

Nox1-evoked ROS causes Fibrosis in Caerulein-Induced Chronic Pancreatitis through the p38/AKT pathway

Inflammation of the pancreas can occur in two distinct forms, either in the acute form (AP) or the chronic form (CP). AP is a short-term inflammation that develops suddenly. By contrast, CP manifests from a long-term inflammation, which results in significant fibrosis of the pancreatic tissue and permanent organ damage. This is because of pro-inflammatory mediators, including reactive oxygen species (ROS). One of the sources of ROS is NADPH oxidase (Nox) enzymes, which transfer electrons across biological membranes to reduce oxygen to superoxide. The rodent genome encodes four Nox enzymes: Nox1-4. We found that Nox1 is implicated in pancreatic fibrogenesis in a mouse model of CP. Our next goal was to determine which intracellular pathway mediates the effect of Nox1-derived ROS. Several intracellular pathways are activated following Nox1-derived ROS, including c-Jun N-terminal kinase (JNK), p38 MAP kinase, and ERK1/2. Each pathway is also activated following caerulein, a cholecystokinin analogue. Our hypothesis was that repetitive administration of caerulein stimulates Nox1-derived ROS, which causes increased oxidative stress, leading to fibrogenesis through phosphorylation of ERK and JNK, as well as up-regulation of p38. We found that the lack of Nox1 does not affect any intracellular pathway in a mouse model of AP. By contrast, the lack of Nox1 impaired caerulein-induced up-regulation of p38 and phosphorylation of AKT in a mouse model of CP. **Conclusion:** Thus, Nox 1 is most likely not implicated in the pathogenesis of acute pancreatitis; however, it is shown to mediate fibrogenesis through the p38/AKT pathway in mice with chronic pancreatitis induced by caerulein.