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Review Article

The Role of Solute Carrier Family Transporters in Hepatic Steatosis and Hepatic Fibrosis

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Abstract

Solute carrier (SLC) family transporters are crucial transmembrane proteins responsible for transporting various molecules, including amino acids, electrolytes, fatty acids, and nucleotides. To date, more than fifty SLC transporter subfamilies have been identified, many of which are linked to the progression of hepatic steatosis and fibrosis. These conditions are often caused by factors such as non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, which are major contributors to the global liver disease burden. The activity of SLC members regulates the transport of substrates across biological membranes, playing key roles in lipid synthesis and metabolism, mitochondrial function, and ferroptosis. These processes, in turn, influence the function of hepatocytes, hepatic stellate cells, and macrophages, thereby contributing to the development of hepatic steatosis and fibrosis. Additionally, some SLC transporters are involved in drug transport, acting as critical regulators of drug-induced hepatic steatosis. Beyond substrate transport, certain SLC members also exhibit additional functions. Given the pivotal role of the SLC family in hepatic steatosis and fibrosis, this review aimed to summarize the molecular mechanisms through which SLC transporters influence these conditions.

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Introduction

Hepatic steatosis can result from various factors, including metabolic processes, pharmacological agents, alcohol consumption, and other toxins. Among these, metabolically induced non-alcoholic fatty liver disease (NAFLD) is the most common type, with a global prevalence of 30%, a figure that continues to rise, indicating a significant global disease burden.[1,2] NAFLD is characterized by hepatic steatosis, and while its underlying pathogenesis remains unclear, the "multiple-hit" hypothesis is currently the most comprehensive and widely accepted model. This model attributes the development of NAFLD to several factors, including disruptions in lipid metabolism, insulin resistance (IR), adipose tissue dysfunction, dietary composition, alterations in the gut microbiota, as well as genetic and epigenetic influences.[3] In addition, abnormal concentrations of certain metal ions—such as iron, copper, and zinc—in plasma and cells may cause cellular dysfunction, further contributing to NAFLD pathogenesis.[4–6] Hepatic fibrosis, the subsequent stage following hepatic steatosis, is a physiological metabolic response to hepatocellular injury. This process involves mechanisms such as the activation of hepatic stellate cells (HSCs), epithelial-mesenchymal transition (EMT) of hepatocytes, macrophage polarization, and increased secretion of inflammatory factors.[7,8] As hepatic fibrosis progresses, liver function deteriorates, potentially culminating in cirrhosis. This advanced stage is associated with an elevated risk of hepatocellular carcinoma and poor patient prognosis.[9,10] A deeper understanding of the mechanisms underlying steatosis and fibrosis, alongside the development of effective pharmacological interventions, could significantly improve the quality of life and prognosis for patients with these chronic liver diseases.

The solute carrier (SLC) family is estimated to include up to 456 members.[11] These transporters are widely expressed across biological membranes, including cytoplasmic and mitochondrial membranes in various organs. SLC transporters facilitate the transport of a broad range of molecules, including amino acids, electrolytes, nucleotides, saccharides, and other substances.[12] They play crucial roles in numerous physiological and pathophysiological processes, significantly contributing to the development of renal diseases, neurodegenerative disorders, cancer, and metabolic conditions. Mutations in these transporters are also linked to various Mendelian diseases.[13] Several SLC members are expressed in the liver, with some influencing liver pathophysiology. Multidrug transporter proteins, an important subgroup of the SLC family, are particularly regulated by liver function, thereby affecting drug metabolism and efficacy. Additionally, certain SLC members are key mediators of drug-induced liver injury caused by agents such as statins and anti-tuberculosis drugs.[14–16] The SLC family also plays a critical role in hepatic steatosis and fibrosis by modulating the functions of hepatocytes and HSCs through various mechanisms. Notably, several SLC-targeted drugs have been tested in clinical trials, demonstrating significant therapeutic effects in treating NAFLD.[17,18]

Keywords: Solute carrier family transporters; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Hepatic fibrosis; Hepatic steatosis; Lipolysis.
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This review provides a comprehensive overview of the latest developments regarding the role of the SLC family in hepatic steatosis and fibrosis. In particular, it focuses on elucidating the mechanisms of action of various SLC molecules. Unlike previous studies, we conduct a systematic review of all known SLC molecules potentially involved in these processes (summarized in Tables 1 and 2),[19–156] emphasizing their clinical applications or potential. This approach offers new insights into how additional SLC members contribute to liver disease development and highlights their potential as drug targets for NAFLD.

SLC1/2

SLC1 is a type of glutamate transporter protein that helps maintain a gradient in the concentration of glutamate across the cell membrane.[157] SLC1A4 and SLC1A5 are responsible for transporting neutral amino acids into the cell. The ratio of plasma glutamate to glutamine concentrations is elevated and correlates with the degree of hepatic fibrosis in patients with NAFLD. These elevated glutamate levels primarily result from the catabolism of glutamine. In methionine- and choline-deficient-induced NASH mice, the expression of SLC1A5 is increased, and HSCs exhibit enhanced glutamine uptake. Inhibition of glutamine uptake or catabolism shifts activated HSCs to a more quiescent state, thereby alleviating fibrosis. Consequently, inhibiting SLC1A5 may reduce glutamine uptake and potentially slow the progression of NAFLD to NASH.[19] However, bioinformatics analysis reveals that the expression of SLC1A4 is decreased in NAFLD patients and may be associated with M1 macrophage activation and neutrophil infiltration. This suggests that SLC1A4 could contribute to fibrosis through mechanisms independent of its transporter function.[20]

The SLC2 family encodes glucose-fructose transport proteins. SLC2 family members are expressed on hepatocyte membranes, with SLC2A2 (GLUT2) showing the highest expression. Reduced activity of SLC2A2 affects glucose transport to the liver and promotes IR in response to a high-fat-sugar diet. Elevated plasma insulin levels stimulate *de novo* lipogenesis (DNL), further exacerbating hepatic steatosis.[158] The reduction in GLUT2 activity may result from either downregulation of its expression or inhibition of its translocation, depending on its cytomembrane expression levels.[159] Various signaling molecules, including sterol O-acyltransferase 2, protease-activated receptor 2, transmembrane member 16A, low-density lipoprotein receptor-related protein-1, and β-hydroxy-β-methylbutyrate, influence hepatic lipid accumulation by regulating GLUT2 activity.[21–25] A high-fat diet (HFD) reduces cytomembrane GLUT2 levels in NAFLD mice. Interestingly, one study identified elevated hepatic GLUT2 expression in mice with type 2 diabetes and high-fructose-induced diabetes with NAFLD.[26–28] In these mice, increased GLUT2 expression promotes glucose translocation into hepatocytes, indirectly increasing precursors for lipid synthesis and promoting hepatic steatosis. The observed differences in GLUT2 expression may result from varying dietary conditions, which induce different patterns of hepatic steatosis. This is consistent with findings that mice with high-fructose-induced NAFLD exhibit greater insulin sensitivity compared to those with HFD-induced NAFLD.[29] Nevertheless, aberrant GLUT2 activity contributes to hepatic steatosis in both dietary patterns. Reduced GLUT2 expression, along with increased GLUT4 expression, has been observed in cirrhotic patients and senescent hepatocytes, leading to selective IR and poor prognosis. It has been postulated that IR resulting from a decrease in GLUT2 may indirectly impact fibrosis by promoting hepatocyte senescence, although this hypothesis requires further verification.[30]

Unlike GLUT2, SLC2A4/GLUT4 is predominantly intracellular in the unstimulated state and rapidly translocates to the cytomembrane in response to glucose uptake stimuli, such as insulin and ischemia-reperfusion. This represents the first reported instance of GLUT protein activation under stressed conditions.[160] IR resulting from GLUT4 inactivation is caused by oxidative stress in adipose tissue, induced by short-term nutrient excess. This mechanism primarily explains GLUT4's influence on hepatic steatosis. Additionally, GLUT4 translocation to the cell membrane can be mediated by the IGF-1R/IRS1/PI3K/Akt or AMPKα1/PGC-1α signaling pathways.[31–33] GLUT4 expression is more pronounced in male obese spontaneously hypertensive rats compared to females, reflecting sex-based differences in the pathogenesis of hepatic steatosis.[34] Activated AMPK can reduce GLUT4 expression in HSCs, thereby decreasing glucose availability for glycolysis, inhibiting HSC activation, and alleviating hepatic fibrosis.[35] SLC2A1/GLUT1 is a critical transporter for glucose uptake in the brain, induced by hypoxia, and associated with increased glycolysis during carcinogenesis. GLUT1 expression is differentially regulated in hepatocytes and HSCs during liver injury, with each cell type playing distinct roles. Hepatic GLUT1 expression is reduced in NAFLD patients, and *in vitro* knockdown of GLUT1 on hepatocytes increases oxidative stress and lipid accumulation.[36] Notably, increased hepatic GLUT1 expression is observed in hepatic fibrosis mice, primarily in the hepatic sinusoidal region. Mechanistically, activated HSCs secrete GLUT1-containing exosomes in response to hypoxia-inducible factor (HIF) 1, which are subsequently taken up by unactivated HSCs, promoting glucose uptake and glycolysis and facilitating HSC activation.[37] Increased GLUT1 in HSCs can also be induced by TGF-β1 through the Smad, p38 MAPK, and PI3K/AKT pathways.[161] SLC2A5/GLUT5 is widely expressed in intestinal epithelial cells, where it facilitates glucose and fructose absorption. Its intestinal expression is associated with obesity and IR.[162] Recent studies have linked high GLUT5 expression in the intestine to disease progression in NAFLD patients.[38] It is hypothesized that specific inhibition of intestinal GLUT5 may alleviate hepatic steatosis by reducing sugar absorption. SLC2A8/GLUT8 is expressed in hepatocytes and intestinal cells and plays a crucial role in intrahepatic fructose transport. Increased translocation of GLUT8 to the cytomembrane during acute fructose overconsumption is mediated by its transient dissociation from transmembrane 4 L six family member 5.[39] High fructose levels induce endoplasmic reticulum stress and oxidative stress in hepatocytes, promoting DNL, lipid oxidative catabolism, and HSC activity. GLUT8 deletion alleviates hepatic steatosis and fibrosis by counteracting these effects.[29,40] SLC2A9/GLUT9 is a urate transporter protein, and its polymorphisms are associated with NAFLD. Liver-specific knockdown of GLUT9 ameliorates HFD-induced hepatic steatosis in mice by decreasing intrahepatic uric acid and inhibiting lipolysis gene expression.[41] However, a Mendelian randomization study combined with cohort analysis shows that elevated plasma urate concentration is not causally associated with NAFLD.[163] Since GLUT9 is widely distributed in the liver, kidney, and intestine, its liver-specific mediation of urate transfer may significantly contribute to intrahepatic urate levels.

