Inhibition of thioredoxin reductase reduces Nlrp3 inflammasome activation in primary mouse macrophage and in bile duct ligated mice.

**ABSTRACT**

**BACKGROUND**

Cholestatic liver diseases, including Biliary Atresia (BA) and Primary Sclerosing Cholangitis (PSC), are characterized by severe portal inflammation with progression to fibrosis/cirrhosis and ultimately liver failure. Overall, cholangiopathies account for ~16% of all liver transplantations and 50% of pediatric transplants. With only poor therapeutic options available, there is an urgent need for an improved mechanistic understanding of these diseases so that new strategies can be developed.

Chronic cholangiopathies including primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and biliary atresia are diseases of unknown etiology characterized by extensive bile duct injury and destruction of the bile ducts.

- Account for ~16% of all liver transplants and 50% of pediatric transplants.
- Biliary atresia that were performed in the US from 1988-2014.
- With only poor therapeutic options available, there is an urgent need for an improved mechanistic understanding of these diseases so that new strategies can be developed.
- In the liver, inflammasomes are important innate immune sensors that assist in maintaining cellular function in response to cytosolic pathogens or stress signals.
- The macrophage NLR Family Pyrin Domain Containing 3 (Nlrp3) inflammasome complex has been shown to be upregulated in human and murine cholestatic liver disease and plays an integral role in regulating hepatic inflammation and fibrosis by increasing production of pro-inflammatory cytokines (IL-1β).
- Nlrp3 inflammasomes have been shown to be activated in both human and murine models of cholestasis but the mechanisms of activation have not been elucidated.
- Previous research has shown that Nlrp3 inflammasome activation can be regulated by multiple factors including damage- and pathogen-associated molecular patterns (DAMPs & PAMPs) and reactive oxygen species (ROS).
- Recently, members of the thioredoxin redox pathway (TrxR1, TrxR2/TrxR1) and TxnRd1 have emerged as important mediators of macrophage Nlrp3 activation.

**RESULTS**

- In human PSC, thioredoxin and thioredoxin reductase are upregulated whereas TxnRd1 is downregulated.
- Increases in thioredoxin reductase expression are predominantly in hepatic macrophages during cholestasis.
- In mice, acute cholestatic injury (BDL) results in inflammasome activation and increased expression of TxnRd1.
- Nlrp3 inflammasome activation occurs in both hepatocytes and macrophages but the thioredoxin pathway is only upregulated in macrophages following exposure to either TNF or LPS.
- The thioredoxin reductase inhibitor auranofin ameliorates Nlrp3 activation and upregulates thioredoxin in hepatic macrophages.
- Liver specific deletion of Trx1/TrxR1 reduces liver injury following bile duct ligation.

**DIRECTIONS**

The Nlrp3 inflammasome complex plays a critical role in the pathogenesis of cholestatic liver disease. Targeting thioredoxin pathway mediated inflammasome activation may provide therapeutic benefit. Future studies will be focused on understanding the cell specific contribution of the thioredoxin pathway inflammasome activation and hepatic injury during cholestasis.