

## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 26274

**Title:** MicroRNAs in liver fibrosis: Focusing on the interaction with hedgehog signaling

**Reviewer's code:** 03387541

**Reviewer's country:** France

**Science editor:** Jing Yu

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

In this review, Hyun and collaborators discuss the regulation of Hedgehog (HH) pathway by MicroRNA in liver fibrosis. The authors discuss the dysregulation of miRNAs closely associated with fibrotic diseases such as liver fibrosis. Aberrant reactivation of HH pathway has been previously implicated in the reactivation of Hepatic stellate cells (HSCs) during liver fibrogenesis. They review growing evidence showing the association of miRNAs with HH signaling. For instance, recent studies suggest that HH-regulating miRNAs induce inactivation of HSCs, leading to decreased hepatic fibrosis. The topic of this review is interesting but several points should be clarified: - In the paragraph "Signal transduction of the HH signaling pathway", a schematic of the HH pathway could help the reader to better understand this complex pathway (miRNA targeting the different components of the pathway could be also included). In addition, major aspects of the pathway are missing such as 1) the involvement of the primary cilium in mammalian cells and 2) that GLI2 and GLI1 are rather strong transcriptional activators while GLI3 may act as strong transcriptional repressor. - On one hand, the authors describe the differentiation of HSCs into myofibroblast-HSCs (MF-HSCs). On the other hand, they mention the role in EMT in HSCs activation. The link between

these two processes is missing and should be clarified. - In the paragraph “ MiRNAs interacting with HH signaling in liver fibrosis”, the authors describe the anti-fibrotic effects of MiR-378a-3p, which targets GLI2 and GLI3. In the light of GLI3 repressor activity and GLI2 activating properties, the authors should discuss this apparent discrepancy. - In the paragraph “miRNAs interacting with HH signalling in others tissues, besides liver”, the authors mentioned the interaction between miR-21 downstream of TGF-b1 signalling in HVC infections... Basically, they discuss the effects of miRNA targeting both TGF-b1 and HH pathways. To broaden their discussion, the authors could also mention and discuss the fact that the TGF-b pathway can regulate major components of the HH pathway in a smo-independent manner in skin and lung fibroblast, pancreatic cancer cells for examples. - In the paragraph “Improvement of the therapeutic application of miRNAs in liver fibrosis”, the authors mentioned very superficially the other HH pathway inhibitors already validated. They should broaden the discussion to the others inhibitors (not only to cyclopamine). They never also clearly discuss the major caveat of miRNA: their potential to generate false positive by targeting multiples targets in addition of HH pathway components (with regards to the topic of this review).

## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

Hyun et al. wrote a well organized and comprehensive review on the regulation of the Hedgehog signaling pathway by miRNAs in liver fibrosis. I only have one comment: -I would recommend adding a figure explaining graphically how miRNA regulates HSC activation by interacting with Hh signaling pathway. This figure would make clear the significance and impact of this topic for readers.