SLC5/6

Sodium-glucose transporters (SGLTs) encoded by the SLC5 family play a crucial role in metabolic diseases, particularly SLC5A2/SGLT2. SGLT2 has emerged as an effective thera-

Table 1. The role of the SLC family in hepatic steatosis

Gene	Protein	Substrate	Organ	Location	Disease	Effect	Mechanism
SLC2A1	GLUT1	Glucose	Liver	Cytomembrane	NAFLD	Inhibit	SLC2A1 silencing induced increased oxidative stress activity and lipid accumulation[35]
SLC2A2	GLUT2	Glucose	Liver	Cytomembrane	NAFLD	Inhibit	SLC2A2 reduced IR by stimulating glucose transport to the liver in an HFD[21–25]
						Promote	SLC2A2 promoted glucose translocation into hepatocytes, indirectly increasing the precursors of lipid synthesis in a high-sugar diet[26–28]
SLC2A4	GLUT4	Glucose	Adipose tissue	Cytomembrane	NAFLD	Inhibit	SLC2A4, whose translocation was mediated via IGF-1R/IRS1/PI3K/Akt signaling pathway, reduced IR by stimulating glucose transport to adipose tissue[31–34]
SLC2A5	GLUT5	Glucose/ fructose	Intestine	Cytomembrane	NAFLD	Promote	SLC2A5 increased the absorption of various sugars indirectly promoting lipogenesis[38]
SLC2A8	GLUT8	Fructose	Liver	Cytomembrane	NAFLD	Promote	SLC2A8, whose translocation was mediated by binding to TM4SF5, induced endoplasmic reticulum stress and oxidative stress in hepatocytes to promote DNL[29,39]
SLC2A9	GLUT9	Uric acid	Liver	Cytomembrane	NAFLD	Promote	SLC2A9 increased intrahepatic uric acid and promoted the expression of lipolysis genes[41]
SLC5A1	SGLT1	Glucose	Intestine	Cytomembrane	NAFLD	Promote	SLC5A1 promoted glucose absorption[51]
SLC5A2	SGLT2	Glucose	Kidney	Cytomembrane	NAFLD	Promote	SLC5A2 inhibitors ameliorated circulating inflammation and oxidative stress,[42] inhibited LXRα-mediated synthesis of BAs and DNL, reducing intestinal lipid absorption,[43] improved IR and reduced precursors of lipid synthesis[44]
SLC5A5	SGLT5	Fructose	Kidney	Cytomembrane	NAFLD	Inhibit	SLC5A5 silencing may be related to increased GLUT8 translocation[53]
SLC6A4	SERT	Serotonin	Intestinal	Cytomembrane	NAFLD	Inhibit	SLC6A4 silencing-mediated extracellular serotonin aggregation caused serum endotoxin increasing, leading to hepatic inflammation,[54,55] caused intestinal dysbacteriosis, activation of the JNK pathway, IR and increased recruitment of hepatic leukocytes[56–58]
			Liver			Promote	SLC6A4 increased serotonin uptake, while serotonin catabolism and oxidative stress mediated mitochondrial and ultimately hepatocyte damage[59]
SLC6A14	ATB (0,+)	Neutral/ Cationic amino	Intestine	Cytomembrane	NAFLD	Inhibit	SLC6A14 silencing increased food intake, altered plasma amino acid profiles[60]
SLC7A8	LAT-2	Glutamine	Adipose tissue	Cytomembrane	NAFLD	Promote	SLC7A8 silencing improved glucose tolerance by reducing lipid accumulation and weight[72]
SLC7A11	xCT	Cystine-glutamate	Liver	Cytomembrane	NAFLD	Inhibit	SLC7A11 affected hepatic lipid accumulation by regulating the process of ferroptosis,[61,62] and epigenetic regulation of SLC7A11 regulated lipid-associated genes or ferroptosis to influence steatosis[63,64]
SLC9A1	NHE1	Na/H	Liver	Cytomembrane	NAFLD	Promote	SLC9A1 silencing reduced DNL and HSCs activation and increased insulin sensitivity[79]

(continued)

Table 1. *(continued)*

Gene	Protein	Substrate	Organ	Location	Disease	Effect	Mechanism
SLC10A1	NTCP	BAs	Liver	Cytomembrane	NAFLD	Promote	SLC10A1 silencing reduced intestinal fat absorption and increased non-coupled respiration in BAT[76]
SLC10A2	ASBT	BAs	Ileum	Cytomembrane	NAFLD	Promote	SLC10A2 silencing reduced plasma BAs and increased hepatic cholesterol catabolism by inhibiting FXR-FGF15/19 and upregulating ERK/JNK-CYP7A1,[73] reduced fat absorption by altering BAs properties,[74] and enhanced insulin sensitivity[75]
SLC13A5	mIndy	Citrate	Liver	Cytomembrane	NAFLD	Promote	SLC13A5 increased hepatic lipogenesis, prevented IR, and reduced plasma and liver TAG levels which may be caused by upregulated by IL-6-signal transducer and activator of transcription 3 pathway and increased plasma β-hydroxybutyrate and AMPK activation[80–83]
SLC15A1	PEPT1	Peptide	Ileum	Cytomembrane	NAFLD	Promote	SLC15A1 silencing caused decreased systemic IL-6 levels inducing a lack of mucosal structures mediated by reduced intestinal energy absorption leading to weight loss[84]
SLC16A1	MCT1	Lactate	Liver	Cytomembrane	NAFLD	Inhibit	SLC16A1 liver-specific deletion resulted in lactate accumulation in hepatocytes, which led to enhanced PPARα, resulting in decreased expression of lipid oxidation-related genes[86]
						Promote	SLC16A1 partial invalidation prevented LDHB expression, leading to a reduction in pyruvate, which affected ATP production and increased the AMP/ATP ratio to activate AMPK[87–89]
SLC16A11	MCT11	Monocarboxylic	Liver	Cytomembrane	NAFLD	Promote	SLC16A11 knockdown improved IR and reduced TAG accumulation in serum and liver[90]
SLC16A13	MCT13	Monocarboxylic	Liver	Cytomembrane	NAFLD	Promote	SLC16A13 knockdown attenuated hepatic diacylglycerol-PKCε-mediated IR, decreased intracellular lactate availability, leading to increased AMPK activation[91]
SLC17A9	VNUT	Nucleotide	Liver	Vesicular	NAFLD	Promote	SLC17A9 knockdown inhibited intercellular purinergic signaling, reducing the progression of inflammation and fibrosis, decreasing the expression of lipolytic genes and increasing the expression of lipolysis genes[101,102]
SLC19A1	RFC	Folate	Liver	Cytomembrane	NAFLD	Inhibit	SLC19A1 silencing in hepatocytes reduced intracellular folate levels, affected the regulation of genes critical for lipid metabolism like FAS and XBP1, leading to the accumulation of lipid droplets in hepatocytes[103]
SLC22A4	OCTN1	Carnitine	Liver	Cytomembrane	Hepatic steatosis	Inhibit	SLC22A4 reduced lipid accumulation by increasing uptake of carnitine[92–95]
SLC22A5	OCTN2	Carnitine	Liver	Cytomembrane	Hepatic steatosis	Inhibit	SLC22A5 reduced lipid accumulation by increasing uptake of carnitine[94,95]

(continued)

Table 1. *(continued)*

Gene	Protein	Substrate	Organ	Location	Disease	Effect	Mechanism
SLC22A12	URAT1	Uric acid	Kidney	Cytomembrane	NAFLD	Promote	SLC22A12 silencing reduced Ccl2 and TNFα and intracellular ROS production in hepatocytes, improving IR by upregulating UCP1 to induce rebrowning of BAT[97]
SLC22A18	–	–	Liver	Cytomembrane	Hepatic steatosis	Promote	SLC22A18 promoted systemic lipid accumulation in mice, including liver[98,99]
SLC25A1	CIC	Citrate	Liver	Mitochondrial membrane	NAFLD	Promote	SLC25A1 inhibition reduced DNL by decreasing citrate transport to reduce pyruvate, promoted FAS by deacetylating CPT1A, and led to reduced glucose oxidative catabolism by triggering acetylation-induced inactivation of PDHE1α, and also activated the SIRT1/PGC1α pathway to enhance oxidative phosphorylation[120,121]
SLC25A5	ANT2	ATP	Liver	Mitochondrial membrane	NAFLD	Promote	SLC25A5 silencing increased uncoupled respiration and prevented IR[127]
					Alcohol-induced fatty liver	Promote	SLC25A5 was stabilized by Kbhb, which was mediated by HMGCS2, facilitated steatosis via the MAPK/Erk/PPARγ axis in chronic alcohol exposure[128]
SLC25A7	UCP1	LCFA and proton	BAT	Mitochondrial membrane	NAFLD	Inhibit	SLC25A7, which mediated by PPARγ signaling pathway, AMPK, GPR120 and sympathetic nerves inhibited hepatic steatosis through non-shivering thermogenesis and weight loss[105–108]
SLC25A8	UCP2	LCFA and proton	Liver	Mitochondrial membrane	NAFLD	Inhibit	SLC25A8 increased thermogenesis through AMPK-PPARα-UCP2 pathway improving fatty acid metabolism[111–113]
SLC25A9	UCP3	LCFA and proton	Liver/ Skeletal muscle	Mitochondrial membrane	NAFLD/ Alcohol-induced fatty liver	Inhibit	SLC25A9 silencing was related to IR, Akt/PKB, and AMPK signaling blunting and FAO decreasing[115–119]
SLC25A10	mDIC	Dicarboxylic acid	WAT	Mitochondrial membrane	NAFLD	Inhibit	SLC25A10 mediated succinate influx into adipocytes, enhanced SUCNR1 to inhibit lipolysis by dampening the pHSL pathway, and reduced NEFAs for intrahepatic lipid synthesis[122,123]
			Liver	Mitochondrial membrane	NAFLD	Promote	SLC25A10 silencing in hepatocytes may downregulate the lipogenic pathway[124]
SLC25A28	Mitoferrin2	Iron	Liver	Mitochondrial membrane	NAFLD	Inhibit	SLC25A28 deficient female mice exhibited elevated hepatic TAG and altered hepatic lipid metabolism when exposed to a low-iron diet[125]
SLC25A47	-	NAD+	Liver	Mitochondrial membrane	NAFLD	Inhibit	SLC25A47 inhibited lipid accumulation and reduced mitochondrial oxidative stress via the SIRT3-AMPKα-SREBPs pathway[129–131]
SLC27A1	FATP1	FAs	Adipose tissue	Cytomembrane	NAFLD	Inhibit	SLC27A1 led to the redistribution of lipids from adipocyte tissues and muscles to the liver[133]

(continued)

