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Loss of pancreatic autophagy promotes the development of chronic pancreatitis

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Autophagy is a preserved cellular process for maintaining intracellular homeostasis through degradation of long-lived proteins and organelles. It has been implicated in various human diseases, including pancreatitis. In this study, the role of autophagy in sustaining normal pancreatic structure and function was investigated by using an in vivo model with pancreatic autophagy-deficiency.

Mice were generated with autophagic Atg7-specific deletion in the pancreas, followed by an evaluation of tissue morphology, inflammation, fibrosis and cell death markers for necroptosis and apoptosis, using immunofluorescence and WB methods. The Atg7 knockout mice developed pancreatitis spontaneously, with evidence of a progression from acute to chronic pancreatitis. Conditional knockout of the autophagy gene Atg7 exhibited reduced autophagic activity and increased inflammation and fibrosis, as well as severe, gender-independent pancreatic damage and a reduced survival rate. The remarkable damage to pancreatic acinar cells was induced by both apoptotic and necroptotic cell death. Atg7 and autophagy levels in human chronic pancreatitis patients were also examined. Unexpectedly, chronic pancreatitis patients had increased inflammation and fibrosis, but reduced ATG7 levels and autophagic activity in pancreatic tissue. Similar to the conditional Atg7 knockout mouse model, acinar cell death induced by apoptosis and necroptosis, and to a lesser extent ADM, were increased in human CP tissue.

These results suggest that deficiency in autophagy signaling promotes the development of acute and chronic pancreatitis by inducing acinar cell death by necroptosis and apoptosis, and that suppression of necroptosis may be a potentially useful approach to the prevention/treatment of chronic pancreatitis.