CRC liver metastatic tissues analysed. Furthermore, we found lower miR-133b levels in lung metastasis compared with their paired primary CRC tissues although significance was not achieved in this case. In fact, we unexpectedly observed that only two out of the five CRC lung metastatic samples showed miR-133 downregulated and even in one of those cases miR-133b expression was found increased. Moreover, miR-133b showed almost five-fold lower expression levels in liver metastatic tissues compared with lung metastatic tissues.

Altogether, we have confirmed the potential relevance of miR-133b in a larger cohort of CRC patients with liver metastasis and the proposed role for miR-133b in metastatic CRC. In addition, our results would indicate that miR-133b downregulation is more specific of liver CRC metastasis, which indicates that miR-133b might be having a potential role determining the metastatic niche, although further studies are warranted to clarify this issue.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Response to comment on 'TAp63 suppress metastasis via miR-133b in colon cancer cells'

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The work by Cristobal *et al* (2014) is an interesting study that builds on our and other recent work implicating downregulation of miR-133b in CRC and correlate with CRC metastasis (Lin *et al*, 2014). To further confirm the role of miR-133b in the metastatic cohort, expression pattern of 377 mature microRNAs were detected in primary and paired metastatic tissues from 17 CRC patients. The results showed that miR-133b significantly downregulated in liver metastatic tissues compared with their paired primary CRC tissues, and markedly downregulated in all the 12 CRC liver metastatic tissues. The major concern is why the authors only chose to analyse miR-133b expression between liver metastatic tissues and their paired primary CRC tissues? A recent study identified the microRNA signature between colorectal recurrences to lymph nodes and liver and between colorectal liver metastasis and primary hepatic tumour (Drusco *et al*, 2014). Wang *et al* (2013) also chose to reveal has-miR-337-3p expression in the metastatic tissues, lymph node metastatic tissues, and the primary gastric cancer tissues. Therefore, we think it would be more persuasive if this study also analyses miR-133b expression in lymph node metastatic tissues.

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