Table 1. *(continued)*

Gene	Protein	Substrate	Organ	Location	Disease	Effect	Mechanism
SLC27A2	FATP2	FAs	Liver	Cytomembrane	NAFLD	Promote	SLC27A2 silencing reduced hepatic lipid accumulation by inhibiting uptake of FAs[134–138]
SLC27A4	FATP4	FAs	Liver	Mitochondrial membrane	NAFLD	Inhibit	SLC27A4 silencing in hepatocytes led to decreased β-oxidation, increased synthesis and uptake of FAs and as well as lipolysis[139,140]
					NAFLD	Promote	SLC27A4 could increase ACSL activity in response to palmitate stimulation for synthesis of lipids and FAs, resulting in damage to the structure of the endoplasmic reticulum, which was caused by phospholipid composition alteration, and activating the Bax and JNK/PUMA pathways[141,142]
SLC27A5	FATP5	FAs/BAs	Liver	Cytomembrane	NAFLD	Promote	SLC27A5 silencing improved systemic glucose homeostasis[144]
SLC31A1	Ctr-1	Copper	Intestinal	Cytomembrane	NAFLD	Inhibit	SLC31A1 silencing reduced copper-mediated β-oxidation and increased DNL and IR. Hepatic iron overload due to copper deficiency caused mitochondrial dysfunction and inhibition of antioxidant defenses[146,147]
SLC35A1	CST	CMP-sialic	Liver	Golgi apparatus	Hepatic steatosis	Inhibit	SLC35A1 maintained hepatic lipid homeostasis in neonatal mice by enhancing VEGFR2 signaling[154]
SLC39A14	ZIP14	Zinc	Liver	Cytomembrane	NAFLD	Inhibit	SLC39A14, which mediated by UPR-AFT4/6, increased zinc influx followed by decreasing of PTP1B activity affecting the pro-apoptotic p-eIF2α/ATF4/CHOP pathway and DNL,[148] affected PPARγ activity as well as insulin receptor activity,[149,150] prevented iron deficiency-mediated lipid accumulation[151]
SLC43A3	ENBT1	Purine-selective nucleobase	Liver	Cytomembrane	NAFLD	Inhibit	SLC43A3 seemed to regulate FAs flux in adipocytes, functioning as a positive regulator of FAs efflux and a negative regulator of FAs uptake[156]

AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; ANT2, adenine nucleotide translocase-2; ASBT, apical sodium-dependent bile acid transporter; ATB (0,+), amino acid transporter B(0,+); ATP, adenosine triphosphate; BAs, bile acids; BAT, brown adipose tissue; Ccl2, chemokine ligand 2; CIC, citrate/isocitrate carrier; CPT1A, palmitoyl-transferase 1A; CST, CMP-sialic acid transporter; Ctr-1, copper transporter 1; DNL, *de novo* lipogenesis; ENBT1, equilibrative nucleobase transporter 1; FAO, fatty acid oxidation; FAS, fatty acids; FATP1, fatty acid transport protein 1; FATP2, fatty acid transport protein 2; FATP4, fatty acid transport protein 4; FATP5, fatty acid transport protein 5; FXR, farnesoid X receptor; FGF15/19, fibroblast growth factor 15/19; GLUT1, glucose transporter type 1; GLUT2, glucose transporter type 2; GLUT4, glucose transporter type 4; GLUT5, glucose transporter type 5; GLUT8, glucose transporter type 8; GLUT9, glucose transporter type 9; GPR120, G protein-coupled receptor 120; HFD, high-fat diet; IR, insulin resistance; HMGCS2, 3-hydroxy-3-methylglutaryl-coenzyme A synthase 2; HSCs, hepatic stellate cells; IL-6, interleukin 6; JNK, c-Jun N-terminal kinase; Kbhb, global protein lysine β-hydroxybutyrylation; LAT-2, l-type amino acid transporter 2; LDHB, lactate dehydrogenase B; LXRα, liver receptor alpha; MCT1, monocarboxylic transporter 1; MCT11, monocarboxylic transporter 11; MCT13, monocarboxylic transporter 13; mDIC, mitochondrial dicarboxylate carrier; mIndy, mammalian homolog of INDY; NAFLD, non-alcoholic fatty liver disease; NEFAs, non-esterified fatty acids; ACSL, acyl coenzyme A synthase; NHE1, Na(+)/H(+) exchanger 1; NTCP, sodium taurocholate co-transporting polypeptide; OCTN1, organic cation transporter 1; OCTN2, organic cation transporter 2; PDHE1α, pyruvate dehydrogenase E1alpha; PEPT1, peptide transporter 1; pHSL, cAMP-phosphorylated hormone-sensitive lipase; PPARα, peroxisome proliferator-activated receptor alpha; PTP1B, protein-tyrosine phosphatase 1B; RFC, folate carrier; SERT, serotonin transporter; SGLT1, sodium-glucose transporter 1; SGLT2, sodium-glucose transporter 2; SGLT5, sodium-glucose transporter 5; SUCNR1, succinate receptor 1; TAG, triacylglycerol; TNFα, tissue necrosis factor α; TM4SF5, transmembrane 4 L six family member 5; URAT1, urate transporter 1; UCP1, uncoupling protein 1; UCP2, uncoupling protein 2; UCP3, uncoupling protein 3; VEGFR2, vascular endothelial growth factor receptor 2; VNUT, vesicular nucleotide transporter; XBP1, X-box binding protein 1; xCT, cystine-glutamate reverse transporter; ZIP14, Zrt- and Irt-like proteins 14.

Table 2. The role of the SLC family in hepatic fibrosis

Gene	Protein	Substrate	Organ	Location	Disease	Effect	Mechanism
SLC1A4	ASCT1	Neutral amino acid	Liver	Cytomembrane	NASH	Inhibit	SLC1A4 reduced M1 macrophage activation and neutrophil infiltration[19]
SLC1A5	ASCT2	Neutral amino acid	Liver	Cytomembrane	NASH	Promote	SLC1A5 activated HSCs by increasing HSCs glutamine uptake and catabolism[20]
SLC2A1	GLUT1	Glucose	Liver	Cytomembrane	NAFLD	Promote	SLC2A1 could be induced by TGF-β1 through Smad, p38 MAPK and PI3K/AKT pathways.[37] SLC2A1-containing exosomes stimulated by HIF1 were taken up by HSCs facilitating glycolysis and HSCs activation[36]
SLC2A2	GLUT2	Glucose	Liver	Cytomembrane	Cirrhosis	Inhibit	SLC2A2 prevented hepatocyte senescence indirectly affecting fibrotic process by reducing IR[30]
SLC2A4	GLUT4	Glucose	Liver	Cytomembrane	Hepatic fibrosis	Promote	SLC2A4, which could be inhibited by AMPK, facilitated glycolysis and HSCs activation[35]
SLC2A8	GLUT8	Fructose	Liver	Cytomembrane	Hepatic fibrosis	Promote	SLC2A8 promoted lipid oxidative catabolism in HSCs[40]
SLC5A1	SGLT1	Glucose	Intestine	Cytomembrane	NASH	Promote	SLC5A1 increased the expression of genes related to inflammation and hepatic fibrosis[52]
SLC5A2	SGLT2	Glucose	Kidney	Cytomembrane	NASH	Promote	SLC5A2 inhibitors improved blood sugar and lipid levels,[45] affected intestinal flora,[46] influenced miRNA-34a-5p-GREM2-TGFβ or Sirt1/AMPK/ PGC1α/FoxO1 axis impairing HSCs activation,[47,48] reduced inflammation and abnormal lipid degradation by mediating O-GlcNAcylation and activating AMPK-TFEB-induced autophagic fluxes[49]
					Cirrhosis	Promote	SLC5A2 inhibitors attenuated the major fibrotic pathways TGF-β/TGF-βRI/Smad2 and PDGFR-β in HSCs and VEGF-A/VEGFR-2/Shb pathway in hepatic endothelial cells[50]
SLC7A11	xCT	Cystine-glutamate	Liver	Cytomembrane	Hepatic fibrosis	Promote	HIF-1α/SLC7A11, SOCS1/P53/SLC7A11, IRF1/SLC7A11, Beclin1/SLC7A11, ubiquitination of SLC7A11 could all influence fibrosis by regulating ferroptosis in HSCs[65–69]
						Inhibit	In hepatocytes, JNK-c-Jun-SLC7A11 decreased ROS and increased PHD-AMPK-mitochondrial autophagy pathway, leading to NLRP3-mediated IL-1β reduction and finally preventing HSCs activation,[70] facilitating the EMT of hepatocytes through inhibition of AGER1/Sirt4/SLC7A11 pathway promoting ferroptosis[71]
SLC9A1	NHE1	Na/H	Liver	Cytomembrane	NASH	Promote	SLC9A1 silencing reduced DNL and HSCs activation and increased insulin sensitivity[79]
SLC10A1	NTCP	BAs	Liver	Cytomembrane	Hepatic fibrosis	Promote	SLC10A1 promoted BAs uptake which was associated with HSCs activation[77,78]
SLC16A1	MCT1	Lactate	Liver	Cytomembrane	NASH	Promote	SLC16A1 knockdown in HSCs reduced collagen-1 expression and attenuated hepatic fibrosis[85]
					NASH	Inhibit	SLC16A1 knockdown in hepatocytes increased collagen-1 expression and attenuated hepatic fibrosis[85]
SLC17A9	VNUT	Nucleotide	Liver	Vesicular	NASH	Promote	SLC17A9 knockdown inhibited intercellular purinergic signaling, reducing the progression of inflammation and fibrosis, decreasing the expression of lipolytic genes and increasing the expression of lipolysis genes[101,102]

(continued)

