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PANCREATITIS

KMO inhibitor for multi-organ failure in experimental acute pancreatitis

> Acute pancreatitis is a common and serious condition...

Inhibition of kynurenine-3-monooxygenase (KMO) could be a novel treatment approach for multiple organ dysfunction syndrome (MODS) in acute pancreatitis, according to a new study published in *Nature Medicine*. The findings showed that a small-molecule inhibitor of KMO protected against extrapancreatic tissue injury to the lung, kidney and liver in an *in vivo* experimental model of acute pancreatitis with MODS (AP-MODS).

Acute pancreatitis is a common and serious condition, with sudden onset of inflammation of the pancreas as a result of a number of causes, most frequently excess alcohol consumption or gallstones. "Although the local complications of the disease in the pancreas are important, the main factor that determines clinical outcome is the development of MODS, particularly affecting the lungs and kidneys," says first author Damian Mole, University of Edinburgh, UK. "About 1 in 4 persons with acute pancreatitis will develop MODS and need critical care," he adds.

Previous work had identified the kynurenine pathway of tryptophan metabolism as an important contributor to the development of MODS within the context of acute pancreatitis. In the new study, the researchers built on this work by exploring the role of KMO, a key enzyme in the tryptophan metabolism pathway that metabolizes kynurenine, in AP-MODS.

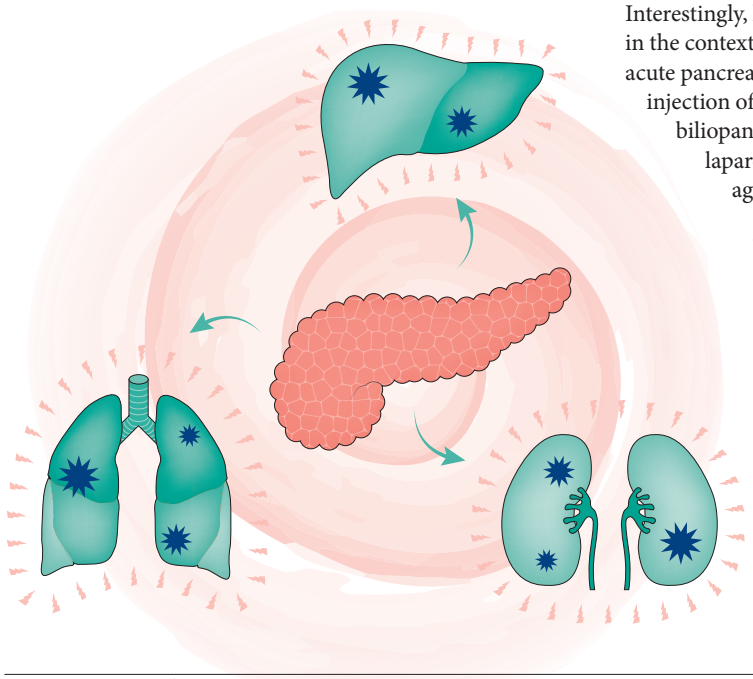
The investigators created a mouse that lacked KMO activity in all tissues and used this mutant mouse to examine kynurenine metabolism pathways, revealing that KMO was the key enzyme that determines the metabolic fate of kynurenine. Interestingly, lack of KMO activity in the context of experimental acute pancreatitis (induced by injection of taurocholate into the biliopancreatic duct during laparotomy) protected against lung, liver and kidney injury (assessed by TUNEL and histological assays, among others). No difference in the level of pancreatic injury (necrosis, interlobular oedema, inflammatory cell infiltrates) was observed between *Kmo*^{null} and wild-type control mice after induction of acute pancreatitis.

A medicinal chemistry strategy identified the oxazolidinone GSK180 as a potent and specific inhibitor of KMO; X-ray crystallography confirmed the binding of the inhibitor in the KMO active site. Crucially, therapeutic administration of GSK180 in a rat model of AP-MODS protected against injury to the lung, liver and kidneys; untreated rats had higher levels of lung, liver and kidney damage.

"While these are exciting findings in rodent models, there is a lot to consider before this approach can be applied to humans," says David Whitcomb (University of Pittsburgh, USA), who was not involved in this new study, citing selection of patients with acute pancreatitis for inclusion in clinical trials and timing of drug delivery as important factors. "Furthermore, human acute pancreatitis is highly heterogenous, and it is not clear that the mechanism of multiple organ failure is the same in everyone," he cautions.

A similar sentiment is held by the investigators. "What we really need to do now is bridge the translation gap," explains Mole. "In order to make an effective and robust translation into the clinic, we need to show further proof-of-concept that KMO is a rational and sensible strategy to pursue in human acute pancreatitis," he concludes, which will be the major focus of future work.

Katrina Ray



Laura Marshall/*NPG*

ORIGINAL ARTICLE Mole, D. J. *et al.* Kynurenine-3-monooxygenase inhibition prevents multiple organ failure in rodent models of acute pancreatitis. *Nat. Med.* http://dx.doi.org/10.1038/nm.4020

FURTHER READING Bakker, O. J. *et al.* Treatment options for acute pancreatitis. *Nat. Rev. Gastroenterol. Hepatol.* **11**, 462–469 (2014)