LETTER to the EDITOR

New Insight of OCT2 Regulation as Mediator for Cisplatin- Induced Nephrotoxicity

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Dear Editor

We read with interest the recently published review article in Asian Pac J Cancer Prev, by Nematbakhsh et al., entitled 'Cisplatin-Induced Nephrotoxicity; Protective Supplements and Gender Differences'(Nematbakhsh et al., 2017). The authors concluded several suggestions that may provide to reduce Cisplatin (CDDP) induced nephrotoxicity (Nematbakhsh et al., 2017). Here, we would like to add one more substantial suggestion to improve the current efforts to overcome the main dosing limiting nephrotoxic effect of CDDP. Cisplatin nephrotoxicity is sex related greater intensity of damage in male than female and these differences may be related to CDDP uptake by OCT2 due to the markedly higher renal expression of Organic cation transporter 2 (OCT2) in male than female rats. The main determinant for sex differences in OCT2 gene expression is testosterone (El-Arabey, 2015a, 2015b) . Furthermore, Study demonstrated that OCT2 level was significantly reduced in mice after castration (Meetam et al., 2009). Hence, regulation of OCT2 expression act as critical mediator for CDDP induced nephrotoxicity. There are some efforts introduced toward study of protective supplement on the regulation of renal organic cation transporters (Ulu et al., 2012; El-Arabey and Salama, 2015; El-Arabey, 2016). Recently, study demonstrated that OCT2 gene variation in the South African bantu-speaking population and functional promoter variants in different populations for drug safety, response and global pharmacogenomics (Wilson et al., 2017). Therefore, we should take in our consideration when explore novel compounds against CDDP induced nephrotoxicity to examine their effects on the regulation of renal OCT2. In addition, research is needed to conduct randomized clinical trials to examine the relevance of sex differences and contribution of the renal expression of OCT2 transporter to the situation of CDDP induced nephrotoxicity in humans.

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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.

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