Table 2. *(continued)*

Gene	Protein	Substrate	Organ	Location	Disease	Effect	Mechanism
SLC22A3	OCT3	Organic cation	Liver	Cytomembrane	Hepatic fibrosis	Inhibit	SLC22A3 silencing led to the upregulation of TGF-β, resulting in the progression of fibrosis[100]
SLC22A4	OCTN1	Carnitine	Liver	Cytomembrane	Hepatic fibrosis	Inhibit	SLC22A4 was upregulated in activated HSCs, resulting in an increased delivery of ERGO, which has a protective effect against hepatic fibrosis[96]
SLC23A2	SVCT2	Vitamin C	Liver	Cytomembrane	Cirrhosis	Promote	SLC23A2 mediated vitamin C influx, assisting hydroxylase to promote HSCs collagen 1 release[104]
SLC25A1	CIC	Citrate	Liver	Mitochondrial membrane	NASH	Promote	SLC25A1 inhibition inhibited M1 pro-inflammatory pathway and the expression of pro-fibrotic genes[121]
SLC25A3	PiC2	Pi and copper	Liver	Mitochondrial membrane	NASH	Inhibit	SLC25A3 silencing impaired ETC by reducing copper in mitochondria, leading to electron leakage and increased mitochondrial ROS production, making hepatocytes more susceptible to oxidative stress[124]
SLC25A7	UCP1	LCFA and proton	BAT	Mitochondrial membrane	NASH	Promote	SLC25A7 was downregulated in NK cells via PPARγ/ATF2 axis, increased FAO exacerbating irreversible mitochondrial damage, leading to necrotic apoptosis in NK cells,[109] reduced uptake of succinate by BAT, activating SUCNR1 in HSCs and macrophages to produce pro-inflammatory effects[110]
SLC25A8	UCP2	LCFA and proton	Liver	Mitochondrial membrane	NASH	Inhibit	Activation of the PPARα-SLC25A8-AMPK pathway in macrophages could inhibit macrophage activation to reduce inflammation and alleviate the progression of fibrosis[114]
SLC25A28	Mitoferrin2	Iron	Liver	Mitochondrial membrane	Hepatic fibrosis	Inhibit	BRD7-p53-SLC25A28 axis led to aberrant accumulation of redox-activated iron and hyperfunction of the ETC, which promoted ferroptosis in HSCs[126]
SLC25A46	–	–	Liver	Mitochondrial membrane	NASH	Inhibit	SLC25A46 affected hepatic mitochondrial fatty acid β-oxidation and lipid metabolism through the ECM2-SLC25A46-Mic19 axis[132]
SLC25A47	–	NAD+	Liver	Mitochondrial membrane	NASH	Inhibit	SLC25A47 inhibited lipid accumulation and reduced mitochondrial oxidative stress via the SIRT3-AMPKα-SREBPs pathway[129–131]
SLC27A4	FATP4	FAs	Liver	Mitochondrial membrane	NASH	Inhibit	SLC27A4 silencing in BMDM and Kupffer cells led to an increased pro-inflammatory response and induced hepatic fibrosis[143]
SLC27A5	FATP5	FAs/BAs	Liver	Cytomembrane	NASH	Inhibit	SLC27A5 downregulation was mediated by RUNX2, leading to the accumulation of hepatic unconjugated bile acids and HSCs activation through upregulation of the expression of EGR3[145]
SLC29A1	hENT1	Nucleoside	Liver	Cytomembrane	NASH	Promote	SLC29A1 silencing inhibited activation of RhoA/ROCK-1 signaling pathway[153]
SLC38A1	SNAT1	Glutamine	Liver	Cytomembrane	NAFLD	Promote	SLC38A1 upregulation mediated by HIF-2α-YAP may involve in glutamine metabolism to activate HSCs[155]
SLC39A14	ZIP14	Zinc	Liver	Cytomembrane	NAFLD	Inhibit	SLC39A14, which upregulated by MTF1, mediated zinc influx in HSCs preventing fibrosis[152]

AMPK, AMP-activated protein kinase; ASCT1, alanine, serine, cysteine transporter 1; ASCT2, alanine, serine, cysteine transporter 2; BAs, bile acids; BAT, brown adipose tissue; BMDM, bone marrow-derived macrophages; CIC, citrate/isocitrate carrier; CPT1A, carnitine palmitoyl-transferase 1A; DNL, *de novo* lipogenesis; EGR3, early growth response protein 3; EMT, epithelial-mesenchymal transition; ETC, electron transport chain; ERGO, ergothioneine; FAO, fatty acid oxidation; FAS, fatty acid synthase; FATP4, fatty acid transport protein 4; FATP5, fatty acid transport protein 5; GLUT1, glucose transporter type 1; GLUT2, glucose transporter type 2; GLUT4, glucose transporter type 4; GLUT8, glucose transporter type 8; hENT1, high human equilibrative nucleoside transporter 1; HIF1, hypoxia-inducible factor 1; HSCs, hepatic stellate cells; IL-1β, interleukin 1-beta; IR, insulin resistance; JNK, c-Jun N-terminal kinase; MCT1, monocarboxylic transporter 1; MTF1, metal-regulatory transcription factor 1; NASH, non-alcoholic steatohepatitis; NHE1, Na(+)/H(+) exchanger 1; NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3; NTCP, sodium taurocholate co-transporting polypeptide; OCT3, organic cation transporter 3; OCTN1, organic cation transporter 1; PDHE1α, pyruvate dehydrogenase E1alpha; PiC2, mitochondrial Cu+ transporter; ROS, reactive oxygen species; RUNX2, RUNX family of transcriptional repressors 2; SGLT1, sodium-glucose transporter 1; SGLT2, sodium-glucose transporter 2; SNAT1, sodium-neutral amino acid transporter 1; SUCNR1, succinate receptor 1; SVCT2, sodium-dependent vitamin C transporter 2; TGF-β1, transforming growth factor-beta 1; UCP1, uncoupling protein 1; UCP2, uncoupling protein 2; VNUT, vesicular nucleotide transporter; xCT, cystine-glutamate reverse transporter.

peutic target for diabetes, with well-documented efficacy in reversing hepatic steatosis and fibrosis.[164] A recent five-year follow-up study demonstrated that SGLT2 inhibitors significantly improved hepatic steatosis in patients with diabetes and NAFLD.[42] Mechanistically, SGLT2 inhibitors improve hepatic steatosis through multiple pathways, including the reduction of circulating inflammatory and oxidative stress conditions.[43] For example, dapagliflozin inhibits liver receptor alpha-mediated bile acid (BA) synthesis and DNL, ameliorates BA disruption-induced intestinal dysbiosis, and reduces intestinal lipid absorption.[165] Lugliflozin has been shown to reduce body weight, hepatic gluconeogenesis, and blood glucose levels, primarily improving IR and reducing lipid synthesis precursors.[44] Similarly, a prospective study observed an increased risk of hepatic fibrosis in diabetic patients, which was significantly mitigated by SGLT2 inhibitors.[166] Specifically, SGLT2 inhibitors alleviate fibrosis by improving blood sugar and lipid levels, enhancing the physiological functions of hepatocytes and HSCs, modulating intestinal flora, and facilitating vascular remodeling.[45,46] Additionally, SGLT2 inhibitors downregulate miRNA-34a-5p expression in HSCs, which increases Gremlin 2-mediated inactivation of TGF-β, resulting in impaired HSC activation. The Sirt1/AMPK/PGC1α/FoxO1 axis is also involved in the inactivation of HSCs by SGLT2 inhibitors.[47,48] Additionally, SGLT2 inhibitors reduce glucose surplus-induced O-GlcNAcylation, which decreases the expression of inflammatory and fibrosis-related genes and activates AMPK-TFEB-induced autophagic flux, preventing autophagy dysfunction that leads to abnormal lipid degradation and increased inflammatory cytokines.[49] Empagliflozin (EMPA) treatment has been shown to attenuate key fibrotic pathways, including TGF-β/TGF-βRI/Smad2 and PDGFR-β in HSCs, accompanied by decreased expression of type I collagen (Col 1A1) and extracellular matrix. EMPA treatment also attenuates the VEGF-A/VEGFR-2/Shb pathway, which induces angiogenesis in hepatic endothelial cells, improving vascular remodeling and portal hypertension. Notably, no toxic effects of EMPA on the kidneys have been observed.[50] Given the mitigating effect of SGLT2 on hepatic fibrosis and its improvement of sodium retention and solution volume redistribution *in vivo*, this represents a novel approach to cirrhosis treatment. Two additional SLC5 family members have been linked to hepatic steatosis and fibrosis. SLC5A1, which encodes SGLT1, is predominantly expressed in the intestinal epithelium and mediates glucose uptake. SGLT1 levels are higher in patients with NAFLD compared to healthy controls and correlate with the degree of hepatic fibrosis.[167] Consistently, SGLT1 inhibition ameliorates NAFLD by reducing glucose absorption and downregulating genes related to inflammation and hepatic fibrosis.[51,52] SLC5A5, encoding SGLT5, is a fructose-transporting protein expressed in the kidneys that mediates fructose reabsorption. However, a high-fructose diet-induced hepatic steatosis is exacerbated in SGLT5-deficient mice, possibly due to increased translocation of GLUT8.[53]

The SLC6 family mediates the transport of various neurotransmitters.[168] The serotonin transporter (SERT) protein, encoded by SLC6A4, is responsible for serotonin transport. In fructose-fed mice, a decrease in intestinal SERT protein leads to extracellular serotonin aggregation, resulting in transmural transport, decreased occludin expression, and increased intestinal permeability. This is followed by elevated serum endotoxin levels, ultimately triggering hepatic inflammation exacerbated by lipid accumulation. Similar effects are observed in glucose-fed and Western diet-fed mice following SERT knockout.[54,55] Additional mechanisms through which SERT exerts its effects include intestinal dysbiosis, activation of the c-Jun N-terminal kinase (JNK) pathway, IR, and increased recruitment of hepatic leukocytes.[56–58] However, one study shows that hepatic SERT expression is elevated in HFD-induced NASH mice, increasing serotonin uptake. Serotonin catabolism and oxidative stress mediate mitochondrial damage, ultimately leading to hepatocyte injury. However, SERT levels are not elevated in human samples.[59] In conclusion, the expression levels of SERT in the liver and intestine may vary during the progression of NAFLD. In systemic SERT knockout mice, intestinal SERT effects may outweigh hepatic SERT effects. Nonetheless, aberrant expression of SERT in both the intestine and liver contributes to lipid accumulation and inflammation in the liver. SLC6A14, a Na/Cl-coupled transporter for neutral/cationic amino acids, is expressed in the intestine. HFD-induced mice that undergo SLC6A14 knockout exhibit increased food intake, exacerbated hepatic steatosis with altered plasma amino acid profiles, and a greater prevalence of these effects in males, indicating a potential involvement of SLC6A14 in hepatic steatosis.[60]

