Nature Reviews Nephrology | Published online 4 Dec 2017; doi:10.1038/nrneph.2017.168

PHARMACOLOGY

Investigating nephrotoxicity with an integrated liver–kidney chip

Although nephrotoxins pose a substantial threat to human health, ethical concerns often hinder the study of precise toxicological mechanisms in humans. Now, using a dual organs-on-chips approach, David Eaton, Ed Kelly, Jonathan Himmelfarb, Victoriya Sidorenko and colleagues elucidate the specific steps in the liver and kidney that lead to aristolochic acid-induced nephrotoxicity and thereby evaluate the utility of this method for preclinical pharmacology and toxicology studies.

The researchers connected human primary hepatic parenchymal cells to proximal tubular epithelial cells in an *ex vivo* microphysiological system and found that biotransformation of aristolochic acid involves nitroreduction followed by sulfate conjugation in the liver. Hepatic and renal membrane transporters efficiently mediate liver cell efflux and kidney cell influx of the sulfate conjugate, respectively. Toxicity in the kidney is caused by accumulation and dissociation of the unstable sulfate conjugate to a reactive metabolite that binds to DNA and proteins.

In the future, the researchers plan to investigate the role of the liver in the metabolism of other known nephrotoxins. "Once the mechanisms of action in both liver and kidney have been elucidated, the nephrotoxicity of drugs could be substantially reduced by pharmacologically targeting hepatic xenobiotic-metabolizing enzymes and/or hepatic or renal transporters," comments Eaton. Furthermore, they intend to explore the role of genetic polymorphism in response to xenobiotics, either by screening for donors of select genotypes or by using CRISPR–Cas9 gene editing of pluripotent stem cells followed by directed differentiation.

"Pharmacological studies using human organs-on-chips will enable improvements in preclinical drug development and better assessment of human health hazards from environmental exposures," concludes Eaton.

Jack M. Heintze

ORIGINAL ARTICLE Chang, S.-Y. *et al.* Human liver–kidney model elucidates the mechanisms of aristolochic acid nephrotoxicity. *JCI Insight* **2**, e95978 (2017)

"the nephrotoxicity of drugs could be substantially reduced by pharmacologically targeting hepatic xenobiotic-metabolizing enzymes and/or hepatic or renal transporters"