Reply to: "New Insight of OCT2 Regulation as Mediator for Cisplatin- Induced Nephrotoxicity"

Dear Editor

We read the interesting letter entitled "New insight of OCT2 Regulation as Mediator for Cisplatin- Induced Nephrotoxicity " by Amr Ahmed EL-Arabey and Mohnad Abdalla in response to our review article (Nematbakhsh et al., 2017) about the role of OCT2 in cisplatin nephrotoxicity. Firstly, we appreciate the response.

The first author previously wrote about OCT2 and his suggestion that the main determinant for sex differences in OCT2 gene expression is testosterone (El-Arabey AA, 2015). The role of OCT2 expression in cisplatin nephrotoxicity is documented. Yonezawa et al reported that renal rat OCT2 expression is the major determinant of cisplatin-induced nephrotoxicity (Yonezawa et al., 2005). However Sprowl et al., (2013 and 2014). concluded that clinical exploration of OCT2 inhibitors may not protect the kidney against cisplatin induced nephrotoxicity unless the p53 pathway is antagonized, and therefore Formononetin was suggested by Huang et al., (2017).

The nephron-protective role of OCT2 inhibitor like cimetidine has been also been reported (Sprowl et al., 2013; Katsuda et al., 2010).

OCT2 has no expression in tumors and OCT2 inhibitors have no effect on tumor tissue. In human being, in observational studies, expression of OCT2 has been linked to cisplatin nephrotoxicity. It seems that the suggestions for use of OCT2 inhibitors in different sexes might be relevant.

References

El-Arabey AA (2015). Sex and age differences related to renal OCT2 gene expression in cisplatin-induced nephrotoxicity. *Iran J Kidney Dis*, **9**, 335-6.

Huang D, Wang C, Duan Y, et al (2017). Targeting Oct2 and P53: Formononetin prevents cisplatin-induced acute kidney injury. *Toxicol Appl Pharmacol,* **326**, 15-24.

Katsuda H, Yamashita M, Katsura H, et al (2010). Protecting cisplatin-induced nephrotoxicity with cimetidine does not affect antitumor activity. *Biol Pharm Bull,* **33**, 1867-71.

Nematbakhsh M, Pezeshki Z, Eshraghi JF, et al (2017). Cisplatin-Induced Nephrotoxicity; Protective Supplements and Gender Differences. *Asian Pac J Cancer Prev*, **18**, 295-314.

Sprowl JA, van Doorn L, Hu S, et al (2013). Conjunctive therapy of cisplatin with the OCT2 inhibitor cimetidine: influence on antitumo*r efficacy and systemic clearance. Clin Pharmacol Ther,* **94**, 585-92.

Sprowl JA, Lancaster CS, Pabla N, et al (2014). Cisplatin-induced renal injury is independently mediated by OCT2 and p53. *Clin Cancer Res*, **20**, 4026-35.

Yonezawa A, Masuda S, Nishihara K, et al (2005). Association between tubular toxicity of cisplatin and expression of organic cation transporter rOCT2 (Slc22a2) in the rat. *Biochem Pharmacol*, **70**, 1823-31.

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