Stearoyl-CoA desaturase 1 deficiency protects mice from immune-mediated liver injury

Dechun Feng¹, Ying Wang², Yunhua Mei², Yan Xu¹, Heng Xu¹, Yun Lu¹, Qingqiong Luo², Shupe Zhou³, Xiangyin Kong¹ and Lingyun Xu^{1,2}

Immunity and metabolism are closely linked. The liver is an important metabolic organ in the body. However, the interactions between hepatocytes and the immune system are poorly understood. In mice developing concanavalin A (ConA)-induced hepatitis (CIH), we found extensive lipid accumulation in hepatocytes. Critical enzyme involved in fat synthesis such as stearoyl-CoA desaturase 1 (SCD1) was upregulated. When we injected ConA to SCD1-deficient mice, we found these mice to be highly resistant to CIH. The mechanisms of the protective effect of SCD1 deficiency might be attributed to the reduced leptin levels in those mice, which modulated critical cytokines and signaling pathways in CIH pathogenesis. In conclusion, our study suggests that SCD1 deficiency protects mice from liver injury in a leptin-dependent manner.

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Accumulated evidence has indicated that immunity and energy metabolism are closely linked. Starvation and malnutrition can suppress immune responses and increase susceptibility to infections, whereas obesity is associated with a state of aberrant immune activity and increased risk for inflammatory diseases.¹ The liver is the largest and very important metabolic organ in the body. It processes the major categories of nutrients after their absorption from the digestive tract, and stores glycogen, fats and vitamins. In recent years, the role of the liver as a major immune organ has been increasingly recognized.²

Immune cells, including Kupffer cells and lymphocytes, constitute approximately 45% of the total nonhepatocytes cells of a normal liver.³ These cells play critical roles in immune defenses against invading pathogens. Mice with high-fat diet-induced hepatic steatosis show decreased natural killer T-cell (NKT cell) proportions in the liver, and are sensitive to lipopolysaccharide (LPS)-induced liver injury.^{4,5} Moreover, in hepatosteatotic mice developing concanavalin A

(ConA)-induced hepatitis (CIH), T-cell differentiation is strongly shifted toward a Th1 profile. In addition, severe liver injury and high production of proinflammatory cytokines, including tumor necrosis factor- α (TNF- α) and interferon- γ (IFN- γ), have been observed in hepatosteatotic mice.⁶ Therefore, metabolic syndromes have been proposed as risk factors in immune-mediated liver inflammation and injury.⁵ However, the manner in which inflammation influences lipid metabolism in the liver and the interactions between immune cells and hepatocytes are still poorly understood.

In our study with CIH in mice, we noticed extensive lipid accumulation in hepatocytes. The critical enzyme involved in fat synthesis, stearoyl-CoA desaturase 1 (SCD1), was greatly upregulated. In attempting to induce CIH in SCD1-deficient mice, we found these mice to be highly resistant to CIH. The mechanisms leading to CIH resistance in SCD1-deficient mice were then elucidated. Our results add another line of direct evidence that hepatosteatosis greatly influences immune responses in the liver. Thus, we suggest that

¹Institute of Health Sciences, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai Jiaotong University School of Medicine, Shanghai, China; ²Shanghai Institute of Immunology, Shanghai Jiaotong University School of Medicine, Shanghai, China and ³Department of Laboratory Animal Science, Health Science Center, Peking University, Beijing, China

Correspondence: Professor L. Xu, Shanghai Institute of Immunology, Shanghai Jiaotong University, 225 South Chongqing Road, Building I Room 308, Shanghai 200025, China.

E-mail: lyxu@sibs.ac.cn

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modulation of fat metabolism be further explored as a potential strategy for intervention and treatment of inflammatory liver diseases.

MATERIALS AND METHODS

Animal Treatment

C57BL/6 male mice, 8–10 weeks of age, were purchased from Shanghai SLAC Laboratory Animal CO LTD (Shanghai, China). ab^{Xy^k} mice (back crossed to Balb/c mice, F2 generation) with the spontaneous dysfunction of SCD1 have been described previously.⁷ Mice were housed in the animal facilities of Shanghai Institutes for Biological Science, Chinese Academy of Sciences, under pathogen-free conditions according to the Institutional Animal Care and Use Committee guidelines. Mice were fed *ad libitum* a standard laboratory chow diet provided by SLAC Laboratory Animal CO LTD.

CIH Induction

Mice were injected via the tail vein with a single dose (15 mg/kg of body weight) of ConA to produce the CIH model.

