This letter is to address the major comment raised by Dr. Paola Perego (Department of Experimental Oncology and Molecular Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy) that the decreased sensitivity to cisplatin treatment in gastric cancer cells is mainly mediated by AKT instead of MDR1 activation (1).

MDR1 is shown to confer survival advantage and this function may be functionally linked to its elevation by YB1 through Akt activation. Furthermore, our study identified Akt-YB1 and MDR1 axis as a downstream target of RecQL4, and it is difficult to assess the relative importance and influence of each of these components in cisplatin resistance (2). As we have not carried out the absorption as well as efflux of cisplatin in this study, we have based our discussion on our suggestive correlation observed between RecQL4 and the Akt-YB1 and MDR1 axis rather than MDR1 alone.

While I agree with the fact that cisplatin is not a substrate for P-glycoprotein, the efflux efficiency may vary for various cell types, particularly cancer cells. MDR1 inhibitor has been observed to affect the enhanced efflux by cisplatin treatment, and MDR1 expression can be augmented by cisplatin treatment (3). In addition, accumulating evidence has demonstrated the association between MDR1 activation and cisplatin resistance in a variety of cancer cells (4–6).

To further address the above issue, we have examined the level of AKT activation in gastric cancer cell lines by Western blotting (data not shown). We observed that four cell lines (MGC-803, AGS, SNU-1, and NCI-N87) showed a consistency between p-AKT levels and their sensitivity to cisplatin treatment; however, inconsistency between p-AKT and sensitivity to cisplatin was also observed in other three GC cell lines. For example, SNU-16 cell line was shown to be highly resistant to cisplatin (1), but had a low level of p-AKT. In contrast, although HGC-27 and MKN45 cell lines had a high level of p-AKT, their resistant capability to cisplatin was only marginally increased in comparison with AGS and NCI-N87 cells (2). Therefore, these observations strongly support that both AKT activation and RecQL4 overexpression should exist for the eventually enhanced YB1 and MDR1 activation and cisplatin-resistant phenotype in human GC cells.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References

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