Letter to the Editor

Reevaluation of the Roles of ABCG2 in the Disposition of Genistein

The purpose of this letter is to clarify some assessments in the article by Yang et al. (2012), in which they questioned the credibility of a conclusion in our recently published article (Alvarez et al., 2011). Yang et al. (2012) did provide a new insight, according to which increased exposure of aglycone in Bcrp1(−/−) mice might arise from the hydrolysis of glucuronide conjugates. However, they additionally claimed that “this is very different from the current understanding that an increased level of aglycone comes directly from impaired aglycone efflux transport of these conjugates.” Thus, the title of the article by Yang et al. (2012), which involves a clear allusion to our study, seems to be excessive. In brief, it is erroneous to read the final conclusion in our article as being that enhanced exposure to systemic metabolites in Bcrp1(−/−) can be attributed to increased intestinal absorption of genistein.


Yang et al. (2012), our article (Alvarez et al., 2011) also included references to a possible direct effect of Bcrp on the increased levels of the conjugates in Bcrp1(−/−) mice, since we stated in the discussion that “our results indicated a direct and conclusive Bcrp I efflux action on phase II metabolites of these isoflavones in vivo, and suggested a possible novel concept for ABCG2/BCRP as part of a metabolism-driven efflux transport of these conjugates.” Thus, the title of the article by Yang et al. (2012), which involves a clear allusion to our study, seems to be excessive. In brief, it is erroneous to read the final conclusion in our article as being that enhanced exposure to systemic metabolites in Bcrp1(−/−) can be attributed to increased intestinal absorption of genistein.

Authorship Contributions
Wrote or contributed to the writing of the manuscript: Alvarez, Vallejo, Barrera, Merino, Prieto, Tomas-Barberan, and Espin.

References

Response to Letter to the Editor on “Breast Cancer Resistance Protein (ABCG2) Determines Distribution of Genistein Phase II Metabolites: Reevaluation of the Roles of ABCG2 in the Disposition of Genistein”

The purpose of this letter is to respond to a comment made by Dr. Alvarez to our recently published article (Yang et al., 2012). We thank Dr. Alvarez for her interest and comments.

We take this opportunity to reemphasize that the conclusion of our article breaks away from a conventional wisdom, and we showed that higher systemic exposures to a conjugate did not have to come from an increased amount of aglycone available for conjugation or increased rates of conjugation. In fact, we have showed that a higher systemic exposure (i.e., higher blood concentrations) could be caused by preferred distribution of conjugates to the systemic circulation.

We arrived at our conclusion even though most of our pharmacokinetic results are consistent with those provided by Alvarez et al. (2011) and Enokizono et al. (2007). Our result is not inconsistent with the earlier research article by Alvarez et al. (2011), which showed that Bcrp has direct and conclusive effects on conjugate efflux. However, we did arrive at a very different interpretation of the pharmacokinetic results based on additional mechanistic studies. We made the decision to highlight our differences because speculation/hypothesis put forth by previous publications was taken as truth by other researchers and one reviewer of our manuscript.