Quantitative Systems Toxicology (QST) Modeling of Drug-Induced Acute Proximal Tubule Epithelial Cell Injury and Associated Renal Hemodynamic Responses

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PURPOSE

Renal proximal tubule epithelial cells (RPTEC) are vulnerable to drug-induced toxicities which often result in acute kidney injury (AKI).
Drug toxic effects range from mild RPTEC injuries to cellular death via multiple cellular damage mechanisms. At the systems level, decline in glomerular filtration rate (GFR) is a common manifestation of AKI.
The complexity of pathophysiological responses (cellular, neurohormonal, hemodynamic) that lead to impaired filtration pose a challenge for reliable prediction of AKI. level manifestations of AKI. Quantitative systems toxicology (QST) a promising tool to predict drug-induced AKI was employed by computationally translating in vitro cellular-level renal damage assays and kidney tissue. exposure predictions into systems.

OBJECTIVE

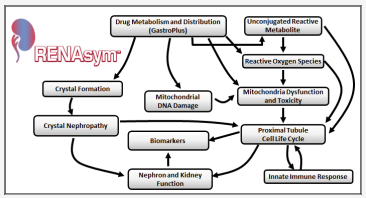
The aim is to develop a QST model of drug-induced AKI (RENAsym) to mechanistically determine the level of cellular injury and predict the subsequent changes in renal hemodynamic responses.

METHODS

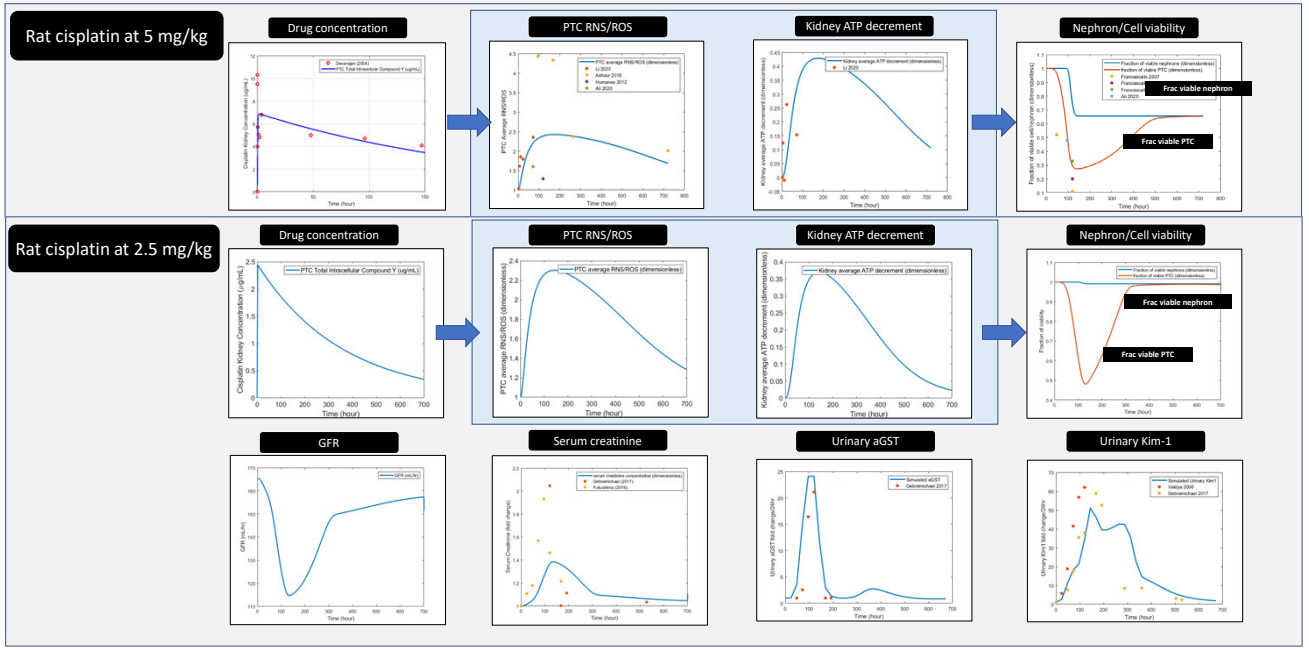
At the cellular level, RENAsym represents RPTEC life cycle, bioenergetics, and immune responses to renal toxicity. In vitro assays were used to parameterize key cellular injury mechanisms.
At the systems level, RENAsym model represents renal function and feedback mechanisms including tubuloglomerular feedback (TGF) and renin-angiotensin-aldosterone systems (RAAS).
RENAsym was employed to characterize the renal hemodynamic responses of drug induced RPTEC injury in humans and rats treated with nephrotoxic drugs including cisplatin.

RESULTS

Toxicity mechanism in RENAsym were initially parameterized using the in vitro measurements of oxidative stress and mitochondrial dysfuction in RPTEC exposed to cisplatin
The model was then calibrated with preclinical cellular measurements and organ-wide toxicity measures in rats
RENAsym can recapitulate the timing of injury in cisplatin-treated rats when only ROS-generating toxicity mechanism was included
AT the cellular level, specific biomarkers such as Kim-1 and aGST were employed to represent the level injury to RPTEC
At the systemic level, functional biomarkers such as GFR and serum creatinine were used to represent the hemodynamic response of nephrotoxic drugs
Biomarker submodels were implemented in RENAsym and calibrated with preclinical data mostly available in rats



- Simulated rat cisplatin model compares well to the observed data for functional and urinary biomarkers at two different doses
  - Simulated viability at 2.5 mg/kg cisplatin in rats predicts a mild injury and recovery of PTC loss and GFR loss compared to 5 mg/kg cisplatin where PTC loss is not fully recovered representing a stronger injury
  - Functional biomarkers (e.g. serum creatinine) as well as urinary biomarkers (e.g. urinary aGST and Kim-1) are recapitulated for cisplatin-mediated injury in RENAsym



CONCLUSION

Cisplatin-mediated toxicity were evaluated dose-dependently in rats using a quantitative systems toxicology model of drug-induced acute kidney injury (RENAsym).

RENAsym represents kidney function at cellular and organ levels in healthy and pathologic states caused by nephrotoxic toxic drug such as cisplatin.

Nephrotoxic drugs other than cisplatin are also represented in RENAsym.
RENAsym can predict drug induced cellular injury and subsequent hemodynamic impairments, and evaluate preclinical and clinical outcomes during AKI using functional and urinary biomarkers

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