The liver is the central regulator of iron metabolism and accordingly, chronic liver diseases often lead to systemic iron overload due to diminished expression of the iron-regulatory hormone hepcidin. To study the largely unknown regulation of iron metabolism in the context of hepatic disease, we used two established models of chronic liver injury, i.e., repeated carbon tetrachloride (CCl₄) or thioacetamide (TAA) injections. To determine the impact of CCAAT/enhancer-binding protein (C/EBP)-homologous protein (CHOP) on hepcidin production, the effect of a single TAA injection was determined in wild-type and CHOP knockout mice. Furthermore, CHOP and hepcidin expression was assessed in control subjects and patients with alcoholic liver disease. Both chronic injury models developed a distinct iron overload in macrophages. TAA-, but not CCl₄ - injected mice displayed additional iron accumulation in hepatocytes, resulting in a significant hepatic and systemic iron overload which was due to suppressed hepcidin levels. C/EBP? signalling, a known hepcidin inducer, was markedly inhibited in TAA mice, due to lower C/EBP? levels and overexpression of CHOP, a C/EBP? inhibitor. A single TAA injection resulted in a long-lasting (> 6 days) suppression of hepcidin levels and CHOP knockouts (compared to wild-types) displayed significantly attenuated hepcidin
down-regulation in response to acute TAA administration. CHOP mRNA levels increased 5-fold in alcoholic liver disease patients versus controls (p< 0.005) and negatively correlated with hepcidin expression. Our results establish CHOP as an important regulator of hepatic hepcidin expression in chronic liver disease. The differences in iron metabolism between the two widely used fibrosis models likely reflect the differential regulation of hepcidin expression in human liver disease.