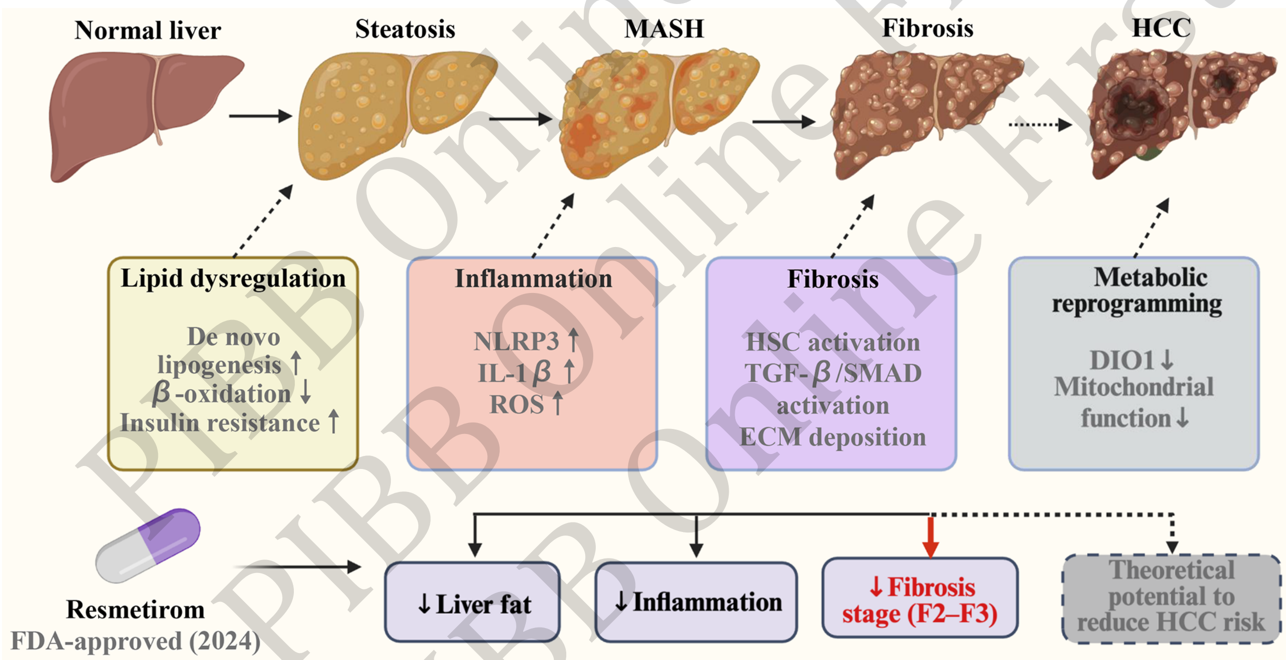
生物化学与生物物理进展
Progress in Biochemistry and Biophysics
XXXX，XX(XX)：1~19
www.pibb.ac.cn

Thyroid Hormone Network Regulation in MASLD: Mechanisms and Targeted Therapies*

XIAO Wen-Ping[1)**], MA Yang[1)**], GUAN Heng[1)], WAN Sha[2)], HAN Wen[1)], LUO Bing-Bing[3)], WANG Wu-Feng[3)], LIU Fang[1,4)***]

([1)]*Department of Human Anatomy, College of Basic Medicine, Guilin Medical University, Guilin* 541199, China;
[2)]*Taikang Center for Life and Medical Sciences, Wuhan University, Wuhan* 430071, China;
[3)]*College of Basic Medicine, Guilin Medical University, Guilin* 541199, China;
[4)]*Center of Diabetic Systems Medicine, Guangxi Key Laboratory of Excellence, Guilin Medical University, Guilin* 541199, China)

Graphical abstract



Abstract Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the most prevalent chronic liver disease worldwide, affecting approximately 32% – 38% of the adult population and posing a growing public health burden. MASLD represents a continuous disease spectrum ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), progressive hepatic fibrosis, cirrhosis, and ultimately hepatocellular carcinoma (HCC). The pathological core of MASLD lies in disruption of hepatic lipid metabolic homeostasis, characterized by an imbalance among *de novo* lipogenesis, fatty acid β-oxidation,

* This work was supported by a grant from The National Natural Science Foundation of China (82160063).
** These authors contributed equally to this work.
*** Corresponding author.
Tel：86-773-5595243，E-mail：fang.liu@msn.com
Received：October 28，2025 Accepted：January 29，2026

and very-low-density lipoprotein (VLDL) – mediated lipid export. This metabolic disequilibrium subsequently drives inflammatory injury and fibrotic progression. Among the multiple regulatory pathways involved, thyroid hormone (TH) signaling has emerged as a central regulator of hepatic metabolic homeostasis. The liver is a major peripheral target organ of TH action, where TH predominantly exerts its metabolic effects through thyroid hormone receptor β (TRβ). Large-scale epidemiological studies and meta-analyses have demonstrated that hypothyroidism is significantly associated with increased MASLD prevalence, more severe histological injury, and advanced hepatic fibrosis, suggesting that dysregulation of TH signaling may participate throughout the entire MASLD disease spectrum. At the molecular level, TH regulates hepatic lipid metabolism by coordinating suppression of lipogenesis, enhancement of mitochondrial fatty acid oxidation, and promotion of VLDL assembly and secretion through integrated genomic actions of the T3 – TRβ axis and non-genomic signaling pathways. Across different stages of MASLD, TH signaling exerts stage-dependent protective effects. In the steatosis stage, TH improves metabolic flexibility by modulating insulin sensitivity, glucose metabolism, and lipid droplet clearance, thereby alleviating early lipotoxic stress. During progression to MASH, TH attenuates inflammatory amplification by improving mitochondrial homeostasis, suppressing activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, and modulating the gut – liver axis microenvironment. In advanced stages, TH signaling influences hepatic stellate cell activation and extracellular matrix deposition, partly through interaction with the transforming growth factor-β (TGF-β)/SMAD pathway, while alterations in intrahepatic TH availability, mediated by dynamic changes in iodothyronine deiodinase 1 (DIO1), contribute to fibrosis progression and hepatocellular dedifferentiation. In hepatocellular carcinoma, coordinated downregulation of TRβ and DIO1 establishes a tumor-associated hypothyroid state that promotes metabolic reprogramming and tumor progression. The clinical relevance of TH signaling in MASLD has been underscored by the recent approval of Resmetirom, a liver-targeted TRβ-selective agonist, for the treatment of non-cirrhotic MASH with moderate-to-severe fibrosis (F2 – F3). This approval represents a landmark transition from mechanistic understanding to metabolism-centered precision therapy in MASLD. Clinical trials have demonstrated that Resmetirom not only improves key histological endpoints, including MASH resolution and fibrosis regression, but also favorably modulates atherogenic lipid profiles, highlighting the therapeutic potential of selectively targeting hepatic TH pathways. This review systematically summarizes the multidimensional regulatory roles of TH across the MASLD disease spectrum and discusses emerging diagnostic and therapeutic implications of TH-based interventions, aiming to inform future mechanistic research and optimize clinical management strategies.

Key words　metabolic dysfunction-associated steatotic liver disease, thyroid hormone, thyroid hormone receptor β, hepatic lipid metabolism, thyroid hormone receptor agonist

DOI：10.3724/j.pibb.2025.0466　　**CSTR**：32369.14.pibb.20250466

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the most prevalent chronic liver disease worldwide, with an adult prevalence of approximately 32% – 38%. In Chinese urban populations, the prevalence is similarly close to 30%, with 10% – 20% developing fibrosis, representing an increasingly substantial disease burden[1-3]. MASLD manifests as a continuous disease spectrum, progressing from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), hepatic fibrosis/cirrhosis, and potentially culminating in hepatocellular carcinoma (HCC) [4-6]. The pathological core lies in the disruption of hepatic lipid metabolic homeostasis, whereby an imbalance among *de novo* lipogenesis, fatty acid β-oxidation, and very-low-density lipoprotein (VLDL) -mediated lipid export leads to ectopic lipid deposition, triggering inflammatory and fibrotic cascades[5].

Among the multiple regulatory pathways involved, thyroid hormone (TH) signaling is recognized as a pivotal regulator of hepatic metabolic homeostasis. Through its predominant hepatic receptor, thyroid hormone receptor β (TRβ), TH regulates key lipid metabolic processes including synthesis, mitochondrial biogenesis, β-oxidation, and VLDL secretion. Additionally, by promoting lipophagy, TH may play a direct role in regulating lipotoxicity. Meta-analyses encompassing over 76.5 million individuals have demonstrated that hypothyroidism is significantly associated with an increased risk of MASLD development, as well as more severe histological injury and hepatic fibrosis, suggesting that TH signaling dysregulation may be implicated throughout the entire disease progression of MASLD[7-8].

Based on these insights, TRβ -targeted

therapeutic strategies have garnered increasing attention. The oral TRβ agonist Resmetirom, currently the only agent granted accelerated approval by the U. S. Food and Drug Administration (FDA) for adult MASH patients with non-cirrhotic moderate-to-severe fibrosis (F2 – F3), represents a development toward metabolism-centered precision interventions in the MASLD treatment landscape. However, its long-term efficacy and safety require further validation through real-world studies[9].

Therefore, this review systematically summarizes the multidimensional regulatory roles of TH across distinct stages of the MASLD disease spectrum, including steatosis, inflammation, fibrosis, and carcinogenesis, and further discusses the potential value of thyroid function-related biomarkers in MASLD diagnosis and risk stratification, aiming to provide insights for deepening mechanistic understanding and optimizing targeted therapeutic strategies.

1 Molecular basis of hepatic TH signaling

Understanding the multidimensional regulatory roles of TH in MASLD requires elucidation of its fundamental mechanisms of action in the liver. This section systematically delineates the molecular basis of TH uptake by hepatocytes, local activation, and nuclear receptor signaling transduction.

1.1 Cellular transport and local activation of TH

The liver serves as a central organ for peripheral TH metabolism. Circulating thyroxine (T4) enters hepatocytes *via* specific membrane transporters, including organic anion transporting polypeptides and monocarboxylate transporters[10-11]. Within hepatocytes, the iodothyronine deiodinase (DIO) family determines local TH bioactivity: DIO1 and DIO2 are responsible for converting T4 into the biologically active triiodothyronine (T3), whereas DIO3 mediates its inactivation[12]. In MASLD, hepatic DIO1 expression undergoes dynamic alterations: compensatory upregulation occurs in early-stage steatosis, however, with progression to advanced MASH, DIO1 expression and activity decline, resulting in reduced local T3 availability despite normal circulating thyroid-stimulating hormone (TSH) levels[13].

