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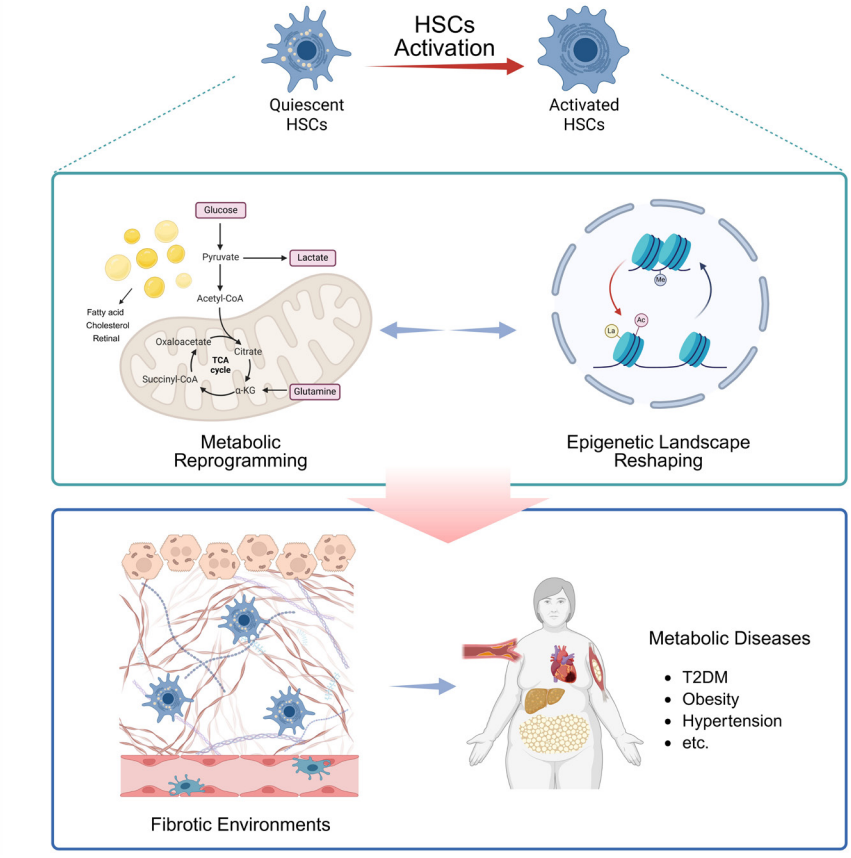

Highlights

- **HSC activation involves coordinated metabolic and epigenetic reprogramming.**
- **Altered fuel metabolism induces major metabolic shifts in HSCs.**
- **These shifts alter the epigenetic landscape via histone, DNA, and transcription changes.**
- **Metabolic-epigenetic changes trigger HSC activation and fibrosis-linked diseases.**

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Metabolic Sparks in the Liver: Metabolic and Epigenetic Reprogramming in Hepatic Stellate Cells Activation and Its Implications for Human Metabolic Diseases

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The liver plays a fundamental role in metabolic homeostasis, integrating systemic fuel utilization with the progression of various metabolic diseases. Hepatic stellate cells (HSCs) are a key nonparenchymal cell type in the liver, which is essential for maintaining hepatic architecture in their quiescent state. However, upon chronic liver injury or metabolic stress, HSCs become activated, leading to excessive extracellular matrix deposition and pro-fibrotic signaling, ultimately positioning them as key players in liver pathology. Emerging evidence highlights the critical roles of metabolic reprogramming and epigenetic regulation in HSCs activation. HSCs activation is driven by both intrinsic fuel metabolism reprogramming and extrinsic metabolic cues from the microenvironment, while the metabolic intermediates actively reshape the epigenetic landscape, reinforcing fibrogenic transcriptional programs. In this review, we summarize recent advances in understanding how metabolic and epigenetic alterations drive HSCs activation, thereby shaping transcriptional programs that sustain fibrosis, and discuss potential therapeutic strategies to target these interconnected pathways in human metabolic diseases.

Keywords: Epigenomics; Hepatic stellate cells; Metabolic diseases; Metabolic reprogramming

INTRODUCTION

The liver plays central roles in systemic homeostasis by regulating fuel utilization, detoxification, bile production, and immune function. Its functional relevance in these processes closely links it to various endocrine and metabolic diseases [1], including metabolic dysfunction-associated fatty liver disease (MAFLD), diabetes, obesity, chronic kidney disease, and cardiovascular diseases.

Among them, MAFLD stands out as a key player, serving as a critical link between metabolic disorders and liver pathology. This condition displays a progressive spectrum, where liver dysfunction and metabolic imbalances fuel disease advancement as MAFLD progresses, liver fibrosis, characterized by excessive extracellular matrix (ECM) accumulation and impaired regenerative capacity, marks as a decisive and irreversible turning point, ultimately leading to significant hepatic dysfunction, and lasting functional impairment. Given its central roles in disease progression, unraveling the mechanisms underlying the pathogenesis of liver fibrosis and developing precise and targeted therapeutic strategies remain essential.

Hepatic stellate cells (HSCs) are key mediators of liver fibrosis. Under normal condition, HSCs resides in the space of Disse, surrounding hepatocytes, and primarily exists in as quiescent HSCs (qHSCs), which play a systemic role in the storage and metabolic regulation of lipids and vitamin A. qHSCs are also essential for maintaining liver homeostasis by interacting with other hepatic cells through various cytokines, chemokines, and growth factors. For instance, qHSCs-derived hepatocyte growth factor modulates Kupffer cell activity by attenu-

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ating inflammatory responses, and promotes liver tissue repair [2]. In addition, qHSCs regulate ECM turnover by secreting matrix metalloproteinases which degrade excess ECM and counteract fibrogenic signaling, thereby preventing ECM accumulation and maintaining the liver microenvironment [3].

In response to liver injury, HSCs undergo activation (aHSCs), transitioning from a quiescent to a pro-fibrotic phenotype, a process essential for tissue repair and characterized by increased proliferation, lipid droplet (LD) depletion and enhanced ECM production. However, under condition of chronic liver damage, inflammation, or metabolic imbalance, aHSCs transdifferentiate into myofibroblastic HSCs (mHSCs), which exhibit abberant ECM production and enhanced pro-fibrotic activity, ultimately leading to fibrosis. This phenotypic transition is tightly regulated by a complex network of cytokines, growth factors, and metabolic adaptations, which collectively drive fibrogenic activity.

Recently, the roles of metabolic reprogramming in HSCs activation have gained considerable attention, revealing its impact beyond its traditional bioenergetic function. In this context, alteration of fuel metabolism—such as glycolytic adaptation, glutaminolysis, lipid metabolism, and mitochondrial remodeling—are being actively uncovered [4,5]. Moreoever, emerging evidence underscores the intricate interplay between metabolic changes and epigenetic modifications, where metabolic changes actively remodel epigenetic landscapes, reinforcing fibrogenic gene expression through a positive feedback loop. This metabolism-epigenetics crosstalk has emerged as a key regulatory axis in HSCs activation, influencing signaling pathways beyond direct metabolic adaptation.

In this paper, we aim to provide a comprehensive overview of metabolic alteration occurred during HSCs activation, the relevant epigenetic reprogramming driven by these metabolic changes. Furthermore, we will discuss potential therapeutic strategies for targeting these processes, with a particular focus on precise and targeted approaches to disrupt the fibrogenic cascade, thereby mitigating progression of various metabolic diseases and its complications.