Leptin Replacement

ab^{Xy^k}/ab^{Xy^k} mice received 1 mg/kg recombinant murine leptin (R&D Systems, MN, USA) or PBS by intraperitoneally injection twice a day for 5 days. Subsequently, ConA was injected into all the mice.

Alanine Aminotransferase Measurement

Plasma was obtained approximately 17 h after ConA injection. Alanine aminotransferase (ALT) levels were determined using the ALT detection kit (Shanghai Yihua Medical Science & Technology, Shanghai, China) according to manufacturer's instructions.

Histology

Livers were removed after perfusion with PBS, fixed with 4% phosphate-buffered paraformaldehyde, and embedded in paraffin. Tissue sections (5 μ m) were prepared, stained with Haematoxylin & Eosin (H&E), and examined under light microscopy. A total of 10 tissue sections were analyzed for each animal.

TUNEL Staining

Paraffin-embedded liver tissues were assayed for DNA fragmentation using a terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) reaction according to the manufacturer's instructions (Roche Molecular Biochemicals, IN, USA). Sections were then examined under light microscopy. A total of 10 tissue sections were analyzed for each animal.

Oil Red O Staining

Frozen liver sections (8 μ m) were stained with Oil Red O (Sigma, MO, USA) for 10 min, and then counterstained with hematoxylin for 45 s. Sections were then examined under

light microscopy. A total of 10 tissue sections were analyzed for each animal.

Analysis of Plasma Cytokines

Plasma concentrations of TNF- α , IFN- γ and leptin were determined using specific enzyme-linked immunosorbent assay kits (R&D Systems) according to the manufacturer's instructions.

RNA Extraction and Reverse Transcription

Total RNA was isolated from cell pellets and liver tissues using the RNeasy Mini Kit (Qiagen, Hilden, Germany). Genomic DNA was removed from total RNA before cDNA synthesis using the RNase-free DNase set for DNase digestion during RNA purification (Qiagen). RNA was stored at -80°C . First-strand cDNA synthesis was performed for each RNA sample using Sensiscript RT Kit (Qiagen). Random hexamers were used to prime cDNA synthesis.

Real-Time PCR

Gene expression of inducible nitric oxide synthase (iNOS), interferon-induced protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 α (MIP-1 α), SCD1 and leptin mRNA was performed by real-time PCR using SYBR Green master mix (Applied Biosystems, Foster City, CA, USA). Thermocycler conditions included an initial holding period at 50°C for 2 min, then 95°C for 10 min. This was followed by a two-step PCR program consisting of 95°C for 15 s, and 60°C for 60 s for 40 cycles. Data were collected and quantitatively analyzed using an ABI Prism 7900 sequence detection system (Applied Biosystems). The β -actin was used as an endogenous control to normalize for differences in the amount of total RNA in each sample. All quantities were expressed as number of fold relative to the expression of β -actin.

β -actin:

sense 5'-TGTCCACCTTCCAGCAGATGT-3';
anti-sense 5'-AGCTCAGTAACAGTCCGCCTAGA-3'.

MIP-1 α :

sense 5'-CACCTCTGTACCTGCTCAA-3';
anti-sense 5'-ATGGCGCTGAGAAGACTTGGT-3'.

IP-10:

sense 5'-GCCGTCATTTTCTGCCTC-3';
anti-sense 5'-ATGGCGCTGAGAAGACTTGGT-3'.

iNOS:

sense 5'-GCCACCAACAATGGCAACA-3';
anti-sense 5'-CGTACCGGATGAGCTGTGAATT-3'.

MCP-1:

sense 5'-AAAAACCTGGATCGGAACCAA-3';
anti-sense 5'-CGGGTCAACTTCACATTCAAAG-3'.

Leptin:

sense 5'-TGCACCCTATGTCACCATCAAA-3';
anti-sense 5'-CAGAGCTGAGCACGAACTGTG-3'.

Figure 1 Lipid accumulation in CIH. Four groups of C57BL/6 mice ($n = 5$) received a ConA (15 mg/kg) injection via the tail vein. (a) Representative photomicrographs are shown depicting Oil Red O staining of liver sections. Increased fat (red) in hepatocytes 2–24 h after ConA injection as compared to a quiescent condition (0 h). (b) Liver mRNA expression of SCD1, FAS, ACC1 and Elov16. Results are shown as mean $\pm$ s.d. Data are representative of five experiments.

