Deletion of I?B? activates RelA to reduce acute pancreatitis in mice through up-regulation of Spi2A.

The transcription factor nuclear factor-?B (NF-?B) (a heterodimer of NF-?B1p50 and RelA) is activated rapidly in acute pancreatitis (AP). However, it is not clear whether NF-?B promotes or protects against AP. We used the NF-?B inhibitor protein, inhibitor of ?B (I?B)?, to study the roles of NF-?B in the development of AP in mice. I?B? or the combination of I?B? and RelA selectively were deleted from pancreas of mice using the Cre/locus of cross-over P strategy; cerulein or L-arginine were used to induce AP. We performed microarray analyses of the I?B?- and RelA-deficient pancreata. DNA from healthy individuals and patients with acute or chronic pancreatitis were analyzed for variants in coding regions of alpha-1-antichymotrypsin. Mice with pancreas-specific deletion of I?B? had constitutive activation of RelA and a gene expression profile consistent with NF-?B activation; development of AP in these mice was attenuated and trypsin activation was impaired. However, AP was fully induced in mice with pancreas-specific deletion of I?B? and RelA. By using genome-wide expression analysis, we identified a cluster of NF-?B-regulated genes that might protect against the development of AP. The serine protease inhibitor 2A (Spi2a) was highly up-regulated in I?B?-deficient mice. Lentiviral-mediated expression of
Spi2A reduced the development of AP in C57BL/6 and RelA-deficient mice. However, we did not correlate any variants of alpha-1-antichymotrypsin, the human homologue of Spi2a, with acute or chronic pancreatitis. Pancreas-specific deletion of I?B? results in nuclear translocation of RelA and reduces AP induction and trypsin activation in mice after administration of cerulein or L-arginine. Constitutive activation of RelA up-regulates Spi2A, which protects mice against the development of AP.