News Release

Title

Iron-Rich Kupffer Cells Exhibit Phenotypic Changes during the Development of Liver Fibrosis in NASH

Key Points

- Kupffer cells are magnetically divided into Fe-hi and Fe-lo fractions in a NASH model
- Iron-rich Kupffer cells exert proinflammatory and profibrotic properties in NASH
- MiT/TFE transcription factors mediate iron-induced Kupffer cells' phenotypic changes
- MiT/TFE transcription factors are activated in Kupffer cells in murine and human NASH

Summary

Although recent evidence suggests the involvement of iron accumulation in the pathogenesis of nonalcoholic steatohepatitis (NASH), the underlying mechanisms remain poorly understood. Previously, we reported a unique histological structure termed "crown-like structure (CLS)", where liver-resident macrophages (Kupffer cells) surround dead hepatocytes, scavenge their debris, and induce inflammation and fibrosis in NASH. In this study, using magnetic column separation, we show that iron-rich Kupffer cells exhibit proinflammatory and profibrotic phenotypic changes during the development of NASH, at least partly, through activation of MiT/TFE transcription factors. Activation of MiT/TFE transcription factors is observed in Kupffer cells forming CLSs in murine and human NASH. Iron chelation effectively attenuates liver fibrosis in a murine NASH model. This study provides insight into the pathophysiologic role of iron in NASH. Our data also shed light on a unique macrophage subset rich in iron that contributes to CLS formation and serves as a driver of liver fibrosis.

Research Background

Nonalcoholic fatty liver disease (NAFLD) is commonly observed in patients with the metabolic syndrome and is one of the most prevalent chronic liver diseases in the world. The term NAFLD refers to a spectrum of chronic liver disease ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), the latter of which predisposes patients to cirrhosis and hepatocellular carcinoma. Amongst various etiologies, aberrant iron metabolism is also considered to be a "hit" in the pathogenesis of NASH. However, the underlying mechanism(s) and the responsible cell type(s) are incompletely understood. In murine and human NASH, there is a unique histological structure termed "crown-like structure (CLS)", in which dead hepatocytes with large lipid droplets are surrounded by CD11c-positive liver-resident macrophages (Kupffer cells). During the maturation of CLSs, Kupffer cells become positive for CD11c through crosstalk with dead hepatocytes, and acquire proinflammatory and profibrotic properties. Thus, CD11c-positive Kupffer cells may be a novel macrophage subset crucial for liver fibrosis in NASH. However, the molecular mechanism underlying the phenotypic changes of Kupffer cells remains to be elucidated.

Research Results

This study provided evidence on the role of iron accumulation in Kupffer cells during the development of liver fibrosis in NASH. Our findings demonstrate that: (i) proinflammatory and profibrotic CD11c-positive Kupffer cells in NASH comprise the Fe-hi fraction, (ii) iron accumulation in Kupffer cells activates MiT/TFE transcription factors to increase proinflammatory and profibrotic properties, (iii) activated MiT/TFE transcription factors are observed in Kupffer cells forming CLSs in mouse models of NASH and human NASH, and (iv) iron chelation attenuated liver fibrosis in a murine NASH model. Thus, we defined Kupffer cells as a target cell type responsible for iron accumulation–mediated chronic inflammation in NASH. This study provides insight into the molecular mechanism underlying the pathogenesis of NASH.

Research Summary and Future Perspective

It is an important future issue to understand how iron accumulates in a particular group of Kupffer cells during the development of NASH. We previously reported that Kupffer cells give rise to formation of CLSs, where they scavenge debris of dead hepatocytes and residual lipids, and thus gradually become positive for CD11c during CLS maturation, probably through interaction with dead cells. Given that CD11c-positive Kupffer cells in CLSs comprise the Fe-hi fraction, iron may accumulate in these Kupffer cells in a phagocytosis-dependent manner. In the next step, we need to elucidate the causality of aberrant iron metabolism in Kupffer cell polarization *in vivo* during the development of NASH.

Publication

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