1.2 Classical genomic actions of TH

T3, as the primary active form of TH, binds to its nuclear receptors (thyroid hormone receptor, TR) to precisely regulate hepatic lipid metabolism at the transcriptional level. TR comprises two isoforms, TRα and TRβ. In the liver, TRβ1 is the predominant isoform and serves as the key receptor governing lipid and cholesterol metabolism[13-14]. The classical mechanism of this pathway is illustrated in Figure 1: in the absence of T3, TR/retinoid X receptor (RXR) heterodimers bound to thyroid hormone response elements (TREs) on DNA preferentially recruit nuclear receptor corepressor (NCoR), silencing mediator of retinoid and thyroid hormone receptors (SMRT), and histone deacetylase 3 (HDAC3), leading to chromatin condensation and transcriptional repression of target genes[15-17].

Upon T3 binding, receptor conformation changes, releasing the corepressor complex and recruiting coactivators such as steroid receptor coactivator-1 (SRC-1) and CREB-binding protein/ E1A-binding protein p300 (CBP/p300) [14, 18-19]. This process promotes histone acetylation and chromatin opening, thereby initiating transcriptional programs for genes involved in lipid synthesis, fatty acid oxidation, and cholesterol metabolism[14, 18].

Through this precise molecular switch, the T3 – TRβ axis directly governs the dynamic equilibrium between lipid anabolism and catabolism. Disruption of this signaling pathway is considered a pivotal molecular event driving hepatic steatosis and subsequent metabolic dysregulation.

Schematic illustration of thyroid hormone signaling through TR/RXR-dependent transcriptional regulation of hepatic metabolic genes. T4, thyroxine. T3, triiodothyronine. TR, thyroid hormone receptor. RXR, retinoid X receptor. TRE, thyroid hormone response element. TATA boxes, core promoter DNA element (distinct from TRE). MCT8, monocarboxylate transporter 8. NCoR, nuclear receptor corepressor. SMRT, silencing mediator of retinoid and thyroid hormone receptor. HDAC3, histone deacetylase 3. CBP, CREB-binding protein. SRC-1, steroid receptor coactivator-1. SREBP-1c, sterol regulatory element-binding protein-1c. FASN, fatty acid synthase. CPT1, carnitine palmitoyltransferase 1. LDLR, low-density lipoprotein receptor. HMGCR, HMG-CoA reductase. OATP1B1/1B3, organic anion transporting polypeptide 1B1/1B3. DIO1/DIO2, iodothyronine deiodinase 1/2.

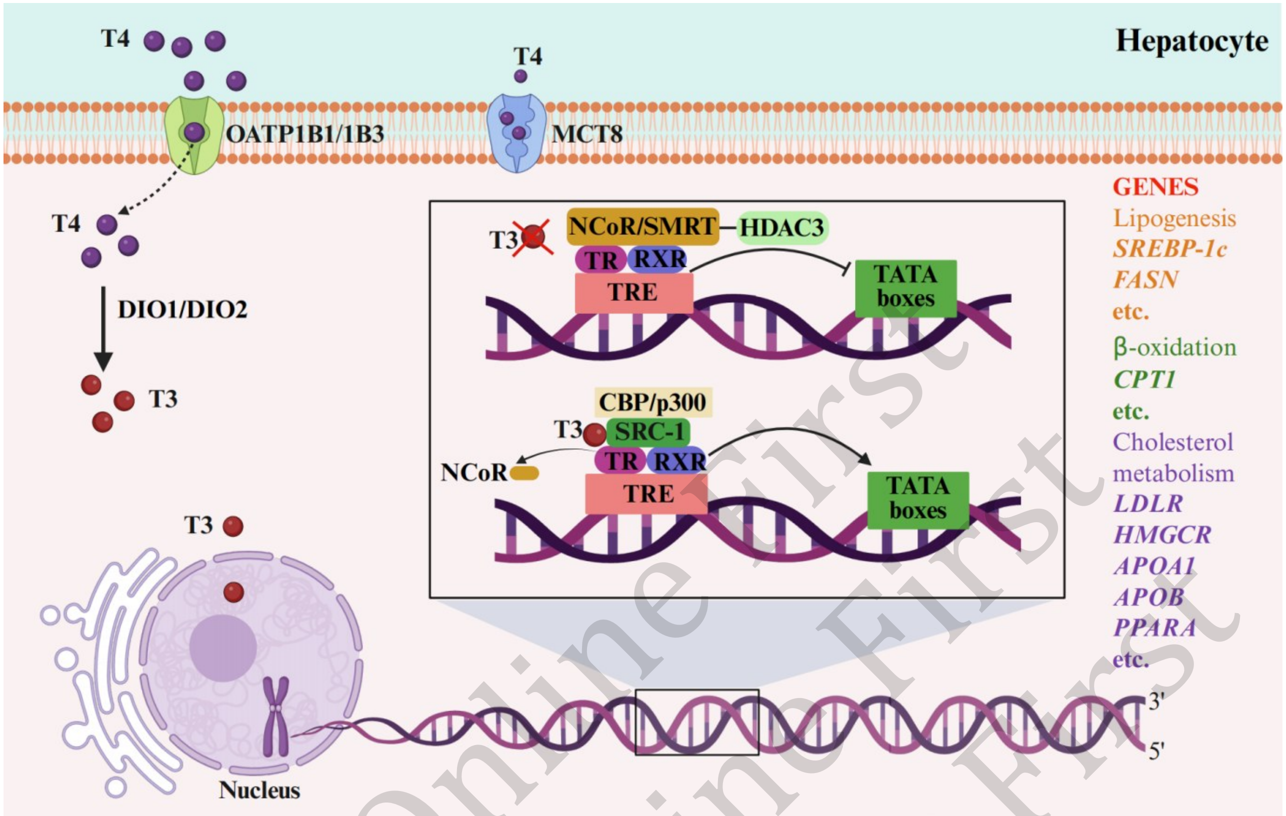


Fig. 1　Regulation of lipid-related gene expression by TH in hepatocytes

1.3　Non-genomic actions of TH

Beyond classical genomic transcriptional regulation, TH mediates rapid cellular signaling responses through non-genomic mechanisms. For instance, TH can activate kinase cascades such as phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase (MAPK) *via* cell surface integrin αvβ3[15, 20-21], thereby rapidly modulating mitochondrial function[22] and cytoskeletal remodeling[23-24].

This dual "genomic - non-genomic" regulatory mode confers TH with flexibility to respond to acute metabolic stress (such as lipotoxic episodes), and the synergy between these two mechanisms is essential for maintaining metabolic homeostasis in the challenging microenvironment of MASLD.

2　Multidimensional TH regulatory network across the MASLD disease spectrum

The pathological progression of MASLD represents a continuous dynamic process, initiating from simple steatosis, advancing through MASH, and ultimately culminating in hepatic fibrosis and HCC. The TH signaling axis spans this entire continuum, counteracting pathological progression through multidimensional molecular mechanisms.

2.1　Steatosis stage: regulation of insulin sensitivity and lipid homeostasis

Simple steatosis represents the initial stage of MASLD, characterized by lipid metabolic imbalance in the context of systemic and hepatic insulin resistance (IR), leading to progressive accumulation of triglycerides (TG) within hepatocytes[25-26]. At this stage, recent evidence suggests that TH may modulate hepatic lipid homeostasis by influencing insulin sensitivity, lipid metabolic regulatory networks, and lipid droplet clearance processes, thereby mitigating the early lipotoxic burden to a certain extent[27-28].

2.1.1　Insulin resistance-related signaling and glucose metabolic regulation

Hepatic insulin resistance is a central driver of MASLD pathogenesis, characterized by impaired insulin signaling that promotes excessive hepatic glucose production and dyslipidemia[29-30]. Increasing evidence indicates that TH modulates hepatic insulin resistance through regulation of canonical insulin signaling pathways and glucose metabolic transcription factors, although most mechanistic insights are derived from animal and in vitro studies, with limited validation in human MASLD.

Enhancement of canonical insulin signaling. Under physiological conditions, insulin binding to its receptor activates a phosphorylation cascade involving insulin receptor substrate-1 and -2 (IRS-1/2), PI3K/Akt, and downstream effectors such as the mammalian target of rapamycin complex 2 (mTORC2) [31]. In MASLD, impaired IRS-1 phosphorylation and Akt activation contribute to hepatic steatosis and glucose homeostatic dysfunction. Experimental studies suggest that TH potentiates this signaling axis by upregulating insulin receptor and IRS-1 expression *via* T3 – TRβ – dependent transcriptional regulation, thereby enhancing insulin signaling capacity in hepatocytes[32]. In addition, TH-activated PI3K – Akt signaling suppresses glycogen synthase kinase 3 beta (GSK3β) activity through phosphorylation at Ser9, promoting anabolic metabolic processes[33]. Collectively, these effects may improve hepatic insulin signaling efficiency, although direct clinical evidence in MASLD remains limited.

Regulation of FoxO1 and glucose metabolic transcription. Beyond proximal signaling events, TH also influences hepatic glucose metabolism through the transcriptional regulation of forkhead box O1 (FoxO1). Under fed conditions, T3 modulates FoxO1 activity via coordinated sirtuin 1 (SIRT1) -mediated deacetylation and Akt-dependent phosphorylation, facilitating FoxO1 nuclear export and degradation and thereby suppressing gluconeogenic gene expression[34-35]. This integrated post-translational regulation enables TH to restrain pathological hepatic gluconeogenesis, a hallmark of insulin resistance in MASLD.

Additionally, T3-induced phosphorylation of GSK3β (Ser9) suppresses its kinase activity and promotes hepatic glycogen synthesis[36-37], which may redirect acetyl-CoA away from de novo lipogenesis. However, whether these TH-mediated effects on glucose homeostasis translate into clinically meaningful metabolic improvements in MASLD patients requires further investigation.

2.1.2 Classical hepatic lipid metabolism regulatory networks

Targeting intrahepatic lipid accumulation, TH exerts pleiotropic effects on lipid homeostasis through both genomic (TRβ -mediated transcriptional regulation) and non-genomic (rapid signaling pathway activation) mechanisms, encompassing suppression of lipogenesis, enhancement of fatty acid oxidation, and facilitation of lipid export.

Suppression of de novo lipogenesis. In MASLD, insulin signaling dysregulation leads to excessive activation of the transcription factor sterol regulatory element-binding protein 1c (SREBP-1c), which drives the expression of key lipogenic genes including fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC) [38]. TH reduces hepatic lipogenesis through coordinated metabolic reprogramming rather than direct transcriptional suppression of SREBP-1c. The primary mechanism involves T3-mediated activation of AMP-activated protein kinase (AMPK), which catalyzes the inhibitory phosphorylation of ACC at Ser79, thereby blocking conversion of acetyl-CoA to malonyl-CoA[39-40]. Importantly, reduced malonyl-CoA levels simultaneously relieve the allosteric inhibition of carnitine palmitoyltransferase 1 (CPT1), creating a metabolic switch that suppresses lipid synthesis while promoting fatty acid oxidation. Additionally, TRβ -mediated enhancement of fatty acid oxidation pathways creates a metabolic environment that indirectly attenuates SREBP-1c-mediated lipogenic gene expression through substrate depletion and metabolic feedback signals[39].

