Dokumenttyp: journal article

Autor(en) des Beitrags: Li, Ning; Wu, Xuefeng; Holzer, Ryan G; Lee, Jun-Hee; Todoric, Jelena; Park, Eek-Joong; Ogata, Hisanobu; Gukovskaya, Anna S; Gukovsky, Ilya; Pizzo, Donald P; VandenBerg, Scott; Tarin, David; Atay, Cİdem; Arkan, Melek C; Deerinck, Thomas J; Moscat, Jorge; Diaz-Meco, Maria; Dawson, David; Erkan, Mert; Kleeff, Jörg; Karin, Michael


Abstract: Chronic pancreatitis is an inflammatory disease that causes progressive destruction of pancreatic acinar cells and, ultimately, loss of pancreatic function. We investigated the role of I?B kinase ? (IKK?) in pancreatic homeostasis. Pancreas-specific ablation of IKK? (Ikk?(?pan)) caused spontaneous and progressive acinar cell vacuolization and death, interstitial fibrosis, inflammation, and circulatory release of pancreatic enzymes, clinical signs resembling those of human chronic pancreatitis. Loss of pancreatic IKK? causes defective autophagic protein degradation, leading to accumulation of p62-mediated protein aggregates and enhanced oxidative and ER stress in acinar cells, but none of these effects is related to NF-?B. Pancreas-specific p62 ablation prevented ER and oxidative stresses and attenuated pancreatitis in Ikk?(?pan) mice, suggesting that cellular stress induced by p62 aggregates promotes development of pancreatitis. Importantly, downregulation of IKK? and accumulation of p62 aggregates were also observed in chronic human pancreatitis. Our studies demonstrate that IKK?, which may control autophagic protein degradation.
through its interaction with ATG16L2, plays a critical role in maintaining pancreatic acinar cell homeostasis, whose dysregulation promotes pancreatitis through p62 aggregate accumulation.