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Metabolic memory and immune evasion in MASLD-HCC progression

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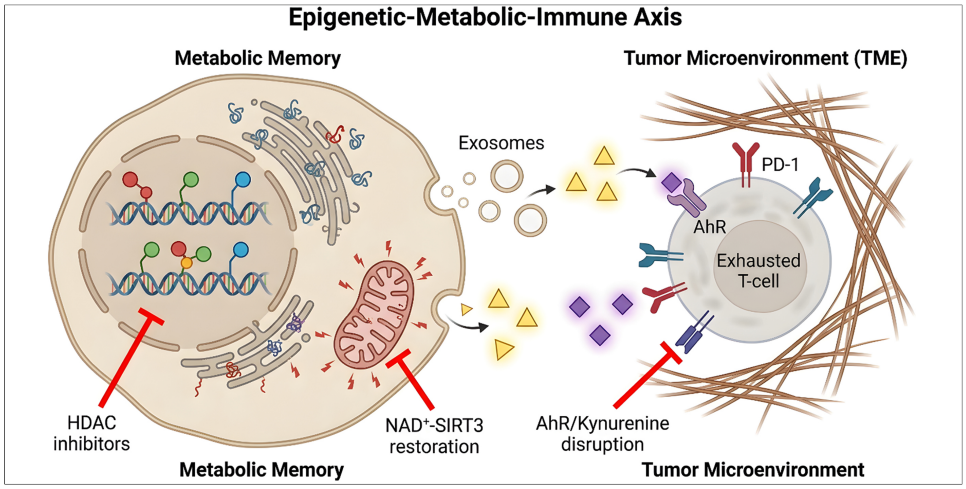

Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of hepatocellular carcinoma (HCC). Central to its pathogenesis is "metabolic memory" - the persistence of pro-tumorigenic alterations after resolution of the initial metabolic insult. This review examines how metabolic memory, encoded across multiple layers of the epigenome - including DNA methylation, repressive histone modifications, and non-coding RNA networks - and propagated through mitochondrial dysfunction and lipotoxic metabolites, sustains a locked immunosuppressive state that drives immune evasion in MASLD-HCC. We delineate convergent pathways - including the unfolded protein response, dysregulated autophagy, tryptophan-kynurenine-aryl hydrocarbon receptor (AHR) signaling - that couple metabolic memory to immune checkpoint upregulation and T-cell exhaustion. We further discuss how metabolic byproducts such as lactate drive immunosuppression through histone lactylation, and how extracellular vesicles transmit metabolic stress signatures to remotely reprogram immune cells within the tumor microenvironment. From a therapeutic perspective, we evaluate strategies targeting the reversibility of this memory, including NAD^+-SIRT3 axis restoration and epigenetic modulators such as HDAC inhibitors, and discuss their potential to sensitize tumors to immunotherapy. We also explore emerging approaches aimed at disrupting the kynurenine-AHR axis and overcoming fibrotic barriers to immune infiltration. Disrupting this "epigenetic-metabolic-immune axis" may be essential for halting disease progression.

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INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as the leading cause of chronic liver disease worldwide, affecting approximately 30% of the global adult population[1,2]. Driven by the escalating epidemics of obesity, type 2 diabetes mellitus, and metabolic syndrome, the disease burden of MASLD continues to rise[3]. Within the natural history of MASLD, approximately 20% of patients progress to metabolic dysfunction-associated steatohepatitis (MASH), and a subset of these cases further advance to cirrhosis and ultimately hepatocellular carcinoma (HCC)[4]. Notably, a substantial proportion of patients with MASLD-associated HCC (MASLD-HCC) do not traverse a clinically evident cirrhotic stage, suggesting the existence of non-canonical carcinogenic pathways[5]. This distinctive feature renders traditional cirrhosis-based surveillance strategies inadequate for the early detection of such HCC cases, which are often associated with a poorer clinical prognosis.

Despite the efficacy of metabolic interventions - including lifestyle modifications, insulin sensitizers, and lipid-lowering agents - in ameliorating hepatic steatosis and inflammation, epidemiological evidence indicates that prior or resolved MASLD continues to confer a persistently elevated risk of HCC development[6,7]. In other words, even when the metabolic derangements are seemingly "corrected", the liver appears to retain a form of "traumatic memory" that sustains malignant transformation[8,9]. This phenomenon bears a striking resemblance to the well-established concept of "metabolic memory" in diabetes research, wherein early exposure to hyperglycemia instigates epigenetic modifications that drive the relentless progression of vascular and neurological complications despite subsequent glycemic control[10,11]. In the context of hepatic oncology, two critical questions warrant systematic investigation: Does a parallel "metabolic memory" operate in the liver? And if so, what are its molecular vectors?