METABOLIC REPROGRAMMING ASSOCIATED WITH HSC ACTIVATION

Metabolic reprogramming is widely recognized as a critical driver of HSCs activation and consequent liver fibrosis progression. Accumulating evidence has revealed the pivotal role of altered fuel metabolism in orchestrating the phenotypic transition of qHSCs to aHSCs. This section discusses a thorough overview of the metabolic reprogramming observed in essential fuel metabolism during HSC activation (Fig. 1).

Glucose metabolism

Glucose metabolism serves a fundamental fuel source for virtually all cell types and organisms on earth, integrating various anabolic and catabolic pathways to maintain cellular homeostasis. As a central metabolic hub, glycolysis breaks down glucose to produce adenosine triphosphate (ATP), and provide essential intermediates for biosynthetic processes, including nucleotide, amino acid, and lipid synthesis. Under homeostatic condition, qHSCs primarily rely on oxidative phosphorylation to maintain energy homeostasis. However, upon activation, they undergo a metabolic switch to aerobic glycolysis, a shift that provides both rapid energy production and biosynthetic support for proliferation and ECM production. This metabolic adaption characterized by increased glucose uptake and its conversion to lactate, even in the presence of oxygen is a hallmark of the Warburg effect, a phenomenon primarily observed in cancer cells.

The glycolytic reprogramming of HSCs is driven by coordinated transcriptional and metabolic events. Primarily, transcriptional activation of glucose transporters (GLUTs), including GLUT1, GLUT2, and GLUT4 significantly increase glucose uptake [6,7]. Expression of key rate limiting enzymes, such as hexokinase 2 (HK2) and pyruvate kinase M2 (PKM2), is also significantly upregulated, contributing to the enhanced glycolytic flux [8]. In contrast, gluconeogenic enzymes including phosphoenolpyruvate carboxykinase (PCK1) and fructose bisphosphatase (FBP1) are downregulated, thereby reinforcing the glycolytic phenotype.

Reprogramming of glucose metabolism also include various signaling pathways. For example, Hedgehog (Hh) signaling through Gli and leptin converge upon the transcription factor hypoxia-inducible factor 1α (HIF-1α), a master regulator of metabolic changes, upregulating expression of GLUTs and glycolytic enzymes.

Additionally, platelet-derived growth factor (PDGF) upregulates the phosphoinositide 3-kinase (PI3K)-protein kinase B (Akt)-mechanistic target of rapamycin (mTOR) signaling cascade, thereby enhancing the expression of key glycolytic enzymes, including GLUT1 and PKM2. Notably, PDGF activation of glycolytic flux is further amplified by the production of

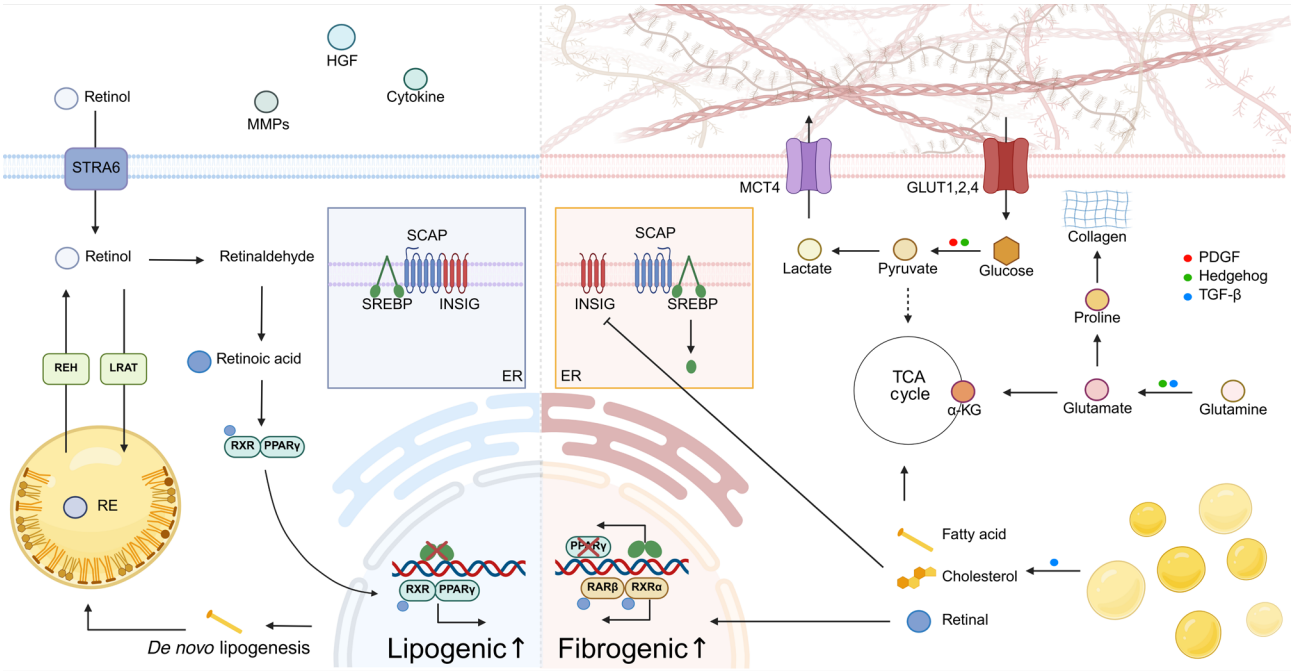

Fig. 1. Metabolic changes and fuel utilization in hepatic stellate cells (HSCs) activation. Quiescent HSCs play a crucial role in storing lipids and vitamins through the regulation of peroxisome proliferator-activated receptor gamma (PPARγ) and sterol regulatory element-binding protein (SREBP). During the activation into activation HSC, various signals, such as transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF), trigger metabolic changes to provide the energy and metabolic intermediates required for fibrogenesis. Key characteristics of this process include enhanced aerobic glycolysis, glutaminolysis, and lipolysis. Each signal is marked with a dot on the arrows where it induces metabolic changes. HGF, hepatocyte growth factor; MMP, matrix metalloproteinase; STRA6, stimulated by retinoic acid gene 6; REH, retinyl ester hydrolase; LRAT, lecithin retinol acyltransferase; SCAP, SREBP cleavage-activating protein; INSIG, insulin-induced gene; ER, endoplasmic reticulum; RE, retinyl esters; RXR, retinoid X receptor; MCT, monocarboxylate transporter; GLUT, glucose transporter; TCA, tricarboxylic acid; α-KG, α-ketoglutarate; RARβ, retinoic acid receptor β.

Extracellular vesicles (EV) containing glycolysis-related enzymes, such as GLUT1 and PKM2, which transfers to other qHSCs. These transferred EVs ultimately modulate the glucose metabolism and promoting activation [9], thereby contributing to the heterogeneity of HSCs activation between the pericentral and periportal regions.

Lactate, the main product of glycolysis catalyzed by lactate dehydrogenase (LDH), may also play a significant role in HSCs activation. In aHSCs, the high glycolytic flux leads to lactate accumulation, and the lactate stabilizes HIF-1α by inhibiting prolyl hydroxylases, creating a feed-forward loop that sustains glycolytic flux [10]. Additionally, lactate can be exported via monocarboxylate transporter 4 (MCT4), establishing an acidic niche that promotes pro-fibrotic M2 macrophage polarization by inducing α-ketoglutarate (α-KG) production [10].

Glutamine metabolism

Glutamine is an amino acid that serves as a critical metabolic substrate in various cellular processes, including energy production, nucleotide biosynthesis, and redox homeostasis. In rapidly proliferating cells, glutamine metabolism plays key roles in sustaining anabolic and bioenergetic demands.