Enhancement of mitochondrial β -oxidation. Addressing the mitochondrial dysfunction commonly observed in MASLD, TH significantly upregulates peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) through direct TRβ -mediated transcription. This activation further engages mitochondrial transcription factor A (TFAM) and the deacetylases SIRT1/3, thereby promoting expression of the rate-limiting enzyme CPT1 and accelerating long-chain fatty acid entry into mitochondria for oxidation[41]. Concurrently, AMPK activation by TH enhances this pathway through non-genomic mechanisms: by reducing malonyl-CoA levels to relieve CPT1 allosteric inhibition, and by promoting SIRT1/3 activity to improve mitochondrial respiratory chain efficiency[40, 42]. This represents convergent regulation where genomic and non-genomic pathways synergistically enhance fatty acid oxidation to effectively ameliorate metabolic dysfunction.

Facilitation of VLDL assembly and secretion. Hepatic lipid export relies on the synergistic actions of apolipoprotein B (ApoB) and microsomal triglyceride transfer protein (MTP), processes often impaired in MASLD[43-44]. T3 induces expression of both ApoB and MTP *via* TRβ binding to thyroid hormone response elements in their promoter regions, promoting triglyceride packaging into nascent VLDL particles and their subsequent secretion, thereby reducing intrahepatic lipid burden[45] (Figure 2).

2.1.3 Regulation of autophagy and organelle interactions

Beyond classical nuclear receptor effects, TH further reduces lipid droplet burden and stabilizes organellar function through autophagy modulation and potential effects on organelle crosstalk.

(1)Regulatory role in lipophagyDuring MASLD progression, sustained mechanistic target of rapamycin complex 1 (mTORC1) activation suppresses autophagy initiation and exacerbates lipid droplet accumulation[46]. TH-mediated AMPK activation can inhibit mTORC1 signaling, potentially restoring autophagic flux[47]. Given that late endosomal/lysosomal adaptor, MAPK and mTOR activator 1 (LAMTOR1) inhibition[48] and transcription factor EB (TFEB) activation[49] have been shown to restore lipophagic flux in MASLD models, and considering the established role of TH in autophagy regulation[28, 50-51], the TH–TFEB pathway represents a mechanistically plausible therapeutic target. Specifically, TH has been shown to activate TFEB transcriptional activity by inhibiting mTORC1[45], thereby promoting lysosomal biogenesis and lipophagic flux. However, direct evidence linking T3 to LAMTOR1 downregulation remains to be established. Furthermore, detailed mechanistic studies on TFEB nuclear translocation dynamics and its regulation of adaptor protein (PLIN2/p62) interactions in human hepatocytes require further validation. Such validation should employ TFEB knockout models and live-cell imaging approaches (Figure 2).

(2)Potential regulation of organellar contact sitesDysregulation of endoplasmic reticulum-mitochondria contact sites (MCS) has been implicated in altered lipid handling and may contribute to endoplasmic reticulum (ER) stress in MASLD[52-54]. While TH improves mitochondrial function through the SIRT1/PGC-1α pathway[51, 55] and AMPK-mediated mTORC1 inhibition may reduce ER stress[47], direct evidence for TH regulation of MCS structural components or contact site dynamics remains limited. The hypothesis that TH indirectly stabilizes MCS by reducing oxidative stress and improving organellar bioenergetics requires experimental validation.

(3)Evidence limitations and research perspectivesCurrent evidence is primarily derived from rodent models, with applicability to MASLD patients facing challenges including species differences and chronic exposure safety concerns. Priority should be given to investigating TFEB responsiveness in human primary hepatocytes, validation through liver-specific TFEB knockout models, and clinical correlation analyses of TFEB expression in MASLD patients, thereby providing the theoretical foundations for autophagy-targeted therapeutic strategies.

Schematic overview of thyroid hormone–mediated control of lipid metabolism, including lipogenesis, mitochondrial β-oxidation, VLDL assembly and secretion, and autophagy-related pathways. TR, thyroid hormone receptor. FA, fatty acid. VLDL, very-low-density lipoprotein. ApoB100, apolipoprotein B100. MTP, microsomal triglyceride transfer protein. mTORC1, mammalian target of rapamycin complex 1. TFEB, transcription factor EB. PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha. PPARα, peroxisome proliferator-activated receptor alpha. TFAM, mitochondrial transcription factor A. SIRT1/3, sirtuin 1/3. CPT2, carnitine palmitoyltransferase 2. CACT, carnitine–acylcarnitine translocase. TG, triglycerides. AMPK, AMP-activated protein kinase. ACC, acetyl-CoA carboxylase. CPT1, carnitine palmitoyltransferase 1. SREBP-1c, sterol regulatory element-binding protein 1c.

2.2 MASH stage: sustained inflammatory response and gut–liver axis alterations

The MASH stage is characterized by immune activation, inflammatory storms, and cell death. When simple steatosis encounters "multiple hits" including lipotoxicity and oxidative stress, the disease rapidly

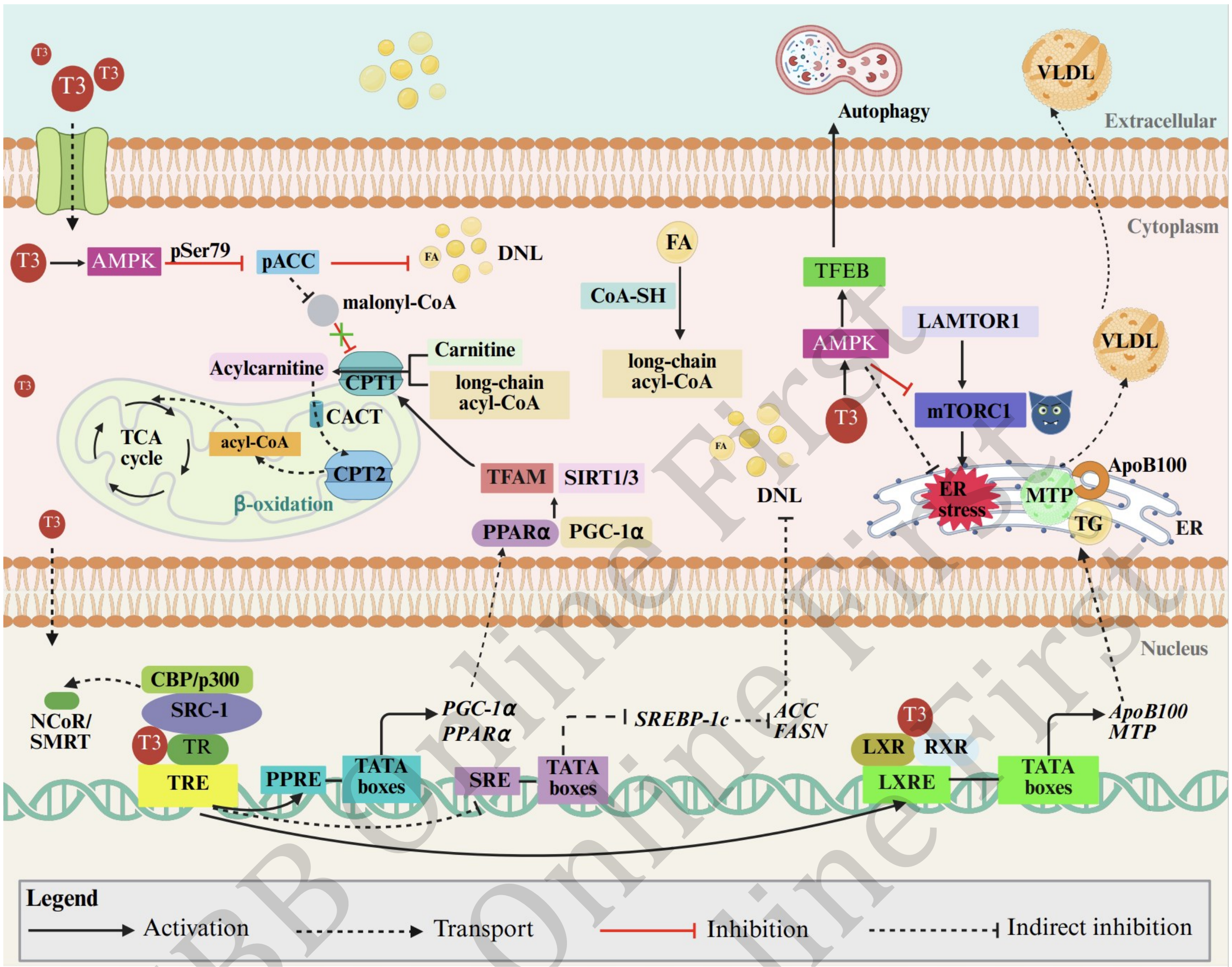


Fig. 2 Molecular Mechanisms of TH Regulation in Hepatic Lipid Homeostasis

progresses to MASH. At this stage, TH functions not only as a metabolic regulator but also as a pivotal anti-inflammatory factor, demonstrating potential in experimental models to suppress inflammatory cascades by blocking pyroptotic pathways and remodeling the gut－liver axis microenvironment.

2.2.1 NLRP3 inflammasome and pyroptosis

Aberrant activation of the nucleotide-binding domain leucine-rich repeat and pyrin domain-containing receptor 3 (NLRP3) inflammasome and downstream gasdermin D (GSDMD) -mediated pyroptosis constitute the core mechanisms driving uncontrolled inflammation in MASH[56]. Under lipotoxic stimuli, damaged hepatocytes release ROS and mitochondrial DNA (mtDNA), which activates the NLRP3 complex, leading to GSDMD cleavage, plasma membrane rupture, and IL-1β/IL-18 release, and thereby triggering immune cell infiltration[57-58].

Animal studies suggest that TH may modulate this pathway through multiple steps: First, TH potentially reduces reactive oxygen species (ROS) signaling for NLRP3 activation by inducing mitophagy and upregulating PGC-1α-mediated SOD2 expression[59-60]. Second, TRβ agonists can downregulate NLRP3, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and caspase-1 expression while suppressing interleukin-1β (IL-1β) release[61-63], although the specific transcriptional regulatory mechanisms remain unclear. Notably, current studies are primarily based on acute inflammatory models, and their efficacy in the chronic inflammatory environment of MASLD requires further validation.

2.2.2 Gut－liver axis microenvironment regulation

Gut microbiota dysbiosis and intestinal barrier disruption represent important external drivers of

MASH progression[64]. Increased intestinal permeability resulting from tight junction disruption facilitates translocation of bacterial lipopolysaccharide (LPS) into the liver via the portal circulation, leading to Kupffer cell activation and pro-inflammatory cytokine release, including tumor necrosis factor-α (TNF-α)[65].

