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EDITORIAL

Alcohol-Induced Pancreatitis: A Critical Role for TFEB in Maintaining Lysosomal Biogenesis and Autophagic Clearance

Aside from gallstone-induced disease, alcohol abuse is the most common cause of acute pancreatitis and is the single most common cause of chronic pancreatitis in human beings. The deleterious effects of alcohol on pancreatic acinar cell function have been recapitulated in animal models, although chronic alcohol feeding of rodents itself does not typically cause pancreatitis, but rather requires an additional perturbation such as stimulation with the cholecystokinin analog cerulein or exposure to enterotoxin to induce disease.[1] In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Wang et al[2] show the Gao-binge model of alcohol feeding alone is sufficient to induce mild edematous acute pancreatitis in mice. They established that chronic alcohol consumption using the Lieber–DeCarli liquid diet for only 10 days combined with a single dose of orally gavaged ethanol on the last day causes pancreatitis by 8 hours with significant histologic damage, edema, increased serum amylase and lipase, cytokine expression, immune cell infiltration, and enhanced autophagy activity.

This group previously identified a role for the transcription factors EB and E3 (TFEB and TFE3, respectively) in the development of experimental pancreatitis in mice.[3] TFEB and TFE3 are members of the microphthalmia family of basic helix–loop–helix–zipper transcription factors, termed the MiT/TFE family, which play a major role in lysosomal biogenesis.[4] Impaired lysosomal function leading to an inhibition of macroautophagy is recognized as a major pathogenic event in the development of experimental pancreatitis.[5] In the present study, Wang et al[2] provide evidence that the Gao-binge model of alcoholic pancreatitis results in a significant reduction in lysosome number and expression of lysosomal proteins, consistent with a loss of TFEB. Furthermore, they also noted an accumulation of zymogen granules (ZGs) in acinar cells, a fraction of which colocalize with autophagosomal and lysosomal markers. Based on studies that alcohol increases the fragility of ZGs, they theorized that these compromised ZGs are cleared by autophagy. To confirm these findings, inducible acinar-specific TFEB knockout mice were challenged with the Gao-binge model, resulting in a more severe pancreatitis phenotype. Unexpectedly, they found that acinar-specific TFEB knockout mice fed the Lieber–DeCarli control diet replacing ethanol with maltose dextrin also caused pancreatitis. However, knockout mice fed a normal chow diet showed little or no pancreatic damage, indicating a component of the Lieber–DeCarli diet other than ethanol is able to stress the pancreas.

These data clearly support that loss of TFEB in alcoholic pancreatitis is involved in the pathogenesis of disease, but do not solidify a causative role for TFEB in the pathology. Thus, a key series of experiments also are provided, showing that adenoviral overexpression of TFEB by tail injection in vivo significantly ameliorates alcohol-induced pancreatitis. Indeed, TFEB overexpression attenuated histologic damage, serum amylase and lipase levels, and partially prevented the loss of lysosomal proteins. Supporting the translational significance of these findings to human disease, analysis of samples from normal healthy donors and patients with alcoholic pancreatitis indicated the presence of autophagic vacuoles containing ZGs, a reduction in lysosomal associated membrane protein 1 (LAMP1) and 2 (LAMP2), immune cell infiltration, and reduced TFEB nuclear staining in alcoholic vs healthy pancreas. Collectively, this study reinforces the significance of TFEB-induced lysosomal biogenesis in maintaining acinar homeostasis in response to stresses caused by alcohol consumption and provides a new and much-needed model of alcoholic pancreatitis in rodents that more closely recapitulates the human condition.

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Conflicts of interest
The author discloses no conflicts.

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