In aHSCs, glutaminolysis, the conversion of glutamine to α-KG, is significantly elevated [11]. The accumulation of α-KG as a product of the increased glutaminolysis, supports proliferation and fibrogenic activity by serving as a fuel for the tricarboxylic acid (TCA) cycle, particularly when glucose is predominantly utilized for aerobic glycolysis.

Glutamine uptake in HSCs is primarily mediated by the solute carrier family 1 member 5 (SLC1A5) transporter, whose expression increases during activation [12]. Once inside the cell, glutamine is converted to glutamate, catalyzed by glutaminase

(GLS), the rate limiting step of glutaminolysis. Glutamate is then further processed by glutamate dehydrogenase (GLUD1) or transaminases (GOT1/GOT2) and converted to α-KG, which enters the TCA cycle. aHSCs exhibit upregulated expressions of GLS, GLUD1, and GOT1/2 at both mRNA and protein levels, correlating with increased α-KG flux. Several signaling pathways act as upstream regulators of the glutaminolysis in this context. For example, Yes-associated protein 1 (YAP)/WW-domain-containing transcription regulator 1 (TAZ), which mediates cell proliferation and apoptosis, promotes the transcription of glutaminolytic enzymes, including GLS and GOT1, by binding to transcriptional enhanced associated domain (TEAD) family proteins [13,14]. Hh signaling cooperates with YAP to amplify glutaminolytic flux. When the Hh pathway is activated, its downstream smoothened (SMO) facilitates the expression and nuclear localization of YAP [14,15]. This activation promotes the transcription of YAP target genes, thereby reinforcing the glutaminolytic phenotype of activated HSCs. Blocking Hh-YAP axis has been shown to prevent liver fibrosis; genetic ablation of YAP or pharmacological inhibition (e.g., verteporfin) reduces glutamine uptake and α-KG levels, impairing HSCs proliferation [16]. In murine models, Hh inhibition (e.g., cyclopamine) or HSCs specific SMO knockout attenuates GLS activity and fibrosis progression [15,17,18]. However, some studies have reported contradictory findings where dimethyl α-ketoglutarate, a cell-permeable ester form of α-KG, displays inhibitory effects on fibrosis and autophagy in HSCs [19,20]. One possible explanation is that extracellular α-KG plays distinct roles compared to intracellular α-KG.

Glutamine can also serve as a precursor for proline synthesis, contributing to the production of collagen, a major component of the ECM in liver fibrosis [21,22]. The increased glutamine conversion to proline supports the fibrogenic activity of HSCs. Additionally, the downregulation of proline oxidase (POX) expression during HSCs activation may lead to an accumulation of free proline, further reinforcing collagen synthesis and deposition [23].

Lipid and vitamin A metabolism

qHSCs account for approximately 80% to 90% of vitamin A storage and regulation in the body, serving as the primary systemic reservoir of vitamin A [24]. Vitamin A is not merely stored in HSCs, it actively participate in maintaining HSCs quiescence [25-27].

Vitamin A, in the form of retinoids conjugated to retinol-binding protein, is transported into HSCs through stimulated by retinoic acid gene 6. Once internalized, lecithin retinol acyltransferase (LRAT) esterifies retinoids with fatty acid to form retinyl esters (RE), which are subsequently stored in LDs [28]. In addition to RE, LDs contain triglycerides and cholesterol esters serving as energy reservoirs [29,30]. These droplets are highly dynamic organelles, with their composition and turnover closely linked to HSCs activation. Upon activation, HSCs lose their LDs, consequently their stored vitamin A, leading to enhanced fibrogenic activity; LDs are mobilized and transported to autophagosomes, where they undergo lipophagy, a selective form of autophagy that degrades LDs to release free fatty acids (FFAs) and free cholesterol [31-34]. The protein autophagy-related gene 7 (ATG7) plays a crucial role in this process by facilitating the formation of autophagosomes [35]. Once released, the FFAs are transported to mitochondria, where they undergo β-oxidation to generate ATP, providing the energy required for HSCs proliferation and ECM production. In this context, β-oxidation, a metabolic pathway that integrates long chain fatty acid (LCFA) into mitochondrial metabolism, is upregulated in aHSCs reinforcing the metabolic shift from lipid storage to energy production, thereby supporting fibrosis as an energy-intensive processes. Additionally, retinyl ester hydrolase (REH) promotes the breakdown of fatty acids bound to REs, regenerating retinol. Retinol is further catabolized into retinoic acid (RA), a bioactive metabolite of vitamin A that acts as a signaling molecule to maintain the quiescent phenotype of HSCs [36,37]. Retinoic acid receptors (RAR) and retinoid X receptors (RXR) are nuclear receptors activated by retinoids and play significant roles in suppressing fibrogenic genes [38,39].

Elevated free cholesterol levels contribute to HSCs activation by enhancing the expression of toll-like receptor 4 (TLR4), a pattern recognition receptor that increases the cells sensitivity to transforming growth factor-beta (TGF-β), a key cytokine that drives fibrogenesis [40]. This heightened sensitivity amplifies HSCs responses to fibrogenic stimuli, leading to ECM deposition and tissue remodeling. Cholesterol accumulation in HSCs is also regulated by low-density lipoprotein receptor (LDLR), which facilitates cholesterol uptake of cholesterol from circulating low-density lipoproteins (LDL), and miR-33a, a microRNA that modulates cholesterol homeostasis by suppressing cholesterol efflux [41]. Furthermore, oxidized LDL (oxLDL), a modified form of LDL, has been shown to induce HSCs activation through Wnt signaling pathway, further reinforcing fibrogenesis [42]. OxLDL also binds to scavenger re-

ceptors on the HSCs surface, triggering intracellular signaling cascades that upregulate fibrogenic gene expression and enhance collagen production [43]. Targeting cholesterol metabolism in HSCs may represent a promising therapeutic approach for targeting liver fibrosis [44]. This is further supported by interesting observations showing that inhibition of acyl-CoA: cholesterol acyltransferase 1 (ACAT1), an enzyme responsible for the esterification of free cholesterol, mitigates free cholesterol accumulation in HSCs, thereby suppressing fibrotic progression [45].

Two major transcription factors are known to regulate lipid metabolism in qHSCs; peroxisome proliferator-activated receptor gamma (PPAR-γ) and sterol regulatory element-binding protein 1 (SREBP1) [46,47]. PPAR-γ is activated with its specific ligands such as fatty acids, eicosanoids and functions as heterodimer with RXR [38]. This heterodimer complex translocates to the nucleus and upregulates fat storage gene expression by binding to the peroxisome proliferator-responsive element sequence. SREBP is a master regulator of fatty acid and lipid synthesis. Under normal condition, SREBP remains in an inactive state in the endoplasmic reticulum (ER) membrane, bound to SREBP cleavage-activating protein (SCAP) and insulin-induced gene (INSIG), which acts as lipid sensors. However, when intracellular levels of fatty acids and cholesterol decline, ubiquitin-X domain-containing protein 8 (UBXD8) recognizes INSIG and promotes its ubiquitination and extraction from the ER membrane, leading to its proteasomal degradation [48]. As a result, SREBP is liberated from the complex, translocates to the golgi where it undergoes proteolytic cleavage by site-1, 2 proteases to generate its functional form. This cleaved transcription factor, corresponding to the N-terminal portion of SREBP, binds to sterol regulatory element (SRE), facilitating transcription of lipid synthesis genes.