SCD1:

sense 5'-AAGTTCTCAGAAACACACGCCG-3';

anti-sense 5'-TTCCGCCCTTCTCTTTGACAG-3'.

Immunoblot Analysis

Immunoblot analysis were performed using whole liver cell extract samples resolved by electrophoresis on a 10% SDS-polyacrylamide gel and transferred to PVDF membrane. STAT1, phospho-STAT1 (Thr-701), STAT3 and phospho-STAT3 (Tyr-705) were visualized using antibody from BD Bioscience (CA, USA).

Electrophoretic Mobility Shift Assay

Nuclear extracts of liver tissues were prepared as described previously.⁸ NF- κ B-binding consensus single-strand oligo nucleotide (5'-AGTTGAGGGGACTTCCAGGC-3') was first annealed with the complement oligonucleotide (5'-GCCTGGGAAAGTCCCTCAACT-3'). The annealed DNA fragment was labeled with [γ -³²P] dATP (Amersham, Piscataway, NJ, USA) using T4 Polynucleotide Kinase (Promega, Madison, WI, USA). Nuclear proteins (15 μ g) were incubated with 2.5 ng ³²P-labeled double-stranded oligonucleotide probes for 30 min at room temperature. The mixture was resolved by electrophoresis on 4% polyacrylamide gels with 0.5 $\times$ Tris-borate-ethylenediaminetetraacetic acid buffer at 4°C.

Statistical Analysis

All the results were expressed as mean $\pm$ s.d. Statistical comparisons between two groups were made using Student's *t*-test after analysis of variance. The level of significance was set at $\alpha = 0.05$. All the tests were two-sided.

RESULTS

ConA Treatment Increases Fat Accumulation in the Liver

CIH is a widely used animal model of immune-mediated liver injury and can be induced by intravenous injection of ConA into mice. We found that as early as 2 h after ConA injection, fat accumulation was observed in hepatocytes as indicated by Oil Red O staining (Figure 1a). Meanwhile, the critical enzyme involved in fat synthesis, SCD1, was upregulated (Figure 1b). We also found that other key lipogenic genes including fatty acid synthase, acetyl-CoA carboxylase 1 and Elov16 showed a similar expression pattern with SCD1 (Figure 1b). Thus, at the early phase of CIH induction, in tandem with the development of tissue damaging immune responses, there arose increased fat synthesis and accumulation.

Deficiency of SCD1 Protects Mice from CIH

SCD1 plays a crucial role in lipid metabolism.^{9,10} SCD1-deficient mice manifest defective hepatic cholesterol ester and triglyceride synthesis,^{11,12} thus exhibiting reduced liver steatosis. The ab^{xyk} mice⁷ are newly characterized asebia mice with a spontaneous dysfunction mutation of the SCD1 gene. We used these mice for induction of CIH. Their littermates

Figure 2 SCD1-deficient mice are resistant to ConA-induced hepatitis. SCD1-deficient mice (ab^{Xyk}/ab^{Xyk}) and littermate control mice (+/?) ($n = 5$) received a ConA injection (15 mg/kg) via the tail vein. Oil Red O staining of liver sections 4 h after ConA injection (a). Seventeen hours after ConA injection, plasma was obtained and ALT levels were measured (b). At the same time, livers were removed and fixed in 4% paraformaldehyde. Liver H&E (c) and TUNEL (d) staining were performed and results examined using light microscopy (magnification $\times 200$). Results are shown as mean $\pm$ s.d. Data are representative of five experiments. ** $P < 0.01$.

with normal phenotype (+/+ or +/ab^{Xyk} mice, shown as +/?) were used as controls.

Four hours after CIH induction, significantly less hepatosteatosis was observed in ab^{Xyk}/ab^{Xyk} mice as compared with +/? mice (Figure 2a). Serum was collected 17 h after ConA administration for the measurement of ALT to verify liver damage severity. We found that serum ALT was dramatically increased after CIH induction in +/? mice (9183 ± 1629 , U/L), indicating severe liver damage in these mice. However, in ab^{Xyk}/ab^{Xyk} mice, ConA-induced serum ALT increase was markedly blocked (88 ± 50 , U/L; $P < 0.01$) (Figure 2b). Microscopic examination of liver sections from +/? mice with CIH revealed severe pathological changes, characterized by widespread inflammatory lesions (Figure 2c, H&E staining) and hepatocyte death (Figure 2d, TUNEL staining). In contrast, few inflammatory or necrotic lesions were observed in ab^{Xyk}/ab^{Xyk} mice (Figure 2c and d). Therefore, mice deficient in SCD1 appeared highly resistant to CIH.

