Cyclophilin A is a damage associated molecular pattern that mediates paracetamol-induced liver injury

James Dear¹,³, Ken Simpson², Melianthe Nicolai¹, James Catterson¹, Tineke Huizinga¹, Kevin Dhaliwal⁶, Sheila Webb⁴, D Nick Bateman³, David J Webb¹

¹Clinical Pharmacology Unit, Edinburgh University, Edinburgh, United Kingdom, ²Centre for Inflammation Research, Edinburgh University, Edinburgh, United Kingdom, ³National Poisons Information Service, Edinburgh, United Kingdom, ⁴MRC Human Genetics Unit, Edinburgh, United Kingdom

The innate immune system is alerted to cell injury by damage associated molecular patterns (DAMPs) - intracellular molecules that are released following damage to the cell membrane. Cyclophilin A (CypA) is a novel inflammatory mediator we previously identified as important in the pathophysiology of sepsis. As necrotic cell death is typical of severe paracetamol poisoning, we hypothesised that CypA may be an important mediator of liver injury by virtue of it being a novel DAMP.

This translational study used both mouse models and human samples. We generated a mouse lacking the gene for CypA (CypA KO) to investigate its role in paracetamol poisoning (induced by 350mg/kg intra-peritoneal injection). Furthermore, we determined the effect on paracetamol poisoning of blockade of the extra-cellular receptor for CypA (CD147) with a specific antibody. We generated necrotic cells from the liver of wild-type (WT) and KO mice and quantified the inflammatory response when necrotic cells were injected into WT mice. With ethics approval, urine was collected from patients attending the Royal Infirmary of Edinburgh with varying degrees of paracetamol-induced liver injury and the CypA concentration was measured.

CypA KO mice were resistant to paracetamol poisoning (ALT values 24 hrs post-paracetamol injection: KO 1096 ± 501u/l n=24; WT 4244 ± 1266u/l n = 15, p=0.01). Inhibition of CD147 also significantly reduced paracetamol-induced liver injury. Six hours after injection into WT mice, CypA KO necrotic liver cells induced less of an inflammatory response than WT cells. Inhibition of CD147 also significantly reduced the host inflammatory response to necrotic liver cells. Urine from patients with paracetamol-induced liver injury had significantly elevated CypA compared to patients without evidence of liver injury.

CypA is a critical mediator of paracetamol-induced liver injury. Our data support its pathophysiological mechanism being a DAMP. In humans, this protein is released into the urine of patients with liver injury and it may represent a biomarker in addition to a novel therapeutic target.