CompCyst outperforms the standard-of-care paradigm

CompCyst had a significantly higher accuracy than the standard-of-care for classification into the surgery, surveillance and discharge groups (69% versus 56%; $P=0.000073$).

The authors also used a conceptually similar artificial intelligence-based approach to define a composite marker panel for predicting cyst type, which was significantly more accurate than conventional clinical and imaging criteria for cyst diagnosis ($P=0.01$).

Overall, by integrating, rather than replacing, conventional tools with molecular data, CompCyst outperforms the standard-of-care paradigm for management of patients with pancreatic cysts.

“The next step is a multicentre study to prospectively compare CompCyst with current tools in all patients with pancreatic cysts — we expect to start enrolment within the next 12 months,” concludes author Anne Marie Lennon.

Conor A. Bradley

ORIGINAL ARTICLE Springer, S. et al. A multimodality test to guide the management of patients with a pancreatic cyst. *Sci. Transl. Med.* **11**, eaav4772 (2019)

Credit: Laura Marshall/
Springer Nature Limited

Finally, PADI4-deficient mice fed a lithogenic diet to induce gallstones had substantially reduced gallstone formation compared with wild-type mice fed the same diet, despite no differences in bile composition. In wild-type mice fed a lithogenic diet, a PADI4 inhibitor and an agent that impairs the activity and migration of neutrophils both markedly impaired gallstone formation, as well as the progression of gallstones that had already formed.

Together, these findings suggest that NETs foster the assembly of biliary cholesterol and calcium crystals into larger aggregates and gallstones. “Hypothetically, it seems possible to take these results as a basis for therapeutic interventions,” concludes Herrmann. “This is especially important for patients with relapsing disease.”

Iain Dickson

ORIGINAL ARTICLE Muñoz, L. E. et al. Neutrophil extracellular traps initiate gallstone formation. *Immunity* <https://doi.org/10.1016/j.immuni.2019.07.002> (2019)

Improving hepatic ischaemia–reperfusion injury outcomes

Two new studies have extended our understanding of hepatic ischaemia–reperfusion injury (IRI), demonstrating how antibiotic pretreatment can improve outcomes in liver transplant recipients and finding that the administration of small-molecule inhibitors of cyclophilin D (CypD) can protect against this injury in mice.

Hepatic IRI is a pro-inflammatory response initiated when blood circulation is restored to tissues after a period of ischaemia. Despite being a major cause of early allograft dysfunction (EAD) following liver transplantation, and contributing to the problem of donor organ shortage, the mechanisms of IRI are not well understood and new treatment and prevention strategies are needed.

In the first of the new studies, a team of researchers built on other experimental studies that showed an effect of the microbiota in the survival of skin and heart allografts. Here, they examined how modifications of the gut microbiota with antibiotic pretreatment might affect hepatic IRI and liver transplantation outcomes.

First, using a clinically relevant allogeneic mouse model of orthotopic liver transplantation, 10-day antibiotic pretreatment in recipients was found to increase gut-derived prostaglandin E2 (PGE2) serum levels and the subsequent hepatic expression of the PGE2 receptor, EP4. In an EP4-dependent manner, antibiotic pretreatment decreased and increased markers of endoplasmic reticulum (ER) stress and autophagy, respectively, which are thought to protect against hepatic IRI. Indeed, 10-day antibiotic pretreatment in recipients conferred IRI protection in this mouse model, whereas an EP4 antagonist restored ER stress, decreased autophagy and recreated hepatic IRI.

In humans, the investigators found that patients who received a prolonged antibiotic regimen (≥ 10 days) prior to liver transplantation recapitulated the findings related to ER stress and autophagy from the mouse model, which coincided with improved liver function and a decreased incidence of EAD. Concluding their work on IRI and liver transplantation, the researchers say, “by integrating mouse and human data, our study clearly underscores the benefits of extended recipient antibiotic pretreatment.”

One mechanism for IRI involves mitochondrial dysfunction, in which CypD-regulated mitochondrial permeability transition pore (mPTP) opening is increased. In the second new study, the effects of nine small-molecule inhibitors of CypD were examined in cell models and in livers of mice undergoing hepatic IRI.

The researchers first identified the most potent CypD inhibitor in mouse livers and primary human hepatocytes. Using an assay of CypD activity with isolated hepatic mitochondria, the effects of the inhibitors on mPTP opening were assessed by measuring mitochondrial swelling and calcium retention.

The investigators then induced IRI in the livers of mice and administered an inhibitor or vehicle before and during reperfusion, collecting samples of blood and liver for histological analyses. In mice with hepatic IRI, they found that administration of the potent CypD inhibitor restored hepatic calcium retention capacity and oxidative phosphorylation parameters, and reduced liver damage compared with vehicle. The authors suggest that these compounds could be developed to protect patients from IRI after liver surgery or for other disorders related to mPTP opening.

Iain Dickson

ORIGINAL ARTICLES Nakamura, K. et al. Antibiotic pretreatment alleviates liver transplant damage in mice and humans. *J. Clin. Invest.* **129**, 3420–3434 (2019) | Panel, M. et al. Small-molecule inhibitors of cyclophilins block opening of the mitochondrial permeability transition pore and protect mice from hepatic ischemia–reperfusion injury. *Gastroenterology* <https://doi.org/10.1053/j.gastro.2019.07.026> (2019)