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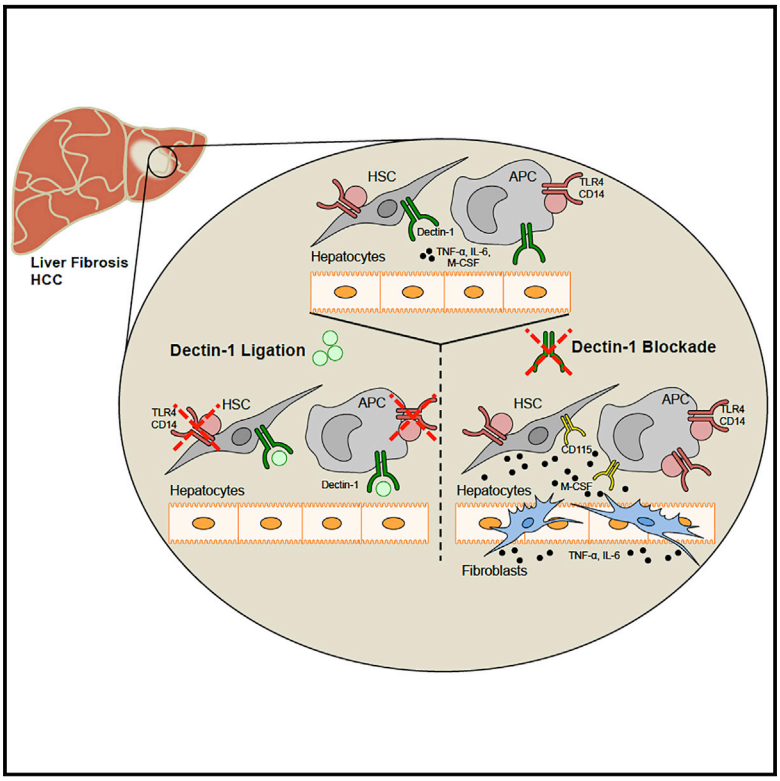
Dectin-1 Regulates Hepatic Fibrosis and Hepatocarcinogenesis by Suppressing TLR4 Signaling Pathways

Graphical Abstract



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In Brief

Seifert et al. show Dectin-1 protects against chronic liver disease by suppressing TLR4 signaling via CD14 and M-CSF. This suggests that Dectin-1 is an attractive target for experimental therapeutics in hepatic fibrosis and transformation with implications for a role for Dectin-1 in suppression of sterile inflammation, inflammation-induced oncogenesis, and endotoxemia.

Highlights

- Dectin-1 expression is upregulated in hepatic fibrosis and liver cancer
- Deletion of Dectin-1 exacerbates liver fibrosis and accelerates hepatocarcinogenesis
- Dectin-1 protects against liver disease by suppressing TLR4 signaling
- Dectin-1 mitigates TLR4 and CD14 expression, which is regulated by M-CSF expression

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Dectin-1 Regulates Hepatic Fibrosis and Hepatocarcinogenesis by Suppressing TLR4 Signaling Pathways

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SUMMARY

Dectin-1 is a C-type lectin receptor critical in antifungal immunity, but Dectin-1 has not been linked to regulation of sterile inflammation or oncogenesis. We found that Dectin-1 expression is upregulated in hepatic fibrosis and liver cancer. However, Dectin-1 deletion exacerbates liver fibro-inflammatory disease and accelerates hepatocarcinogenesis. Mechanistically, we found that Dectin-1 protects against chronic liver disease by suppressing TLR4 signaling in hepatic inflammatory and stellate cells. Accordingly, *Dectin-1*$^{-/-}$ mice exhibited augmented cytokine production and reduced survival in lipopolysaccharide (LPS)-mediated sepsis, whereas Dectin-1 activation was protective. We showed that Dectin-1 inhibits TLR4 signaling by mitigating TLR4 and CD14 expression, which are regulated by Dectin-1-dependent macrophage colony stimulating factor (M-CSF) expression. Our study suggests that Dectin-1 is an attractive target for experimental therapeutics in hepatic fibrosis and neoplastic transformation. More broadly, our work deciphers critical cross-talk between pattern recognition receptors and implicates a role for Dectin-1 in suppression of sterile inflammation, inflammation-induced oncogenesis, and LPS-mediated sepsis.

INTRODUCTION

Hepatic fibrosis—the end result of repeated liver injury—is one of the most significant public health concerns worldwide (Lim and Kim, 2008). Liver injury resulting from a variety of etiologies, including viral hepatitis, toxins, or metabolic disorders, primes hepatocytes to regenerate to replace necrotic or apoptotic hepatic parenchymal cells and simultaneously triggers a robust inflammatory response, which induces hepatic stellate cells (HSCs) to transdifferentiate and express extracellular matrix (ECM) proteins. If injury persists, regeneration eventually fails, and the hepatocytes are replaced by abundant ECM leading to fibrosis and eventually cirrhosis (Bataller and Brenner, 2005). Liver fibrosis is clinically associated with the development of hepatocellular carcinoma (HCC), the third leading cause of cancer-related death worldwide (Franceschi and Raza, 2009).

Toll-like receptor (TLR) ligation is a primary mechanism by which intra-hepatic innate inflammatory cells and HSCs are activated after hepatic injury (Paik et al., 2003; Seki et al., 2007). TLRs belong to a broader category of evolutionarily conserved pattern recognition receptors (PRRs), which link inflammatory responses to pathogenic or sterile inflammatory stimuli (Kawai and Akira, 2010). A primary role of TLR4 expressed on innate hepatic leukocytes is to respond to lipopolysaccharide (LPS) (De Creus et al., 2005). In addition, in the context of chronic liver injury, TLRs can ligate intra-hepatic "danger molecules," which include by-products of inflammatory injury and cellular necrosis, collectively denoted damage-associated molecular patterns (DAMPs) (Paik et al., 2003; Seki et al., 2007). As such, TLR ligation has a critical role in perpetuating sterile inflammation and tissue damage in chronic liver disease. For example, ligation of either TLR4 or TLR9 markedly promotes liver fibrosis, whereas deletion of either receptor is protective (Aoyama et al., 2010). Similarly, TLR4 ligation by LPS derived from selected intestinal microbiota promotes hepatocellular carcinogenesis (Dapito et al., 2012).

Dectin-1 is a trans-membrane receptor and member of the C-type Lectin family of PRRs. Dectin-1 is required for the innate immune response to fungal pathogens (Vautier et al., 2012). Ligation of fungal wall β-glucans by Dectin-1 recruits the CARD9 adaptor protein, which phosphorylates Syk, thereby initiating an anti-fungal immune response (Gross et al., 2006; Strasser et al., 2012). However, Dectin-1 does not have an established role in modulating sterile inflammation in liver fibrosis