During HSCs activation, the expression of PPAR-γ decreases [49], whereas SREBP is upregulated in aHSCs and facilitates lipid remodeling that supports ER expansion and cell proliferation. In particular, SREBP2 plays a key role in maintaining cholesterol homeostasis essential for preserving the quiescent phenotype of HSCs [50,51], Disruptions in this pathway result in the accumulation of free cholesterol, thereby promoting HSC activation [52,53]. Notably, several studies have shown that reintroducing PPAR-γ into aHSCs can restore them to a quiescent, less fibrogenic state, indicating its potential as a therapeutic target [54,55]. Furthermore, pharmacological or genetic inhibition of SREBP signaling has been shown to effectively suppress HSC activation [56,57]. Collectively, these findings suggest that targeting lipid metabolism through the modulation of key transcription factors such as PPAR-γ and SREBP holds therapeutic promise for the treatment of liver fibrosis.

METABOLIC REPROGRAMMING-DRIVEN EPIGENETIC CHANGES IN HSCs ACTIVATION

As previously stated, HSCs activation is accompanied by substantial metabolic alterations. Emerging evidence emphasizes the intricate crosstalk between metabolic alterations and epigenetic modifications as the key drivers of phenotypic switch of quiescent, vitamin A-storing cells to proliferative, contractile, ECM-producing aHSCs. This crosstalk collectively regulates the transcriptional reprogramming necessary for HSCs activation.

In this section, we specifically focus on how metabolic alterations shape the epigenetic landscape during HSCs activation, through various post-translational modifications of histones and DNA, as well as the regulation of nuclear receptors (Fig. 2).

Histone acetylation

Histone modifications play pivotal roles in regulating chromatin structure and gene expression. Various metabolic substrates are used to modify the histone tails and the structured globular domain of nucleosome core particles. Histone acetylation, in particular, is a critical epigenetic modification mediated by a wide range of histone acetyltransferases (HATs) This process alters chromatin architecture by relaxing its structure, allowing for transcription factors access to DNA, thereby promoting gene expression.

Enhanced glycolysis in activated HSCs serves as a predominant fuel source for the synthesis of acetyl-coenzyme A (CoA), a metabolic substrate of histone acetylation [58]. A recent study has shown that PDGF-stimulated glycolysis in aHSCs fuels histone acetylation, particularly at histone H3 lysine 9 (H3K9), on the promoter regions of EV-related genes, leading to increased expression of genes, such as ras related protein 31 [9]. This epigenetic changes result in the increased release of EVs, which are enriched with fibrogenic proteins and amplify liver fibrosis [9]. Conversely, sirtuins (SIRTs), which exerts deacetylase activity in an nicotinamide adenine dinucleotide, oxidized form-dependent manner, also link cellular metabolism to epigenetic states. Given the possibility that increased glycolytic flux in

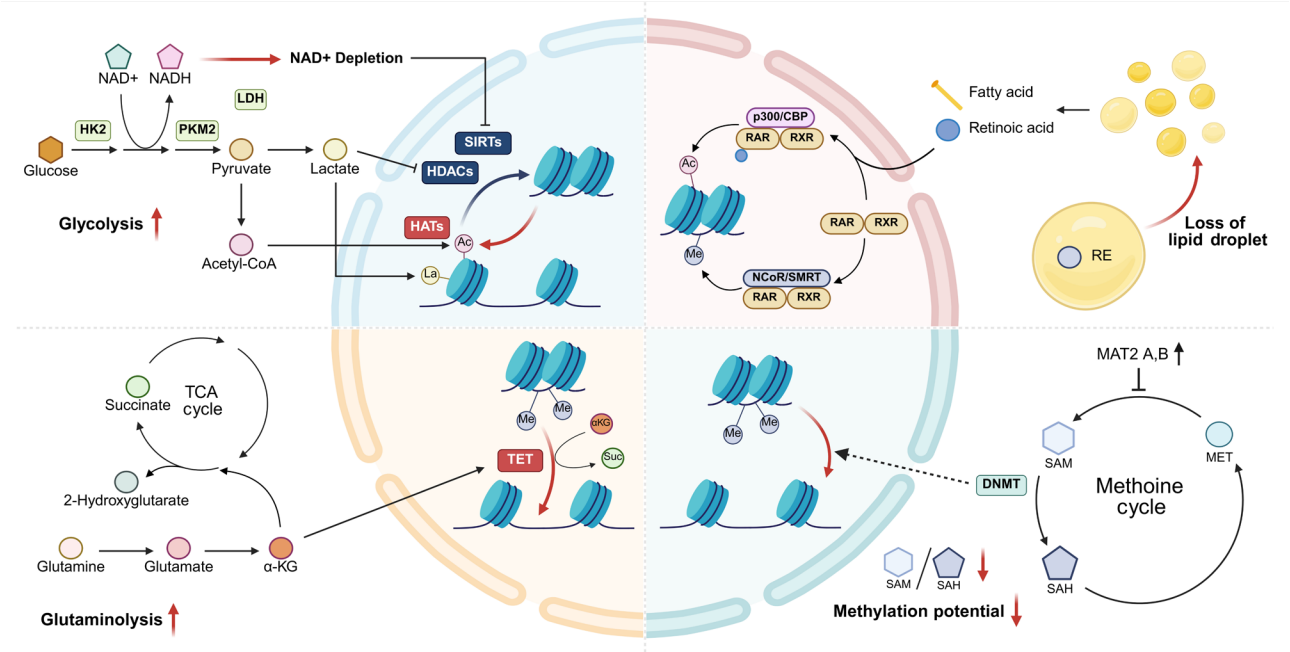

Fig. 2. Metabolic reprogramming-driven epigenetic modifications in hepatic stellate cells (HSCs) activation. Intricate crosstalk between metabolic reprogramming and epigenetic modifications is essential in HSCs activation. Key metabolic alterations, including enhanced glycolysis, glutaminolysis, and loss of lipid droplets, drive histone and DNA modifications that regulate HSCs activation and fibrosis progression. Histone acetylation, lactylation, and DNA methylation are dictated by availability of metabolic intermediates such as acetyl-coenzyme A (CoA), lactate, S-adenosylmethionine (SAM), and α-ketoglutarate (α-KG). Additionally, nuclear receptor signaling modulates chromatin remodeling in response to retinoic acid and free fatty acids, thereby reinforcing transcriptional programs associated with HSCs activation. NAD+, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide, reduced form; LDH, lactate dehydrogenase; HK2, hexokinase 2; PKM2, pyruvate M2; SIRT, sirtuin; HDAC, histone deacetylase; HAT, histone acetyltransferases; TCA, tricarboxylic acid; TET, ten-eleven translocation; CBP, CREB-binding protein; RAR, retinoic acid receptor; RXR, retinoid X receptor; NCoR, nuclear receptor corepressor; SMRT, silencer mediator of retinoid and thyroid hormone receptor; RE, retinyl esters; DNMT, DNA methyltransferase; MAT, methionine adenosyltransferase; SAH, S-adenosylhomocysteine.

aHSCs leads to NAD+ depletion, aHSCs may exhibit impaired SIRT activity, thereby contributing to fibrotic phenotypes through enhanced histone acetylation [59].

These functional connection between glucose metabolism and histone acetylation is further elaborated upon by a line of investigation demonstrating that specific glycolytic enzymes, such as PKM2 and LDH modulates the metabolic-epigenetic link, and inhibition or modulation of these enzymes attenuate HSCs activation and liver fibrosis [60,61].

For example, dimerized PKM2, which is significantly enriched in aHSCs, promotes aerobic glycolysis, and upregulates specific transcription factors via histone H3 modification, thus driving HSCs activation [60]. However, PKM2 tetramerization, induced by the allosteric agent thienopyrrolopyridazinone, inhibits HSCs activation by reducing aerobic glycolysis and decreasing expression of myelocytomatosis oncogene and cyclin D1 through the regulation of histone H3K9 acetylation. Both TEPP-46 and the PKM2 inhibitor attenuated liver fibrosis *in vivo* in a mouse model [60].