Concurrently, immune evasion constitutes a cardinal hallmark of tumorigenesis[12]. In the setting of MASLD, the hepatic immune microenvironment undergoes a profound remodeling from "metainflammation" to a state of "immune paralysis"[13,14]. Lipotoxic metabolites, oxidative stress, and chronic endoplasmic reticulum (ER) stress not only inflict hepatocellular injury but also reprogram infiltrating and resident immune cells toward suppressive phenotypes. More critically, these aberrant alterations in the immune microenvironment may persist long after the resolution of the initial metabolic insult, thereby establishing a form of "mnemonic immune evasion"[15]. However, a systematic mechanistic integration of how metabolic memory - through epigenetic regulation, metabolite signaling, and intercellular crosstalk - perpetuates this locked state of immunosuppression remains conspicuously absent.

Before dissecting the mechanisms, it is essential to clarify the terminology that underpins this review. In the context of chronic metabolic diseases, three related but mechanistically distinct concepts are frequently conflated: metabolic reprogramming, metabolic-immune coupling, and metabolic memory. Metabolic reprogramming refers to the adaptive alterations in cellular metabolic pathways - such as the shift from oxidative phosphorylation (OXPHOS) to glycolysis (the Warburg effect) - that enable cells to survive and function under altered environmental conditions. This is a dynamic, reversible, and often homeostatic response to ongoing metabolic stress. Metabolic-immune coupling describes the real-time regulation of immune cell phenotype and function by metabolites; for instance, succinate can acutely stabilize hypoxia-inducible factor 1 alpha (HIF-1α) in pro-inflammatory macrophages, and lactate can immediately suppress T-cell effector function. This coupling is stimulus-dependent and typically resolves once the metabolic stimulus is removed. In contrast, metabolic memory, as operationally defined in this review, refers specifically to the persistence of pro-tumorigenic cellular alterations - encoded through stable epigenetic

modifications, durable mitochondrial dysfunction, and self-sustaining metabolic byproduct signaling - that remain long after the initial metabolic insult has been corrected or resolved. Therefore, the aims of this review are fourfold: (1) To systematically delineate the mechanisms underpinning metabolic memory in MASLD-HCC progression, with a particular emphasis on epigenetic modifications, mitochondrial dysfunction, and the enduring effects of metabolic byproducts; (2) To dissect the immune evasion pathways driven by metabolic memory, including sustained upregulation of immune checkpoints, metabolic competition, and lactate-mediated immunosuppression; (3) To explore the critical nodes of convergence between these two pathogenic axes [e.g., ER stress-unfolded protein response (UPR), autophagy, AHR signaling]; and (4) To summarize potential therapeutic strategies targeting the metabolic memory-immune evasion axis and to highlight current knowledge gaps and future research directions. By integrating these advances, we aim to provide novel insights into the distinctive biological behavior of MASLD-related HCC and to establish a theoretical foundation for the development of combined metabolic-immunotherapeutic strategies.

METABOLIC REPROGRAMMING AND METABOLIC MEMORY IN MASLD-HCC

Accumulation of lipotoxic metabolites

The aberrant accumulation of lipotoxic metabolites represents a central mechanism driving metabolic reprogramming and disease progression during the transition from MASH to HCC. These metabolites, which include free fatty acids, cholesterol, and ceramides, not only inflict direct hepatocellular injury but also foster tumorigenesis by remodeling the hepatic microenvironment[16]. Leng *et al.* demonstrated that the LIX1L protein is markedly upregulated in liver tissues from patients with MASH, in murine models of the disease, and in hepatocytes subjected to palmitate stimulation. Mechanistically, LIX1L promotes CD36 expression by stabilizing CD36 mRNA, thereby exacerbating hepatic lipid accumulation, inflammation, and fibrosis[17]. As a key fatty acid translocase, elevated CD36 expression facilitates enhanced free fatty acid uptake, thereby establishing a lipotoxic positive feedback loop[18]. Furthermore, multi-omics analyses have revealed that lipotoxic species, such as ceramides and diacylglycerols, accumulate significantly in cardiac tissue under conditions of aging and metabolic stress, suggesting that analogous mechanisms of lipotoxic metabolite accrual may play a pivotal role in the establishment of hepatic metabolic memory[19,20]. The persistent presence of these lipid species underpins a pro-inflammatory and pro-fibrotic microenvironment that primes the liver for HCC development.

