

## ANSWERING REVIEWERS

22<sup>th</sup> of December 2013



Dear Editor,

Thank you very much for giving us the opportunity to revise our manuscript. We appreciate very much the Reviewers' valuable comments, and we have reviewed the comments by the reviewers, found them to be very clear and insightful, and have revised the manuscript accordingly. We detail our point-by-point responses in the following pages. We hope that our revised manuscript will be accepted by the World Journal of Gastroenterology editorial team. If you still have any questions to our responses, don't hesitate to inform us, and we will answer them as soon as possible. **The revised parts are highlighted in red font in the revised manuscript.** Please find enclosed the edited manuscript containing an electronic copy of the full-text manuscript in Word format (file name: **wjg-5825-Review.doc**).

**Title:** New insights into the functions and localization of the homeotic gene CDX2 in gastric cancer

**Author:** Lin-Hai Yan, Wei-Yuan Wei, Yu-Bo Xie, Qiang Xiao

**Manuscript No:** 5852

The manuscript has been improved according to the suggestions of reviewers:

- 1. Format has been updated.**
- 2. Revision has been made according to the suggestions of the reviewer:**

**Reviewer: 01016438**

**The comments of the reviewer 01016438 are extremely valuable.**

*Comments (1):* This is a timely and fairly thorough review, which makes the point on an important topic namely the role of CDX2 in the gastric carcinoma, still far from being fully elucidated.

*Responses 1:* We really appreciate the positive comments and suggestions on revising our article from Reviewer 01016438.

*Comments (2):* Authors, when commenting on their work should speak in the second person plural (we), instead of saying "Xiao and colleagues".

*Responses 2:* The reviewer is right that we were sloppy on our way of presentation which causes confusion to the readers. We have removed the 'Xiao and colleagues', and added a clearly word 'we' to instead. If you still think some words should be replaced, don't hesitate to inform us, and we will change them as soon as possible.(see line 58, 86 and 267)

*Comments (3):* Authors should put a question mark in the title of the last paragraph "CDX2 is important in diagnosis and prognosis of gastric cancer" as, according to them, CDX2 has no prognostic value.

*Responses 3:* This is a very good point and we thanks for reviewer's comments. We have removed the sentence 'CDX2 is important in diagnosis and prognosis of gastric cancer' from the title of the last paragraph, and added a clearly Objective sentence (CDX2 IS A USEFUL MAKER FOR FUTURE DRUG AND GENE THERAPY IN GASTRIC CANCER) to describe

the function of CDX2 in gastric. If you still think some words should be replaced, don't hesitate to inform us, and we will change them as soon as possible.(see line 262)

**Reviewer: 00505502**

**The comments of the reviewer 00505502 are extremely valuable.**

*Comments (1):* 1. This manuscript mentioned that CDX2 is associated with various factors, MAPK signaling, Reg IV, MDR1, ERK and mTOR pathways and etc. Therefore, the authors should address the correlation diagram of the CDX2.

*Responses 1:* This is a very good point and we thanks for reviewer's comments. Form the published articles, we just can mentioned that CDX2 is associated with MAPK, Reg IV, MDR1, ERK and mTOR directly or indirectly. We are still deciphering the precise mechanisms behind how and why CDX2 is associated with MAPK, Reg IV, MDR1, ERK and mTOR, Therefore, it is hard to address the precise correlation diagram of the CDX2 now.

*Comments (2):* CDX2 plays opposing roles in the biological effects. One role is tumorigenesis and cell growth and the other is tumor cell apoptosis. Therefore, there is lack of cohesiveness in the whole flow and conclusion of this manuscript. The authors should describe each main point separately about an opposite effect in conclusion.

*Responses 2:* The reviewer is absolutely correct, we should describe opposite effect in conclusion. But, from the published articles, There are 12 researches indicating that CDX2 is anti-oncogene, and 5 supporting CDX2 is cancer gene. We can't arbitrarily infer the roles of CDX2 play in different biological

behaviors because of the number of research. Furthermore not every research on the biological behavior can be comparatively described. According to the published document and our research on the CDX2, we temporarily conjecture that regulation of CDX2 is affected by positive and negative feedback simultaneously. Over-expression or low-expression CDX2 both can produce the same effects in some certain biological behavior (such as: apoptosis, proliferation et al). This inference surely need to be proved in the following researches, therefore, we make a synthesis description of the published articles.

**Comments (3):** The authors suggested that “anti-CDX2 therapy may be beneficial for patients with intestinal-phenotype gastric cancer” in Core tip and Conclusion. However, if anti-CDX2 therapy inhibits an apoptotic effect, it doesn’t know whether to necessarily lead to a prognostic improvement. So, you should not propose the possibility of anti-CDX2 therapy for gastric cancer.

**Responses 3:** This is a valid point by the reviewer and we thanks for reviewer’s comments. this sentence is based on the published articles and the researches we have done, but we don’t have any clear evidence to prove this. we were sloppy on our way of presentation which causes confusion to the readers about this sentence. We have removed the sentence ‘anti-CDX2 therapy may be beneficial for patients with intestinal-phenotype gastric cancer’ from Core tip and Conclusion, and added a clearly Objective sentence to describe the function of CDX2 in gastric. If you still think some content should be added to Core tip and Conclusion section, don't hesitate to inform us, and we will add them as soon as possible.(see line 50)

**Comments (4):** The authors showed the relation between Helicobacter

pylori infection and intestinal metaplasia. There have been some manuscripts about the relation between CDX2 and Helicobacter pylori, so the authors should suggest their association drawing these manuscripts.