Similarly, LDH inhibition protects against hepatic fibrosis by regulating the metabolic reprogramming of HSCs in both *in vitro* and *in vivo* models [61]. Its protective effects are presumably mediated through disrupted NAD+ recycle and reduced nuclear lactate levels, both of which are linked to potential epigenetic changes. In particular, since lactate is an endogenous inhibitor of histone deacetylase (HDAC), LDH inhibition also increases HDAC activity, followed by decrease of histone acetylation, particularly at the c-Myc promoter region [61]. The downregulation of c-Myc further suppresses the expression of GLS2 and the glutamine transporter (SLC1A5), thereby re-

stricting glutaminolysis and contributing to HSCs inactivation [61].

These findings suggest that metabolic reprogramming during HSCs activation induces histone acetylation, which in turn drive additional metabolic changes, creating a feedback loop that amplifies HSCs activation and fibrosis progression.

Histone lactylation

Histone lactylation is another histone modification that links metabolic reprogramming to HSCs activation. Traditionally considered a by-product of glycolysis, lactate has recently been recognized as a direct regulator of gene transcription by modifying histone lysine residues at target gene promoter regions. A recent study demonstrated that insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2) functions a key regulator in HSCs activation and liver fibrosis by upregulating aldolase A, a key glycolytic enzyme, thereby enhancing glycolytic flux into lactate production [62]. Furthermore, MCTs, especially MCT1, facilitate the intracellular and potentially nuclear transport of lactate, enabling lactate accumulation in the nucleus [63]. Once inside the nucleus, lactate can be locally converted to lactyl-CoA by nuclear-localized acyl-CoA synthetases or metabolized by nuclear LDH activity, providing substrates for histone lactylation [64,65]. This leads to elevated histone lactylation in aHSCs, particularly H3K18 lactylation (H3K18la), which is enriched in the promoter regions of genes associated with HSCs activation. Inhibition of glycolysis using 2-deoxy-D-glucose reduces histone lactylation *in vitro* and ameliorates liver fibrosis by suppressing HSCs activation *in vivo* [62].

Similarly, HK2 expression also increases during HSCs activation, contributing to lactate accumulation and histone H3K18la [66]. Deletion of the *Hk2* gene or inhibition of lactate production reduces H3K18la and suppresses HSCs activation, while, exogenous lactate, but not acetate, rescues the activating capacities of Hk2-deficient HSCs. Notably, class 1 HDAC inhibition increases H3K18ac, whereas reducing H3K18la, ultimately suppressing HSCs activation [66]. These findings revealed the competitive relationship between histone lactylation and acetylation in the regulation of HSCs activation. However, as previously mentioned, histone acetylation has also been implicated in promoting HSCs activation; Therefore, the intricate balance between lactylation and acetylation may play a crucial role in determining HSCs activation and fibrosis progression.

Beyond histone lactylation, various metabolic byproducts can also link metabolic reprogramming to epigenetic modifications [67]. For instance, β-hydroxybutyrylation (BHB), a systemic fuel source under starvation condition, fuels histone BHBylation, which is associated with gene activation in response to energy stress and metabolic adaptation [68]. Given that HSCs undergo significant metabolic shifts during activation and are located adjacent to hepatocytes, the primary site of BHB production, BHB may influence fibrogenic gene expression and cellular plasticity by manipulating epigenetic landscapes. Further studies are needed to elucidate the role of metabolite-driven histone modifications and their balance in HSCs activation and liver fibrosis progression.

DNA methylation

HSCs activation is accompanied by extensive remodeling of the DNA methylation landscape, driven by increased DNA methyltransferase (DNMT) activity and reduced expression of ten-eleven translocation (TET) enzyme which functions as a DNA demethylase [69]. This shift leads to elevated promoter methylation of anti-fibrotic genes, suppressing their expression, while simultaneously reducing methylation of pro-fibrotic genes, leading to their upregulation. Concurrently, global levels of DNA hydroxy-methylation decline, limiting the dynamic regulation of DNA methylation [69]. Genome-wide analyses have revealed distinct DNA methylation patterns between qHSCs and aHSCs, suggesting that epigenetic regulation of DNA methylation plays a crucial role in HSCs activation and fibrosis progression [69]. HSCs activation entails a metabolic rewiring of the methionine cycle that influences the cellular S-adenosylmethionine (SAM)/S-adenosylhomocysteine (SAH) ratio, also known as the methylation potential. Hepatocytes predominantly express methionine adenosyltransferase 1A (MAT1A), which encodes methionine adenosyltransferase (MAT) enzymes responsible for SAM synthesis. However, during hepatic fibrosis and HSCs activation, MAT1A expression decreases whereas MAT2A and MAT2B, which encode alternative MAT isoforms, are upregulated [70]. MAT2A encodes the catalytic β2 subunit of MATII, the enzyme responsible for SAM biosynthesis in HSCs, while MAT2B encodes a regulatory α subunit, which binds to MAT2A to form a hetero-oligomeric complex. This interaction increases feedback inhibition by SAM, leading to reduced MATII enzymatic activity and lower intracellular SAM levels, despite the upregulation of MATII subunits [70]. The decline in SAM levels reduces the SAM/SAH ratio, influencing gene expression and promoting a fibrogenic phenotype. This paradox—higher MAT2A/B ex-

pression but lower SAM availability—is a hallmark of chronic liver fibrosis [70]. Silencing MAT2A in activated HSCs further depletes SAM and suppresses proliferation, indicating that a sufficient SAM pool is necessary for maintaining the activated phenotype [70]. Conversely, perturbations in methionine/SAM metabolism alter DNA methylation, where a higher SAM/SAH ratio favors methylation and a more qHSCs state, while SAM depletion or SAH accumulation inhibits DNMT activity, leading to hypomethylation of fibrogenic genes [70]. A recent study showed that oroxylin A, a flavonoid derived from *Scutellaria baicalensis* with anti-fibrotic properties, inhibits MAT2A expression, reducing SAM levels, and suppressing DNMT3A activity, leading to cyclic GMP-AMP synthase (cGAS) gene hypomethylation [71]. As a result, cGAS-stimulator of interferon genes (STING) signaling is activated, promoting HSCs senescence, which serves as a novel anti-fibrotic mechanism [71].

During activation, HSCs generate α-KG through glutaminolysis, which is essential for maintaining the activity of α-KG–dependent dioxygenases, including TET enzymes which catalyze DNA demethylation by oxidizing 5-methylcytosine (5mC) [72]. Sufficient α-KG facilitates the demethylation of promoter regions, whereas α-KG depletion or accumulation of succinate and 2-hydroxyglutarate, the metabolic byproducts that inhibit α-KG–dependent dioxygenases activity, can impair TET activity, leading to aberrant DNA hypermethylation [73]. However, direct evidence demonstrating that α-KG drives the demethylation specifically at pro-fibrotic gene promoters in HSCs remains limited. While α-KG is known to support TET enzyme activity broadly, further research is required to confirm whether it directly modulates the epigenetic regulation of fibrogenic genes in HSCs. Nonetheless, given its role in DNA demethylation, α-KG may contribute to the activation of fibrogenic genes in HSCs. Thus, glutamine metabolism, which primarily regulates the α-KG pool in HSCs, may influence the epigenetic landscape and activation of fibrogenic pathways in HSCs.