Epigenetically mediated metabolic memory

Metabolic stress-induced epigenetic alterations constitute a fundamental mechanism for the establishment of "metabolic memory" - a phenomenon whereby gene expression patterns remain persistently altered long after the resolution of the initial insult, thereby propelling the progression from MASLD to HCC[8]. This memory is encoded across multiple layers of the epigenome. Gradual DNA methylation changes have been documented across the histological spectrum of MASLD, correlating with accelerated epigenetic aging[21]. Repressive histone modifications, such as H3K9me3 and H3K27me3, silence tumor suppressors and immunomodulatory genes, linking nutrient excess to durable chromatin remodeling[22]. In addition to these transcriptional controls, this form of cellular memory extends beyond transcriptional regulation to encompass non-coding RNAs and extensive reprogramming at the post-transcriptional level. Studies have demonstrated that chronic ER stress, triggered by prolonged exposure to a high-fat diet (HFD), elicits a distinct post-transcriptional regulatory landscape. Remarkably, approximately 70% of HFD-induced changes in gene expression are governed at the translational level. MicroRNAs and long non-coding RNAs have emerged as critical carriers of metabolic memory, regulating gene expression both intracellularly and via extracellular vesicles (EVs)[23,24]. A specific subset of mRNAs, characterized by suboptimal codon usage and short poly(A) tails under normal dietary conditions, becomes selectively activated via HFD-induced poly(A) tail lengthening[25]. These transcripts are enriched for genes involved in cell cycle regulation, immune

response, fibrogenesis, and tissue remodeling, and their expression levels correlate positively with the histologic severity of MASH in both murine models and human biopsy specimens. This mode of regulation - orchestrated by the coordination of polyadenylation and deadenylation via *cis*-acting elements within the 3' untranslated region (UTR) - represents a crucial "memory" mechanism at the epitranscriptomic level. Together with the DNA methylation and histone modifications described above, these non-coding RNAs and post-transcriptional mechanisms form a multilayered epigenetic network that enables hepatocytes to adapt to sustained metabolic pressure while potentially locking in pro-carcinogenic gene expression programs[26].

The vicious cycle of mitochondrial dysfunction and oxidative stress

The self-perpetuating vicious cycle established between mitochondrial dysfunction and excessive production of reactive oxygen species (ROS) serves as another critical vector of metabolic memory in MASLD-HCC progression. Persistent metabolic insults, including lipotoxicity and ER stress, compromise mitochondrial integrity, leading to elevated ROS generation. In MASLD, mitochondrial dysfunction manifests through multiple interconnected defects - including β-oxidation imbalance, impaired mitophagy, and mitochondrial DNA (mtDNA) mutations - that collectively drive disease progression from steatosis to HCC[27]. In turn, excessive ROS inflicts further damage upon mtDNA and proteins, thereby establishing a self-amplifying cycle of destruction that can be conceptualized as a form of enduring cellular memory[28]. Notably, mtDNA released from damaged mitochondria can activate the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) signaling pathway, upregulating programmed death-ligand 1 (PD-L1) expression and directly linking mitochondrial dysfunction to immune evasion during MASLD malignant transformation[29]. These hepatic findings are consistent with multi-omics studies conducted in aging cardiac tissue, where electron microscopy has revealed structurally impaired and enlarged mitochondria, while proteomic analyses have documented widespread mitochondrial dysregulation and impaired ATP production[30,31], suggesting that mitochondrial dysfunction represents a conserved feature of metabolic memory across organ systems. Although these findings are derived from cardiac research, analogous mechanisms are pervasive in the metabolically stressed liver. Hepatic lipid overload impairs mitochondrial OXPHOS and compromises quality control mechanisms, while mitochondrial oxidative stress in turn promotes genomic instability and creates a pro-tumorigenic microenvironment - establishing a self-reinforcing loop that links metabolic dysregulation to hepatocarcinogenesis[28]. ROS-mediated mtDNA damage is cumulative and largely irreversible, potentially leading to permanent mutations or altered expression of genes encoding critical OXPHOS proteins, thereby chronically compromising cellular energy metabolism and redox homeostasis. This mitochondrial "memory" not only attenuates normal hepatocellular function but also sustains a microenvironment conducive to genomic instability and malignant transformation through the continuous production of ROS and pro-inflammatory signals, thereby accelerating the trajectory toward HCC[32,33]. The core mechanisms and pathological consequences of metabolic memory in MASLD-HCC progression are summarized in Table 1.