Potential interactions between TH and the gut microbiota. Observational studies indicate that hypothyroidism is associated with reduced gut microbial diversity and an altered Firmicutes/Bacteroidetes ratio[66]. Mechanistically, TH suppresses cholesterol 7α-hydroxylase (CYP7A1) expression and reduces total bile acid synthesis in human hepatocytes, which may indirectly influence the gut microbiota composition by altering bile acid profiles[67-68]. Conversely, microbiota-derived short-chain fatty acids (SCFAs) can modulate hepatic gene expression through epigenetic mechanisms, including histone deacetylase inhibition, and may thereby influence hepatic TH signaling[69]. However, current evidence is largely correlative, and whether TH-mediated microbiota changes represent direct effects or secondary consequences of metabolic improvement remains unclear.

Evidence gaps. Although interventions such as probiotics or fecal microbiota transplantation (FMT) can improve microbiota composition and attenuate hepatic inflammation[70], no studies have directly demonstrated that TH-based interventions reverse microbiota dysbiosis in MASH. Further mechanistic and clinical studies are required to clarify causal relationships within the TH – gut microbiota axis (Figure 3).

2.3 Fibrosis stage: evidence related to HSC functional state transitions

The fibrosis stage is characterized by hepatic stellate cells (HSC) activation, excessive extracellular matrix (ECM) deposition, and hepatic microenvironment remodeling[71]. When MASH-associated inflammation persists chronically, the hepatic microenvironment gradually transitions from a metabolic stress and inflammation-dominated state to a repair-scarring phenotype. Activation and myofibroblastic transdifferentiation of quiescent HSCs constitute the central events driving excessive ECM deposition[72]. The degree of hepatic fibrosis is closely associated with adverse long-term outcomes in patients with chronic liver disease, including decompensated cirrhosis and hepatocellular carcinoma, representing a critical watershed in disease progression from relatively reversible to irreversible stages[73]. TH and its receptors have been observed in various experimental models to influence HSC activation status. While TRβ mediates TH effects in hepatocytes, recent evidence indicates that TRα is the predominant isoform in HSCs and functions by inhibiting transforming growth factor-beta (TGF- β) signaling and fibrogenic activation[72, 74-75].

2.3.1 Evidence related to HSC functional state transitions

Hepatic fibrosis regression depends on the resolution of activated HSCs through terminal fates such as apoptosis, senescence, or reversion to quiescence[72, 75]. Senescent HSCs participate in fibrosis regression through reduced ECM synthesis capacity and senescence-associated secretory phenotype (SASP) factor release[73, 75]. However, the associated inflammatory and tumorigenic risks require careful evaluation.

Limitations of cross-organ studies. Currently, direct evidence for TH-induced hepatic HSC senescence is limited, with existing inferences primarily derived from pulmonary fibrosis studies where T3 attenuates fibrosis primarily through improving epithelial mitochondrial function and modulating fibroblast activation[76-79]. However, pulmonary fibroblasts and HSCs exhibit significant differences in vitamin A metabolism, sinusoidal capillarization, and other functions, and the fibrotic microenvironments of these two organs are markedly distinct, precluding direct extrapolation.

Potential mechanisms and validation pathways. Based on the metabolic regulatory effects of TH, we hypothesize that it may influence HSCs through several mechanisms, including ameliorating steatosis to indirectly reduce profibrotic signals such as TGF-β, affecting HSC metabolic reprogramming via AMPK/PGC-1α, and directly regulating senescence genes via TR-mediated transcription, with TRα likely being the primary mediator given its predominance in HSCs. Validation of these hypotheses requires determining TRα and TRβ expression levels in HSCs to clarify the predominant isoform, assessing the effects of T3 on senescence markers in primary HSCs, and evaluating antifibrotic efficacy in HSC-specific TR knockout mice, with particular attention to TRα given its predominance in HSCs.

2.3.2 TGF-β/SMAD signaling and ECM alterations

The transforming growth factor-beta (TGF-β)/SMAD family protein (TGF-β/SMAD) signaling pathway is a key profibrotic mechanism maintaining HSC activation status and sustained ECM deposition. This pathway drives the transcription of fibrosis-related genes including collagen type I alpha 1 chain (Col1a1), collagen type III alpha 1 chain (Col3a1), and alpha-smooth muscle actin (α-SMA), a regulatory pattern conserved across chronic liver injuries of different etiologies[80-81]. Multiple in vitro experiments and animal studies suggest that T3 may functionally interact with TGF-β/SMAD signaling axis *via* TRβ. In these models, T3 treatment reduces SMAD2/3 phosphorylation levels, accompanied by attenuated TGF-β-induced ECM gene transcriptional activity[82]. Furthermore, in various experimental fibrosis models, T3 intervention leads to reduced tissue scarring. It should be noted that these findings primarily derive from animal models and in vitro studies, and their relevance to MASLD-associated hepatic fibrosis requires further investigation (Figure 3).

2.4 HCC stage: TH/TRβ signaling dysregulation and tumor progression

When MASLD progresses to the hepatocellular carcinoma (HCC) stage, the TH/TRβ signaling axis undergoes functional dysregulation. Although observational studies suggest a potential association between hypothyroidism and elevated HCC risk, causal relationships remain unclear[83-84]. At the molecular level, downregulated TRβ expression and attenuated TH signaling activity in HCC tissues have been widely observed, and this "tumor-associated hypothyroid" state may contribute to tumor progression by promoting metabolic reprogramming[85].

2.4.1 Intratumoral TH signaling disruption: synergistic dysregulation of TRβ and DIO1

HCC tissues exhibit concurrent alterations characterized by downregulated TRβ expression and diminished DIO1 activity[86-87]. TRβ downregulation may be associated with promoter methylation, upregulation of transcriptional repressors, or receptor mutations. Meanwhile, significantly reduced expression and activity of DIO1, which primarily catalyzes the outer ring deiodination of T4 to produce active T3, leads to decreased T3 bioavailability within tumor tissues. Notably, DIO expression shows dynamic changes across the MASLD spectrum, with initial compensatory upregulation in early stages followed by progressive downregulation during MASH and HCC development[88]. This biphasic pattern and its specific relationship with MASH-HCC progression require further investigation. This synergistic dysregulation of receptors and metabolic enzymes collectively impairs intracellular TH signal transduction in tumor cells, establishing a foundation for metabolic reprogramming.

Overview of thyroid hormone (TH) – mediated regulation of hepatic metabolism, inflammation, fibrogenesis, and tumor-associated metabolic reprogramming across the MASLD disease spectrum, from steatosis to hepatocellular carcinoma. TRα/β, thyroid hormone receptors alpha and beta; IRS, insulin receptor substrate; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; AMPK, AMP-activated protein kinase; PPARα, peroxisome proliferator-activated receptor alpha; SREBP-1c, sterol regulatory element-binding protein-1c; VLDL, very-low-density lipoprotein; ApoB100, apolipoprotein B100; MTP, microsomal triglyceride transfer protein; ROS, reactive oxygen species; mtDNA, mitochondrial DNA; NLRP3, NOD-like receptor family pyrin domain-containing 3; GSDMD, gasdermin D; IL, interleukin (including IL-1β and IL-18); TNF-α, tumor necrosis factor-alpha; LPS, lipopolysaccharide; ZO-1, zonula occludens-1; TGF-β, transforming growth factor-beta; SMAD, mothers against decapentaplegic homologs; HSC, hepatic stellate cell; ECM, extracellular matrix; α-SMA, alpha-smooth muscle actin; TFEB, transcription factor EB; mTORC1, mechanistic target of rapamycin complex 1; DIO1, iodothyronine deiodinase 1; SASP, senescence-associated secretory phenotype.

2.4.2 Metabolic reprogramming and therapeutic resistance

Attenuated TH signaling plays a pivotal role in metabolic reprogramming in HCC. This process is characterized by mitochondrial dysfunction, including the downregulation of genes such as PGC-1α and reduced mitochondrial number, impaired oxidative phosphorylation (OXPHOS) due to decreased respiratory chain complex expression and OXPHOS efficiency, enhanced glycolysis marked by

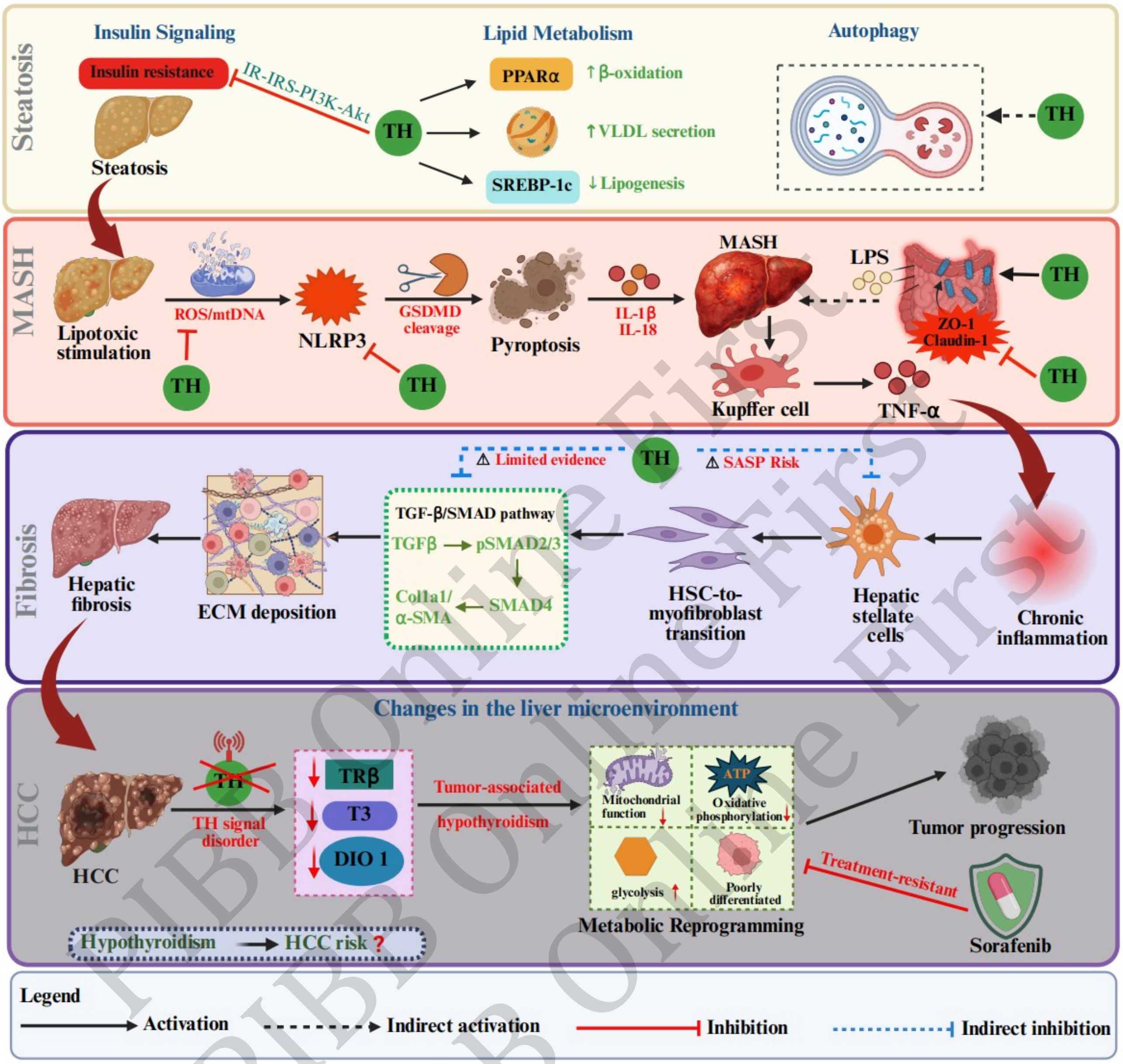


Fig. 3 The multidimensional regulatory network of TH during the progression of the MASLD disease spectrum

upregulation of rate-limiting enzymes such as hexokinase 2 (HK2) and lactate dehydrogenase A (LDHA), consistent with the Warburg effect, and reduced cellular differentiation associated with downregulation of hepatocyte nuclear factor 4 alpha (HNF4α) and increased tumor aggressiveness[85, 89-90]. This metabolic reprogramming may be associated with therapeutic resistance, as similar metabolic phenotypes have been linked to reduced sorafenib sensitivity in preclinical models. Furthermore, TRβ signaling deficiency may contribute to enhanced tumor invasiveness, potentially through modulation of the epithelial-mesenchymal transition and related invasiveness pathways[86]. Given that the TRβ agonist Resmetirom has been approved for MASH treatment, it may theoretically reduce HCC incidence risk in MASH patients by improving metabolic homeostasis. However, this long-term benefit currently lacks prospective evidence.