*Responses 4:* This is a very good point and we thanks for reviewer's comments. From the published articles, we objectively describe the relation among CDX2, Helicobacter pylori infection and intestinal metaplasia, but we can't arbitrarily infer that there must be relation among CDX2, Helicobacter pylori infection and intestinal metaplasia because the relation among them isn't clear yet. Based on reliable published researches, we respectively describe the relation among CDX2, Helicobacter pylori infection and intestinal metaplasia instead of inferring their relation arbitrarily in our article.

*Comments (5):* In paragraph of 'CDX2 INDUCES DRUG RESISTANCE IN GASTRIC CANCER', this manuscript mentioned that CDX2 protein directly regulates Reg IV expression and Reg IV activates the EGFR/Akt/AP-1 signaling pathway. On the other hand, in paragraph of 'CDX2 IS AN ONCOGENE IN GASTRIC CANCER', it was written that apoptosis induced by PTEN upregulation which has been shown to be dependent on CDX2, by triggering PI3K/Akt inactivation. So, the authors should discuss about this contraindication.

*Responses 5:* This is a very good point and we thanks for reviewer's comments. In the published articles we find that CDX2 can affect both drug

resistance pathway leading by P-gp and apoptosis pathway involved with survivin, cyclin D1, and c-Myc (Yan LH, Wang XT, Yang J, Lian C, Kong FB, Wei WY, Luo W, Xiao Q, Xie YB. Reversal of multidrug resistance in gastric cancer cells by CDX2 downregulation. World J Gastroenterol. 2013 Jul 14;19(26):4155-65). Apoptosis is a factor related to drug resistance, However, there's no verdict on whether apoptosis is bound to affect drug resistance in published articles. Therefore, we won't subjectively relate apoptosis and drug resistance because of their joint effects on Akt, instead, we respectively describe the roles CDX2 plays in apoptosis and drug resistance. We will research the relation between apoptosis and drug resistance next.

**Reviewer: 00051382**

**The comments of the reviewer 00051382 are extremely valuable.**

*Comments (1):* The running title is "CDX2 and gastric cancer". However, in abstract, the authors only refer the functions of CDX2, not mentions anything about gastric cancer.

*Responses 1:* The reviewer is right that we were sloppy on our way of presentation which causes confusion to the readers about our abstract. We have rewrited the Part of abstract, and added some content about gastric cancer, If you still think some words should be replaced, don't hesitate to inform us, and we will change them as soon as possible.(see line 33)

*Comments (2):* 2. When first mentioned the abbreviation, the full name should be used, such as caudal-related homeobox transcription factor 2(CDX2) and multidrug resistance 1(MDR1)

*Responses 2:* This is a very good point and we thanks for reviewer's comments. We have carefully checked the whole paper to make sure when

first mentioned the abbreviation, the full name be used. If you still think some words should be replaced, don't hesitate to inform us, and we will change them as soon as possible.(see line 34, 40, 84)

*Comments (3):* the first sentence of the first paragraph: “CDX2 is a member of the caudal-related homeobox transcription factor gene family” should be changed to Caudal-related homeobox transcription factor 2 (CDX2) is a member of the cadual type homeobox gene family.

The fourth sentence of the first paragraph : “Overexpression of CDX2 in HT-29 cells revealed increased resistance to the known substrates of multidrug resistance protein (MDR)1” should be changed to “Overexpression of CDX2 in HT-29 cells revealed increased resistance to the known substrates of multidrug resistance protein (MDR1)”;

the fifth sentence of the first paragraph: “However, high expression of CDX2 significantly reducestumorigenicity in BGC-823 cells” should be changed to “However, high expression of CDX2 significantly reduces tumorigenicity in BGC-823 cells”;

*Responses 3:* This is a valid point by the reviewer. We have changed the sentences. If you still think some sentences should be deleted, don't hesitate to inform us, and we will remove them as soon as possible. (see line 54, 60, 63)

*Comments (4):* If the article can be illustrated then will be more highlights. The article writing is not fully in accordance with the

format of our journal. This review has a lot of mistakes and shortcomings, the author should revise carefully.

**Responses 4:** The reviewer is absolutely correct that we have submitted our manuscript to professional English language editing company (Jing-Yun Ma Editorial Office) to English proof-read our manuscript. Please see the editing certificate which is from English language editing company(Fig 1). It can verify that our final manuscript has been English proof-read by that company.



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EDITORIAL CERTIFICATE  
(Ref. 2013-09-419)

To whom it may concern at *World Journal of Gastroenterology (WJG)*:

We herein certify that we have edited the following manuscript by both our native English speaking editor and Chinese expert. The edited paper has reached grade A in language evaluation for SCI journals.

Manuscript title: Functions and localization of the homeotic gene CDX2 in gastric cancer

First author and affiliations: Lin-Hai Yan, Department of Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China

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Fig.1 editorial certificate

### 3. References and typesetting were corrected



Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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