THE HEPATIC IMMUNE MICROENVIRONMENT IN THE CONTEXT OF MASLD

The state of "immune paralysis"

During the progression of MASLD, the hepatic immune microenvironment undergoes a complex transition from chronic metainflammation to a state of profound immunosuppression. This shift, frequently termed "immune paralysis", constitutes a critical foundation for both the development of MASLD-HCC and resistance to immunotherapy[34]. Central to the pathophysiology of MASLD is dysregulated lipid metabolism, which not only directly induces hepatocellular steatosis and injury but also profoundly remodels the tissue microenvironment to favor tumor growth and metastasis[35]. Persistent lipid overload and metabolic stress engender a chronic, low-grade inflammatory state (i.e., metainflammation), characterized by the sustained release of pro-inflammatory cytokines and chemokines. However, in contrast to classical acute inflammation,

Table 1. Core mechanisms and pathological consequences of metabolic memory in MASLD-HCC progression

Mechanism category	Key mediators/effectors	Functional impact on hepatocytes	Contribution to immune evasion	Ref.
Lipotoxic metabolite accumulation	Free fatty acids, ceramides, cholesterol, DAGs	Induces hepatocellular injury, ER stress, and steatosis; Upregulates CD36 via LIX1L stabilization	Establishes a pro-inflammatory and pro-fibrotic niche that impairs immune surveillance	[16-18]
Epigenetic & epitranscriptomic reprogramming	DNA methylation, repressive histone modifications (H3K9me3, H3K27me3), poly(A) tail lengthening (HFD-induced), HDAC activation, ncRNAs	Locks pro-carcinogenic gene expression programs; Selectively activates translational machinery for cell cycle and fibrosis genes	Sustains high expression of PD-L1 and immune checkpoint molecules; Represses MHC-I transcription via HDAC-mediated chromatin compaction	[21,22,25,26,54,58,59]
Mitochondrial dysfunction & ROS	mtDNA damage, impaired mitophagy and OXPHOS, excess ROS generation, mtDNA leakage (cGAS-STING activation)	Compromises ATP production and redox homeostasis; Creates a self-amplifying cycle of organelle destruction	Sustains release of DAMPs and ROS, promoting genomic instability; Upregulates PD-L1 via cGASSTING, driving M2-like macrophage polarization	[28-30,33,34]

cGAS: Cyclic GMP-AMP synthase; DAGs: diacylglycerols; DAMPs: damage-associated molecular patterns; ER: endoplasmic reticulum; HDAC: histone deacetylase; HFD: high-fat diet; MHC-I: major histocompatibility complex class I; mtDNA: mitochondrial DNA; ncRNAs: non-coding RNAs; OXPHOS: oxidative phosphorylation; PD-L1: programmed death-ligand 1; ROS: reactive oxygen species; STING: stimulator of interferon genes.

this protracted inflammatory stimulus fails to effectively mobilize antitumor immunity. Instead, it progressively establishes an immunosuppressive niche by driving metabolic reprogramming and functional exhaustion of immune cells[36]. This transition is reinforced by an age-dependent immunometabolic vicious cycle, in which hepatocyte-derived ROS promotes immune cell senescence while senescent immune cells in turn release pro-inflammatory cytokines that further impair hepatocyte mitochondrial function[37]. For instance, hypoxia-inducible factors (HIFs), which are activated under the hypoxic and oxidative stress conditions prevalent in MASLD, not only orchestrate cellular metabolic adaptation but also profoundly modulate immune cell function to promote the acquisition of immunosuppressive phenotypes[38]. The resulting immunosuppressive microenvironment is characterized by dysfunctional $CD8^+$ T cells, altered myeloid compartments, and heterogeneous immune cell populations that collectively facilitate hepatocarcinogenesis even in the absence of advanced fibrosis[34,39]. This transition from inflammation to immunosuppression renders the liver incapable of mounting effective immune surveillance and clearance in the face of preneoplastic lesions or nascent tumor cells, thereby facilitating the initiation and progression of HCC.

