#209 Jodi-Ann Edwards Advisor(s): Chongmin Huan

Targeting ATF6 is a novel potential strategy for the treatment of acute pancreatitis

INTRODUCTION
Acute pancreatitis (AP) remains a clinical challenge due to the lack of an effective treatment. Novel therapy protecting against acinar cell damage in AP is urgently needed. Endoplasmic reticulum (ER) stress in acinar cells is commonly induced by different AP risk factors. Severe and persistent ER stress leads to cellular injury if not relieved by the unfolded protein response (UPR). Activating transcription factor 6 (ATF6) is a well-known UPR regulator, but has an unclarified role in AP. Here we show that acinar cell specific ATF6 deficiency worsens AP in mice. Consistently, similar to the published therapeutic effects of targeting ATF6 on other ER stress-associated disease models, pharmaceutical activation of ATF6 significantly relieves AP.
METHODS
ATF6 gene deletion in acinar cells of Cela1-Cre/ERT/ATF6flox/flox mice was induced by Tamoxifen intraperitoneal (75mg/kg/day for 5 days). ATF6flox/flox mice served as controls. AA147, an ATF6 activator, was administered (2mg/kg, intraperitoneal) concurrently with AP induction (cerulein 50μg/kg, 7 hourly intraperitoneal). Blood and pancreatic tissues were harvested for histological and biochemical analysis next day.
RESULTS
Pancreatic tissue staining showed less acinar cell damage in ATF6flox/flox mice compared to Cela1-Cre/ERT/ATF6flox/flox mice, and in AA147-treated mice compared to untreated mice. AA147 treatment consistently reduced serum amylase and lipase. Western blots and RT-PCR showed that the expressions of the regenerating protein family, which is protective and anti-inflammatory in AP, were significantly reduced in ATF6 deficient pancreatic tissues.

CONCLUSION
ATF6-regulated UPR transcriptionally regulates the regenerating protein family and protects against acinar cell damage in AP. Targeting ATF6 is a potential strategy for AP treatment.

Additional contributors to this project:
Nadlie Toussaint
Sue Dong
Cathy Mueller
Joshua Zhang
Samantha Shakhvorostova
Peiqi Ou
Lisa Dresner
Alexander Schwartzman
Albert Stanek
Chongmin Huan