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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 4978
Title: Expression and Significance of LG2013-08-07 20:13, an Intestinal Stem Cell Marker, During Each Stage of Gastric Cancer Tumorigenesis
Reviewer code: 00073423
Science editor: Gou, Su-Xin
Date sent for review: 2013-08-07 20:13
Date reviewed: 2013-08-11 23:40

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[Y] Grade C: a great deal of language polishing	[ ] No records	[ ] Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
The paper presents interesting data on LGR5 expression in tissues representing different stages of gastric carcinogenesis. LGR5 is a promising stem cell marker, that has been assess in normal gastric mucosa and gastric adenocarcinoma, however, the data on LGR5 expression in intermediate stages of carcinogesis (IM, dysplasia) are lacking. The data presented by the paper provide some novel information on LGR5 expression at these stages, however the authors tend to overstate their findings. Major comments: 1) The authors tend to overstate the findings observed in their study. The only performed immune-histochemistry of LGR5 in tissues with gastric pathologies, but at many point they state: "our data show that LGR5 is a markers of stem cells in gastric tissues" – the study was not empowered do this. The discussion and conclusion section of the article should avoid the statements "Our findings indicated that LGR5 is a special and sensitive marker for intestinal stem cell and it might be closely related to the intestinal type gastirc cancer; LGR5 aslo plays as an intestinal stem cell marker, and intestinal metaplasia appears to be a precancerous condition but not a carcinoma precursor" – the methodology used by the authors did not allow them to analyze wheather LGR5 was expressed on intestinal stem cells, therefore, these statements are only hypothetical and should be disccused in the right manner. The authors should resctrict the discussion to statements saying that LGR5 has different expression in different gastric diseases. 2) Language - poor: English language has to be revised by a person with high proficiency of English language. There are multiple errors in sentence structure and grammar throughout the text that than need to be corrected. Some sentences are very hard to comprehend e.g. page 3, ln 35. "We aimed to give an indication for the carcinogenic process of gastric cancer with respect to a cancer stem cell hypothesis."; pg. 8, line

18 ?That's why we found in our study, but it may be a precancerous condition but not a precursor for gastric carcinoma rather excluding some rare types". There are also some typos that need to be revised e.g. pg7. Ln14 ?In this condition, We indicated that the overexpression of LGR5 may be an early event in tumorigenesis with good reproducibility and differentiability" 3) The authors miss out some important citations on LGR5 in gastric tissues and need to discuss their findings in the light of these studies: Nam KT et al. 2012 Gut; Simon E et al. 2012 PLOS One Minor Comments: 1) Abstract: Background part of the abstract does not contain the part, which would refer to background, only the aim is stated. The sentence in the conclusion section "LGR5 aslo plays as an intestinal stem cell marker, and intestinal metaplasia appears to be due to abnormal stem cell differentiation by frequently expressing LGR5, but not a carcinoma precursor" is hard to coprehend and needs to be revised. 2) P values are missing at some points in Table 1

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Title: Expression and Significance of LG2013-08-07 20:13, an Intestinal Stem Cell Marker, During Each Stage of Gastric Cancer Tumorigenesis
Reviewer code: 00009417
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ]Rejection
[ ] Grade E (Poor)		[ ] Existed	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS
In this study expression of Lgr5 is characterized in gastric tissues and gastric adenocarcinomas by immunohistochemistry. The findings are correlated to clinical data. The authors suggest Lgr5 as a marker to monitor carcinogenesis. Comments: Anti-Lgr5 immunostaining should be verified by an additional method, e.g. Lgr5 mRNA in situ hybridisation. Anti-Lgr5 immunostained cells in normal gastric mucosa should be further characterized. Is there any difference in Lgr5 expression between low and high grade dysplasia? Titel should changed, because EACH stage of gastric cancer tumorigenesis is probably not addressed.