Nuclear receptor mediated epigenetic modifications

As previously mentioned, HSCs activation is characterized by the loss of LDs, leading to the subsequent release of retinoids and FFAs [74]. RA, derived from RE, binds to RARs (RARα/β/γ), which dimerize with RXR to regulate gene transcription [75].

In qHSCs, ligand-unbound RAR/RXR complexes recruit corepressors nuclear receptor corepressor (NcoR)/silencer mediator of retinoid and thyroid hormone receptor (SMRT), HDACs and polycomb repressive complexes (PRC2), leading to chromatin condensation and gene silencing via histone modifications such as H3K27 trimethylation (H3K27me3) [76-79]. This repressive state maintains quiescence-associated genes, including PPARγ and RARβ. However, as RA level increase during HSCs activation, the complex undergoes a conformational change that releases corepressors and recruits co-activators such as p300/CREB-binding protein, which possess HAT activity [80]. This shift promotes histone acetylation (H3/H4ac) and the increase of gene-activating marks such as H3K4 tri-methylation (H3K4me3), opening chromatin structure and allowing transcription of RA-target genes that counteract early-stage HSCs activation. The subsequent loss of RA during later stage HSCs activation diminishes this transcriptional control, leading to hypermethylation of quiescence-associated genes including *PPARγ* and *RARβ*, reinforcing the fibrogenic phenotype [81].

Additionally, FFAs serve as ligands for nuclear receptors, including PPARs and RXR [75]. In qHSCs, PPARγ forms a heterodimer with RXR to regulate lipid metabolism and storage, thereby suppressing HSCs activation. However, during HSCs activation, PPARγ expression is epigenetically repressed through DNA hypermethylation and histone modifications such as H3K9me3, H3K27me3, at its promoter regions, leading to the loss of FFA-mediated anti-fibrotic signaling [79]. Notably, certain polyunsaturated fatty acids (PUFAs), such as docosahexaenoic acid (DHA) and arachidonic acid (AA), can directly bind and activate RXR, regulating gene expression. RXR, as a heterodimeric partner for multiple nuclear receptors, including PPAR, farnesoid X receptor, liver X receptor, RAR, functions as a central hub for shaping lipid metabolism and fibrosis regulation [82]. The alteration of FFA availability during HSCs activation modulates HSCs activation through disruption of RXR signaling, followed by epigenetic changes.

THERAPEUTIC STRATEGIES TO INHIBIT HSCs ACTIVATION IN METABOLIC DISEASES

As discussed in the previous sections, metabolic reprogramming in HSCs drives their transition into aHSCs, by (1) fueling biosynthetic pathways and mitochondrial energetics, and (2) shaping the epigenetic landscape, both of which are closely linked to signaling pathways and transcriptional regulation. Given these tightly interconnected mechanisms, pharmaco-

Table 1. Pharmacological strategies for hepatic stellate cell activation in metabolic diseases

Causes of HSCs activation	Therapeutics		Reference
	Medications	Mechanisms	
T2DM			
Hyperglycemia Insulin resistance Adipokines dysregulation AGE/RAGE signaling	Metformin	AMPK↑, mTOR↓, succinate-GPR91↓, electron transport chain↓	[85,86]
	Thiazolidinediones (Pioglitazone)	PPAR-γ↑	[87-89]
	SGLT2 inhibitor (Empagliflozin, Tofogliflozin)	miR-34a-5p↓, hedgehog-YAP pathway↓, Hippo signaling↑	[90-92]
	DPP-4 inhibitors	ERK1/2, p38 and Smad2/3 phosphorylation↓, mitochondrial dysfunction↓, ROS↓	[93-95]
	GLP-1 receptor agonists	RAGE/NOX2↓, ROS↓	[96,97]
Obesity			
α-SMA/MMP9/STAT3 signaling Inflamation TGF-β signaling Lipotoxicity	Statin	Modulating PPAR balance, Ferroptosis↑	[107,108]
	J2H-1702	NF-κB signaling↓, Smad3/TGF-β signaling↓	[109]
	Adiponectin, SR1664	PPAR-γ↑	[110,111]
Hypertension			
Oxidative stress	Losartan	NADPH oxidase↓, ROS↓	[115,116]
Renin-angiotensin system	Perindopril	Inhibiting ACE	[117]

HSC, hepatic stellate cell; T2DM, type 2 diabetes mellitus; AGE/RAGE, advanced glycation end-products/receptor for advanced glycation end-products; AMPK, AMP-activated protein kinase; mTOR, mechanistic target of rapamycin; GPR91, succinate-G protein-coupled receptor 91; PPAR-γ, peroxisome proliferator-activated receptor gamma; SGLT2, sodium-glucose cotransporter 2; YAP, Yes-associated protein; DPP-4, dipeptidyl peptidase-4; ERK1/2, extracellular signal-regulated kinase 1/2; ROS, reactive oxygen species; GLP-1, glucagon-like peptide-1; NOX2, NADPH oxidase 2; α-SMA, alpha-smooth muscle actin; MMP9, matrix metalloproteinase-9; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor-beta; NF-κB, nuclear factor kappa B; NADPH, nicotinamide adenine dinucleotide phosphate; ACE, angiotensin-converting enzyme.

logical interventions targeting both metabolic reprogramming and fibrogenic signaling in HSCs may represent promising therapeutic strategies. This section explores how different pharmacological agents inhibit HSCs activation, primarily from a metabolic perspective and within disease-specific contexts, with a focus on their mechanistic actions in type 2 diabetes mellitus (T2DM) and other components of metabolic syndrome including obesity, adipose tissue dysfunction, and hypertension (Table 1).

Type 2 diabetes mellitus

T2DM is a complex metabolic disorder characterized by multiple symptoms including chronic hyperglycemia, insulin resistance, and adipokine imbalances, which collectively drive HSCs activation; High blood glucose levels result in oxidative stress and formation of advanced glycation end-products (AGEs), which binds to receptor for AGEs (RAGE) expressed on HSCs, triggering fibrotic responses [83,84].

Insulin resistance in T2DM leads to excess FFAs and hepatic steatosis, causing lipotoxic hepatocyte injury and release of pro-fibrotic cytokines such as TGF-β1 [85,86]. In this environment, HSCs undergo activation, and subsequently produce collagen, a key structural component of the ECM. Adipokine imbalance may further contribute to HSCs activation. A study has shown that obese T2DM patients often have elevated leptin (a pro-fibrogenic adipokine) and reduced adiponectin (an anti-fibrotic adipokine), presumably shifting HSCs toward an activated state [87], as leptin directly stimulates HSCs via Janus tyrosine kinase (JAK)/signal transducer and activator of transcription (STAT) and TGF-β pathways, whereas adiponectin normally induces PPARγ in HSCs to maintain their quiescence [88-90]. Collectively, the metabolic disturbance creates a persistently pro-fibrotic milieu in T2DM, thereby driving HSCs activation, and fibrosis progression.

Several antidiabetic agents mitigate pro-fibrotic pathways in T2DM by directly targeting HSCs activation. For example, Metformin has been shown to activate the energy sensor AMP-activated protein kinase (AMPK) in HSCs, which in turn coun-

teract HSCs activation by reducing alpha-smooth muscle actin (α-SMA) expression and inhibiting HSCs proliferation [91]. Mechanistically, AMPK activation by metformin disrupts the succinate–succinate-G protein-coupled receptor 91 (GPR91) signaling axis, a metabolic pathway that drives HSCs activation, thereby attenuating mHSCs trans-differentiation [92]. In addition, metformin reduces AGE accumulation and RAGE signaling, leading to the suppression of nuclear factor kappa B (NF-κB)-mediated inflammatory signaling in HSCs. Through these mechanisms, metformin alleviates hyperglycemia-driven oxidative stress and AGE/RAGE pathways, both of which contribute to HSCs activation in T2DM.

