Author's response to reviews

Title: Expression of BRCA1 and ERCC1 mRNA Level is Associated to Lymph Node Metastasis in Chinese Colorectal Cancer Specimen

Authors:

yuanming LU (yuanming_lu@hotmail.com)
Jingyan Gao (gaojy@163.com)
Baorong Song (sbr@163.com)
Junjie Peng (pengjj@163.com)
Ye Xu (Xuye@163.com)
Sanjun Cai (bohojn@hotmail.com)

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Author's response to reviews: see over
Author’s response to reviews

Title: Expression of BRCA1 and ERCC1 mRNA Level is Associated to Lymph Node Metastasis in Chinese Colorectal Cancer Specimen
Authors: Yuanming Lu, Jingyan Gao, Baorong Song, Junjie Peng, Ye Xu and Sanjun Cai

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Author’s response to reviews: see over
Reviewer's report

Title: Expression of BRCA1 and ERCC1 mRNA Level is Associated to Colorectal Cancer Metastasis: The importance to the initial evaluation of clinical outcome of colorectal cancer patients

Version: 1 Date: 22 January 2012
Reviewer: Adam Vilmar

Reviewer's report:

The purpose of this study is to correlate ERCC1 and BRCA1 as effective biomarkers in CRC by RT-PCR analysis of 120 freshly frozen tissue resection samples from patients with and without LNM. This an important area of research in the area of tailored treatment. However, the authors fail to explain why. Is it to obtain prognostic or predictive information, why have they chosen these two biomarkers since both ERCC1 and BRCA1 potentially predict platinum sensitivity??

We have revised based on the reviewers’ comments in background…
Both ERCC1 and BRCA1 are essential component in multiple DNA damage repair pathways which involved in homologous recombination repair, non-homologous repair and nucleotide excision repair, it is considered to be a differential modulator of survival with cisplatin and taxanes. Preclinical and clinical studies have reported that BRCA1 level is associated with cisplatin and taxanes chemo sensitivity. Although above studies suggested that both ERCC1 and BRCA1 may serve as effective biomarkers for chemo sensitivity in cancer patients with primary tumor, the information on these biomarkers is still limited in metastases. In consideration of ERCC1 and BRCA1 act in two complete different signal pathway, explore these two biomarkers as predict factors in CRC metastasis maybe possible to increase the effective and sensitive in individual diagnostic and treatment.
The method section seems relative robust but suddenly the authors describe Western Blotting and TRAP-1 immunohistochemistry without explaining why. Please state the reason, if relevant, and include results in both results and discussion!! In the patients characteristics section, information is required concerning which patients recived adjuvant chemotherapy and how this could influence the results, especially in relation to ERCC1 being predicitve of platinum resistance.

1. about the TRAP1, we have revised in the part of material and methods.
2. in part of materials and methods, a total 120 colorectal carcinoma samples were collected after obtaining informed consent in our hospital. None of the patients received chemotherapy or radiotherapy before surgery, for that we can study them in the same standard lines.

From the results the authors conclude that the two biomarkers are significantly associated with LNM by down regulation which naturally translates into poor survival.
In the discussion section the authors fail to report limitations of their study, doesn’t compare their results to other similar papers and need to put their findings into perspective including a theoretical explanation of the results and where to go next. For example: down-regulation of ERCC1 in LNM+ CRC is very interesting because this could explain why these patients often will benefit from adjuvant chemotherapy including oxaliplatin.

We have revised these in the part of discussion based on the reviewers: for example, In this study, we suggest that ERCC1 and BRCA1 are the potential candidates by showing their down-expression and association with a poor prognosis in CRC…We found that the negatively expression of… implying that ERCC1 might be involved in CRC metastasis, suggesting that reduced expression of proteins may be an early event in colorectal carcinogenesis… On the other hand, proteins of the nucleotide excision repair (NER) pathway are thought to repair DNA damage cause by platinum agents and several studies demonstrated the inverse relationship between impaired DNA-repair capacity and increased response rates to platinum drug. It has been reported that
colorectal cancer patients whose tumor showed low levels of ERCC1 gene amplification had superior overall survival while treated with fluorouracil/oxaliplatine. However, we only investigate one gene in NER pathway. Metastasis is impacted with many factors. ERCC1 could be restrained or promoted by other genes, which has influenced lymph node metastasis somehow. Advanced research has already started and it will help us to know the way of metastasis more clearly.

There are a number of spelling mistakes and poor usage of the English language which will confuse the reader: For example line 6 in Background section, line 2 in RNA-isolation… section, line 6 i Confirmation of…section etc.

All the problems about language have been corrected as reviewer's instruction.

In conclusion this is an interesting topic with cumbersome and admirable lab-work. However, the manuscript needs major reconstruction before it can be considered for publication and even be reviewed properly.

**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests.
Reviewer's report

Title: Expression of BRCA1 and ERCC1 mRNA Level is Associated to Colorectal Cancer Metastasis: The importance to the initial evaluation of clinical outcome of colorectal cancer patients

Version: 1 Date: 23 January 2012
Reviewer: Rafael Rosell

Reviewer's report:
- Major Compulsory Revisions
  None.
- Minor Essential Revisions
  The study is well carried out. The only caveat is that there are other studies including melanoma, head and neck among others, in which overexpression of DNA repair genes such as BRCA1 and ERCC1 are associated with risk of progression to metastasis. The authors found the opposite results. Is there any correlation between the expression of BRCA1 and ERCC1?

  Although ERCC1 and BRCA1 have the similar roles in DNA repair systems, our data show that these two factors might be involved in CRC metastasis. However these two factors show different effects, for example, the BRCA1 does not show more sensitive in early stage like what the ERCC1 does. Thus we compare them and could suggest which one in its pathway is more effective for clinical diagnosis as biomarker. Our data show a relationship between expression of ERCC1 and BRCA1 in colorectal cancer metastasis, imply that both ERCC1 and BRCA1 might be involved in CRC metastasis, suggest that reduced expression of these proteins may be an early event in colorectal carcinogenesis.

  On page 5 TRAP-1 is mentioned and throughout the manuscript there is no further mention of this. It seems something is lacking or misleading. The authors should be very careful and justify this point.

  Yes, we have deal with it carefully.
- Discretionary Revisions

None.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.