Dysregulation of key immune cell populations

The immunosuppressive characteristics of the hepatic immune microenvironment in MASLD stem from the functional dysregulation of multiple key immune cell subsets. First, the function of cytotoxic $CD8^+$ T cells is severely compromised. The lipotoxic milieu can directly induce $CD8^+$ T cell exhaustion and apoptosis. Moreover, the accumulation of lactate, a byproduct of metabolic reprogramming in tumor cells and stromal cells, depletes metabolic resources available to $CD8^+$ T cells, competitively inhibits their proliferation and effector functions, and thereby cripples their antitumor capacity[39]. Second, regulatory T cells (Tregs) exhibit a relative increase in abundance and altered functionality within the MASLD liver. Although Treg numbers are elevated, their immunosuppressive function may be impaired within the MASLD microenvironment, rendering them incapable of effectively restraining excessive inflammation while potentially facilitating tumor immune evasion through the suppression of effector T cell activity[40]. Furthermore, Tregs play a dichotomous, "double-edged sword" role in the transition from MASLD to HCC, as they may both suppress pro-tumorigenic inflammation and promote cancer cell escape[41]. Third, the functions of innate lymphoid cells, including natural killer T (NKT) cells and mucosal-associated invariant T (MAIT) cells, are also compromised, further attenuating innate immune surveillance in the liver[42]. Finally, phenotypic polarization

of macrophages constitutes a cornerstone of the immunosuppressive microenvironment[43]. Driven by lipid loading, hepatic macrophages - comprising both resident Kupffer cells and recruited monocyte-derived macrophages - polarize toward an immunosuppressive and pro-fibrotic M2-like phenotype, frequently designated as tumor-associated macrophages (TAMs)[44,45]. This polarization is regulated by molecular axes such as the TRIM38-HSPA5 pathway, and M2-polarized macrophages create a permissive environment for tumor growth and metastasis by secreting immunosuppressive factors and facilitating tissue remodeling[45]. Collectively, the dysregulation of these immune cell populations constructs an immunosuppressive niche conducive to tumor initiation and progression.

Hepatic stellate cells and extracellular matrix remodeling constitute a physical barrier

In addition to immune cell dysregulation, the activation of hepatic structural cells - specifically hepatic stellate cells (HSCs) - and the subsequent remodeling of the extracellular matrix (ECM) establish critical physical and biochemical barriers within the immune microenvironment of MASLD-HCC. During the progression of MASLD to MASH and fibrosis, persistent inflammatory and injurious signals trigger the activation of quiescent HSCs[46]. Upon activation, HSCs transdifferentiate into myofibroblasts, which engage in robust synthesis and deposition of ECM components such as collagen, culminating in hepatic fibrosis[47]. This excessive ECM deposition not only alters the physical architecture of the liver and increases tissue stiffness but also directly impedes the infiltration and contact of immune cells - particularly cytotoxic T lymphocytes - with neoplastic foci, thereby creating a form of physical sequestration[48]. Moreover, activated HSCs themselves serve as immunomodulatory hubs. They secrete a repertoire of cytokines and chemokines, including transforming growth factor-beta (TGF-β), which further promotes the polarization of M2-like macrophages and the recruitment and functional potentiation of Tregs. Consequently, this superimposes biochemical immunosuppressive signals upon the pre-existing physical barrier[49,50]. In the context of MASLD, HSC activation and the immunosuppressive microenvironment engage in a positive feedback loop. For instance, in models of colorectal cancer liver metastasis, activated HSCs and cancer-associated fibroblasts (CAFs) produce hyaluronan via hyaluronan synthase 2, facilitating ECM remodeling and modulating immune cell behavior to collectively impair antitumor immunity[51]. Thus, HSC activation and ECM remodeling are not merely hallmarks of hepatic fibrosis; they are also pivotal processes that sculpt the immunosuppressive tumor microenvironment (TME) in MASLD-HCC, thereby promoting immune evasion and tumor progression.