SCD1 Deficiency Suppresses Inflammatory Molecules in CIH Pathogenesis

Levels of serum TNF- α and IFN- γ , which are crucial in the pathogenesis of CIH, were measured as well. Compared with those in +/? mice, the increases in TNF- α and IFN- γ production were greatly attenuated in ab^{Xyk}/ab^{Xyk} mice (Figure 3a and b). The expression of several major inflammatory mediators including iNOS, IP-10, MCP-1, MIP-1 α , which were reported to be important in CIH pathogenesis,

was also examined. Expression of all these inflammatory mediators was found significantly lower in ab^{Xyk}/ab^{Xyk} mice than in +/? mice after CIH induction (Figure 3c–f).

SCD1 Deficiency Suppresses NF- κ B and STAT1 Transcriptional Pathways

Alterations of molecular pathways involved in CIH pathogenesis were then determined. First, NF- κ B activity was measured by electrophoretic mobility shift assay (EMSA). We found that DNA-binding activity of NF- κ B was strongly reduced in ab^{Xyk}/ab^{Xyk} mice as compared with that in +/? mice (Figure 4a). Next, we determined phosphorylated and nonphosphorylated STAT1 and STAT3 levels by immunoblot analysis. The protein levels of STAT1 in the liver were lower in ab^{Xyk}/ab^{Xyk} mice than in +/? mice. At the same time, phosphorylation of STAT1 was also suppressed in ab^{Xyk}/ab^{Xyk} mice. No significant difference of total protein levels and the phosphorylated form of STAT3 were observed in +/? and ab^{Xyk}/ab^{Xyk} mice with CIH (Figure 4b). These results indicate that reduced proinflammatory cytokine production and impaired pathogenic signaling pathways in ab^{Xyk}/ab^{Xyk} mice made these mice resistant to liver damage induced by ConA challenge.

Reduced Leptin Levels Mediate Resistance to CIH in SCD1-Deficient Mice

Leptin is a well-characterized adipokine and is considered as a proinflammatory cytokine which mediates the crosstalk between metabolism and immunity.¹³ Previous studies have

Figure 3 SCD1-deficient mice with CIH produced less inflammatory molecules. SCD1-deficient mice (ab^{Xyk}/ab^{Xyk}) and littermate control mice (+/?) (*n* = 5) received a ConA injection (15 mg/kg) via the tail vein. Plasma TNF-α levels (a) 2 h after ConA injection and IFN-γ levels (b) 8 h after ConA injection were measured using ELISA. Liver mRNA expressions of iNOS (c), IP-10 (d), MCP-1 (e) and MIP-1α (f) were quantitatively analyzed using real-time PCR. Results are shown as mean ± s.d. Data are representative of five experiments. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

shown significantly reduced leptin levels in SCD1-deficient mice on chow and high-fat diet.¹⁴ Moreover, mice deficient in leptin are resistant to CIH induction.¹⁵ Therefore, we investigated whether leptin was involved in the resistance to CIH in ab^{Xyk}/ab^{Xyk} mice. First, we examined leptin mRNA expression in adipose tissues, as well as its protein concentration in serum in ab^{Xyk}/ab^{Xyk} mice. Consistent with previous studies, both mRNA and protein levels of leptin were decreased significantly in these mice (Figure 5a). Leptin replacement experiments were then carried out. ab^{Xyk}/ab^{Xyk} mice received recombinant murine leptin (1 mg/kg) or PBS injection twice a day for 5 days, and CIH was subsequently induced in all the mice. As a result, leptin administration significantly restored the ability of ConA to induce hepatotoxicity in ab^{Xyk}/ab^{Xyk} mice (Figure 5b). There was small areas of centrilobular necrosis in leptin-treated SCD1-deficient mice with CIH, whereas no necrosis was observed in PBS-treated SCD1-deficient CIH mice (Figure 5c). We also measured inflammatory mediators expression in the liver. The levels of IFN-γ, IP-10, MCP-1, MIP-1α were significantly higher in leptin-treated SCD1-deficient CIH mice (Figure 5d). Therefore, leptin, at least partially, mediated the resistance to CIH in SCD1-deficient mice.

