Divergent Injury Effects of Cisplatin Treatment on Promoting Cyst Formation in Adult *Pkd2* Mutant Mouse Model

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Introduction: Cisplatin is an antitumor drug used widely in the treatment of a variety of malignancies but also has severe side effects, which could result in acute or chronic kidney injury. Links between cyst formation and renal injuries have been reported in multiple PKD animal models, but the effect of cisplatin-induced injury on cyst formation has not been investigated. Here we evaluate the effect of two different regimens of cisplatin treatment on renal injury and cyst formation in *Pkd2* mutant mouse models.

Methods: To test the effects of cisplatin injury on cyst formation, we tested two regimens of cisplatin treatment (1X 9.0mg/kg and 4X 5.0mg/kg body weight, IP) to cause injury in adult-induced conditional *Pkd2* mouse model. The study design including tamoxifen induction and cisplatin treatment is shown in Experimental Design below. Multiple features including renal injury, proliferation, fibrosis, macrophage accumulation, and cystic index were analyzed to investigate the effect of cisplatin-induced injury on cyst growth.

Results: Analysis of the cystic phenotype showed that both cisplatin regimens significantly accelerated cyst formation in *Pkd2* mutant mice comparing to PBS-treated group. Interestingly, the cystic index is markedly increased in mutant mice given a single cisplatin treatment compared to the multiple cisplatin treatment group. More importantly, kidneys from mice with a single cisplatin treatment displayed decreased levels of fibrosis and macrophage accumulation, but increased proliferation at end-time points compared to the multiple cisplatin treatment group.

Conclusion: Our date show both a single treatment and multiple doses of cisplatin result in accelerated cyst formation in pkd2 mutant mice. More important, these data suggest that different injury forms (acute or chronic) could have distinct effects on cyst formation.

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