MECHANISMS OF IMMUNE EVASION DRIVEN BY METABOLIC MEMORY

Epigenetically locked immunosuppressive phenotypes

Metabolic memory perpetuates immunosuppressive phenotypes by "locking" them into cellular identity through epigenetic mechanisms, ensuring that this state of inhibition persists long after the resolution of the initial metabolic insult (e.g., high-fat or high-glucose environments). DNA methylation and histone modifications orchestrate this process in HCC by silencing immune-related genes - such as CXCL10 and MHC-I - while maintaining PD-L1 expression, thereby shaping a TME characterized by T-cell exhaustion and myeloid-derived suppressor cell (MDSC) enrichment[52]. A principal manifestation of this process is the sustained upregulation of immune checkpoint molecules. For instance, within the TME, elevated expression of PD-L1 on the surface of cancer cells engages programmed cell death protein 1 (PD-1) on T cells, thereby suppressing T cell activation and effector function to facilitate immune evasion[53]. Such upregulation may be instigated by antecedent metabolic perturbations - including hypoxia and lactate accumulation - and subsequently entrenched through epigenetic modifications such as histone alterations or DNA methylation, thus constituting a form of long-term cellular memory[54]. Notably, recent work has identified that RNA-binding proteins can recruit histone methyltransferases to the PD-L1 locus to maintain its sustained expression in HCC, exemplifying the direct coupling of metabolic stress to epigenetic immune checkpoint regulation[55]. Furthermore, alterations in the activity of histone deacetylases (HDACs) represent another

critical mechanism. HDACs catalyze the removal of acetyl groups from histones, leading to chromatin compaction and the protracted transcriptional repression of genes essential for antigen presentation, including major histocompatibility complex class I (MHC-I) molecules[56]. The consequent downregulation of MHC-I expression renders tumor cells incapable of effectively presenting tumor antigens to $CD8^+$ T cells, culminating in a failure of immune surveillance[57]. This HDAC-mediated epigenetic silencing thus erects a durable barrier to antitumor immunity that is underpinned by metabolic memory.

Metabolic byproducts as immune evasion signals

Metabolic byproducts generated by dysregulated metabolism are not merely terminal waste products of energy exchange; they function as potent immunomodulatory signals. In the context of MASLD, sustained metabolic stress induces hepatocellular senescence, which is characterized by the secretion of a panoply of inflammatory cytokines and chemokines collectively termed the senescence-associated secretory phenotype (SASP)[58]. The persistent secretion of SASP components, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), may continue even after the inciting stressor has subsided, creating a state of chronic inflammation within the hepatic microenvironment via paracrine signaling[59]. This chronic inflammation not only inflicts direct hepatocellular injury and promotes fibrosis but also actively suppresses antitumor immunity, thereby sculpting a microenvironment permissive for HCC initiation and progression. This exemplifies the non-cell-autonomous, pro-carcinogenic effects of metabolic memory. On a parallel front, lactate - produced in abundance due to enhanced glycolysis - not only engenders an acidic milieu but also directly modulates gene expression through a process known as lactylation. Histone lactylation is an emerging epigenetic modification wherein elevated lactate levels promote the lactylation of histones, thereby upregulating the transcription of genes associated with immunosuppression[60]. In gastrointestinal cancers, aberrant histone lactylation has been shown to drive M2 macrophage polarization, increase PD-L1 expression, and diminish cytotoxic immune cell infiltration[61]. In HCC specifically, lactylation-driven upregulation of the major vault protein (MVP) inhibits PD-L1 degradation, thereby stabilizing PD-L1 expression and contributing to immunotherapy resistance[62]. This can potentiate the function of Tregs and increase the expression of arginase 1 (Arg1). Arg1 subsequently depletes arginine within the microenvironment, a process that stifles the metabolism and function of effector T cells, thereby reinforcing the immunosuppressive network and transducing the memory of metabolic dysregulation into a sustained immune evasion signal[63].