Thiazolidinediones (TZDs), such as rosiglitazone and pioglitazone, are PPARγ agonists that directly target HSCs' transcriptional program [93]. In T2DM, aHSCs exerts a reduced PPARγ expression and activity, whereas TZD treatment reactivates PPARγ, inducing an adipogenic gene profile that mitigates fibrogenesis. Additionally, in a rat HSCs cell line, rosiglitazone treatment upregulates PPARγ expression and significantly decreases α-SMA and type I collagen synthesis [94]. Moreover, it also inhibits HSCs proliferation and even promotes apoptosis of activated HSCs. Interestingly, this mechanism overlaps with adiponectin's anti-fibrotic effect, as adiponectin requires intact PPARγ signaling to exert its suppressive effects on HSCs activation [95]. Thus, TZDs pharmacologically mimic the adiponectin-PPARγ axis to reverse HSCs activation in T2DM.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors (e.g., empagliflozin) have been reported to exert liver-protective, anti-fibrotic effects beyond glucose control. Specifically, studies have shown that SGLT2 inhibition attenuates HSCs activation primarily through metabolic and signaling pathways.

For example, empagliflozin has been shown to downregulate miR-34a-5p, a microRNA highly enriched in HSCs from a mouse model of diabetic liver fibrosis that promotes TGF-β signaling [96]. By lowering miR-34a, empagliflozin restores the expression of its target gene gremlin 2, an antagonist of TGF-β, thereby reducing Smad-mediated fibrogenic gene expression [96].

SGLT2 inhibitors have also been shown to interfere with the Hh-YAP pathway in HSCs [97], In addition, empagliflozin treatment in fibrotic rats suppressed key components of Hh signaling pathway, including Patched1, SMO, Gli2, thereby mitigating this pro-fibrotic metabolic programming [98]. By inhibiting Hh-YAP signals, SGLT2 inhibitors reduce HSCs glutaminolysis and proliferation, contributing to fibrosis attenuation [98]. This observation aligns with the previously discussed intricate connection between Hh-YAP axis and glutamine metabolism. Taken together, SGLT2 inhibitors directly target HSCs activation in T2DM, by inhibiting miR-34a-TGF-β and Hh-YAP axis, exerting metabolic and transcriptional modulation.

Dipeptidyl peptidase-4 inhibitors (DPP-4i), such as sitagliptin, gemigliptin and vildagliptin, have also been shown to exhibit anti-fibrotic activity in diabetes-related liver disease by targeting HSCs activation [99-101]. Studies have demonstrated that sitagliptin suppresses HSCs activation by inhibiting multiple kinase cascade pathways [99]. In aHSCs, DPP-4 inhibition attenuated PDGF-BB-induced proliferation, and reduced TGF-1 signaling and collagen I gene expression. Mechanistically, sitagliptin prevented the phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 mitogen-activated protein kinase and of Smad2/3, the key effectors of TGF-β signaling pathway [99]. Inhibiting p38 and Smad2/3 activation interrupts the pro-fibrotic gene program in aHSCs and attenuates the trans-differentiation. DPP-4is also mitigate the insulin resistance-associated inflammation and TGF-β signaling pathway, both of which drive HSCs activation. Notably, DPP-4i also increase endogenous glucagon-like peptide-1 (GLP-1) levels, which may further benefit the liver by reducing lipotoxicity and inflammation.

GLP-1 receptor agonists (e.g., liraglutide) have emerged as anti-fibrotic agents due to their effects on hepatic metabolism and inflammation. While GLP-1 agonists are primarily known for improving insulin sensitivity and promoting weight loss, they have also been shown to directly modulate stress pathways in HSCs [102].

In a study using diet-induced nonalcoholic steatohepatitis (NASH) models, liraglutide lowered reactive oxygen species (ROS) levels and suppressed the upregulation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 1/2/4 (NOX1/2/4) NADPH oxidases and RAGE in the liver, thereby attenuating HSCs activation. Liraglutide's anti-fibrotic effect was also confirmed *in vitro*, where it was blunted upon RAGE or NOX2 overexpression, indicating that the mechanisms involves disrupting the ROS–RAGE feed-forward loop that drives HSCs activation [102]. GLP-1 agonism also shifts macrophages toward an anti-inflammatory phenotype and may enhance adiponectin release, further alleviating HSCs activation [103]. Through these mechanisms including reducing

ROS, inhibiting RAGE/NF-κB signaling, and improving the metabolic environments, GLP-1 receptor agonists disrupt key links between T2DM and HSCs activation.

Other components of metabolic syndrome

Metabolic syndrome encompasses obesity, insulin resistance, adipose dysfunction, and hypertension which play key roles in creating a pathological milieu that drives HSCs activation [104,105]. These metabolic disturbances coordinately converge to generate lipotoxic, inflammatory, and hormonal signals, ultimately, contributing to liver fibrosis. While the precise molecular mechanisms remain under investigation, several key biological components, including metabolism and the relevant signaling pathways, are implicated in these processes, offering potential targets for therapeutic intervention in HSCs activation and liver fibrosis.

Obesity and adipose tissue dysfunction

Excess caloric intake leads to dysregulated hepatic lipid metabolism, which drives HSCs activation through oxidative stress and inflammation, representing a pivotal mechanisms in the pathogenesis of liver fibrosis [105]. In addition to these inflammatory signals, chronic overnutrition induces systemic insulin resistance and lipid overload, leading to shifts in hepatic fuel metabolism, such as enhanced glycolysis, glutaminolysis, and lipid accumulation [9,106,107]. These metabolic alterations not only provide biosynthetic precursors and energy that fuel fibrogenic processes but also influence epigenetic regulatory mechanisms, thereby sustaining HSCs activation.

The hepatic accumulation of FFAs and cholesterol results in peroxidation injury, releasing damage-associated molecular patterns (DAMPs) that activate Kupffer cells and recruit inflammatory cells [108,109]. This process is exacerbated by lipid peroxidation products and ROS, which stimulate TLR4 on both Kupffer cells and HSCs, triggering NF-κB-mediated inflammatory signaling [40,110].

Additionally, adipose tissue dysfunction plays a critical role in HSCs activation. Visceral fat produces excess pro-inflammatory adipokines (e.g., leptin, resistin) while only few adipokines with anti-inflammatory properties (e.g., adiponectin) [111,112]. For example, high leptin levels derived from visceral fat in obesity have pro-fibrogenic effects by directly activating HSCs and increasing TGF-β1 secretion, thereby promoting collagen production [111]. Conversely, hypoadiponectinemia removes an important brake on HSCs activation, since adiponectin normally upregulates PPARγ in stellate cells to maintain their quiescent, lipid-storing state [112].

Statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors), while developed for dyslipidemia, also exhibit anti-fibrotic properties in the liver [113]. One mechanism involves induction of ferroptosis, an iron-dependent form of cell death triggered by lipid peroxidation. aHSCs are susceptible to ferroptosis when their antioxidant defenses are impaired. Statins, by blocking the mevalonate pathway, deplete downstream products, such as geranylgeranyl pyrophosphate and coenzyme Q10, which are crucial for neutralizing lipid ROS in HSCs [113]. Simvastatin, a commonly used lipophilic statin, enhances lipid peroxidation of HSCs, thereby inducing ferroptotic cell death. Consequently, statin treatment makes HSCs more sensitive to ferroptosis and ameliorates experimental fibrosis [113]. Additionally, statins' pleiotropic effects improve endothelial function and reduce hepatic inflammation, indirectly inactivating HSCs. There is also evidence that statins may modulate PPAR signaling in the liver [114]. For instance, some class of statins can activate PPARα, improving fatty acid oxidation and thereby reducing lipotoxic stress on the liver. Additionally, statins' pleiotropic effects improve endothelial function and reduce hepatic inflammation, indirectly inactivating HSCs. Taken together, the lipid-lowering, anti-oxidative, and HSC-cytotoxic effects of statins help counteract the lipid-driven HSC activation in metabolic syndrome.

