

ABSTRACT NO. 14

BILE-PANCREATIC DUCT LIGATION IN MICE IS ASSOCIATED WITH STRESS KINASE ACTIVATION AND ACUTE INFLAMMATORY CHANGES IN BOTH THE PANCREAS AND LUNG

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Acute lung injury is a major determinant of outcomes in acute pancreatitis. Stress kinases are involved in activation of proinflammatory pathways. We evaluated acute lung injury and stress kinase activation in a mouse model of acute pancreatitis induced by 24 h of duct ligation (n=5/group). In sham controls the duct was dissected but not ligated. The pancreas and lung were excised. Blinded morphometric scoring of slides was performed by a pathologist (1st author) from five randomly selected high power fields (60x objective) and scores averaged for each tissue. Pancreatic neutrophil infiltration, macrophage infiltration, and interstitial edema were significantly elevated after duct ligation (Student's t, $p < 0.05$). Additional pancreatic changes with ligation included vascular congestion with marginating neutrophils. Of particular importance, duct ligation was also associated with pulmonary morphologic changes indicative of acute lung injury, such as interstitial septal thickening due to vascular congestion and increased cellularity from marginated or extravasated neutrophils. Immunohistochemistry for neutrophils (MPO) followed by morphometric quantitation confirmed significant increases in neutrophil infiltration in the pancreas and lung following duct ligation. Immunoblotting using specific antibodies against p-ERK, p-p38, and p-JNK showed activation of all three stress kinases in the pancreas after duct ligation, without increases in total ERK, total p38, or total JNK. Additionally, we detected ERK activation in the lung after duct ligation.

Conclusions: Bile and pancreatic duct ligation in the mouse is associated with pancreatic and pulmonary stress kinase activation and acute inflammatory changes consistent with early acute pancreatitis and acute lung injury. Our findings are especially important as acute lung injury increases death in clinical acute pancreatitis and as stress kinases are established mediators of proinflammatory pathways in pancreatitis and the systemic inflammatory response syndrome.