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Modeling Organ-Specific Aristolochic Acid Toxicity Using an Integrated Liver-Kidney Organotypic System

Elijah Weber
Problem: Aristolochic Acid Nephropathy (AAN)

Aristolochia clematidis

Aristolochic Acid (AA-I)

- Chinese-herb nephropathy (CHN) / Balkan endemic nephropathy (BEN)
- Chronic kidney disease (CKD) and upper urinary tract urothelial carcinoma (UUC)

IARC classifications:

Herbal remedies containing plant species of the genus *Aristolochia* are carcinogenic to humans (Group 1).

Naturally occurring mixtures of AA are probably carcinogenic to humans (Group 2).
• Can we model AAN using an ex vivo organotypic system?

• Direct and functional coupling of liver → kidney to recapitulate 1st pass metabolism/bioactivation
Platform: Nortis Microphysiological System (MPS)

Technical details:

- Gas-permeable PDMS silicone, polycarbonate base, collagen type I ECM, with a microscope coverslip
- Incorporation of “bubble traps” (port 1) at media entry point, as well as option for “ablumenal” flow (ports 2/4)
- Diameter of “tubule” is ~120 µM with an internal volume of ~70 nL
- Typical flow rate of 0.5-1.0 µL/min
- A 6 mm tubule contains ~5000 PTECs
Development of a microphysiological model of human kidney proximal tubule function

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What is the role of the liver in AA-I first-pass metabolism?
Study Design
AA-nephrotoxicity via hepatic bioactivation
DNA adduct formation from bioactivated AA-I
The role of the liver in bioactivation of AA-I

Aristolochic Acid-I (AA-I)

LIVER

NQO1
Nitroreduction

AL-I-NOH
SULTs
Sulfation

CYP1As
Demethylation

AL-I-NOSO₃

LIVER→KIDNEY

Efflux→Uptake (Hepatic MRPs) (Renal OATs)

Transporters

Kidney Toxicity (Geno-/Cyto-)

Alternative Metabolic Fate (NOT Geno- or Cytotoxic)
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