In the context of aberrant inflammation, novel anti-inflammatory agents targeting HSC-intrinsic stress pathways are under investigation. One example is J2H-1702, a potent 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor [115]. 11β-HSD1 in liver tissue generates active cortisol, which can drive gluconeogenesis and also local inflammation. In HSCs, excess glucocorticoid signaling via 11β-HSD1 may support a pro-fibrogenic state in aHSCs by interacting with inflammatory pathways. In a recent study, inhibiting 11β-HSD1 with J2H-1702 'reprogrammed' HSCs, decreasing their activation markers and inflammatory signaling [115]. The mechanism underlying J2H-1702 inhibition of HSCs activation also involves suppressed phosphorylated Smad3 (downstream of TGF-β) and reduced NF-κB-related gene expression, which led to lower α-SMA and collagen I expression, indicating HSCs were reverting toward quiescence. In diet-induced NASH models, J2H-1702 significantly alleviates liver steatosis and fibrosis, supporting its therapeutic potential. Given the 11β-HSD1 role in promoting hepatic gluconeogenesis, J2H-1702 may indi-

rectly exert its suppressive effects on glycolytic flux in HSCs, thereby reinforcing HSCs inhibition. This exemplifies a strategy of targeting intra-hepatic inflammation and metabolism to prevent HSC activation.

Therapeutic interventions in metabolic syndrome aim to target these upstream drivers to mitigate HSCs activation. Strategies to amplify adiponectin signaling or PPARγ activity can reverse the HSC activation due to obesity and adipose tissue dysfunction. Adiponectin itself has been shown to protect against fibrosis; transgenic mice overexpressing adiponectin are resistant to liver fibrosis, whereas adiponectin-knockout mice develop more severe fibrosis [116]. Adiponectin binding to its receptors on HSCs activates AMP kinase and stimulates PPARγ expression, which reprograms HSCs toward a less fibrogenic, more lipid-storing phenotype [116]. Pharmacologically, this is mimicked by PPARγ agonists (TZDs) and newer selective PPARγ modulators. For example, the experimental modulator SR1664 significantly reduced fibrosis in obese mouse models without typical TZD side effects [117]. SR1664 and similar agents directly act on HSCs to induce PPARγ-target genes, thereby inhibiting collagen deposition [117]. In diet-induced NASH, SR1664 decreased activated HSCs numbers (α-SMA-positive cells) and collagen I content, confirming that PPARγ reactivation can therapeutically disable HSCs [117]. Thus, pharmacological restoration of the adiponectin-PPARγ axis, either directly or indirectly, may address the adipokine deficiency that drives HSCs activation in metabolic syndrome.

Hypertension

The renin-angiotensin system (RAS) is often overactive in metabolic syndrome primarily due to adipose-derived angiotensinogen and systemic hypertension, leading to elevated angiotensin II (Ang II) [118]. Elevated Ang II levels in hypertension stimulate glycolysis and mitochondrial ROS production in HSCs via angiotensin II type 1 (AT1) receptors, fueling fibrogenic processes via TGF-β1/Smad3 signaling [119]. Additionally, systemic insulin resistance associated with hypertension leads to lactate accumulation, which induces histone lactylation and sustains HSCs activation [120]. These findings suggest that hypertension is not only a cardiovascular disorder but also a metabolic driver of liver fibrosis, emphasizing the need for therapeutic strategies targeting hypertension-induced metabolic and epigenetic dysregulation in HSCs.

Renin-angiotensin system blockers (ARBs) attenuate fibrosis by disrupting Ang II/AT1 pro-fibrotic signaling in HSCs [121]. Losartan, an AT1 receptor antagonist, has demonstrated antifibrotic efficacy in both animal models and clinical studies. By blocking AT1 receptor on HSCs, losartan prevents Ang II-induced NOX activation, calcium influx, and TGF-β1 upregulation, thereby inhibiting HSCs activation [121]. In a T cell-mediated fibrosis model, losartan treatment alleviates fibrogenesis and significantly downregulated TGF-β1 expression, resulting in reduced HSCs activation and proliferation [121]. Losartan also appears to exert PPARγ-agonistic effects, further suppressing HSC activation [122].

Similarly, perindopril, an angiotensin-converting enzyme (ACE) inhibitor, achieves upstream blockade of Ang II production. In bile duct-ligated rats, perindopril markedly reduced hepatic hydroxyproline content and collagen gene expression, whereas reducing number of HSCs that produce α-SMA [123]. Perindopril also diminished oxidative stress markers in the liver [123].

Taken together, by relieving HSCs from continuous Ang II stimulation, ARBs and ACE inhibitor reduce the contractile and pro-fibrotic phenotype of HSCs by disrupting the Ang II–TGF-β loop of HSCs activation, offering therapeutic benefits for patients with metabolic syndrome.

CONCLUSIONS

Liver fibrosis, driven by HSC activation, represents a critical and irreversible stage in the progression of a myriad of metabolic diseases. These metabolic diseases are commonly associated with chronic metabolic dysregulation including high blood glucose level, insulin resistance, lipid accumulation, and systemic inflammation, all of which significantly contribute to HSCs activation. Once activated, HSCs further exacerbate these metabolic disturbances, thereby creating a pathological cycle that accelerates disease progression. This review highlights recent findings on the central role of metabolic reprogramming in HSCs activation, where alterations in various aspects of fuel utilization, including glycolysis, glutaminolysis, and lipid metabolism, contribute to the pro-fibrotic phenotype. Furthermore, the interplay between metabolism and epigenetic modifications further reinforces the fibrogenic cascade, establishing a feed-forward loop that sustains disease progression.

While various omics approaches including transcriptomics, epigenetics, and proteomics have been extensively applied to elucidate the mechanisms underlying HSC activation, metabolomics-based investigations remain largely unexplored. Given

the metabolic plasticity of HSCs, precise metabolomic approaches are essential to fully understand the metabolic drivers of HSC activation. Stable isotope tracing analysis, both *in vivo* and *in vitro*, particularly in primary HSCs and mouse models of various metabolic diseases, may be essential for precisely mapping fuel metabolism dynamics and identify key metabolic flux alterations in aHSCs. Additionally, nuclear metabolomics can provide critical insights into how metabolic changes influence epigenetic regulation, which is largely determined by the availability of nuclear metabolic substrates for histone and DNA modification. This approach provides a deeper understanding of the tightly interconnected epigenetic and transcriptional landscape that mediates HSCs activation. However, due to the inherently low abundance of HSCs in the liver, traditional bulk metabolomics approaches may lack the sensitivity required for accurately capturing cell-type-specific metabolic rewiring. Therefore, the adoption of advanced single-cell metabolomics techniques will be required for dissecting the heterogeneity of HSCs metabolic states in both *in vivo* and *in vitro* settings. Future research should focus on integrating these advanced metabolomics approaches with other omics platforms to provide a comprehensive understanding of HSCs activation, ultimately facilitating the development of targeted and effective therapeutic strategies for liver fibrosis and metabolic diseases.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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