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Shicheng Guo <shg047@eng.ucsd.edu>

Thank you for the review of JTO-D-15-01271

1 message

Journal of Thoracic Oncology <em@editorialmanager.com>
Reply-To: Journal of Thoracic Oncology <mary.todd@iaslc.org>
To: Shicheng Guo <shg047@eng.ucsd.edu>

Mon, Dec 28, 2015 at 11:30 AM



RE: JTO-D-15-01271, entitled Silencing NKD2 by promoter region hypermethylation promotes esophageal cancer progression by activating Wnt signaling, by Professor Mingzhou Guo

Dear Dr Guo,

The editors have made a decision on the above-referenced manuscript that you previously reviewed for JTO. The decision letter is included below. If you have any questions or comments please feel free to contact the journal office via email to Mary.Todd@iaslc.org.

Thank you for your time and efforts,

Mary Sharkey Todd, MFA
Managing Editor
Journal of Thoracic Oncology

To: *****
cc: *****
From: "Journal of Thoracic Oncology" mary.todd@iaslc.org
Subject: Editorial Decision for JTO-D-15-01271
CC: *****



Dec 28, 2015

RE: JTO-D-15-01271, entitled "Silencing NKD2 by promoter region hypermethylation promotes esophageal cancer progression by activating Wnt signaling"

Dear ***** ,

Congratulations your manuscript has been found to be acceptable pending revision. Please completely address the concerns raised by the reviewers in your revised manuscript. I anticipate that you will easily be able to answer the criticisms of the reviewers in a satisfactory manner. I will verify that this has been done upon receipt of the revised manuscript. Please find the comments of the reviewers listed below.

Please include the following materials when you submit your revision:

Completed ICMJE forms for each co-author.

An itemized, point-by-point response to the comments of the reviewers. (Label file "Response to Reviewers")

One version of the revised manuscript that includes continuous line and page numbers; these numbers should be used in the "Response to Reviewers" to indicate where specific changes have been made in response to the editorial feedback and reviews. This version should also include "highlighting" in the manuscript to highlight new material. This feature can be found on the formatting toolbar in Microsoft under highlight. (Label file "Highlighted Version")

Finally, please include a version of the manuscript without highlighting and line numbers. (Label file "Revised Version")

Color figures will be published online at no charge. Color figures will be published in print at the discretion of the Editor. The publisher will convert color figures to grayscale figures for print publication. Therefore, you should submit the color version of your figures as you would like it to appear online.

The revisions should be completed within four weeks to avoid being considered as a new submission.

To submit a revision, go to <http://jto.edmgr.com/> and log in as an Author. You will see a menu item called "Submission Needing Revision." Please click on this item to obtain your submission record and begin the revision process.

Your username is: *****

Your password is: *****

With Kind Regards,

David G. Beer
Associate Editor
Journal of Thoracic Oncology

Reviewer Comments:

Reviewer #1: Comments to the Authors,

This manuscript "Silencing NKD2 by promoter region hyper-methylation promotes esophageal cancer progression by activating Wnt signaling" reported a comprehensive description to the epigenetic abnormal of NKD2 and its regulation role in esophageal cancer was related to one of most important cancer relevant signal pathway of Wnt. The study was performed rigorously and the findings sound very interesting. What's more, it would be an exciting example to explore the mechanism of the epigenetic silence of gene expression and then caused cancer development. The biological and biomedical evidence provided by the authors has been very solid. In general, I'd recommend publication if the authors can address the following concerns and to strengthen the reproducibility and credibility of the manuscript.

Major Compulsory Revisions

1, Please collect genome-wide DNA methylation and gene expression data from GEO or arrayexpress (such as RRBS, MBD-seq or BS-seq data in ESCA) to find the evidence that genome-wide methylation and gene expression data were supporting to the present discovery. In addition, TCGA has provided large number of ESCA data, the methylation and gene expression status for NKD2 should be described.

2, please provide the reason how to select the genomic region to conduct the methylation detection. There are at least two CpG islands, which one to choose? In addition, why choose CpG Island, rather than CpG shore or CpG shelf?

3, Any GWAS evidence shown NKD2 were related with ESCA? If there is no any such evidence, how to interpret such phenomenon?

4, please read this paper "DNA demethylation by 5-aza-2'-deoxycytidine is imprinted, targeted to euchromatin, and has limited transcriptional consequences" and discuss the 5-aza section of the study.

Reviewer #2: Cao et al. found significant effects of NKD2 on esophageal squamous cell carcinoma, both in vitro and in vivo, using a variety of experimental methodology as well as clinical samples, and concluding that loss of NKD2 expression by methylation was a notable phenomenon associated with poorer prognosis.

This is an excellent paper and written well. However, although this MS will give us valuable information, following points should be revised to make this MS more valuable.

1. PLA should be spelled out.
2. In Material and Methods. Antigen retrieval condition of immunohistochemistry should be described.
3. In table 1. P-values should be rounded to two significant figures.
4. In figure 3. In figure legend of 3C, authors should describe what each curve mean.
5. In figure 4C. If the relationship between NKD2 and MMPs in human tissue samples can be assessed by immunohistochemistry, please show the results. Furthermore, authors should discuss the role of MMPs in esophageal squamous cell carcinoma by citing references.
6. In figure 5, Wnt signals is analyzed using β -catenin, cyclin D1, and c-myc. Why the three molecules were selected? Is it possible to evaluate Wnt signals in esophageal cancer tissues?
7. In figure 6A, tumor site and the difference between the two mice are not clear macroscopically. Please explain in detail using arrowheads etc. in the picture.
8. In figure 6D, the immunostained pictures of each molecule should be shown using semi-serial section. Immunostained picture for total β -catenin is required to be added to support Wnt signal activation.
9. In xenograft mice experiment, NKD2 unexpressed cell (KYSE150) and overexpressed cell are used. Can opposite results be obtained by using NKD2 expressed cells and knockdown cells?
10. In the first paragraph of Discussion, authors does not discuss about their own results. This paragraph may be included in the Introduction section, rather than Discussion. In the second paragraph, authors just summarize their results but does not discuss enough. Please discuss in detail about obtained results point by point.

Complete Revision Instructions:

PRELIMINARY STEPS:

1. Click on the "Submissions Needing Revision" link.
2. To view the previous decision letter and reviewer comments, please click the blue decision term listed under the View Decision menu.
2. If you would like to download the previous manuscript in order to make revisions, click on "Download Files" under the Action menu.

RESUBMISSION STEPS:

3. To BEGIN the RESUBMISSION: Click "Submit Revision" under the Action menu.
4. Proof each screen to ensure the information is still correct (the Title, Authors, etc), then click Next at the bottom of each page.
5. On the Attach Files screen, be sure to click beside each previous submission item that you would like included in the following submission. BE SURE TO CHOOSE TO CARRY OVER YOUR COPYRIGHT FORM.
6. Now, as you did previously, simply upload the parts of your manuscript. When you are finished, please click Next.
7. Click "Build PDF for My Approval."
8. Click "Go to Submissions Waiting for Authors Approval."
9. Wait for the PDF to Build. When it has been built, you will see the link "View Submission" in the Action menu. Click "View Submission," and open the manuscript in order to proof your work.
10. If you find problems with the manuscript, please click "Edit Submission" from the Action menu. Make the appropriate changes, beginning again at step 3.
11. If you find no problems with the manuscript, please click "Approve Submission" from the Action menu. Your re-submission is now complete!