Cisplatin-induced renal injury promotes cyst formation in adult cilia mutant mouse model

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Introduction: Multiple renal cystic diseases, including PKD, are caused by dysfunction of the primary cilium on the tubule epithelium. Renal injury exacerbated the rate of cyst formation suggesting the cilium may regulate injury response and repair processes. Cisplatin is a widely used antitumor drug that is also known to be nephrotoxic. Here we evaluate whether a Cisplatin-induced renal injury leads to mal-repair of the kidney and increased cyst formation in mice with cilia disruption.

Methods: To test the effects of cisplatin-induced renal injury on cyst formation, we treated conditional Ift88 mutant mice with a low-dose of Cisplatin. To evaluate the impact of cilia disruption on renal injury and repair following Cisplatin treatment, we preformed immunofluorescence staining for injury markers Kim1 and Sox9, and FACS analysis of macrophages on kidneys following cisplatin treatment. We also analyzed cystic phenotypes after 9 weeks to evaluate the consequence of cisplatin-induced injury on cyst formation.

Results: Expression of Kim1 and Sox9 increased three days after Cisplatin treatment but decreased 14 days post treatment in Ift88 mutant mice compared to control. F4/80+ macrophages accumulated around injured tubules although no significant increase in total macrophage numbers was observed based on FACS analysis. More importantly, there was a marked increase in cyst severity in Ift88 mutant kidneys comparted to vehicle treated mice 9 weeks after Cisplatin treatment. Cysts were mainly located at cortical area, similar to the observed regions of Kim1 and Sox9 expression.

Conclusion: Low-dose Cisplatin treatment caused renal injury and enhanced cyst formation in cilia mutant mouse models suggesting that Cisplatin injury can be used as an alternative to IRI to accelerate cyst formation in mouse models. Additionally, these data indicate that cilia function is important in regulating repair processes following injury, defects in which contribute to more aggressive rates of cystogenesis.

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