Author's response to reviews

Title: Vascular endothelial growth factor C promotes cervical cancer metastasis via up-regulation and activation of RhoA/ROCK-2/moesin cascade

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Author's response to reviews: see over
To Melissa Norton, MD  
Editor-in-Chief  
BMC Cancer

Dear Dr. Norton,

I am pleased to resubmit to BMC Cancer the revised manuscript 1328914674337961 R1:

“Vascular endothelial growth factor C promotes cervical cancer metastasis via up-regulation and activation of RhoA/ROCK-2/moesin cascade”

According to all the queries raised by the reviewers, we have supplemented new data and added new relevant contents in this revised version of the MS.

Detailed responses can be found in the enclosed point-by-point rebuttal letter.

The MS complies with all the BMC Cancer editorial rules, and we thus hope that it will be now fit for publication on the BMC Cancer.

Please, be assured that the manuscript has not been published nor is being considered for publication elsewhere in whole or in part, in any language.

Please be assured that all the authors have read and approved the manuscript. The manuscript, in whole or in part, has not been published or submitted to any other journal.

Sincerely,

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Rebuttal Letter

BMC Cancer Manuscript: 1328914674337961 - Vascular endothelial growth factor C promotes cervical cancer metastasis via up-regulation and activation of RhoA/ROCK-2/moesin cascade

RESPONSE TO REVIEWER 1

We are grateful to the reviewer for taking the time to look at our paper and for the many useful comments. Here are the detailed responses to the reviewer’s questions 2, 6, 7, 9:

Reviewer: Johanna Tuomela
Reviewer's report:
This manuscript by He and coworkers investigates the role of VEGF-C in progression of cervical cancer.

2. Are the methods appropriate and well described? YES: The methods are appropriate and well described. However, the authors should briefly define in “Transfection experiments” first paragraph how the cells were treated. Or remove the description of the treatments to this paragraph. I suggest that the last unnecessary sentence of “Cell immunofluorescence”: “Pictures were photographed.” should be deleted.

R: Thanks for the reviewer’s advice. Now we have added the information about how the cells were treated in “Transfection experiments” Section. And we deleted the sentence “Pictures were photographed” as the reviewer suggested.

6. Are limitations of the work clearly stated? YES: However, the authors could discuss about in vivo experiments. Could these in vitro results be confirmed with in vivo experiments?

R: As the reviewer pointed out, our conclusion is mainly based on in vitro findings. Whether these in vitro results happen in vivo remains obscure. Now we have stated this limitation in Discussion Section. Please see the Text.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Reference Joukov et al. 1996 should be added, when discussed of VEGF-C and its receptors.

R: We now have added the reference “Joukov, V et al 1996. A novel vascular endothelial growth factor, VEGF-C, is a ligand for the Flt4 (VEGFR-3) and KDR (VEGFR-2) receptor tyrosine kinases” as the reference 4 when we discuss the VEGF-C and its receptors in Introduction Section.

9. Is the writing acceptable? YES: The manuscript is mainly well-written, but needs some minor language check.

R: We have checked the whole manuscript and corrected the grammar with the help of an English expert.

SUGGESTED REVISIONS:
Minor Essential Revisions:
Please, answer my questions above (in 2, 6, 7 and 9).
The actin rearrangement is detected already in 24h. It would be interesting to add time points between 0h and 24h in order to see in which time-point the changes in cytoskeletal remodeling can be seen. Please, add at least one time-point.

**R:** As the reviewer suggested, we have added 2 time points (6 h, 12 h) and it shows that the changes in cytoskeletal remodeling could be observed at 12 h, while not 6 h. Please see the new data in *Fig 1D.*
RESPONSE TO REVIEWER 2

Many thanks for the reviewer revising the MS. Please find below the responses:

Reviewer: Tommaso Simoncini
Reviewer's report:
The paper by Dr Mian He et al. describes original information on how VEGF-C modulates and controls cervical cancer cell movement, that could be relevant to understand the role of this angiogenic and growth factor in the development and spread of cervical cancer.

In general the experiments are well-conducted, the methods are adequate and the paper is well written. The reference list is comprehensive.

I have some minor points for the authors:
In fig.1A a small sign in the cell migration pictures indicating what is the point considered by the authors as the maximum migration could be helpful to better understand how the exp was performed.

R: Thanks for the useful advice. Now we have added a small sign indicating the maximal migration point as the reviewer suggested. Please see it in Figure Section.

In fig 1D small arrows to indicate the specialized cell membrane structures might as well help the reader, the same applies to Fig 2D, as well.

R: We have added arrows to indicate the specialized cell membrane structures like lamellipodia, pseudopodia and focal adhesion complexes in Fig 1D and Fig 2D.

In fig 5A the quantitative migration distance is not readily visible, do you want to change the magnification or to add a marker of maximal migration, as in fig 1?

R: As the reviewer suggested, we have added the sign indicating the maximal migration point as in Fig 1D. Please see it in Figure Section.

Please provide more contrast to Fig 6A, as the image is a bit hazy.

R: Now we have modified the image and provided more contrast to Fig 6A. Please see it in Figure Section.