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(–/–) 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 in Bcrp1(–/–) mice (Alvarez et al., 2011).” They also stated that “Alvarez et al. (2011) further proposed that improved bioavailability of genistein glucuronides and sulfates could be explained by increased exposure level of genistein aglycone to UGTs and SULTs in Bcrp1 knockout mice.” In this regard, we mentioned in our Short Communication (Alvarez et al., 2011) that an “impaired Bcrp-mediated efflux of genistein and daidzein could increase their exposure to UGT and SULT, and eventually produce greater amounts of metabolites,” simply as a potential additional factor for explaining the increased levels of genistein and its conjugates in Bcrp1(–/–), but we never proposed it as the main cause. We would like to mention that the role of Bcrp1 in genistein absorption was not known when our manuscript was written, and our assessment should thus be considered as a possibility that was open at that moment. Unfortunately, Yang et al. (2012) seem to have overstated the case. Their article is the first demonstration of the absence of the involvement of Bcrp1 in the intestinal absorption of genistein. In agreement with Yang et al. (2012), our article (Alvarez et al., 2011) also included references to a possible direct effect of Bcrp1 on the increased levels of the conjugates in Bcrp1(–/–) mice, since we stated in the discussion that “our results indicated a direct and conclusive Bcrp1 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.

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Wrote or contributed to the writing of the manuscript: Alvarez, Vallejo, Barrera, Merino, Prieto, Tomás-Barberán, and Espín.

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Letter to the Editor

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.

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