DISCUSSION

This study was prompted by our observation of extensive lipid accumulation in the livers of CIH mice. Previous studies have pointed out the connection between hepatic steatosis and liver inflammatory damage. NKT cells are selectively reduced in fatty liver of diet-induced obesity mice, promoting Th1 polarization of and sensitization to LPS-induced liver injury.^{4,5} A similar phenomenon observed in hepatosteatotic mice induced with CIH favored a Th1 response. Enhanced liver injury was found in these mice.⁶ A newly published study suggests that the loss of regulatory T cells in fatty liver may be one reason for enhanced inflammatory damage in fatty liver.¹⁶ Moreover, chronic infectious liver diseases caused by viruses, including HBV and HCV, are frequently associated with hepatic steatosis.¹⁷ Severe hepatic steatosis has also been seen in various animal models of liver injury, such as those induced by LPS,¹⁸ alcohol¹⁹ and CCl₄ (our unpublished data). Because hepatic steatosis presents frequently as a condition leading to liver inflammation, fibrosis and cancer, it would appear that interference with lipid metabolism may indeed represent a useful and novel strategy for prevention and treatment of liver disease.

Along with lipid accumulation, we found enhanced SCD1 expression in the liver of CIH mice. SCD1 is a central lipogenic enzyme converting saturated long-chain fatty acids into monounsaturated fatty acids (MUFAs).²⁰ Then we asked how CIH would manifest in SCD1-deficient mice. As expected, SCD1-deficient mice were highly resistant to CIH as indicated by serum ALT measurement and liver histological examination. Although a recently published report showed that SCD1-deficient mice showed increased severity in a dextran sulfate sodium-induced acute colitis model.²¹ The influence of SCD1 deficiency on immune-mediated liver injury was not known. Our findings indicate that SCD1, a key enzyme involved in fat metabolism, is involved in immune-mediated liver injury. We then went further to explore the underlying mechanism.

Immune activation elicited by ConA results in the elevation of various plasma cytokines, which then leads to immune assault upon hepatocytes. TNF-α is secreted from liver macrophages (Kupffer cells) as early as 2 h after CIH induction.²² Pretreatment of mice with anti-mouse TNF-α anti-serum or TNF-α inhibitor protected them from CIH.²³ In addition, depletion of IFN-γ resulted in a marked reduction in ConA-induced liver injury and inflammation.^{24,25} IFN-γ can synergize with TNF-α to induce production of several chemokines and adhesion molecules.²⁶ In CIH-induced mice, the release of NO into plasma and the expression of iNOS mRNA in liver was found to be increased.^{24,27} The involvement of the toxic effect of iNOS-derived NO in the development of CIH has been emphasized recently.^{28,29} NO mediates tissue injury through pathways including inhibition of mitochondrial respiration, inactivation of proteinase inhibitors and formation of free radicals.³⁰ During the first hours after challenge, the production of proinflammatory

Figure 4 Transcriptional pathways. SCD1-deficient mice (ab^{Xy}/ab^{Xy}) and littermate control mice (+/?) ($n = 5$) received a ConA injection (15 mg/kg) via the tail vein. **(a)** Liver nuclear extracts were subjected to NF-κB-specific EMSA. Specificity of the NF-κB and DNA-binding reaction was confirmed by incubation of liver nuclear extracts with increasing concentration of unlabeled ('cold') oligonucleotides for NF-κB and anti-p50 antibody. **(b)** Total liver protein extracts were probed with anti-phospho (p)-STAT1 (Tyr-701), anti-STAT1, anti-phospho (p)-STAT3 (Tyr-705) and anti-STAT3 antibodies and subjected to immunoblot analysis; **(c)** the ratio of band intensity was quantified and calculated by Biorad-Image for Windows Program (BioRad GS-800 Calibrated Densitometer). Results are shown as mean $\pm$ s.d. Data are representative of five experiments. *** $P < 0.001$.

cytokines is followed by activation of chemotactic factors such as IP-10, MCP-1 and MIP-1 α , which attract more leukocytes to the liver to amplify local inflammation and damage.^{31,32} IP-10 plays an important role in hepatic neutrophil influx in CIH.³¹ Although CIH is developing, IP-10 expression has been found to increase.³³ In MIP-1 α —/— mice, CIH has been shown to be markedly decreased, indicating that MIP-1 α is significantly involved in the pathogenesis of the disease.³⁴ Our observation of reduced production of all the above inflammatory molecules in SCD1-deficient mice after CIH induction suggests that the absence of SCD1 abrogates immune-induced hepatocytic injury and inflammation cascade. In other words, in the setting of T-cell-mediated liver injury, increased SCD1 expression and lipid accumulation may promote proinflammatory cytokine production.