SLC7/9/10/13/15

SLC7 mediated the transport of various amino acids. The cystine-glutamate reverse transporter (xCT), encoded by SLC7A11, is a cystine-glutamate antiporter that mediates the import of cysteine and export of glutamate. This is followed by the generation of glutathione and activation of glutathione peroxidase 4, which plays a critical role in protecting cells from ferroptosis.[169] Alterations in iron metabolism and lipid peroxidation during ferroptosis may be pathophysiologically related to lipid accumulation in NAFLD. Liraglutide and RBM34 have been shown to influence hepatic lipid accumulation by regulating the ferroptosis process mediated by SLC7A11.[61,62] Additionally, epigenetic regulation of SLC7A11 may impact hepatic steatosis. Previous studies have demonstrated that DNA methylation of SLC7A11 is associated with a reduced risk of hepatic steatosis in NAFLD patients, potentially through the regulation of lipid-associated genes.[63] Consistently, methylation of SLC7A11 can also promote ferroptosis and exacerbate the development of NAFLD when regulated by obesity-related protein.[64] SLC7A11 is also a key component in various pathways by which drugs and proteins regulate ferroptosis in HSCs to achieve antifibrosis. These pathways include the sorafenib-induced HIF-1α/SLC7A11 pathway, wogonoside-induced SOCS1/P53/SLC7A11 pathway, ginsenoside Rh2-induced IRF1/SLC7A11 pathway, ginsenoside Rb1-induced Beclin1/SLC7A11 pathway, and tripartite motif 26-induced ubiquitination of SLC7A11.[65–69] Interestingly, SLC7A11 also exerts an inhibitory effect on hepatic fibrosis independent of ferroptosis. Increased SLC7A11 expression has been observed in liver samples from NASH patients. Mechanistically, lipid accumulation-induced activation of the JNK-c-Jun pathway increases SLC7A11 expression in hepatocytes. SLC7A11 reduces reactive oxygen species (ROS) levels and enhances α-ketoglutarate/prolyl hydroxylase activity, activating the AMPK-mitochondrial autophagy pathway. This ultimately leads to a reduction in NOD-, LRR-, and pyrin domain-containing protein 3 inflammasome-mediated interleukin (IL) 1-beta production, preventing myeloid cell recruitment and HSC activation.[70] In summary, an SLC7A11 inhibitor seems to be a potential therapeutic target for alleviating fibrosis progression. However, it is crucial to consider that SLC7A11 expression in HSCs is significantly higher than in hepatocytes under acute liver injury conditions, making HSCs more sensitive to these inhibitors. In the context of chronic liver injury, prolonged TGF-β stimulation induces EMT in hepatocytes, enhancing their sensitivity to

SLC7A11. Administering an SLC7A11 inhibitor at this stage may not only worsen liver injury but also reduce the efficacy of the inhibitor in alleviating hepatic fibrosis.[170] Moreover, inhibition of the AGER1/SIRT4/SLC7A11 pathway in hepatocytes induces ferroptosis, promoting hepatocyte EMT.[71] Therefore, designing effective SLC7A11 inhibitors to alleviate hepatic fibrosis should prioritize specificity for HSCs to minimize hepatocyte damage. Other members of the SLC7 family also influence hepatic steatosis. Knockdown of SLC7A3 in mice or human hepatocytes reduces arginine transport, leading to decreased NO production and subsequent 3′,5′-Cyclic guanosine monophosphate synthesis. This impairs fatty acid (FA) oxidation, which is activated by AMPK-PPARα signaling, ultimately leading to lipid accumulation under fasting or glucose-starvation conditions.[171] Additionally, deletion of SLC7A8, a glutamine transporter, prevents hepatic steatosis, potentially due to improved glucose tolerance, reduced lipid accumulation, and promoted weight loss.[72]

Members of the SLC10 family are primarily involved in BA transport. Among them, SLC10A2, also known as the apical sodium-dependent bile acid transporter (ASBT), has been most extensively studied in liver diseases. ASBT is responsible for BA reabsorption in the ileum, and its inhibition prevents lipid accumulation by reducing plasma BA, altering BA properties, and enhancing insulin sensitivity.[73] Specifically, the inhibition of ASBT reduces circulating BA, leading to a decrease in ileum receptor farnesoid X receptor-activated fibroblast growth factor (FGF) 15/19. As a result, hepatic ERK and JNK signaling pathways are activated, upregulating cholesterol 7α-hydroxylase activity and enhancing hepatic cholesterol catabolism. A similar mechanism has been observed in alcohol-induced steatohepatitis.[18,74] The degree of hydrophobicity of BAs is also higher after ASBT inhibition, interfering with their ability to efficiently mediate lipid uptake, particularly of saturated fatty acids. This suggests that appropriate dietary FA composition may contribute to the role of ASBT inhibitors.[75] Volixibat, an ASBT inhibitor, has been evaluated in clinical trials for its potential to alleviate NASH, but the efficacy was unfortunately suboptimal.[172] One possible explanation is that, while ASBT inhibitors reduce intrahepatic cholesterol levels, ASBT-mediated cholesterol catabolism leads to an increase in intrahepatic BAs. A recent study using an ASBT inhibitor in combination with FGF15 supplementation in NASH mice found that the combination was more effective than either treatment alone. FGF15 reduced intrahepatic BA accumulation and inhibited the activation of cholesterol 7α-hydroxylase by ASBT, while maintaining its role in inhibiting intestinal BA reabsorption, thus ensuring cholesterol and BA homeostasis.[173] Similarly, the sodium taurocholate co-transporting polypeptide (NTCP), encoded by SLC10A1, is also involved in the uptake and homeostatic regulation of BAs, although it is predominantly expressed in the liver. In NTCP-deficient livers, reduced BA uptake from plasma led to elevated plasma BA levels without causing liver injury. This was accompanied by reduced intestinal fat absorption and increased non-coupled respiration in brown adipose tissue (BAT), which attenuated hepatic steatosis through weight loss.[76] NTCP expression has also been associated with HBV-associated hepatic fibrosis and NASH, and overexpression of NTCP in HSCs promoted BA uptake in the NASH environment, which was associated with HSC activation.[77,78]

Some members of the SLC9, SLC13, and SLC15 families have also been reported to be associated with hepatic steatosis. SLC9A1, also known as $Na^{(+)}/H^{(+)}$ exchanger 1 (NHE1), is an electrically neutral Na/H exchanger. Chronic exposure to an HFD upregulated hepatic NHE1 expression, whereas NHE1 deficiency reduced DNL and HSC activation and increased insulin sensitivity.[79] SLC13A5, the mammalian homolog of INDY (mIndy), is a citrate transporter protein. The increase in hepatic mIndy expression in NAFLD patients was mediated by the IL-6-signal transducer and activator of transcription 3 pathway, promoting increased hepatic lipogenesis.[80] Furthermore, liver-specific knockdown of mIndy prevented IR and reduced plasma and liver triacylglycerol (TAG) levels, potentially due to increased plasma β-hydroxybutyrate and AMPK activation.[81–83] SLC15A1 encodes peptide transporter 1 (PEPT1), a high-capacity, low-affinity peptide transporter responsible for the uptake of dipeptides and tripeptides in the intestine, kidney, and liver. PEPT1 knockdown was associated with weight loss and amelioration of hepatic steatosis, potentially due to a reduction in systemic IL-6 levels, leading to a lack of mucosal structures and decreased intestinal energy absorption.[84] Additionally, hepatocyte-expressed PEPT1 may facilitate the entry of specific peptides, such as fish-arginine-derived peptides, to alleviate hepatic steatosis.[174]

SLC16/17/19/22/23

SLC16 encodes the monocarboxylic transporter (MCT), which plays a critical role in the transport of essential cellular nutrients, as well as in cell metabolism and acid-base balance. SLC16A1/MCT1 mediates the influx and efflux of lactate.[175] In healthy livers, intracellular lactate content was found to be proportional to MCT1 expression levels. However, in chronic liver disease, a post-transcriptional modification-associated decrease in MCT1 content correlated with the severity of liver disease, accompanied by intrahepatic lactate accumulation, particularly in alcoholic liver disease. This suggests that post-transcriptional modification of MCT1 may be involved in the pathological processes of liver disease development.[176] In NASH mice, knockdown of MCT1 in HSCs reduced collagen-1 expression and attenuated hepatic fibrosis, while knockdown in hepatocytes had the opposite effect.[85] These findings suggest that reduced MCT1 expression in hepatocytes may significantly contribute to the accelerated progression of liver disease. The role of MCT1 in hepatic steatosis remains inconclusive. Liver-specific MCT1 deletion resulted in lactate accumulation in hepatocytes, leading to enhanced polyubiquitination-mediated degradation of peroxisome proliferator-activated receptor alpha (PPARα), resulting in decreased expression of lipid oxidation-related genes and exacerbation of HFD-induced hepatic steatosis.[86] However, another study showed that reduced lactate uptake in hepatocytes from partial MCT1 knockout mice prevented high lactate dehydrogenase B expression under HFD conditions. This reduction in lactate led to decreased pyruvate levels, affecting ATP production, increasing the AMP/ATP ratio, and activating AMPK to alleviate hepatic steatosis. Conversely, upregulation of MCT1 expression had the opposite effect.[87–89] The present study indicated that abnormalities in MCT1-mediated lactate influx and efflux may contribute to hepatic steatosis, though the specific regulatory mechanisms underlying the role of MCT1 in lactate transport remain to be elucidated. SLC16A11 and SLC16A13, members of the same family of monocarboxylic transporters as MCT1, have also been linked to susceptibility to type 2 diabetes mellitus. Hepatic expression of SLC16A11 was higher in HFD-fed mice, and its knockdown improved IR and reduced TAG accumulation in both serum and liver.[90] Similarly, SLC16A13 knockdown attenuated hepatic diacylglycerol-PKCε-mediated IR in the setting of HFD and decreased intracellular lactate availability led to increased AMPK activation and reduced hepatic lipid accumulation.[91]

The SLC22 family is distributed in tissues such as the kid-

ney and liver.[177] The proteins organic cation transporter 1 (OCTN1) and organic cation transporter 2 (OCTN2), encoded by SLC22A4 and SLC22A5, belong to the same group of carnitine transporter proteins and play a critical role in cellular metabolism. Carnitine improves mitochondrial dysfunction, reduces IR, and thus alleviates NAFLD.[178] Meta-analysis showed that carnitine supplementation improved liver function and lipid accumulation in patients with NAFLD.[92] Carnitine deficiency, resulting from the downregulation of OCTN1 and OCTN2, may reduce the transfer of long-chain fatty acids from the cytoplasm to the mitochondria, limiting their oxidation. During the progression of liver disease, OCTN1 and OCTN2 appear to serve as binding sites for various drugs that influence hepatic steatosis, such as Cynara cardunculus extract, clozapine, and olanzapine.[93–95] OCTN1 was upregulated in activated HSCs, resulting in increased delivery of its substrate, the antioxidant ergothioneine, which protected against hepatic fibrosis.[96] Other members of the SLC22 family have also been implicated in hepatic steatosis and fibrosis. SLC22A12/Urate transporter 1, a uric acid transporter, is predominantly expressed in the epithelial cells of the renal proximal tubules, where it is responsible for the reabsorption of uric acid. Elevated blood urate promotes oxidative stress and increases the production of pro-inflammatory cytokines, leading to IR and hepatocellular lipid accumulation.[179,180] Consistent with this, selective inhibitors of urate transporter 1 reduced inflammatory factors like chemokine ligand 2 and tumor necrosis factor α, as well as intracellular ROS production in hepatocytes, ameliorating hepatic steatosis and improving IR by upregulating uncoupling protein (UCP) 1 to induce the rebrowning of BAT.[97] SLC22A18 was thought to be an organic cation-transporting protein, although its physiological substrates remain unclear. Furthermore, studies have demonstrated that overexpression of SLC22A18 promoted systemic lipid accumulation in mice, including in the liver.[98,99] SLC22A3/Organic cation transporter 3 is an organic cation transporter protein, and deletion of hepatocyte organic cation transporter 3 led to the upregulation of TGF-β, resulting in fibrosis progression.[100]

