Immunopathogenesis of liver fibrosis in steatotic liver disease

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Abbreviations:
SLD, steatotic liver disease; 2-AG, 2-arachidonoylglycerol; HSC, hepatic stellate cell; ER, endoplasmic reticulum; ROS, reactive oxygen species; PAMP or DAMP, pathogen-or damage-associated molecular pattern; AT, adipose tissue; IFN-γ, interferon-γ; NK, natural killer; mGluR5, metabotropic glutamate receptor 5; qHSC, quiescent HSCs; aHSC, activated HSCs; CCL2, C-C motif chemokine 2; CXCL1, CXC motif chemokine ligand 1; TLR, toll-like receptor; TNF, tumor necrosis factor; IL, interleukin; PDGF, platelet-derived growth factor; MPO, myeloperoxidase; TGF, transforming growth factor; TNF-related apoptosis-inducing ligand, TRAIL; Fas ligand, FasL; MMP, metalloproteinase; RAE-1, retinoic acid early inducible 1; SOCS1, suppressor of cell signaling 1.
Recently, a new term steatotic liver disease (SLD) has been introduced to the field of hepatology to encompass the various etiologies of steatosis.\textsuperscript{1,2} Hepatic steatosis having an excessive fat accumulation has been considered as a key factor for the progression of serious liver disease such as hepatic inflammation, fibrosis/cirrhosis, and hepatocellular carcinoma.\textsuperscript{2-4} It could be initiated by overload of nutrition (e.g. glucose, free fatty acid), intoxicants (e.g. alcohol and endocannabinoid-mediated metabolic dysfunction) or genetic factors.\textsuperscript{3-5} Interestingly, lines of evidence have suggested that beyond its role as a metabolic organ, the liver is considered an immunological and neurological organ due to its diverse metabolic functions, enriched immune cells (e.g. innate and adaptive immune cells), and production and release of hepatotransmitter such as glutamate or 2-arachidonoylglycerol (2-AG).\textsuperscript{4-6} So, these factors might affect the progression of SLD, from simple steatosis to steatohepatitis and fibrosis by regulating activation of hepatic stellate cells (HSCs).

It has been reported that inflammation and subsequent liver fibrosis occur due to various immune-mediated activation of HSCs through eating habit-mediated metabolic dysfunction (e.g. obesity, type 2 diabetes, or chronic alcohol consumption), sedentary behavior, and genetic predisposition.\textsuperscript{4,5} Steatohepatitis may be triggered by prolonged multiple stresses in fat storing hepatocytes, such as endoplasmic reticulum (ER) stress, mitochondria dysfunction, and oxidative stress including alcohol-induced reactive oxygens species (ROS) and lipotoxicity.\textsuperscript{5,6} These cellular stresses combined with diverse harmful factors, such as inflammatory cytokines, adipokines, short chain fatty acids, and pathogen-or damage-associated molecular patterns (PAMPs or DAMPs) originated from adipose tissue (AT) and intestine, may cause hepatocyte death and inflammation.\textsuperscript{7} Recently, an interesting study suggested glutamate-mediated cross-talk between AT and liver, in which hypoxic adipocyte excreted glutamate through xCT transporter and the resulting production of interferon-γ (IFN-γ) in natural killer (NK) cells by metabotropic glutamate receptor 5 (mGluR5), subsequently leading to the augmentation of adipose macrophage activation and steatohepatitis in obese mice and patients.\textsuperscript{8}

By these cellular responses and organ cross-talks, inflammatory immune cells migrate nearby damaged hepatocytes, and stimulate the transformation from quiescent HSCs (qHSCs) into activated HSCs (aHSCs) by producing various mediators including cytokines, chemokines or extracellular vesicles. Injured fat-storing hepatocytes produce chemokines, such as C-C motif chemokine 2 (CCL2) and CXC motif chemokine ligand 1 (CXCL1) to recruit pro-inflammatory macrophages and neutrophils, respectively. After migration, macrophages,
neutrophils and resident Kupffer cells are stimulated by DAMPs (e.g. ATP, mitochondrial DNA or double-stranded RNA), PAMPs (e.g. LPS, CpG DNA, Flagellin), or cytokines through specific receptors including P2X purinoceptor 7 and toll-like receptors (e.g. TLR2, TLR3, TLR4, TLR5, and TLR9). Then, produced tumor necrosis factor (TNF)-α, interleukin (IL)-1β, platelet derived growth factor (PDGF), IL-17A, myeloperoxidase (MPO), transforming growth factor (TGF)-β1 and ROS by these cells lead to the activation of qHSCs. Moreover, several types of lymphocytes, such as Th17 cells, γδT cells and B cells, augment HSC activation by producing IL-17, TNF-α, and IL-6.

In contrast, several types of cells, such as NK cells and restorative macrophages can kill aHSCs or suppress HSC activation by producing death ligands including TNF-related apoptosis-inducing ligand (TRAIL) and Fas ligand (FasL), IFN-γ, anti-inflammatory IL-10, and matrix metalloproteinases (MMPs). Once activated HSCs express retinoic acid early inducible 1 (RAE-1), a specific ligand for NKG2D, NK cells specifically produce IFN-γ, TRAIL, or FASL through NKG2D-RAE-1 interaction. In addition, Ly6C^low F4/80^CD11b^+ macrophages can induce fibrosis resolution by producing MMPs or Gr1^+CD11b^+ bone marrow cells inhibit inflammation by IL-10 production in the early stage of liver fibrosis. However, prolonged injuries (e.g. chronic alcohol consumption) cause HSCs to have the ability to avoid this cytotoxicity by increasing TGF-β production and suppressor of cell signaling 1 (SOCS1) expression in aHSCs. Moreover, ROS might deplete NK subpopulations or suppress NK cytotoxicity in the advanced liver fibrosis. A recent study suggested an interesting solution how to overcome HSC evasion against NK cytotoxicity, in which mGluR5 activation in NK cells by hepatic glutamate, a hepatotransmitter, further enhanced NK cytotoxicity to aHSCs, resulting in the attenuation of liver fibrosis. Accordingly, the delivery of mGluR5-stimulated NK cells through tail vein improved liver fibrosis in mice, suggesting a therapeutic intervention of liver fibrosis in patients.

In the past, SLD was somewhat neglected, but as viral hepatitis has been recently overcome, the possibility of SLD progression to serious chronic liver disease has emerged. Despite of pro-inflammatory immune responses for SLD progression to liver fibrosis, it is noteworthy that certain immune cells (e.g. NK cells or restorative macrophages) may have strong anti-fibrotic functions. In particular, new therapeutics can be developed by carefully looking at intrahepatic neurological signaling (e.g. 2-AG production in HSCs and mGluR5 activation in NK cells). Therefore, precise molecular pathways related to immunopathogenesis of liver fibrosis should...
be extensively investigated. Notably, further research will be needed to determine how neuro-
metabo-immune axis, still minimally investigated, influences SLD and liver fibrosis.

**Author’s contribution**

C.W. Concept of the work, manuscript draft, figure generation. W.I.J. Concept of the work, Writing, Revision and Approval of the manuscript.

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**Conflict of Interest**

The authors have no conflict to disclose
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