Author's response to reviews

Title: Correlation of NF-kappaB signal pathway with tumor metastasis of human head and neck squamous cell carcinoma

Authors:

Ming Yan (yanming8012@hotmail.com)
Qin Xu (xuqin_2004@hotmail.com)
Ping Zhang (pingzhang73@hotmail.com)
Xiaojian Zhou (zhouxiaojian@hotmail.com)
Zhiyuan Zhang (zhzhy@omschina.org.cn)
Wantao Chen (chenwantao2002@hotmail.com)

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Author's response to reviews:

Dear Prof. Frank Pajonk and Reviewers:

Thank you for your letter of 04/24/2006 indicating our paper The NF-kappaB pathway is associated with metastasis of head and neck cancer and decreased its activity in xenograft tumor models inhibits hematologic and lymphatic metastasis (MS: 2789586737120835) by YAN, et al can be resubmitted with revision. We do appreciate the prompt and constructive review. We have do our best to revise the manuscript as indicated in yellow colour as suggested by reviewers. Point-by-point responses include the following:

Editorial requests:

#1) Please can you re-write the title of your manuscript to ensure that it makes sense in English and accurately reflects the contents of the manuscript.

# Following the editorial suggestions, we have re-written the title and make it more concise and accurate.

#2) Please include a Methods section in your Abstract and ensure that it conforms to our guidelines.

# Sorry for missing the Methods section in our Abstract, we have added the section in the revised manuscript.

Reviewer: Cun-Yu Wang

1) Title is too long and should be more concise.

# Similar to the editorial request, we have re-written the title.

2) The manuscript should be carefully edited before the publication.

# Following the reviewers request, we have carefully edited the manuscript. In addition, the English language of our revised manuscript has been edited by AJE editors.

# We reviewed the paper mentioned (e.g., Science. 274: 784-787, 1996, Nature Med. 13:62-69, 2007) and agree with the reviewer’s comments, we have supplemented these contents in the revised manuscript.

Reviewer: Chann Lagadec

Major compulsory revisions:

1. Carcinoma collected are for 50% only tongue cancers… so authors should diversified the samples to heterogenize and to obtain homogenous distribution of cancer types through the different squamous carcinoma samples.

# Following the reviewers suggestion, we diversified the samples to two groups, tongue and other sites of head and neck. The nuclear positive rate of p65 was analyzed in the two groups individually.

2. Authors should compare NF-kB and carcinoma localization before to be able to claim that nuclear localization of NF-kB is available for all type of squamous carcinomas...

# We agree with the reviewers comments, and the statistic analysis was taken for squamous cell carcinomas in tongue and in other sites of head and neck individually. The similar results showed that the nuclear positive rates of NF-κB p65 in Lm and Tm groups were higher than Tn group (Wilcoxon rank-sum test; #2=14.573, df=2, p=0.001 in tongue SCC group and #2=22.425, df=2, p=0.0001 in SCCHN of other sites, respectively). These data demonstrate that NF-κB/relA activity can be correlated with SCCHN metastasis.

3. Authors should explain why Aurun et al. 2009 could explain that NF-kB inhibition induced a dramatique decrease of viability? Could identical genetic background (cells coming from the same parental line) explain this specificity? Authors should used others established cells lines (TSCC and OSC-4).

# Concerning to this question, we have reviewed the paper mentioned (Arun P, et al. Clin Cancer Res, 2009) and agree with the reviewer’s comments that NF-kappa B inhibition induced a dramatic decrease of viability. Our results have not been conflict with the paper from Arun et al, the rate of apoptosis in Tca8113 and TL cells treated with PDTC or BAY 11-7085 was increased compared to the control group, and significantly increased in TNF# plus PDTC or plus BAY 11-7085 group. However, we found that the lower metastatic cell line Tca8113 and higher metastatic cell line TL had the similar response to the NF-kB inhibitors. So we considered that there was some other mechanism for inhibiting Tb and TL cells metastasis to lung or lymph nodes by NF-kappa B inhibition besides inducing cell apoptosis (e.g. VEGF and MMP9 down-regulation or p65 phosphorylation at serine 539). Furthermore, we agree with the reviewer’s concern, identical genetic background of the Tca8113 and TL cells may be one of the reasons. Our previous data of apoptosis analysis show that similar results have been attained in TSCC and OSC-4 cell lines (data not shown), in this
manuscript we have only presented the results from Tca8113 and TL cells since
the manuscript page limited.

Minor essential revisions:
1. Some problems with fonts (ex: page 2 line 20)
   # Sorry for the problems, we have corrected them in the revision.
2. Introduction is missing some references to be more contextual.
   As the reviewer suggestion, we have added some references to the introduction
   section.
3. Error in corresponding author email.
   # So sorry, we have corrected the problem in the revision.
4. Fig 1A bottom right… not good magnification.
   # Sorry, we have corrected the problem in the revision.
5. Fig 2B error in graph legend
   # Sorry for the misplacement of graph legend of figures 2B and 2C in the
   previous version, we have changed them.
6. Fig 2D need legend and not number for line
   # We have added the legend instead of number.
7. Fig 3 pictures are not align at all!
   # We have corrected these mistakes in the revised manuscript.
8. Fig 4 graph pictures have to be re-size to be not deformed
   # We have re-sized the Fig 4 graph pictures.

Corresponding author, Wantao Chen