In summary, in-depth understanding of the "tumor-associated hypothyroid" phenomenon specifically in MASH-HCC will provide critical foundations for developing TH signaling-based prevention and therapeutic strategies (Figure 3).

3 Diagnostic significance of thyroid function indices in MASLD

3.1 Association between conventional thyroid function indices and MASLD

Clinically, overt hypothyroidism manifests as elevated TSH with reduced free thyroxine (FT4), while subclinical hypothyroidism (SCH) presents as elevated TSH with normal FT4[91]. Hyperthyroidism manifests as decreased TSH with elevated FT4 and/or free triiodothyronine (FT3) [92]. Multiple epidemiological studies suggest that thyroid dysfunction correlates with MASLD occurrence and severity. Both overt hypothyroidism and SCH are associated with increased MASLD incidence risk[8, 93]. Even within euthyroid populations, FT4 in the low-normal range or TSH in the high-normal range correlates with elevated hepatic steatosis risk, potentially reflecting early metabolic abnormalities[94].

3.2 Stage−specific thyroid function changes and sensitivity indices

Thyroid function indices exhibit variations across the MASLD spectrum. Elevated TSH is more commonly observed in simple steatosis[95]. MASH is associated with reduced FT3 and impaired thyroid hormone sensitivity[95]. In patients with hepatic fibrosis, lower FT3 levels and related sensitivity indices demonstrate a graded correlation with fibrosis severity and adverse outcomes[95-96], suggesting that thyroid function parameters may hold potential prognostic value in MASLD staging and risk assessment.

In recent years, composite indices reflecting thyroid hormone sensitivity, such as the FT3/FT4 ratio, thyroid feedback quantile-based index (TFQI), and thyroid-stimulating hormone index (TSHI), have garnered increasing attention. These indices comprehensively reflect peripheral hormone conversion efficiency and central-peripheral feedback regulatory status. Emerging evidence demonstrates that impaired thyroid hormone sensitivity, as assessed by these composite indices, is independently associated with the presence and severity of hepatic fibrosis in euthyroid MASLD patients. Studies have shown that reduced central sensitivity to FT3 correlates with MASLD progression to liver fibrosis[96], while elevated TFQI and TSHI values exhibit graded associations with advanced fibrosis stages[97-98]. These indices demonstrate a potential for stronger risk discrimination capacity compared to conventional thyroid parameters[96-98], reflecting the limitations of conventional thyroid function tests and the importance of tissue-level thyroid hormone availability in MASLD progression[99], which may provide quantitative tools for assessing "intrahepatic thyroid hormone relative insufficiency" and identifying patients at higher risk for disease progression (Table 1).

Table 1 Biological significance and potential clinical utility of TH−related indicators across different stages of MASLD

Indicator	Biological significance	Association with MASLD	Disease stage	Clinical utility	References
TSH	Central thyroid axis status; hypothyroid tendency	Elevated TSH linked to higher MASLD risk and severity	Steatosis to MASH	Risk assessment; identification of thyroid dysfunction	[8, 93]
FT4	Circulating; TH supply	Lower FT4 linked to higher steatosis risk	Steatosis	Early indicator of low TH status	[94, 99]
FT3	Active TH output	Decreased FT3 linked to advanced fibrosis and poor outcomes	MASH to fibrosis/cirrhosis	Auxiliary marker for fibrosis severity	[95-96]
FT3/FT4 ratio	Peripheral TH conversion efficiency and deiodinase activity	Peripheral deiodinase activity marker linked to metabolic risk and fibrosis severity	Entire spectrum	Understanding metabolic adaptation and decompensation	[96-98]
TFQI, TSHI	Central-peripheral TH feedback and sensitivity	Elevated indices trend with increased fibrosis	Under investigation in MASLD	Exploratory marker for heterogeneity and treatment response	[96-98]

Notes: FT3, free triiodothyronine. FT4, free thyroxine. TFQI, thyroid feedback quantile-based index. TSH, thyroid-stimulating hormone. TSHI, thyroid-stimulating hormone index. TH, thyroid hormone. MASLD, metabolic dysfunction - associated steatotic liver disease. MASH, metabolic dysfunction - associated steatohepatitis.

3.3 Limitations of the current evidence and future research directions

However, current evidence has several limitations. First, most studies are cross-sectional, limiting causal inference. Second, the association between TSH and hepatic steatosis shows ethnic heterogeneity. Thresholds may differ between Asian and Western populations, yet large-scale prospective validation in diverse populations is lacking. Third, whether serum TH levels accurately reflect intrahepatic TH signaling remains controversial, as individual variability in hepatic deiodinase activity, which is influenced by genetic and metabolic factors, may cause dissociation between circulating markers and local biological effects. While composite sensitivity indices may partially address the issue of serum-hepatic dissociation, they lack standardized reference ranges and require validation across MASLD stages.

Therefore, before clinical implementation, future research should prioritize prospective cohort studies to establish causality, multi-ethnic validation of reference ranges, mechanistic studies that integrate serum biomarkers with hepatic tissue assessment, and intervention trials evaluating thyroid-targeted therapies, including thyroid hormone replacement and TRβ-selective agonists, for MASLD-related outcomes.

4 Therapeutic strategies targeting the TH pathway

4.1 Development of the TRβ agonists

Owing to the important role of TRβ in regulating hepatic lipid metabolism, maintaining mitochondrial function, and promoting cholesterol clearance, therapeutic strategies targeting TRβ have long been considered promising for treating MASLD/MASH[100]. However, early non-selective thyroid hormone analogs (e. g., Eprotirome) also activated TRα, which is widely expressed in multiple tissues including the heart, bone, and skeletal muscle, leading to cardiovascular and bone metabolism-related adverse effects in clinical studies, which limited further development of these agents[101]. These experiences prompted a shift in the development of next-generation TRβ agonists, focusing on improving TRβ selectivity and enhancing hepatic targeting and first-pass extraction (e. g., Resmetirom, VK2809) to achieve relatively liver-targeted action while reducing systemic exposure risk[102-103]. This strategy reflects the gradual evolution of TH pathway-targeted therapy from broad systemic effects toward organ-selective intervention[104] .

4.2 Phase III clinical trials of resmetirom: efficacy and metabolic improvement

Resmetirom is an oral, liver-targeted TRβ agonist approved for adults with non-cirrhotic MASH and moderate-to-severe fibrosis[9, 102]. In the Phase III MAESTRO-NASH randomized controlled trial, after 52 weeks of Resmetirom treatment, a proportion of patients achieved MASH resolution without fibrosis progression, or improvement in fibrosis stage from baseline, at rates higher than the placebo group[102, 105]. Beyond histological endpoints, the drug significantly improved lipid metabolism parameters (marked reductions in LDL-C, triglycerides, and ApoB)[102, 105]. HbA1c levels remained relatively stable in patients with T2DM during the 52-week trial period. However, the trial did not include specific measures for assessing systemic insulin sensitivity (e. g., clamp techniques), thus precluding definitive conclusions regarding direct effects on extrahepatic insulin resistance. Given its liver-selective design, systemic metabolic improvements are more likely indirect consequences of restored hepatic function.

4.3 Safety profile and target population

Based on current clinical evidence, resmetirom is indicated primarily for adults with non-cirrhotic MASH and moderate-to-severe fibrosis (F2 – F3 stage)[9]. Subgroup analyses from MAESTRO-NASH demonstrated consistent efficacy across diverse metabolic phenotypes, with similar rates of MASH resolution and fibrosis improvement regardless of comorbid diabetes, dyslipidemia, or the concurrent use of glucose-lowering therapies. While patients with these comorbidities typically presented with more advanced metabolic dysfunction and higher cardiovascular risk at baseline, the lipid-lowering effects of resmetirom remained beneficial across all subgroups, though long-term cardiovascular outcome data are still awaited.

Regarding safety, clinical trial data indicate that resmetirom is generally well tolerated. Common adverse effects include diarrhea and nausea, typically occurring early in treatment and mostly mild to moderate in severity[105]. Potential drug-drug interactions should be considered in clinical practice.

As Resmetirom is primarily metabolized *via* the CYP2C8 pathway, co-administration with strong CYP2C8 inhibitors (*e. g.*, gemfibrozil) should be avoided. Additionally, use in patients with decompensated cirrhosis (Child – Pugh B/C) is currently not recommended due to insufficient safety data and significantly increased drug exposure[9].

Ongoing cardiovascular safety considerations. Although Resmetirom is designed to be liver-selective, participants in the MAESTRO trial were predominantly middle-aged individuals with multiple cardiometabolic risk factors (67% with type 2 diabetes, 78% with hypertension, 71% with dyslipidemia) and intermediate cardiovascular risk (estimated 10-year ASCVD risk ~14% – 15%), and follow-up duration was relatively limited at 52 weeks[102]. Notably, trial data showed no adverse effects on heart rate, blood pressure, or arrhythmias, with major adverse cardiovascular events (MACE) occurring at similarly low rates across all groups (0.3% in each).

In real-world settings, patients with MASLD frequently have comorbid cardiovascular disease and higher risk profiles. While the high THR-β selectivity of resmetirom is designed to minimize cardiac THR-α -mediated effects such as tachycardia or arrhythmias, and its LDL-C reduction (13% – 16%) may confer protective effects, the net cardiovascular impact in higher-risk populations requires validation through dedicated cardiovascular outcomes trials with longer follow-up.

