Impaired autophagy induces chronic atrophic pancreatitis in mice via sex- and nutrition-dependent processes.

Little is known about the mechanisms of the progressive tissue destruction, inflammation, and fibrosis that occur during development of chronic pancreatitis. Autophagy is involved in multiple degenerative and inflammatory diseases, including pancreatitis, and requires the protein autophagy related 5 (ATG5). We created mice with defects in autophagy to determine its role in pancreatitis. We created mice with pancreas-specific disruption of Atg5 (Ptf1aCreex1; Atg5F/F mice) and compared them to control mice. Pancreata were collected and histology, immunohistochemistry, transcriptome, and metabolome analyses were performed. ATG5-deficient mice were placed on diets containing 25% palm oil and compared with those on a standard diet. Another set of mice received the antioxidant N-acetylcysteine. Pancreatic tissues were collected from 8 patients with chronic pancreatitis (CP) and compared with pancreata from ATG5-deficient mice. Mice with pancreas-specific disruption of Atg5 developed atrophic CP, independent of ?-cell function; a greater proportion
of male mice developed CP than female mice. Pancreata from ATG5-deficient mice had signs of inflammation, necrosis, acinar-to-ductal metaplasia, and acinar-cell hypertrophy; this led to tissue atrophy and degeneration. Based on transcriptome and metabolome analyses, ATG5-deficient mice produced higher levels of reactive oxygen species than control mice, and had insufficient activation of glutamate-dependent metabolism. Pancreata from these mice had reduced autophagy, increased levels of p62, and increases in endoplasmic reticulum stress and mitochondrial damage, compared with tissues from control mice; p62 signaling to Nqo1 and p53 was also activated. Dietary antioxidants, especially in combination with palm oil-derived fatty acids, blocked progression to CP and pancreatic acinar atrophy. Tissues from patients with CP had many histologic similarities to those from ATG5-deficient mice. Mice with pancreas-specific disruption of Atg5 develop a form of CP similar to that of humans. CP development appears to involve defects in autophagy, glutamate-dependent metabolism, and increased production of reactive oxygen species. These mice might be used to identify therapeutic targets for CP.