Author's response to reviews

Title: LY294002 may overcome 5-FU resistance via down-regulation of activated p-AKT in Epstein-Barr virus-positive gastric cancer cells

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Author's response to reviews: see over
Dear Editor-in-Chief

I respectfully submit the enclosed paper titled: “LY294002 may overcome 5-FU resistance via down-regulation of activated p-Akt in EBV-positive gastric cancer cells”. It was written by J.Y. Shin and J.H. Kang et al.. We considered our manuscript for publication in the BioMed Central.

We found that; 1) In EBV positive gastric cancer cells, the resistance of 5-FU is attributed to constitutively activated PI3K/AKT pathway by a viral protein, LMP2A. 2) The sensitivity of 5-FU was greatly enhanced by selective inhibition of activated p-Akt when LY294002, a specific PI3-kinase inhibitor, was sequentially combined with 5-FU.

This paper has not been submitted to any other journals for publication.

We thank you for your consideration of our manuscript and look forward to hearing from you shortly.

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Yours sincerely,

Jung-Young Shin
1. In the whole manuscript (abstract, full text, legends and figures), the acronym “Akt” is not homogeneously written (“Akt” versus “AKT”) → All “Akt”s were homogeneously corrected to AKT.

2. In the introduction, a reference must be put at the end of the sentence: “EBV+ gastric carcinomas tend to express much higher amounts of p53 than do EBV-negative carcinomas” → Reference (2) was inserted at the indicated sentence in introduction.

3. The authors didn’t mention the origin (manufacturer) of the compounds used (5-FU and LY294002). → The origin of the compounds was clearly defined in M&M.

4. Figure 1 should be split in fig 1A and 1B → Figure 1 was split into fig1 A and 1B.

5. In the results and especially in figure 3B, the doses of 5-FU and LY294002 are not mentioned. → The doses of 5-FU and LY294002 were expressed in M&M and figure 3B.

6. “Scrambled siRNA” (also called “Scramble II duplex”) is mentioned in M&M. However in the results (§5 and fig 6A), the authors wrote “scramble LMP2A siRNA”, which doesn’t sounds correct. → In the results (§5 and fig 6A) and legend of fig 6, scramble LMP2A siRNA’s were corrected to scrambled siRNA.

7. Regarding the knockdown of LMP2A expression (§5 results), a control must be performed: i.e., is LMP2A is truly expressed in SNU-719 before the knockdown? What is its expression after knockdown? → Before the knockdown, LMP2A was abundantly expressed in SNU-719. When LMP2A siRNA was transfected in SNU-719 cells, the expression of LMP2A was reduced compared with scrambled siRNA. These data were inserted in Figure 6A.
The authors have reported some interesting, but not new, facts about the gastric carcinogenesis related to EBV infection. The technical approach is very informative but there is no clear link between the Results and Discussion section. Despite of robust results the manuscript don’t show any arrogated clear discussion. Actually, Discussion section is too long and redundant. The presentation should be more concise and the principal findings should highlight the purpose of the work. Some of the authors have already described similar results elsewhere but the references are not cited. The references might be upgraded and several papers of 2009 and 2010 should be included to improve the Discussion.

- No clear link between the Results and Discussion section and Discussion section is too long and redundant.
  → The content of results were indicated as the figure number. We deleted the unnecessary sentences that were not directly concerned with the results and shorten a manuscript to acceptable length.

- The references upgraded and several papers of 2009 and 2010
  → The papers of 2009 and 2010 in discussion were inserted in the references (ref 2, 22, 23, 35).
LY294002 may overcome 5-FU resistance via down-regulation of activated p-AKT in Epstein–Barr virus-positive gastric cancer cells.

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Running title: LY294002 overcome 5FU resistance in EBV (+) gastric cancer.

Key words: Epstein–Barr virus, 5-FU, PI3 kinase inhibitor, drug resistance, gastric cancer