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ESPS Manuscript NO: 4978
Title: Expression and Significance of LG2013-08-07 20:13, an Intestinal Stem Cell Marker, During Each Stage of Gastric Cancer Tumorigenesis
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
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[Y] Grade C (Good)	[Y] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
"In conclusion, we have investigated an increasing expression of a promising cancer stem cell gene, LGR5, in lesions from normal tissues to dysplasia, gastric cancer and finally metastasis, suggesting that it would be served as an important biomarker for early detection of patients at higher risk for gastric tumorigenesis" From your study, we can know that LGR5 is not only expressed in tumor cells, but also normal cells. You said there were statistically significant differences, but you could not draw a solid conclusion and say that LGR5 is a biomarker for early detection of patients at higher risk for gastric tumor genesis. You might use the word 'possible' to describe this connection. To verify your findings, you might do a RT-PCR experiment to detect LGR5 gene expression in different tissues. The manuscript is not well written and clear.

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Title: Expression and Significance of LG2013-08-07 20:13, an Intestinal Stem Cell Marker, During Each Stage of Gastric Cancer Tumorigenesis
Reviewer code: 00052707
Science editor: Gou, Su-Xin
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Date reviewed: 2013-09-01 00:20

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
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		[ ] No records	

COMMENTS TO AUTHORS
To editor/authors: It is very good idea. But, the results seem to be comfused, positive rate of high grade (35.7%) was much lower than those in low grade, intestinal metaplasia and intestinal type cancer (68.0%,72.2% and 58.6%), there is not any good reason. The positive rate of intestinal type gastric cancer without metastasis or recurrence was higher (68.7%), which did not concert with the results in Table 3. The background in figure E is darker than the others.

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[Y] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
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[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

This study investigates the expression and significance of Leucine-rich repeat-containing G protein-coupled receptor 5 (LGR5) in normal gastric tissue, intestinal metaplasia, dysplasia, gastric cancer and distant metastasis. LGR5 was analyzed in 145 normal gastric mucosa, 90 intestinal metaplasia, 53 dysplasia, 180 gastric adenocarcinoma and 15 metastasis in lymph nodes and liver by immunohistochemistry. The relationship between LGR5 expression and clinicopathological features were statistically analyzed. LGR5 was found expressed in 26.9% of normal gastric mucosa, 72.2% of intestinal metaplasia, 50.9% of dysplasia, 52.8% of gastric adenocarcinomas and 86.7% of metastasis in lymph nodes and liver. The positive rate of LGR5 in metastasis, gastric cancer, and dysplasia were much higher than adjacent normal tissues ($p<0.01$). There was an increasing intensity of LGR5 expression in lesions from normal tissue to dysplasia, gastric cancer and finally metastasis but intestinal metaplasia($p<0.001$). The LGR5 positive cells in intestinal metaplasia were more prevalent than normal gastric tissues ($p<0.001$). The expression of LGR5 in gastric cancers appeared to be signi?cantly associated with gender, age, differentiation, Lauren type, and TNM stage ($p<0.05$).The increasing expression of potential cancer stem cell marker LGR5 in lesions from normal tissues to dysplasia, gastric cancer and finally metastasis, suggest that it would be served as an important biomarker for early detection of patients at higher risk for gastric tumorigenesis.LGR5 could be a candidate target for future diagnosis and tailored management in gastric cancer. Major Comments: 1) This is a very interesting study which showed a sequence of expression LGR-5 from early cancerous state to metastasis in gastric cancer tissues as demonstrated by immunohistochemical techniques. 2)I was not sure whether or not the authors have looked into the APC mutations and Wnt

signaling in these tissues. 3) Please clarify the following statements since it is confusing with regard to the conclusions: "that LGR5 expression was higher in low grade dysplasia than high grade in this study. The reason could be the current morphologic criteria of different grade dysplasias which actually include a mix of architectural and cytologic features but functional character, because it was easily-confused diagnosis with intestinal metaplasia that low grade dysplasia preserved some ability of intestinal metaplasia in develpement". This brings doubt that whether or not this increasing expression of LGR-5 could serve potentially as a marker for gastric cancer since this membrane receptor has been shown to be overexpressed in colon cancer including the entire GI tract. 4)Thus the conclusion of the study is very tentative and will require appropriate modifications. Minor comments: There are numerous spelling errors which will need to be fixed. A thorough editing will be necessary.