DISRUPTION OF BOTH HFE AND TFR2 CAUSES IRON-INDUCED LIVER INJURY

Roheeth Delima1,2, Anita Chua1, Janina E. Tirmnitz-Parker1,3, Kevin Croft4,2, Ross Graham1, John K. Olynyk1,3, Debbie Trinder1,3;
1School of Medicine & Pharmacology, University of Western Australia, Nedlands, WA, Australia; 2Gastroenterology, Fremantle Hospital, Fremantle, WA, Australia; 3Western Australian Institute of Medical Research, Perth, WA, Australia; 4Curtin Health Innovation Research Institute, Perth, WA, Australia

Hereditary haemochromatosis (HH) is a common iron overload disorder caused by mutations in HFE or TFR2, which impair the liver iron regulatory hormone, hepcidin (Hamp). This study aimed to examine the effects of disruption of Hfe and Tfr2 on liver iron loading and injury in mouse models of HH. Methods: Iron status was determined in single mutant (Hfe-/- and Tfr2Y245X) and double mutant (Hfe-/-xTfr2Y245X) mice (10-14 weeks of age) by measuring plasma and liver iron concentration. Hamp expression was measured by real-time PCR. Liver injury was evaluated by measuring serum alanine transaminase (ALT) activity, hepatic histology, collagen deposition (Sirius red) and iron levels (Perls). Hepatic oxidative stress was determined by measuring F2-isoprostane, a marker of lipid peroxidation, by gas chromatography-mass spectrometry and anti-oxidant enzyme, superoxide dismutase (SOD). Results: Hfe-/-xTfr2Y245X mice had significantly elevated hepatic iron levels (1.5-fold; P<0.01) with a periportal iron distribution, increased plasma iron (1.7-fold; P<0.01) and transferrin saturation (1.3-fold; P<0.01) compared with Hfe-/- and Tfr2Y245X mice, which in turn, were increased compared with wild-type mice. Hamp was significantly reduced in Hfe-/- and Tfr2Y245X mice to 30% (P<0.01) and in Hfe-/-xTfr2Y245X mice to 1% (P<0.01) compared with wild-type mice. Hfe-/-xTfr2Y245X mice had elevated serum ALT activity (2 fold; P<0.001) compared with wild-type mice. Hfe-/-xTfr2Y245X mice had scattered lobular aggregates of mononuclear inflammatory cells, steatosis and increased portal tract collagen deposition. By contrast, Hfe-/- and Tfr2Y245X mice showed minimal hepatic inflammation, with no increased collagen deposition in Tfr2Y245X mice. F2-isoprostane levels were significantly elevated in Hfe-/-xTfr2Y245X (4.2-fold; P<0.001), Tfr2Y245X mice (3.2-fold; P<0.001) and Hfe-/- mice (2.0-fold; P<0.01) and SOD was increased in Hfe-/-xTfr2Y245X (1.5-fold; P<0.05) compared with wild-type mice. Conclusion: The disruption of Hfe or Tfr2 causes hepatic iron loading and lipid peroxidation. However, the disruption of both Hfe and Tfr2 produces more severe hepatic iron overload and lipid peroxidation, with inflammation, portal fibrosis and steatosis. Hfe-/-xTfr2Y245X mice provide a novel model of iron-induced liver injury.
Disclosures:
John K. Olynyk - Grant/Research Support: Roche, Bayer
The following people have nothing to disclose: Roheeth Delima, Anita Chua, Janina E. Tirmitz-Parker, Kevin Croft, Ross Graham, Debbie Trinder