4.4 Real−world application experience

Real-world studies have revealed practical challenges in the clinical application of resmetirom. Regarding patient selection, a biopsy-validated MASLD cohort study from Turkey found that non-invasive tests struggled to precisely identify patients meeting treatment criteria for significant fibrosis[106]. Similarly, a German steatotic liver disease registry study showed that the proportion of patients actually meeting treatment criteria was lower than expected[107]. For monitoring tools, vibration-controlled transient elastography and magnetic resonance elastography demonstrated good concordance in MASLD fibrosis staging, providing a reliable basis for non-invasive monitoring[108]. A Spanish Hepamet registry study further proposed non-invasive criteria for pharmacotherapy indications in clinical practice[109]. Regarding early application experience, real-world data from the United States showed that Resmetirom was well tolerated[110]. However, challenges such as drug accessibility remain significant barriers[109]. Given the current lack of long-term follow-up data beyond one year[111] there is a need to establish standardized non-invasive monitoring protocols and long-term efficacy assessment systems.

4.5 Exploration of combination therapy strategies

The development and progression of MASH involves multiple metabolic and inflammatory pathways, making single-target interventions unlikely to fully address its complex pathological processes. Studies have shown that VK2809, a highly selective TRβ agonist, significantly reduced hepatic fat content in a Phase 2 randomized, placebo-controlled trial[112]. The multifactorial nature of MASH supports combining TRβ agonists with other metabolic-modulating agents (*e. g.*, GLP-1 receptor agonists or FGF21 analogs), thus representing a rational therapeutic strategy[113]. While direct evidence for such TRβ agonist-based combination therapy is currently limited, the potential for synergistic effects is supported by the complementary mechanisms of these agents in addressing distinct metabolic pathways and the crosstalk between thyroid hormone, GLP-1, and FGF21 signaling[113]. Rigorous preclinical and clinical studies are needed to evaluate the efficacy and safety of these combination regimens, particularly regarding their impact on fibrosis reversal and long-term clinical outcomes (Table 2).

5 Limitations of current research

Despite accumulating evidence supporting a regulatory role of thyroid hormones in MASLD, several important limitations remain. Species differences between humans and rodents, particularly in hepatic deiodinase expression patterns (notably DIO1 activity) and TRβ isoform distribution, may limit the translational relevance of preclinical efficacy and safety data. Long-term safety also remains uncertain, as although Phase 3 trials of 52 – 54 weeks have demonstrated acceptable cardiac function and thyroid axis safety, extended follow-up is required to assess bone health, especially fracture risk, and cardiovascular outcomes in high-risk populations that are underrepresented in clinical trials. Moreover, serum thyroid hormone levels may not accurately

Table 2 Clinical profile, target population, and safety landscape of resmetirom.

Feature	Key content	Clinical significance	References
Core efficacy	MASH resolution and fibrosis improvement versus placebo; favorable lipid effects	Improves hepatic histology and metabolic abnormalities	[102, 105, 114]
Target population	Adults with non-cirrhotic MASH and moderate-to-severe fibrosis (F2-F3)	FDA-approved indication	[9]
Contraindicated population	Decompensated cirrhosis (Child–Pugh B/C)	Lack of safety data	[9]
Safety	Common mild–moderate diarrhea/nausea and avoid strong CYP2C8 inhibitors	Well tolerated; long-term CV safety not fully established	[9, 105]
Real-world data	Safety consistent with registration trials; noninvasive markers show improvement; patient selection remains challenging	Supports clinical feasibility; standardized monitoring protocols needed	[106, 109]
Current limitations	Lack of long-term (>1 year) data Limited drug accessibility	Long-term efficacy evaluation and optimized application strategies required	[109, 111]

Notes: FDA, Food and Drug Administration. MASH, metabolic dysfunction-associated steatohepatitis. CYP2C8, cytochrome P450 2C8. F2, fibrosis stage 2. F3, fibrosis stage 3. CV, cardiovascular.

reflect intrahepatic thyroid signaling status, since local T3 concentrations are tightly regulated by deiodinases such as DIO1 and DIO3 and may not correlate with circulating levels. The absence of validated biomarkers predicting responsiveness to TRβ agonists further limits patient stratification and personalized treatment approaches. In addition, mechanistic understanding of cell-type-specific and zonated hepatic responses to TRβ activation remains incomplete, hindering the optimization of therapeutic strategies, and potential interactions between TH-based therapies and common MASLD comorbidities, including type 2 diabetes and cardiovascular disease, require further investigation to better inform clinical management.

6 Conclusions and future perspectives

The progression of MASLD involves a complex, multifactorial pathophysiology. This review systematically elucidates how the TH/TRβ signaling axis regulates the entire disease spectrum: from lipid metabolism and mitochondrial function in steatosis, through inflammatory modulation and gut barrier maintenance in MASH, to hepatic stellate cell fate determination and ECM remodeling in fibrosis, and ultimately to the tumor microenvironment in HCC. The approval of Resmetirom marks an important step in translating these mechanistic insights into clinical practice.

To realize the full therapeutic potential of TH-targeted therapy, three key areas require further investigation. First, mechanistic precision is needed. Understanding how TH signaling differs across hepatic cell types (hepatocytes, HSCs, Kupffer cells) and lobular zones (periportal versus pericentral) will explain why patients with normal serum TSH may exhibit intrahepatic hypothyroidism. Single-cell and spatial transcriptomic approaches will be instrumental in addressing these questions.

Second, predictive biomarkers must be identified. Integrating genomic markers (THRB and DIO1 polymorphisms), metabolomic profiles (baseline fatty acid signatures), and clinical phenotypes could enable the development of response prediction models that identify patients most likely to benefit. Concurrently, long-term safety monitoring in underrepresented populations, including pediatric, elderly, and those with cardiovascular comorbidities groups—is essential to comprehensively assess adverse event risks.

Third, the development of next-generation therapeutics should advance on multiple fronts: enhancing liver selectivity through prodrug design or hepatotropic ligands. Developing TRβ1-selective molecules with minimal TRβ2 activity to reduce pituitary suppression, and establishing evidence-based combination regimens with GLP-1RAs and FXR agonists to achieve synergistic effects should be prioritized.

As these challenges are addressed, TH-targeted MASLD therapy will transition from empirical treatment to biomarker-guided precision medicine, offering more effective solutions for this pressing global health burden.

References

[1] Hou M, Gu Q, Cui J, *et al*. Proportion and clinical characteristics of metabolic-associated fatty liver disease and associated liver fibrosis in an urban Chinese population. Chin Med J, 2025, **138**(7): 829-837

[2] Rinella M E, Lazarus J V, Ratziu V, *et al*. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol, 2023, **79**(6): 1542-1556

[3] Younossi Z M, Kalligeros M, Henry L. Epidemiology of metabolic dysfunction-associated steatotic liver disease. Clin Mol Hepatol, 2025, 31: S32-S50

[4] Ma Y, Wang J, Xiao W, *et al*. A review of MASLD-related hepatocellular carcinoma: progress in pathogenesis, early detection, and therapeutic interventions. Front Med, 2024, **11**: 1410668

[5] Patel S, Kasem F, Flaherty D, *et al*. HCC in MASLD and ALD: biochemical pathways, epidemiology, diagnosis, and treatment. BioChem, 2025, **5**(3): 19

[6] European Association for the Study of the Liver (EASL), European Association for the Study of the Diabetes (EASD), European Association for the Study of the Obesity (EASO). EASL – EASD – EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol, 2024, **81**(3): 492-542

[7] Labenz C, Kostev K, Armandi A, *et al*. Impact of thyroid disorders on the incidence of non-alcoholic fatty liver disease in Germany. U Eur Gastroenterol J, 2021, **9**(7): 829-836

[8] Mantovani A, Csermely A, Bilson J, *et al*. Association between primary hypothyroidism and metabolic dysfunction-associated steatotic liver disease: an updated meta-analysis. Gut, 2024, **73**(9): 1554-1561

[9] Keam S J. Resmetirom: first approval. Drugs, 2024, **84**(6): 729-735

[10] van der Deure W M, Friesema E C H, de Jong F J, *et al*. Organic anion transporter 1B1: an important factor in hepatic thyroid hormone and estrogen transport and metabolism. Endocrinology, 2008, **149**(9): 4695-4701

[11] Friesema E C H, Ganguly S, Abdalla A, *et al*. Identification of monocarboxylate transporter 8 as a specific thyroid hormone transporter. J Biol Chem, 2003, **278**(41): 40128-40135

[12] Gereben B, Zavacki A M, Ribich S, *et al*. Cellular and molecular basis of deiodinase-regulated thyroid hormone Signaling1. Endocr Rev, 2008, **29**(7): 898-938

[13] Lopez-Alcantara N, Naujack A M, Chen Y, *et al*. Dysregulation of hepatic deiodinase type I in metabolically associated steatotic liver disease. J Mol Endocrinol, 2025, **75**(2): e250096

[14] Zhang J, Lazar M A. The mechanism of action of thyroid hormones. Annu Rev Physiol, 2000, 62: 439-466

[15] Astapova I, Lee L J, Morales C, *et al*. The nuclear corepressor, NCoR, regulates thyroid hormone action *in vivo*. Proc Natl Acad Sci U S A, 2008, **105**(49): 19544-19549

[16] Hörlein A J, Näär A M, Heinzel T, *et al*. Ligand-independent repression by the thyroid hormone receptor mediated by a nuclear receptor co-repressor. Nature, 1995, **377**(6548): 397-404

[17] Chen J D, Evans R M. A transcriptional co-repressor that interacts with nuclear hormone receptors. Nature, 1995, **377**(6548): 454-457

[18] Fondell J D, Ge H, Roeder R G. Ligand induction of a transcriptionally active thyroid hormone receptor coactivator complex. Proc Natl Acad Sci U S A, 1996, **93**(16): 8329-8333

[19] Moore J M R, Galicia S J, McReynolds A C, *et al*. Quantitative proteomics of the thyroid hormone receptor-coregulator interactions. J Biol Chem, 2004, **279**(26): 27584-27590

[20] Bergh J J, Lin H Y, Lansing L, *et al*. Integrin αVβ3 contains a cell surface receptor site for thyroid hormone that is linked to activation of mitogen-activated protein kinase and induction of angiogenesis. Endocrinology, 2005, **146**(7): 2864-2871

[21] Davis P J, Goglia F, Leonard J L. Nongenomic actions of thyroid hormone. Nat Rev Endocrinol, 2016, **12**(2): 111-121

[22] Wrutniak-Cabello C, Casas F, Cabello G. Thyroid hormone action in mitochondria. J Mol Endocrinol, 2001, **26**(1): 67-77

[23] Incerpi S, Gionfra F, De Luca R, *et al*. Extranuclear effects of thyroid hormones and analogs during development: an old mechanism with emerging roles. Front Endocrinol, 2022, **13**: 961744

[24] Tedeschi L, Vassalle C, Iervasi G, *et al*. Main factors involved in thyroid hormone action. Molecules, 2021, **26**(23): 7337