The roles of SLC17, SLC19, and SLC23 in the pathogenesis of hepatic steatosis and fibrosis remain incompletely understood. SLC17A9 encodes the vesicular nucleotide transporter (VNUT) protein responsible for ATP vesicular storage.[181] VNUT-mediated vesicular ATP release promoted very low-density lipoprotein secretion in an autocrine or paracrine manner via metabotropic pyrimidine and purine nucleotide receptors 13 receptor purinergic signaling. VNUT deficiency protected against the development of inflammation and fibrosis in the context of a HFD despite TAG accumulation in the liver. Mechanistically, VNUT knockdown inhibited intercellular purinergic signaling, which reduced the progression of liver inflammation and fibrosis, accompanied by a decrease in the expression of lipolytic genes and an increase in the expression of lipolysis genes.[101] Another study demonstrated that inhibition of glucose-induced ATP release from VNUT vesicles led to decreased intracellular TAG content and secretion in hepatocytes, along with reduced hepatic inflammation and fibrosis,[102] confirming the anti-inflammatory effect of VNUT. However, whether this affected intrahepatic lipid accumulation remains to be further explored. SLC19A1 is responsible for folate transport, and low blood folate levels are associated with the progression of NAFLD. A deficiency in SLC19A1 expression in hepatocytes reduced intracellular folate levels, affecting the regulation of key lipid metabolism genes, such as fatty acid synthase and X-box binding protein 1, leading to the accumulation of lipid droplets in hepatocytes.[103] SLC23A2 is a vitamin C transporter protein. Human HSCs express only one vitamin C transporter, SLC23A2. This protein is elevated in cirrhotic livers and mediates vitamin C influx, assisting hydroxylases in promoting collagen 1 release by HSCs.[104]

SLC25

Members of the SLC25 family transport a variety of compounds across the inner mitochondrial membrane, bridging the mitochondrial matrix and cytosol.[182] The most extensively researched family within this group is the UCP family. SLC25A7/UCP1 is a mitochondrial uncoupling protein expressed in BAT and associated with non-shivering thermogenesis. The beneficial effects on hepatic steatosis were primarily achieved through weight loss. Various drugs affected UCP1 expression through different pathways to achieve weight loss. For example, magnolol and Paeonia lactiflora root increased UCP1 expression through the activation of the PPARγ signaling pathway and AMPK, respectively.[105,106] Loureirin B treatment increased the proportion of ω3 polyunsaturated fatty acids in BAT and white adipose tissue (WAT), which activated the key lipid sensor G protein-coupled receptor 120, in turn upregulating UCP1.[107] In addition, UCP1 expression was involved in the brain-nerve-lipid axis. Moderate alcohol consumption stimulated hypothalamic neural circuits and sympathetic nerves innervating BAT, which significantly increased UCP1 expression and activity in BAT. This may serve as a potential mechanism for metabolic improvement through moderate alcohol consumption.[108] Alterations in UCP1 expression in the liver and BAT were also associated with the fibrotic process. The persistent high-fat environment in advanced NAFLD downregulated UCP1 in NK cells via the PPARγ/ATF2 axis, increasing fatty acid oxidation (FAO) and exacerbating irreversible mitochondrial damage. This, in turn, promoted necrotic apoptosis in NK cells and aggravated fibrosis.[109] UCP1 also mediated the uptake of succinate from the circulation by BAT and WAT, thereby reducing extracellular succinate, which activated succinate receptor 1 in HSCs and macrophages to produce pro-inflammatory effects.[110] The mitochondrial function of SLC25A8/UCP2 is not yet fully understood. As an uncoupling protein homologue of UCP1, it reduced mitochondrial ATP and ROS production, as well as thermogenesis.[183] Polymorphisms in UCP2 and increased hepatic UCP2 expression were associated with a reduced risk of NASH.[184,185] Various drugs could enhance thermogenesis, improve fatty acid metabolism, and lipid synthesis through the AMPK-PPARα-UCP2 pathway.[111–113] Moreover, activation of the PPARα-UCP2-AMPK pathway in macrophages inhibited macrophage activation to reduce inflammation and alleviate fibrosis progression.[114] SLC25A9/UCP3 was primarily expressed in skeletal muscle and prevented lipid-induced mitochondrial damage by promoting FA export from mitochondria. Moderate overexpression of UCP3 could increase mitochondrial oxygen consumption and FAO in muscle and liver.[115,116] Polymorphisms in UCP3 were associated with NASH and IR.[117,118] A progressive increase in IR, accompanied by a gradual decrease in UCP3 levels, has been observed in HFD-fed mice. Meanwhile, Akt/PKB and AMPK signaling were blunted, and FAO was decreased in gastrocnemius muscle, similar changes are seen in alcohol-induced IR.[119,120] Thus, UCP3 may delay the progression of hepatic steatosis by regulating fatty acid metabolism and alleviating IR.

SLC25A1 and SLC25A10 were involved in the development of hepatic steatosis and fibrosis through the transport of carboxylic acids. SLC25A1 was responsible for transporting mitochondrial citrate into the cytoplasm and was highly expressed in the livers of NASH patients. SLC25A1 inhibition

decreased citrate transport and inhibited glycolysis, leading to decreased pyruvate levels. These effects worked together to reduce DNL. It also inhibited the M1 pro-inflammatory pathway as well as the expression of pro-inflammatory and pro-fibrotic genes.[121] Furthermore, SLC25A1 inhibition alleviated HFD-induced hepatic steatosis and IR by altering hepatic protein acetylation patterns. Specifically, under HFD conditions, SLC25A1 inhibition promoted FAO by deacetylating carnitine palmitoyltransferase 1A and reduced glucose oxidative catabolism by triggering the acetylation-induced inactivation of pyruvate dehydrogenase E1α, which caused enhanced glucose uptake and storage in the liver, and activated the SIRT1/PGC1α pathway to enhance oxidative phosphorylation for energy production.[186] SLC25A10, also known as the mitochondrial dicarboxylate carrier (mDIC), was a carrier of dicarboxylic acids on the mitochondrial membrane, predominantly expressed in white adipose tissue (WAT).[187] SLC25A10 mRNA levels in human WAT correlated positively with insulin sensitivity and negatively with intrahepatic TAG levels.[122] Mechanistically, mDIC mediated the influx of succinate into adipocytes, which enhanced succinate receptor 1 to inhibit lipolysis by dampening the cAMP-phosphorylated hormone-sensitive lipase pathway. mDIC deficiency led to increased lipolysis in adipocytes of HFD mice, providing non-esterified fatty acids for intrahepatic lipid synthesis and promoting DNL.[123] However, since mDIC also played a crucial role in providing malate for citrate transport required for fatty acid synthesis its deletion in hepatocytes may downregulate the lipogenic pathway.[124] This suggests that mDIC performs distinct functions in hepatocytes and adipocytes, and its effects on hepatic steatosis may be dominated by its effects in adipocytes.

SLC25A3 and SLC25A28 were implicated in the development of hepatic steatosis and fibrosis by modulating intracellular copper and iron levels, respectively, with low copper and iron being common risk factors for NAFLD. SLC25A3, a mitochondrial inner membrane carrier for inorganic phosphate (Pi) and copper, was observed to be downregulated in the livers of HFD-fed mice. This reduction in SLC25A3 expression impaired the electron transport chain by decreasing copper in mitochondria, leading to electron leakage and increased mitochondrial ROS production. Ultimately, this rendered hepatocytes more susceptible to oxidative stress and potentially facilitated NASH progression.[188] SLC25A28/Mitoferrin2 was a mitochondrial iron-translocation protein essential for hepatocyte regeneration.[189] Mitoferrin2-deficient female mice exhibited elevated hepatic TAG levels and altered hepatic lipid metabolism when exposed to a low-iron diet, suggesting that Mitoferrin2-mediated intrahepatic iron homeostasis plays an important role in lipid metabolism.[125] Additionally, Mitoferrin2-mediated iron transfer was implicated in the pathogenesis of fibrosis by influencing ferroptosis. The elevated expression of bromodomain-containing protein 7 in response to ferroptosis inducers promoted mitochondrial translocation of p53 by directly binding to it, which interacted with SLC25A28 to form a complex that enhanced SLC25A28 activity. This resulted in the aberrant accumulation of redox-activated iron and hyperfunction of the electron transport chain, ultimately promoting ferroptosis in HSCs.[126]

SLC25A5 and SLC25A47 were involved in the development of hepatic steatosis and fibrosis through nucleotide transport. SLC25A5 is a mitochondrial ATP transporter protein that facilitates the exchange of adenosine diphosphate and ATP across the inner mitochondrial membrane. Liver-specific SLC25A5 deficiency increased uncoupled respiration and prevented the development of steatosis and IR in mice.[127] Its role in alcohol-induced fatty liver disease was similar. Alcohol administration triggered global protein lysine β-hydroxybutyrylation (hereinafter referred to as Kbhb) in the liver. Two modifications of SLC25A5 Kbhb, mediated by 3-hydroxy-3-methylglutaryl-coenzyme A synthase 2, prevented SLC25A5 degradation by ubiquitin proteases. The stabilization of SLC25A5 facilitated steatosis via the MAPK/Erk/PPARγ axis under chronic alcohol exposure.[128] SLC25A47 was a hepatocyte-specific mitochondrial carrier that transported NAD+. SLC25A47 mediated the increase of mitochondrial NAD+, activating sirtuin 3 (SIRT3) protein activity, and inhibited lipid accumulation via the SIRT3-AMPKα-SREBPs pathway.[129] Upon activation of SIRT3, hepatocyte mitochondrial oxidative stress was reduced, and mitochondrial dysfunction was alleviated, which reduced hepatocyte apoptosis and alleviated hepatic fibrosis.[130] Similarly, the deletion of SLC25A47 impaired hepatocyte mitochondrial function due to an inability of the mitochondria to cope with the additional metabolic stress induced by high-fat/high-sucrose feeding. This ultimately led to the development of NASH.[131]

The loss of function of SLC25A46, an outer mitochondrial membrane protein, led to alterations in mitochondrial lipid composition and may play a role in membrane remodeling associated with mitochondrial fusion and fission.[190] SLC25A46 was involved in endoplasmic reticulum-mitochondrial contacts through the ECM2-SLC25A46-Mic19 axis. Abnormalities in this pathway resulted in impaired mitochondrial phospholipid metabolism, disrupted mitochondrial membrane organization, and affected hepatic mitochondrial fatty acid β-oxidation and lipid metabolism, potentially contributing to the development of hepatic fibrosis.[132]

