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Molecular Simulation Analysis of Glucuronidation of UDP-glucuronosyltransferase 1A7 and 1A10

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UDP-glucuronosyltransferase 1A (UGT1A) constitute an endoplasmic reticulum (ER) membrane-bound enzyme family whose members catalyze glucuronidation. We previously analyzed the bilirubin glucuronidation by UGT1A isoform 1 (UGT1A1) by means of (1) calculation of 3-D structure of mutant UGT1A1, (2) docking simulation of UGT1A1 and its coenzyme (UDPGA), (3) induced fit of UGT1A1-UDPGA complex, and (4) docking simulation of UGT1A1 and bilirubin. We found that the ratio of the docking when the hydroxyl group of bilirubin oriented toward UDPGA correlated with *in vitro* conjugation capacity report previously [1]. Based on this molecular mechanism that glucuronidation by UGT1A1 requires the hydroxyl group of ligand to locate toward the coenzyme [2], we reported the method to predict the conjugation capacity of UGT1A1 by our molecular simulation [3]. In this study we analyzed the glucuronidation of other UGT1A isoforms (UGT1A7 and UGT1A10) by our molecular simulation. As a result, we found that ratio of the binding of coenzyme to the enzyme in reactive orientation and the ratio of the ligand orientation whose hydroxyl group locate toward the coenzyme also correlated with *in vitro* conjugation capacity [4,5]. This result suggests that the conjugation capacity of other UGT1A isoforms is determined by the similar mechanism as UGT1A1.

[1] Yamamoto K. *et al.,* Contribution of two missense mutations (G71R and Y486D) of the bilirubin UDP glycosyltransferase (UGT1A1) gene to phenotypes of Gilbert's syndrome and Crigler-Najjar syndrome type II, *Biochim Biophys Acta* 1406:267-273, 1998.
[2] Takaoka Y. *et al.*, Ligand orientation governs conjugation capacity of UDP-glucuronosyltransferase 1A1, *Journal of Biochemistry*, 148(1):25-28, 2010.
[3] Takaoka Y. *et al.*, Method for predicting enzyme activity by computer simulation, PCT/JP2009/004286, 2009.
[4] Villeneuve L. *et al.*, Novel Functional Polymorphisms in the UGT1A7 and UGT1A9 Glucuronidating Enzymes in Caucasian and African-American Subjects and Their Impact on the Metabolism of 7-Ethyl-10-hydroxycamptothecin and Flavopiridol Anticancer Drugs, *The Journal of Pharmacology and experimental therapeutics*, 307(1):117-128, 2003.
[5] Dellinger R.W. *et al.*, Importance of UDP-glucuronosyltransferase 1A10 (UGT1A10) in the detoxification of polycyclic aromatic hydrocarbons: decreased glucuronidative activity of the UGT1A10^{139Lys} isoform, *Drug Metabolism and Disposition*, 34(6):943-949, 2006.