Reviewer's report

Title: Epigenetic mechanisms involved in differential MDR1 mRNA expression between gastric and colon cancer cell lines and rationales for clinical chemotherapy

Version: 1 Date: 9 August 2007

Reviewer: Masakazu Yashiro

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General

Lee, et al described the comparison between MDR1 mRNA expression and methylation status at promoter region in gastric and colon cancer cell lines to clarify the reason why chemotherapeutic regimens have been different in gastric and colon cancer. The authors showed that MDR1 mRNA was not detected in the 10 gastric cancer cell lines but variable MDR1 mRNA levels in 7 of 9 colon cancer cell lines. Then, they examined underlying mechanisms in silencing of MDR1 expression by inhibiting methyltransferase inhibitor or histone deacetylase inhibitor. The authors concluded that the MDR1 mRNA levels in gastric cancer cells are low due to different epigenetic regulations such as DNA methylation and/or histone deacetylation.

Although the phenomenon itself seems to be interesting, the data is preliminary. This paper needs a major revise, and is not recommended for publication in this form.

Comments:

1. The data presented in this study is not enough to conclude that their results can provide a better understanding of the efficacy of combined chemotherapy as well as their oral bioavailability.

2. Their findings are not sufficient for definition of chemotherapeutic regimen. No experimental evidence is provided in the effect on 5-FU, platinum agents and topoisomerase inhibitors in animal models.

3. More details of the backgrounds of cancer cell lines used in this study should be addressed. Because the chemo-sensitivity of most cancer cell lines depend on p53 status, p53 status in each cancer cell lines should be addressed.

4. Why were both of semi-quantitative RT-PCR and real-time RT-PCR performed? Some of gastric cancer cell lines such as SNU-668,484 showed relative high expression in semi-quantitative PCR, whereas no expression in real-time RT-PCR in despite of more than 35 cycles. In addition, why did these cell lines show almost same expression ratio as COLO320HSR? Data of Pgp protein expression should be necessary.

5. In the chemo-sensitivity assay, expression of Pgp protein is not associated
with sensitivity for paclitaxel, because IC50 of SNU-668 was more than 10-fold high compared with SNU-C5 which showed no expression of Pgp protein same as SNU-668. In addition, there might be lack in sufficient explanation about dose of paclitaxel in figure 4B. Growth of SNU-668 which IC50 is 200-fold less than Colo320HSR is not suppressed at all, whereas that of colo320HSR is dramatically reduced only by adding Pgp inhibitor.

6. Direct sequencing of promoter region with or without bisulfite treatment might be useful to examine the methylation status at in gastric and colon cancer cell lines.

7. Discussion about treatment with 5AdC and TSA is relative complicated. How is the effect of these treatments on Pgp protein expression or chemo sensitivity? The authors described that MDR1 mRNA expression is differentially regulated in gastric and colon cancer. However, as shown in Table1, SNU-16 (gastric cancer cell line) and SNU-C5 (colon cancer) show similar effect on MDR1 expression as well as SNU-216 and HCT-116.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

What next?: Reject because scientifically unsound

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

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