SLC27/29/31/35/37/38/39/43

The FATP family, encoded by SLC27, is responsible for fatty acid transport, with some members also exhibiting acyl-CoA synthase activity, playing important roles in metabolic diseases.[191] SLC27A1/Fatty acid transport protein 1 is mainly expressed in adipocytes and skeletal muscle tissues, and its loss of function leads to the redistribution of lipids from adipose and muscle tissues to the liver.[133] SLC27A2/Fatty acid transport protein 2 (FATP2) is mainly expressed in the liver and can reduce hepatic lipid accumulation when inhibited. Transmembrane 4 L six family member 5, murine CYP (Cyp2c44), and Forkhead box protein A1 all mitigate hepatic lipid accumulation by downregulating FATP2 expression or interfering with FATP2 translocation.[134–136] Hepatitis B virus X and N-Acetyltransferase-like protein 10 can promote hepatic lipid accumulation by upregulating FATP2 expression or promoting FATP2 stability.[137,138] SLC27A4/Fatty acid transport protein 4 (FATP4) is widely distributed *in vivo*, functioning as an acyl-CoA synthetase on organelle membranes but is relatively poorly expressed in hepatocytes.[192] FATP4 may play a key role in mitochondrial β-oxidation and mediates the transport of fatty acids from lipid droplets to mitochondria for β-oxidation during starvation in myofibroblasts. Conversely, the deletion of FATP4 in hepatocytes decreases β-oxidation and increases fatty acid synthesis and uptake, ultimately elevating hepatocyte and plasma TAG levels.[139,140] Another study found that FATP4 expression was elevated in the livers of NASH mice. Additionally, cells that overexpress FATP4 can increase acyl-CoA synthetase activity in response to palmitate stimulation for β-oxidation, elongation, and desaturation of FAs, as well as synthesis of neutral lipids, sphingolipids, and phospholipids. This results in hepatocellular steatosis, endoplasmic reticulum structural damage due to phospholipid composition changes, and activation of the Bax and JNK/PUMA pathways, which increases

TAG levels in hepatocytes and plasma. Furthermore, downregulation of FATP4 in hepatocytes and adipocytes mediates the protective effects of vitamin D and exercise on obesity and HFD-induced hepatic steatosis.[141,142] FATP4 influences both lipid synthesis and catabolism, with its stable expression being crucial for hepatocyte lipid homeostasis. Additionally, the deletion of FATP4 in bone marrow-derived macrophages and Kupffer cells leads to an increased proinflammatory response and induces hepatic fibrosis in HFD-fed female mutants.[143] SLC27A5/Fatty acid transport protein 5 (FATP5) is associated with BA homeostasis in the liver in addition to fatty acid transport.[193] Knockdown of FATP5 can reverse NAFLD and significantly improve systemic glucose homeostasis.[144] However, reduced hepatic FATP5 expression in NAFLD patients is associated with histologic progression and may contribute to lipid reduction during the progression of NASH to cirrhosis.[194] The possible explanation is that downregulation of FATP5 is mediated by the RUNX family of transcriptional repressors 2, which increases the accumulation of hepatic unconjugated bile acids, especially cholic acid, leading to HSC activation through upregulation of the expression of early growth response protein 3.[145]

SLC31A1 and SLC39A14 influence the development of hepatic steatosis and fibrosis by regulating intracellular metal ion levels. SLC31A1 is a copper-specific transport protein located in the parietal membrane of enterocytes. High-fat-sugar diet inhibited SLC31A1-mediated copper uptake through the intestinal epithelium, leading to blood copper deficiency followed by hepatic copper reduction. This reduction decreased β-oxidation, increased DNL, and contributed to IR. Additionally, hepatic iron overload caused by copper deficiency led to mitochondrial dysfunction and inhibition of antioxidant defenses.[146,147] Blood copper levels also predicted the risk of cardiovascular diseases in NAFLD patients.[195] SLC39A14 (also known as Zrt- and Irt-like protein 14, or ZIP14) is a zinc transporter protein highly expressed in both the intestine and liver. It plays a critical role in regulating manganese and iron homeostasis.[196,197] ZIP14 is upregulated during endoplasmic reticulum stress, where it reduces endoplasmic reticulum stress-induced hepatic steatosis and apoptosis. Mechanistically, the unfolded protein response activates transcription factors ATF4 and ATF6, leading to upregulation of ZIP14 and subsequent zinc influx. This process decreases protein-tyrosine phosphatase 1B activity, which affects the pro-apoptotic p-eIF2α/ATF4/CHOP pathway and DNL, offering protection against endoplasmic reticulum stress.[148] ZIP14-mediated zinc influx also directly influences the activity of PPARγ and insulin receptors, thereby regulating hepatic lipogenesis.[149,150] In addition, ZIP4 may be less induced by long-term HFD, leading to iron deficiency and thus lipid accumulation in hepatocytes.[151] Low zinc levels were associated with an increased risk of hepatic fibrosis, and consistent with this, ZnCl2 treatment could ameliorate hepatic fibrosis by increasing intracellular zinc levels through metal-regulatory transcription factor 1-mediated upregulation of ZIP14 and inhibition of histone deacetylase 4 in combination with ZIP14.[152]

Other SLC family members may also play a role in hepatic steatosis and fibrosis, although reports on them are fewer. SLC29A1 is a nucleoside transporter protein, and miR-126b mimics may alleviate hepatic fibrosis in rats by inhibiting the activation of the RhoA/ROCK-1 signaling pathway through decreased expression of SLC29A1.[153] SLC35A1 encoded a cytidine-5′-monophosphate-sialic acid transporter that mediates the transport of cytidine-5′-monophosphate-sialic acid between the cytoplasm and the Golgi apparatus for protein sialylation. A deficiency in SLC35A1 in liver sinusoidal endothelial cells (LSECs) results in excessive neonatal hepatic lipid deposition and severe hepatic injury. In SLC35A1-deficient mice, vascular endothelial growth factor receptor 2 in LSECs was desialylated, resulting in enhanced vascular endothelial growth factor receptor 2 signaling, which disrupted LSEC recognition and hepatic compartmentalization. This suggests that SLC35A1 plays an important role in maintaining hepatic lipid homeostasis in neonatal mice.[154] SLC38A1 mediates glutamine uptake, and upregulation of HIF-2α inhibited Yes-associated protein phosphorylation in HSCs, leading to the overexpression of enzymes related to glutamine metabolism, including SLC38A1. This enhanced glutamine metabolism and activated HSCs.[19,155] Although the expression level of SLC38A1 in human fibrotic liver remains unclear, it is reasonable to speculate that overexpression of SLC38A1 promoting glutamine uptake might be beneficial for fibrosis progression. Polymorphisms in SLC37A3, SLC38A8, and SLC39A8 have been implicated in NAFLD progression, but their specific regulatory mechanisms in fibrosis progression have yet to be fully clarified.[198–200] SLC43A3 seems to regulate the flux of FAs in adipocytes, functioning as a positive regulator of FA efflux and a negative regulator of FA uptake. Therefore, overexpression of SLC43A3 may be beneficial for FA clearance in hepatocytes.[156]

Future perspectives

As the structure and function of SLC family molecules continue to be elucidated, an increasing number of members have been identified as being involved in the development of hepatic steatosis and fibrosis. Among these, the SLC2, SLC5, SLC7, and SLC25 families are better understood and have been shown to influence hepatocyte and HSC function by mediating saccharide or FA transport and regulating ferroptosis or mitochondrial function. Other SLC family members are also implicated in the development of steatosis or fibrosis through the transport of BAs, metal ions, serotonin, amino acids, carboxylic acids, and nucleotides. However, the specific regulatory mechanisms of these molecules remain to be fully elucidated. Additionally, certain transporters, such as GLUT2, SERT, mDIC, and MCT1, may exhibit distinct patterns depending on the conditions, leading to seemingly contradictory roles in hepatic steatosis and fibrosis. It is likely that these molecules may have different functions at various sites or in different environments. Consequently, it is essential to elucidate the regulatory conditions governing these diverse functions. In future research, we anticipate utilizing a greater number of preclinical models, including organoids, which more closely resemble the actual human environment. These models can simulate the structure and function of these molecules in various states and investigate potential mechanisms, such as epigenetic modifications and stereostructural changes in different environments. The SLC family has considerable potential as therapeutic targets for NAFLD and NASH. However, purifying SLC molecules is difficult due to their structural complexity. Moreover, the fact that their intracellular and extracellular domains are regulated by different post-translational modifications adds to the challenge. Additionally, the structure of SLC molecules is influenced by the surrounding cellular environment. Thus, studies on the structure of SLC molecules must integrate an understanding of the cellular and organismal context. Furthermore, more research should focus on the expression and modification of these molecules in human samples to confirm their expression in extrahepatic tissues and ensure that targeted drugs do not affect other organs. It is anticipated that the utilization of advanced bioinformatics and

