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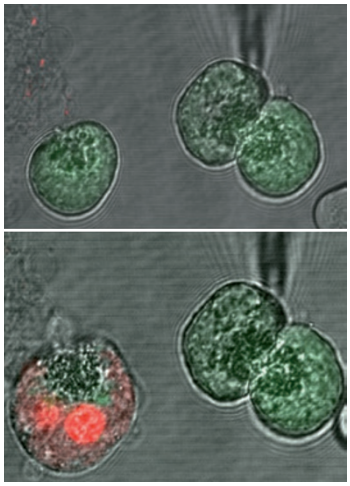
PANCREATITIS

MPTP pore opening proves crucial for experimental pancreatitis

Opening of the mitochondrial permeability transition pore (MPTP) has been shown to be key to the development of experimental acute pancreatitis. The findings pinpoint MPTP as a potential new drug target for the treatment of acute pancreatitis.

Despite extensive research, a specific targeted agent for the treatment of acute pancreatitis is lacking, and management of the disease is usually supportive care (such as pain control or antibiotics). "In my view, there are two principal strategies that can be adopted to develop treatments for acute pancreatitis: the first is to target pancreatic acinar cell injury, the second the resulting immune responses," explains author Robert Sutton.

Previous work had focussed on the early events in pancreatic injury, particularly calcium overload. Interestingly, this calcium overload in the mitochondrial matrix induces MPTP opening (important for mitochondrial membrane potential and ATP production), which has been shown to occur in the context of acute pancreatitis. As the mechanisms underlying this process were unknown, MPTP opening in the pancreas was investigated using a variety of techniques *in vitro* and *in vivo*.



ATP delivered via patch pipette (right) prevents cell death in mouse pancreatic acinar cells; increased cytosolic calcium levels (green) and necrotic cell death pathway activation (red). Image courtesy of R. Sutton.

The researchers found that toxin-induced MPTP opening in acinar cells was induced via second messenger receptor calcium channel release, which led to depleted ATP production and impaired calcium clearance. Consequently, autophagy was then defective and necrosis occurred upon activation of necrotic cell death pathways. Strikingly, intracellular supplementation of ATP mitigated these effects.

In both mouse and human pancreatic acinar cells, pharmacological and genetic inhibition of MPTP prevented toxin-induced mitochondrial impairment (maintaining membrane potential and protecting ATP production) and necrosis. Crucially, the same results were observed *in vivo*. In all four experimental animal models of acute pancreatitis tested (representing the whole spectrum of human acute pancreatitis), immunological and histopathological changes as a result of acute pancreatitis were inhibited, and even abolished.

"Ultimately, we need a therapy for acute pancreatitis and the more targets, compounds, preclinical studies, companies we draw into the field, toxicology packages undertaken, phase I, IIa, IIb and III studies we undertake, the more likely it is that sooner or later we will have a specific, licenced pharmacotherapy for acute pancreatitis," concludes Sutton.

Katrina Ray

Original article Mukherjee, R. *et al*. Mechanism of mitochondrial permeability transition pore induction and damage in the pancreas: inhibition prevents acute pancreatitis by protecting production of ATP. *Gut* http://dx.doi.org/10.1136/gutjnl-2014-308553