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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Lysosome-Associated Membrane Protein-2: A Major Player in the Pathogenesis of Chronic Pancreatitis

The mechanisms involved in the development of either acute or chronic pancreatitis are not well understood, but previous reports have suggested that the pathogenesis of acute pancreatitis may involve a blockade of autophagic flux.[1] In the current issue of *Cellular and Molecular Gastroenterology and Hepatology,* Mareninova et al[2] from the Gukovskaya and Lerch groups have reported the results of studies investigating the role of lysosome-associated membrane protein-2 (LAMP-2) in the development of acute and chronic pancreatitis and in the regulation of successful autophagy in pancreatic acinar cells.

In their report, they show that LAMP-1 and LAMP-2 levels are reduced in pancreas samples obtained from patients with acute pancreatitis, and they also note that similar changes occur during the evolution of five different animal models of acute pancreatitis. They find that this reduction in LAMP-2 levels occurs during the early phases of experimental pancreatitis and that it appears to be the result of LAMP-2 digestion by the lysosomal enzyme cathepsin B. The authors used LAMP-2–deficient mice in an attempt to evaluate whether there may be a cause and effect mechanism involved, and they found that the pancreatic acinar cells in *LAMP-2*$^{-/-}$ mice contain reduced levels of amylase and trypsinogen as well as zymogen granules, suggesting that LAMP-2 is instrumental in maintaining pancreatic acinar cell homeostasis.

The pancreatic acinar cells in *LAMP-2*$^{-/-}$ mice exhibit changes characterized by increased vacuole formation, apoptosis, and necrosis followed by infiltration of the pancreas by inflammatory cells. As these mice age, they develop some characteristics of chronic pancreatitis, including, the presence of activated pancreatic stellate cells, and the presence of CD206-positive macrophages within the pancreas. This elegant study is in agreement with earlier studies indicating that impaired autophagy and depletion of LAMP-2 may play important roles in the development of both acute and chronic pancreatitis.[3,4]

It has been more than 30 years since it was first recognized that, during the early phases of experimental pancreatitis, lysosomal hydrolases and zymogen granule enzymes become colocalized and zymogen granules are engulfed in autophagosomes.[5] While in those initial studies the role of autophagy was suggested, the means to investigate the mechanisms involved were not available. The authors of this current report have previously suggested that this may occur due to incomplete autophagy[1] and provide here further evidence that *LAMP-2* deletion by perturbing autophagic flux may lead to chronic pancreatitis.

Premature proteolytic enzyme activation within pancreatic acinar cells has been considered one of the initial steps in the development of acute pancreatitis. This was found to depend on the activation of trypsinogen by cathepsin B. The authors of the current study also show that the lysosomal enzyme cathepsin B plays an important role in the development of pancreatitis, but they suggest that it does so in a manner independent of its effect on trypsinogen activation.

Inhibiting LAMP-2 function in processing autophagy has been implicated in a number of other diseases as well. For example, mutations on the *LAMP-2* gene were shown to lead to cardiomyopathy in patients with Danon disease,[6] and antibodies against LAMP-2 have been identified in most patients with antineutrophil cytoplasmic antigen-associated vasculitis.[7] In addition, in patients with Parkinson's disease, alpha-synuclein, and leucine-rich repeat kinase 2 mutants have been shown to bind LAMP-2, blocking its function.[8] It will be of great interest to evaluate whether patients with chronic pancreatitis have *LAMP-2* mutations or mutations on genes expressing proteins that bind LAMP-2 and inhibit its function. As efforts are being made to repair and activate the autophagic pathway in other diseases, one can envisage such attempts to alleviate chronic pancreatitis.

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References

1. Mareninova OA, Hermann K, French SW, et al. Impaired autophagic flux mediates acinar cell vacuole formation and trypsinogen activation in rodent models of acute pancreatitis. J Clin Invest 2009; 119:340–355.
2. Mareninova OA, Sendler M, Malla SR, et al. Lysosome-associated membrane proteins (LAMP) maintain pancreatic acinar cell homeostasis: LAMP-2–deficient mice develop pancreatitis. Cell Mol Gastroenterol Hepatol 2015;1:678–694.
3. Fortunato F, Bürgers H, Bergmann F, et al. Impaired autolysosome formation correlates with Lamp-2 depletion: role of apoptosis, autophagy, and necrosis in pancreatitis. Gastroenterology 2009;137:350–360.
4. Diakopoulos KN, Lesina M, Wörmann S, et al. Impaired autophagy induces chronic atrophic pancreatitis in mice via sex- and nutrition-dependent processes. Gastroenterology 2015;148:626–638.

5. Koike H, Steer ML, Meldolesi J. Pancreatic effects of ethionine: blockade of exocytosis and appearance of crinophagy and autophagy precede cellular necrosis. Am J Physiol 1982;242:G297–G307.
6. Nishino I, Fu J, Tanji K, et al. Primary LAMP-2 deficiency causes X-linked vacuolar cardiomyopathy and myopathy (Danon disease). Nature 2000;406:906–910.
7. Kain R, Exner M, Brandes R, et al. Molecular mimicry in pauci-immune focal necrotizing glomerulonephritis. Nat Med 2008;14:1088–1096.
8. Cuervo AM, Stefanis L, Fredenburg R, et al. Impaired degradation of mutant alpha-synuclein by chaperone mediated autophagy. Science 2004;305:1292–1295.

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Conflicts of interest
The author discloses no conflicts.

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2352-345X
http://dx.doi.org/10.1016/j.jcmgh.2015.08.005