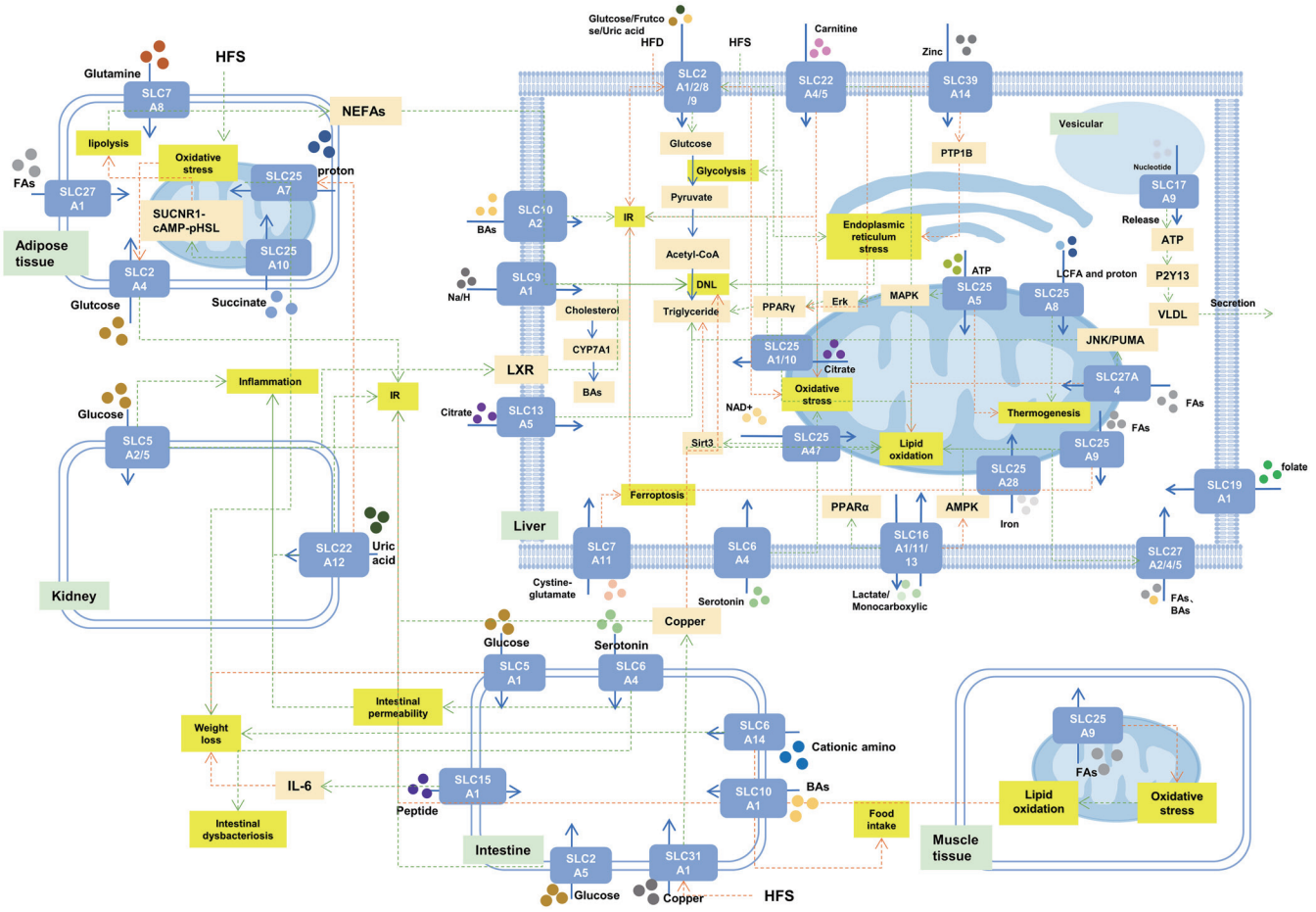

Fig. 1. The role of the SLC family in hepatic steatosis. The blue rectangle represents cells in different tissues, the orange box represents key molecules, the process described in the yellow box is the key process affecting hepatic steatosis, the green arrow represents promotion/up-regulation, and the orange arrow represents inhibition/down-regulation. SLC2/5/27 are distributed across the intestine, kidney, adipose tissue, and liver. They regulate sugar transport, affect insulin sensitivity, and influence fat synthesis by decreasing its precursors, along with hepatic fatty acid transport, which is directly or indirectly regulated by SLC25A8/9. SLC7A11 is primarily found in the liver, where it regulates ferroptosis and influences lipid metabolism. SLC6A14, SLC7A8, SLC10, SLC15A1, and SLC25A7/8 are distributed in the intestine, adipose tissue, and liver, where they regulate bile acid transport, adipose tissue thermogenesis, and intestinal absorption, collectively contributing to weight reduction. SLC13A5, SLC16, and SLC25A5/9 are found in the liver, where they primarily regulate IR. SLC17A9 is located in vesicles and influences the release of VLDL in hepatocytes. SLC19A1 and SLC25A28 are located in the liver and primarily affect the expression of lipid metabolism genes. SLC22A4/5 are also distributed in the liver, where they primarily influence lipolysis through the transport of carnitine. SLC6A4, SLC22A12, and SLC25A47 are found in the liver and kidney, where they regulate hepatic inflammation. SLC9A1, SLC25A1, SLC31A1, and SLC39A14 are distributed in both the liver and intestine and are involved in reducing DNL in the liver. SLC25A10 is located in adipose tissue, where it regulates lipolysis and influences DNL through the regulation of NEFAs. AMPK,AMP-activated protein kinase; ATP, adenosine triphosphate; BAs, bile acids; CYP7A1, cholesterol 7α-hydroxylase; FAs, fatty acids; HFD, high-fat diet; HFS, high fructose diet; P2Y13, purine nucleotide receptors 13; PPARα, peroxisome proliferator-activated receptor alpha; PTP1B, protein-tyrosine phosphatase 1B; LCFA, long-chain fatty acid; LXR, liver receptor; VLDL, very low density lipoprotein; IR, insulin resistance; DNL, *de novo* lipogenesis; NEFAs, non-esterified fatty acids.

imaging techniques, coupled with increased interdisciplinary collaboration, will facilitate a more comprehensive understanding of SLC molecules. Despite numerous obstacles to clinical implementation, some drugs, such as SGLT2 inhibitors and ASBT inhibitors, have already been developed. SGLT2 inhibitors have shown significant potential in inhibiting the progression of NAFLD and NASH.[17,42,166,201] However, clinical studies of SGLT2 inhibitors have been limited to patients with diabetes and NAFLD or NASH, necessitating large, high-quality, randomized controlled trials to explore their effectiveness in all patients with NAFLD or NASH. Additionally, the current maximum follow-up period of five years highlights the need for further investigation into the long-term effects of SGLT2 inhibitors, as well as the optimal dose and duration for treating steatohepatitis in diverse populations or in patients with varying degrees of severity. There is also the possibility that SGLT2 inhibitors could be employed in the treatment of cirrhosis. ASBT inhibitors have also been developed to alleviate steatohepatitis, but their efficacy has been limited.

Conclusions

In summary, SLC family molecules play a crucial role in the development of hepatic steatosis and fibrosis (Figs. 1 and 2). Therefore, further research into the underlying mechanisms and corresponding SLC molecular structures is necessary to develop safe and effective targeted therapies.

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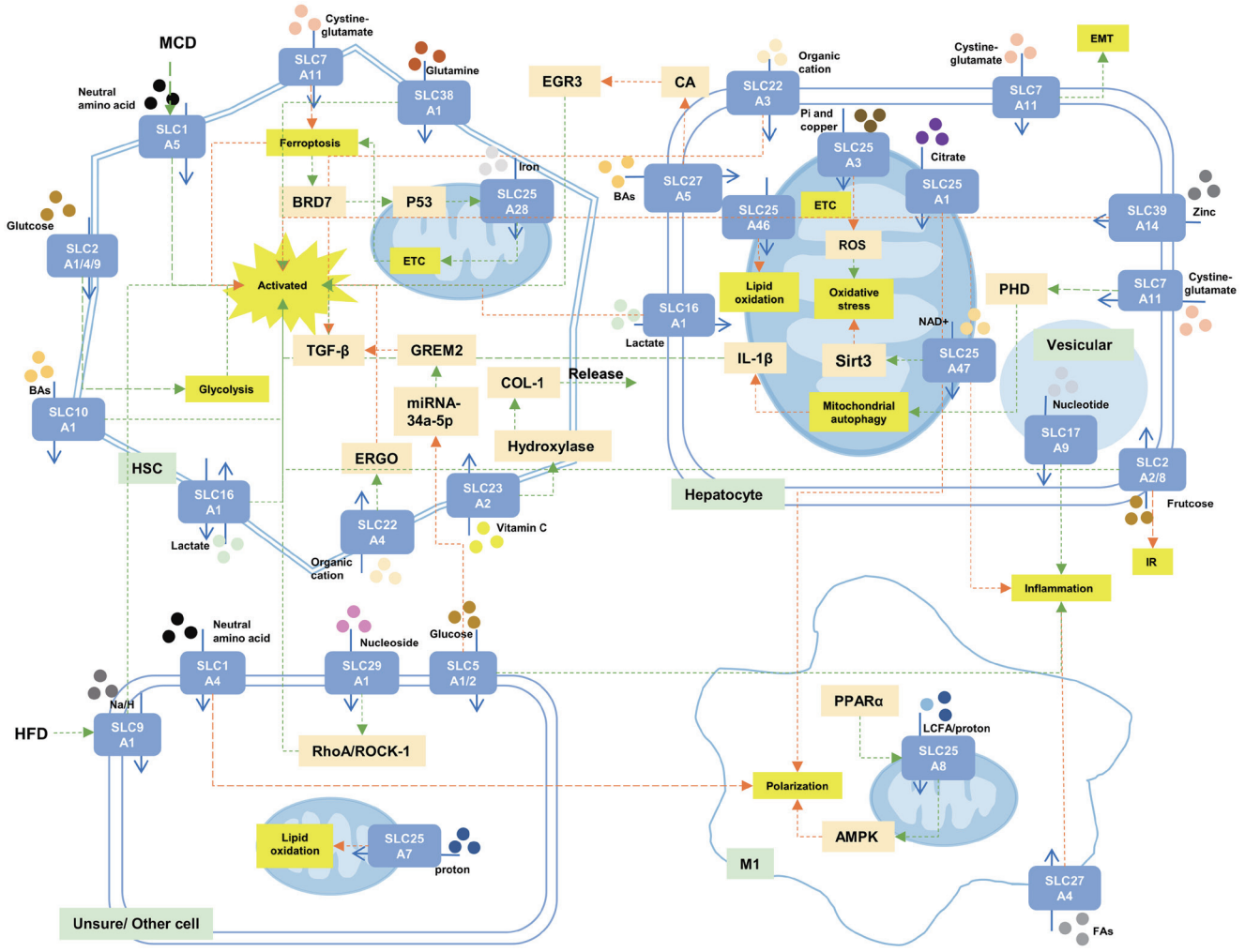

Fig. 2. The role of the SLC family in hepatic fibrosis. The blue polygon represents different cells, the orange box represents key molecules, the process described in the yellow box is the key process affecting hepatic fibrosis, the green arrow represents promotion/up-regulation, and the orange arrow represents inhibition/down-regulation. SLC1A5, SLC2A1/4/9, SLC9A1, SLC10A1, SLC16A1, SLC27A5, SLC38A1, and SLC39A14 are distributed in the kidney and liver, and they influence hepatic stellate cell (HSC) activation through multiple pathways. SLC22A3/4 and SLC5A1/2 influence HSC activation through the regulation of TGF-β. SLC23A2 in HSCs promotes the release of COL-1. SLC1A4, SLC25A1, and SLC25A8 affect macrophage polarization. SLC2A2 modulates insulin sensitivity, while SLC5A1, SLC17A9, and SLC27A4 are distributed in the intestine and liver and are associated with hepatic inflammation. SLC7A11 regulates the ferroptosis of HSCs, as well as the EMT of hepatocytes. SLC25A3/7/46/47 are distributed in the intestine and liver, and they affect mitochondrial function. SLC25A28 promotes the ferroptosis of HSCs. AMPK, AMP-activated protein kinase; BAs, bile acids; CA,COL-1,EGR3, early growth response protein 3; ERGO, ergothioneine; ETC, electron transport chain; GREM2, Gremlin-2; HFD, high-fat diet; IR, insulin resistance; LCFA, long-chain fatty acid; M1, M1 macrophage; MCD, methionine- and choline-deficient diet; PPARα,peroxisome proliferator-activated receptor alpha; ROS, reactive oxygen species; TGF-β, transforming growth factor-beta; EMT, epithelial-mesenchymal transition.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Literature analysis and conceptualization (CZh, XY, YX), original draft preparation and writing (CZh, HL), review, and supervision (CZe, MC). CZh and XY have equally important contributions to the article. All authors have read and agreed to the published version of the manuscript.

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