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Reviewer Invitation for Silencing NKD2 by promoter region hypermethylation promotes esophageal cancer progression by activating Wnt signaling

1 message

Journal of Thoracic Oncology <em@editorialmanager.com> Mon, May 9, 2016 at 5:08 AM
Reply-To: Journal of Thoracic Oncology <mary.todd@iaslc.org>
To: Shicheng Guo <shg047@eng.ucsd.edu>

Journal of Thoracic Oncology

May 09, 2016

Dear Dr Guo,

I am writing in hopes that you may be able to review manuscript JTO-D-15-01271R2, entitled "Silencing NKD2 by promoter region hypermethylation promotes esophageal cancer progression by activating Wnt signaling" by Professor Mingzhou Guo.

Please find the manuscript abstract listed below.

If you should choose to accept this assignment, you will be given 14 days to complete the assignment.

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If for any reason you find it impossible to complete this review, please let us know immediately by clicking here to DECLINE to review this paper:
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Thank you for your time and efforts,

David G. Beer, Ph.D
Associate Editor
Journal of Thoracic Oncology

Reviewer 1: (Previous Version)

The author said there is no any public methylation data for ESCA (such as RRBS, MBD-seq or BS-seq data in ESCA). However, As I know, there are several data existing in GEO. Please answer this question correctly and made the validate analysis carefully.

Reviewer 2: (Previous Version)
JTO-D-15-01271R1

The authors returned the revised MS with the letter. However, the replies were insufficient for acceptance of this MS.

1. There are NKD2 methylation data in TCGA because TCGA used Illumina human methylation 450(K), which includes NKD2.
2. GWAS data can be downloaded from COSMIC using the following URL, where NKD2 data are included
http://cancer.sanger.ac.uk/cosmic/gene/samples?coords=AA%3AAA&src=gene&end=452&ln=NKD2&sn=oesophagus&all_data=&id=5214&seqlen=452&start=1#complete
3. Question 7
The authors state "3. In table 1. P-values should be rounded to two significant figures.
Answer: Thanks for your suggestion. We added the figures (in figure 2) and the manuscript was revised."
However, the figure is still "0.9085".

Additionally, there are many careless grammatical errors.

Introduction: Naked cuticle homolog 2 (NKD2) was found to be frequently methylated in human breast and gastric cancers. However, the epigenetic changes and mechanisms of NKD2 in human esophageal cancer remain unclear. Methods: Nine esophageal cancer cell lines and 154 cases of primary esophageal cancer samples were analyzed using methylation specific PCR, immunohistochemistry, western blot and xenograft mouse models. Results: Loss of NKD2 expression and complete methylation were found in KYSE150 and TE1 cells. Reduced NKD2 expression and partial promoter region methylation were observed in KYSE30, KYSE70, KYSE410, KYSE140 and COLO680 cells. High levels of NKD2 expression and unmethylation were detected in KYSE450 and TE8 cells. Re-expression of NKD2 was induced by 5-aza-2'-deoxycytidine in NKD2 unexpressed cells or cells in which NKD2 expression was reduced. NKD2 was methylated in 53.2% (82/154) of human primary esophageal cancer samples, and promoter region hypermethylation was significantly associated with reduced expression of NKD2 ($p<0.01$). NKD2 methylation was associated with TNM stage and lymph node metastasis ($p<0.01$). Our results suggest that NKD2 is regulated by promoter region methylation, and methylation of NKD2 may serve as a prognostic marker in esophageal cancer. Our further studies demonstrate that NKD2 suppresses cell proliferation, colony formation, cell invasion and migration, as well as induces G1/S check point arrest in esophageal cancer cells. NKD2 suppressed xenograft tumor growth and inhibited Wnt signaling in human esophageal cancer cells. Conclusions: NKD2 is frequently methylated in human esophageal cancer, and the expression of NKD2 is regulated by promoter region methylation. NKD2 suppresses esophageal cancer progression by inhibiting Wnt signaling both in vitro and in vivo.