[25] Truong X T, Lee D H. Hepatic insulin resistance and steatosis in metabolic dysfunction-associated steatotic liver disease: new insights into mechanisms and clinical implications. Diabetes Metab J, 2025, **49**(5): 964-986

[26] Dua A, Kumari R, Singh M, *et al*. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): the interplay of gut microbiome, insulin resistance, and diabetes. Front Med, 2025, **12**: 1618275

[27] Zhou J, Tripathi M, Ho J P, *et al*. Thyroid hormone decreases hepatic steatosis, inflammation, and fibrosis in a dietary mouse model of nonalcoholic steatohepatitis. Thyroid, 2022, **32**(6): 725-738

[28] Sinha R A. Thyroid hormone-mediated selective autophagy and its implications in countering metabolic dysfunction-associated steatotic liver disease. Endocrinol Metab, 2024, **39**(5): 686-692

[29] Perry R J, Samuel V T, Petersen K F, *et al*. The role of hepatic lipids in hepatic insulin resistance and type 2 diabetes. Nature, 2014, **510**(7503): 84-91

[30] Samuel V T, Shulman G I. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. J Clin Investig, 2016, **126**(1): 12-22

[31] Haeusler R A, McGraw T E, Accili D. Biochemical and cellular properties of insulin receptor signalling. Nat Rev Mol Cell Biol, 2018, **19**(1): 31-44

[32] Feng X, Jiang Y, Meltzer P, *et al*. Thyroid hormone regulation of hepatic genes *in vivo* detected by complementary DNA

microarray. Mol Endocrinol, 2000, **14**(7): 947-955

[33] Beurel E, Grieco S F, Jope R S. Glycogen synthase kinase-3 (GSK3): Regulation, actions, and diseases. Pharmacol Ther, 2015, 148: 114-131

[34] Singh B K, Sinha R A, Zhou J, *et al*. FoxO1 deacetylation regulates thyroid hormone-induced transcription of key hepatic gluconeogenic genes. J Biol Chem, 2013, **288**(42): 30365-30372

[35] Singh B K, Sinha R A, Zhou J, *et al*. Hepatic *FOXO1* target genes are co-regulated by thyroid hormone *via* RICTOR protein deacetylation and MTORC2-AKT protein inhibition. J Biol Chem, 2016, **291**(1): 198-214

[36] da Silva Teixeira S, Panveloski-Costa A C, Carvalho A, *et al*. Thyroid hormone treatment decreases hepatic glucose production and renal reabsorption of glucose in alloxan-induced diabetic Wistar rats. Physiol Rep, 2016, **4**(18): e12961

[37] Hiroi Y, Kim H H, Ying H, *et al*. Rapid nongenomic actions of thyroid hormone. Proc Natl Acad Sci U S A, 2006, **103**(38): 14104-14109

[38] Shimano H, Sato R. SREBP-regulated lipid metabolism: convergent physiology—divergent pathophysiology. Nat Rev Endocrinol, 2017, **13**(12): 710-730

[39] Mullur R, Liu Y Y, Brent G A. Thyroid hormone regulation of metabolism. Physiol Rev, 2014, **94**(2): 355-382

[40] Fullerton M D, Galic S, Marcinko K, *et al*. Single phosphorylation sites in Acc1 and Acc2 regulate lipid homeostasis and the insulin-sensitizing effects of metformin. Nat Med, 2013, **19**(12): 1649-1654

[41] Zhang Y, Ma K, Song S, *et al*. Peroxisomal proliferator-activated receptor-γ coactivator-1α (PGC-1α) enhances the thyroid hormone induction of carnitine palmitoyltransferase I (CPT-Iα). J Biol Chem, 2004, **279**(52): 53963-53971

[42] Thakran S, Sharma P, Attia R R, *et al*. Role of sirtuin 1 in the regulation of hepatic gene expression by thyroid hormone. J Biol Chem, 2013, **288**(2): 807-818

[43] Zhenghui G, Simon C, Yao Z. Lipoprotein metabolism in nonalcoholic fatty liver disease. J Biomed Res, 2013, **27**(1): 1

[44] Fujita K, Nozaki Y, Wada K, *et al*. Dysfunctional very-low-density lipoprotein synthesis and release is a key factor in nonalcoholic steatohepatitis pathogenesis. Hepatology, 2009, **50**(3): 772-780

[45] Sinha R A, Singh B K, Yen P M. Direct effects of thyroid hormones on hepatic lipid metabolism. Nat Rev Endocrinol, 2018, **14**(5): 259-269

[46] Marcondes-de-Castro I A, Reis-Barbosa P H, Marinho T S, *et al*. AMPK/mTOR pathway significance in healthy liver and non-alcoholic fatty liver disease and its progression. J Gastroenterol Hepatol, 2023, **38**(11): 1868-1876

[47] Videla L A. T_3-induced liver AMP-activated protein kinase signaling: redox dependency and upregulation of downstream targets. World J Gastroenterol, 2014, **20**(46): 17416

[48] Jang Y, Ko M, Lee J Y, *et al*. Inhibition of lysosomal LAMTOR1 increases autophagy by suppressing the MTORC1 pathway to ameliorate lipid accumulations in MAFLD. Autophagy, 2025, **21**(12): 2633-2649

[49] Lin J, Huang C, Zhao J, *et al*. The novel TFEB agonist desloratadine ameliorates hepatic steatosis by activating the autophagy-lysosome pathway. Front Pharmacol, 2024, **15**: 1449178

[50] Sinha R A, Yen P M. Thyroid hormone-mediated autophagy and mitochondrial turnover in NAFLD. Cell Biosci, 2016, **6**(1): 46

[51] Sinha R A, You S H, Zhou J, *et al*. Thyroid hormone stimulates hepatic lipid catabolism *via* activation of autophagy. J Clin Invest, 2012, **122**(7): 2428-2438

[52] Bezawork-Geleta A, Devereux C J, Keenan S N, *et al*. Proximity proteomics reveals a mechanism of fatty acid transfer at lipid droplet-mitochondria- endoplasmic reticulum contact sites. Nat Commun, 2025, **16**: 2135

[53] Yu H, Liu Y, Gulbranson D R, *et al*. Extended synaptotagmins are Ca^{2+}-dependent lipid transfer proteins at membrane contact sites. Proc Natl Acad Sci U S A, 2016, **113**(16): 4362-4367

[54] Janer A, Morris J L, Antonicka H, *et al*. ESYT1 tethers the ER to mitochondria and is required for mitochondrial lipid and calcium homeostasis. Life Sci Alliance, 2024, **7**(1): e202302335

[55] Nemoto S, Fergusson M M, Finkel T. SIRT1 functionally interacts with the metabolic regulator and transcriptional coactivator PGC-1α. J Biol Chem, 2005, **280**(16): 16456-16460

[56] Chen F, Li S, Liu M, *et al*. Targeting BRD4 mitigates hepatocellular lipotoxicity by suppressing the NLRP3 inflammasome activation and GSDMD-mediated hepatocyte pyroptosis. Cell Mol Life Sci, 2024, **81**(1): 295

[57] Lucas-Ruiz F, Peñín-Franch A, Pons J A, *et al*. Emerging role of NLRP3 inflammasome and pyroptosis in liver transplantation. Int J Mol Sci, 2022, **23**(22): 14396

[58] Li X, Zhang Z, Han Y, *et al*. NLRP3 inflammasome and pyroptosis: implications in inflammation and multisystem disorders. PeerJ, 2025, **13**: e19887

[59] Abu Shelbayeh O, Arroum T, Morris S, *et al*. PGC-1α is a master regulator of mitochondrial lifecycle and ROS stress response. Antioxidants, 2023, **12**(5): 1075

[60] Wulf A, Harneit A, Kröger M, *et al*. T3-mediated expression of PGC-1α *via* a far upstream located thyroid hormone response element. Mol Cell Endocrinol, 2008, **287**(1/2): 90-95

[61] Byrne C D, Targher G, Tilg H. Thyroid hormone receptor-beta agonists: new MASLD therapies on the horizon. Gut, 2024, **73**(4): 573-581

[62] Li L, Song Y, Shi Y, *et al*. Thyroid hormone receptor-β agonists in NAFLD therapy: possibilities and challenges. J Clin Endocrinol Metab, 2023, **108**(7): 1602-1613

[63] Vargas R, Videla L A. Thyroid hormone suppresses ischemia-reperfusion-induced liver NLRP3 inflammasome activation: Role of AMP-activated protein kinase. Immunol Lett, 2017, 184: 92-97

[64] Portincasa P, Bonfrate L, Khalil M, *et al*. Intestinal barrier and permeability in health, obesity and NAFLD. Biomedicines, 2021, **10**(1): 83

[65] Cani P D, Amar J, Iglesias M A, *et al*. Metabolic endotoxemia

initiates obesity and insulin resistance. Diabetes, 2007, **56**(7): 1761-1772

[66] Knezevic J, Starchl C, Tmava Berisha A, *et al*. Thyroid-gut-axis: how does the microbiota influence thyroid function? Nutrients, 2020, **12**(6): 1769

[67] Drover V A B, Agellon L B. Regulation of the human cholesterol 7α-hydroxylase gene (*CYP7A1*) by thyroid hormone in transgenic mice. Endocrinology, 2004, **145**(2): 574-581

[68] Ellis E C S. Suppression of bile acid synthesis by thyroid hormone in primary human hepatocytes. World J Gastroenterol, 2006, **12**(29): 4640

[69] Krautkramer K A, Fan J, Bäckhed F. Gut microbial metabolites as multi-Kingdom intermediates. Nat Rev Microbiol, 2021, **19**(2): 77-94

[70] Zhu Y, Tan J K, Liu J, *et al*. Roles of traditional and next-generation probiotics on non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH): a systematic review and network meta-analysis. Antioxidants, 2024, **13**(3): 329

[71] Akkız H, Gieseler R K, Canbay A. Liver fibrosis: from basic science towards clinical progress, focusing on the central role of hepatic stellate cells. Int J Mol Sci, 2024, **25**(14): 7873

[72] Higashi T, Friedman S L, Hoshida Y. Hepatic stellate cells as key target in liver fibrosis. Adv Drug Deliv Rev, 2017, 121: 27-42

[73] Zhang Y, Ren L, Tian Y, *et al*. Signaling pathways that activate hepatic stellate cells during liver fibrosis. Front Med, 2024, **11**: 1454980

[74] Manka P, Coombes J D, Sydor S, *et al*. Thyroid hormone receptor alpha modulates fibrogenesis in hepatic stellate cells. Liver Int, 2024, **44**(1): 125-138

[75] Zhang M, Serna-Salas S, Damba T, *et al*. Hepatic stellate cell senescence in liver fibrosis: characteristics, mechanisms and perspectives. Mech Ageing Dev, 2021, **199**: 111572

[76] Wang L, Li Z, Wan R, *et al*. Single-cell RNA sequencing provides new insights into therapeutic roles of thyroid hormone in idiopathic pulmonary fibrosis. Am J Respir Cell Mol Biol, 2023, **69**(4): 456-469