Next, we explored further whether key pathogenic signaling pathways in CIH were altered in SCD1-deficient mice.

Because transcription factor NF-κB is involved in the synthesis of TNF- α , IFN- γ and numerous proinflammatory factors, the role of NF-κB in the pathogenesis of CIH has been well recognized. Many drugs show significant protective effects against CIH depending upon their prevention of NF-κB activation.^{35,36} In SCD1-deficient mice, DNA-binding activity of NF-κB after ConA administration was much weaker as indicated by EMSA. Another key pathogenic signaling pathway involved in CIH is IFN- γ /STAT1 signaling. Liver injury induced by ConA was associated with an increase in pSTAT1 levels in the liver. Transgenic mice overexpressing STAT1 under the control of the CD2 promoter enhancer construct showed elevated IFN- γ levels as well as significantly augmented liver injury following administration of ConA. Consistently, STAT1—/— mice were protected from such T-cell-dependent liver injury.²⁵ Here, we observed significantly reduced phosphorylation of STAT1 with ConA treatment in SCD1-deficient mice. These results suggest that

Figure 5 Leptin mediated the resistance to CIH in SCD1-deficient mice. **(a)** Plasma leptin levels of +/? and ab^{Xyk}/ab^{Xyk} mice were measured with ELISA. mRNA expression of leptin in epididymal fat pad was quantitatively analyzed using real-time PCR. Results are shown as mean $\pm$ s.d. ($n = 5$). **(b)** ab^{Xyk}/ab^{Xyk} mice received i.p. injections of either PBS or leptin (1 mg/kg) twice a day for 5 days. Subsequently, CIH was induced in all mice. Plasma ALT levels were measured 17 h later. **(c)** Representative liver H&E staining of **(b)**. Arrows indicates necrotic areas. **(d)** Liver mRNA expression of IFN- γ , IP-10, MCP-1 and MIP-1 α were quantitatively analyzed using real-time PCR. Results are shown as mean $\pm$ s.d. ($n = 5$). Data are representative of three experiments. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

SCD1 deficiency impairs the production of IFN- γ , thus reducing the activation STAT1 in CIH, and protecting mice from immune-mediated liver injury. In addition, we tested the STAT3 pathway which mediates protective effects in CIH.³⁷ We showed that the STAT3 pathway was not significantly influenced in SCD1-deficient mice.

We wondered how SCD1, the enzyme for biosynthesis of MUFAs, might interfere with inflammation. We noticed a report by Ntambi *et al* that leptin production was suppressed in SCD1-deficient mice on chow and high-fat diet.¹⁴ It is well known that leptin is a critical linker between energy metabolism and immunity.¹³ Leptin influences many immune

pathways in a direct or indirect manner. The key pathogenic immune cells in CIH, such as T cells and NKT cells, may be activated by leptin.¹³ Leptin also promotes the production of proinflammatory cytokines such as TNF- α and IFN- γ which are critical in the pathogenesis of CIH.^{13,38} A previous study showed that susceptibility to CIH may be increased by leptin via maintenance of high numbers of hepatic NKT cells as well as by mediation of T-cell activation and cytokine production.¹⁴ Obesity and the metabolic syndrome would therefore put the liver at a heightened risk of immune-mediated damage under a leptin-dependent mechanism.³⁹ Leptin deficiency leads to reduced severity in the CIH model.¹⁵ Here, we observed reduced serum leptin levels and leptin mRNA expression in adipose tissue in SCD1-deficient mice. The replacement experiment further confirmed that reduced leptin levels contributed significantly to the protective role of SCD1 deficiency in CIH induction.

Very recently, several well-known lipid metabolism regulators that stimulate fat oxidation, including metformin and Omega-3 polyunsaturated fatty acids, have shown hepatoprotective activity against immune-mediated liver injury.^{40,41} In this study, we clearly demonstrated that inactivation of SCD1, a key regulator in lipid metabolism, protects mice from CIH. Similar protective effects were also seen after pretreatment of mice with AMPK activator metformin (our unpublished data). Our findings provide direct evidence that regulation of energy metabolism may alter immune responses in the liver, a realization that suggests a new approach to understanding and perhaps controlling crosstalk between energy metabolism and the immune system in the liver. Such an approach may assist and improve liver disease treatment in the future.

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