[77] Yu G, Tzouvelekis A, Wang R, *et al*. Thyroid hormone inhibits lung fibrosis in mice by improving epithelial mitochondrial function. Nat Med, 2018, **24**(1): 39-49

[78] Yang M, Wang D, Gan S, *et al*. Triiodothyronine ameliorates silica-induced pulmonary inflammation and fibrosis in mice. Sci Total Environ, 2021, **790**: 148041

[79] Morris A. Thyroid hormone therapy resolves pulmonary fibrosis in mice. Nat Rev Endocrinol, 2018, **14**(2): 64

[80] Dewidar B, Meyer C, Dooley S, *et al*. TGF-β in hepatic stellate cell activation and liver fibrogenesis—updated 2019. Cells, 2019, **8**(11): 1419

[81] Xu F, Liu C, Zhou D, *et al*. TGF- β/SMAD pathway and its regulation in hepatic fibrosis. J Histochem Cytochem, 2016, **64**(3): 157-167

[82] Alonso-Merino E, Martín Orozco R, Ruíz-Llorente L, *et al*. Thyroid hormones inhibit TGF-β signaling and attenuate fibrotic responses. Proc Natl Acad Sci U S A, 2016, **113**(24): E3451-E3460

[83] Frau C, Loi R, Petrelli A, *et al*. Local hypothyroidism favors the progression of preneoplastic lesions to hepatocellular carcinoma in rats. Hepatology, 2015, **61**(1): 249-259

[84] Hassan M M, Kaseb A, Li D, *et al*. Association between hypothyroidism and hepatocellular carcinoma: a case-control study in the United States. Hepatology, 2009, **49**(5): 1563-1570

[85] Kowalik M A, Puliga E, Cabras L, *et al*. Thyroid hormone inhibits hepatocellular carcinoma progression *via* induction of differentiation and metabolic reprogramming. J Hepatol, 2020, **72**(6): 1159-1169

[86] Davidson C D, Gillis N E, Carr F E. Thyroid hormone receptor beta as tumor suppressor: untapped potential in treatment and diagnostics in solid tumors. Cancers, 2021, **13**(17): 4254

[87] Lin Y H, Lin K H, Yeh C T. Thyroid hormone in hepatocellular carcinoma: cancer risk, growth regulation, and anticancer drug resistance. Front Med, 2020, **7**: 174

[88] Bruinstroop E, Zhou J, Tripathi M, *et al*. Early induction of hepatic deiodinase type 1 inhibits hepatosteatosis during NAFLD progression. Mol Metab, 2021, **53**: 101266

[89] Yen P M. Physiological and molecular basis of thyroid hormone action. Physiol Rev, 2001, **81**(3): 1097-1142

[90] Yang C, Yan Y C, Pan G, *et al*. Thyroid hormones inhibit tumor progression and enhance the antitumor activity of lenvatinib in hepatocellular carcinoma *via* reprogramming glucose metabolism. Cell Death Discov, 2025, **11**: 92

[91] Taylor P N, Medici M M, Hubalewska-Dydejczyk A, *et al*. Hypothyroidism. Lancet, 2024, **404**(10460): 1347-1364

[92] Lee S Y, Pearce E N. Hyperthyroidism: a review. Jama, 2023, **330**(15): 1472

[93] Bano A, Chaker L, Plompen E P C, *et al*. Thyroid function and the risk of nonalcoholic fatty liver disease: the Rotterdam study. J Clin Endocrinol Metab, 2016, **101**(8): 3204-3211

[94] Gu Y, Wu X, Zhang Q, *et al*. High-normal thyroid function predicts incident nonalcoholic fatty liver disease among middle-aged and older euthyroid subjects. J Gerontol A Biol Sci Med Sci, 2022, **77**(1): 197-203

[95] Kim D, Kim W, Joo S K, *et al*. Subclinical hypothyroidism and low-normal thyroid function are associated with nonalcoholic steatohepatitis and fibrosis. Clin Gastroenterol Hepatol, 2018, **16**(1): 123-131.e1

[96] Wan H, Yu G, Xu S, *et al*. Central sensitivity to free triiodothyronine with MAFLD and its progression to liver fibrosis in euthyroid adults. J Clin Endocrinol Metab, 2023, **108**(9): e687-e697

[97] Li R, Zhou L, Chen C, *et al*. Sensitivity to thyroid hormones is associated with advanced fibrosis in euthyroid patients with non-alcoholic fatty liver disease: a cross-sectional study. Dig Liver Dis, 2023, **55**(2): 254-261

[98] Zhou L, Jiang L, An Y, *et al*. Association of sensitivity to thyroid hormones and non-alcoholic fatty liver disease and the severity of liver fibrosis in euthyroid adults: a retrospective study. Diabetes,

Metabolic Syndrome and Obesity, 2025, 18: 479-490

[99] Hatziagelaki E, Paschou S A, Schön M, *et al*. NAFLD and thyroid function: pathophysiological and therapeutic considerations. Trends Endocrinol Metab, 2022, **33**(11): 755-768

[100] Saponaro F, Sestito S, Runfola M, *et al*. Selective thyroid hormone receptor-beta (TRβ) agonists: new perspectives for the treatment of metabolic and neurodegenerative disorders. Front Med, 2020, **7**: 331

[101] Sjouke B, Langslet G, Ceska R, *et al*. Eprotirome in patients with familial hypercholesterolaemia (the AKKA trial): a randomised, double-blind, placebo-controlled phase 3 study. Lancet Diabetes Endocrinol, 2014, **2**(6): 455-463

[102] Zhang F, Meng Y, Zhao B, *et al*. Resmetirom: the first FDA-approved drug for metabolic dysfunction-associated steatohepatitis (MASH) with a perspective on precision medicine. Clin Drug Investig, 2025, **45**(11): 837-845

[103] Kuchay M S, Isaacs S, Misra A. Intrahepatic hypothyroidism in MASLD: Role of liver-specific thyromimetics including resmetirom. Diabetes Metab Syndr Clin Res Rev, 2024, **18**(5): 103034

[104] Sookoian S, Pirola C J. Resmetirom for treatment of MASH. Cell, 2024, **187**(12): 2897-2897.e1

[105] Harrison S A, Bedossa P, Guy C D, *et al*. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. N Engl J Med, 2024, **390**(6): 497-509

[106] Kaya E. Non-invasive tests for resmetirom treatment fail to accurately define the target population: Evidence from a biopsy-proven masld cohort. Hepatol Forum, 2025: 111-115

[107] Messer E K, Petroff D, Schattenberg J, *et al*. Evaluating resmetirom eligibility among patients with MASH: insights from the German steatotic liver disease-registry. Z Gastroenterol, 2025, **63**(8): 836-843

[108] Mathur A, Ozkaya E, Rosberger S, *et al*. Concordance of vibration-controlled transient elastography and magnetic resonance elastography for fibrosis staging in patients with metabolic dysfunction-associated steatotic liver disease. Eur Radiol, 2025, **35**(10): 6507-6515

[109] Shuaibi S, Tobal I, Gore J, *et al*. A real-world experience with resmetirom: tolerability and access. Gastro Hep Adv, 2025, **4**(9): 100709

[110] Ravela N, Shackelford P, Blessing N, *et al*. Early experience with resmetirom to treat metabolic dysfunction – associated steatohepatitis with fibrosis in a real-world setting. Hepatol Commun, 2025, **9**(4): e0670

[111] Vats K, Alam M M. Translating trial to treatment: a scoping review of resmetirom first year in real-world use for moderate to advanced fibrosis in metabolic dysfunction-associated steatohepatitis. Cureus, 2025: **17**(8):e90268

[112] Loomba R, Neutel J, Mohseni R, *et al*. LBP-20-VK2809, a novel liver-directed thyroid receptor beta agonist, significantly reduces liver fat with both low and high doses in patients with non-alcoholic fatty liver disease: a phase 2 randomized, placebo-controlled trial. J Hepatol, 2019, **70**(1): e150-e151

[113] Mahajan S, Malladi N, Banerjee S K. Future potential therapeutics to treat MASH. Drug Discov Today, 2025, **30**(9): 104451

[114] Mousa A M, Mahmoud M, AlShuraiaan G M. Resmetirom: the first disease-specific treatment for MASH. Int J Endocrinol, 2025, **2025**(1): 6430023

代谢功能障碍相关脂肪性肝病的甲状腺激素网络调控：机制与靶向治疗*

肖文萍[1)**] 马 扬[1)**] 官 衡[1)] 万 沙[2)] 韩 文[1)] 罗冰冰[3)] 王武锋[3)] 刘 昉[1,4)***]

([1)] 桂林医科大学基础医学院人体解剖学教研室，桂林 541199；
[2)] 武汉大学泰康生命医学中心，武汉430071；
[3)] 桂林医科大学基础医学院，桂林 541199；[4)] 桂林医科大学广西糖尿病系统医学重点实验室，桂林 541199)

摘要 代谢功能障碍相关脂肪性肝病（metabolic dysfunction-associated steatotic liver disease，MASLD）已成为全球最常见的慢性肝病，其疾病谱可由单纯脂肪变性进展至代谢功能障碍相关脂肪性肝炎（metabolic dysfunction-associated steatohepatitis，MASH）、肝纤维化及肝细胞癌。肝脏甲状腺激素（thyroid hormone，TH）信号紊乱被认为是贯穿该进程的重要机制之一。TH通过其肝脏优势表达的甲状腺激素受体β（thyroid hormone receptor β，TRβ）调控脂质生成、线粒体氧化及极低密度脂蛋白分泌，并维持自噬功能，从而限制早期脂毒性；在炎症阶段，TH通过改善线粒体稳态和抑制核苷酸结合寡聚化结构域样受体蛋白3（NOD-like receptor family pyrin domain containing 3，NLRP3）炎症小体活化、调节肠–肝轴微环境以遏制炎症放大；在纤维化及癌变阶段，TH信号影响肝星状细胞活化、抑制转化生长因子β（transforming growth factor-β，TGF-β）/SMAD驱动的细胞外基质沉积，并与碘甲状腺原氨酸脱碘酶1（iodothyronine deiodinase 1，DIO1）协同调控肝细胞分化状态。随着靶向TRβ的Resmetirom获批用于F2–F3期纤维化的非肝硬化MASH，TH信号研究正由机制阐释迈向精准治疗。本文基于MASLD疾病谱综述TH的多维调控作用及其诊疗意义。

关键词 代谢功能障碍相关脂肪性肝病，甲状腺激素，甲状腺激素受体β，肝脏脂质代谢，甲状腺激素受体激动剂
中图分类号 R575.5;R977.1 **DOI**：10.3724/j.pibb.2025.0466 **CSTR**：32369.14.pibb.20250466

---

* 国家自然科学基金（82160063）资助项目。
** 并列第一作者。
*** 通讯联系人。
Tel：0773-5595243，E-mail：fang.liu@msn.com
收稿日期：2025-10-28，接受日期：2026-01-29