Metabolic competition and nutrient deprivation in the TME

Metabolic competition within the TME constitutes a fundamental physical mechanism through which metabolic memory drives immune evasion. HCC cells, which typically exhibit the Warburg effect, possess an extraordinarily high avidity for key nutrients such as glucose and glutamine, leading to nutrient scarcity within the TME. Infiltrating immune cells, particularly effector T cells and natural killer (NK) cells that demand substantial bioenergetic resources to execute their cytotoxic functions, are consequently subjected to "metabolic starvation." This nutrient deprivation not only constrains energy production but also impairs immune cell proliferation, activation, and cytokine elaboration, ultimately driving functional exhaustion or anergy. For example, $CD200^+$ acute myeloid leukemia stem cells have been shown to suppress T cell function by impairing their OXPHOS metabolic activity[64]. Moreover, aberrations in methionine metabolism constitute another critical facet of this competition. The methionine cycle provides S-adenosylmethionine (SAM), the universal methyl donor required for cellular methylation reactions, including DNA and histone methylation. Competitive uptake of methionine by tumor cells can lead to SAM insufficiency within the TME, thereby perturbing the methylation landscape essential for maintaining the proper epigenetic state and functional integrity of T cells[65]. It is important to recognize that SAM pools are highly compartmentalized in MASLD-HCC: tumor cells often maintain high intracellular SAM levels to sustain their own proliferative epigenetic programs, whereas infiltrating T cells within the TME experience SAM deprivation due to

methionine competition; circulating SAM concentrations, which are influenced by hepatic metabolic status and dietary intake, reflect the net balance of these compartmentalized pools rather than the local TME concentration experienced by immune cells. In MASLD-HCC specifically, elevated circulating SAM levels and SAM/SAH ratios have been independently associated with HCC development, providing clinical evidence that methionine cycle dysregulation is not merely a consequence of tumor metabolism but may actively contribute to hepatocarcinogenesis[66]. Dysregulation of such epigenetic control may render T cells more susceptible to differentiating into an exhausted phenotype or losing effector functionality, thereby consolidating the immunosuppressive microenvironment. More broadly, aberrant methionine metabolism induces T-cell exhaustion, promotes M2 macrophage polarization, and inhibits NK cell activity through epigenetic reprogramming of both tumor and immune cells[67].

EVs as vectors of memory

EVs serve as critical mediators of intercellular communication and play a prominent role in transmitting metabolic memory and sculpting an immunosuppressive microenvironment. During the progression from MASLD to HCC, metabolically stressed adipocytes, hepatocytes, and incipient preneoplastic cells release substantial quantities of EVs[68]. These EVs carry specific "cargo" - including metabolic enzymes, non-coding RNAs (e.g., miRNAs), and even metabolites - which they deliver to immune cells within the TME, thereby remotely reprogramming the functional state of recipient cells[69]. For instance, EVs derived from adipose tissue may transport enzymes that promote fatty acid oxidation or associated miRNAs, inducing the polarization of macrophages toward an anti-inflammatory, M2-like phenotype[70,71]. Similarly, hepatocyte-derived EVs may transfer signaling molecules that suppress antigen presentation or foster Treg differentiation[72]. Emerging evidence highlights that EVs in MASLD carry bioactive microRNAs that influence lipotoxicity, inflammation, and fibrosis progression, functioning as key intercellular messengers that propagate metabolic stress signals throughout the hepatic microenvironment[73]. In HCC, EVs actively contribute to immune evasion by transmitting PD-L1, pro-angiogenic factors, and chemoresistance signals, thereby directly linking metabolic dysregulation in donor cells to immunosuppressive reprogramming in recipient immune cells[74]. This EV-mediated transmission of information possesses inherent memory-like characteristics, as it converts the specific signatures of metabolic stress experienced by donor cells (e.g., insulin resistance, lipotoxicity) into transmissible signals that persistently modulate the metabolic pathways and gene expression profiles of recipient immune cells. Through this mechanism, EVs propagate and entrench the memory of localized metabolic dysfunction systemically within the immune compartment, thereby orchestrating a systemic downregulation of antitumor immune responses and providing an extracellular conduit for immune evasion in HCC.

CONVERGENT PATHWAYS LINKING METABOLIC MEMORY TO IMMUNE EVASION

ER stress and the UPR

Dysregulation of ER function, precipitated by chronic metabolic stress, represents a central nexus in the progression from MASLD to HCC. Persistent lipid overload and inflammatory signaling trigger ER stress, thereby activating the UPR[75]. Within this framework, the inositol-requiring enzyme 1α (IRE1α)-X-box binding protein 1 (XBP1) signaling axis plays a dual role, serving as a critical molecular bridge that couples metabolic memory to immune evasion. In HCC, phosphorylated PERK and spliced XBP1 are markedly overexpressed, and their dysregulation is associated with aggressive tumor phenotypes, therapeutic resistance, and immune evasion[76]. On one hand, activated IRE1α catalyzes the non-canonical splicing of *XBP1* mRNA to generate the spliced isoform XBP1s. As a potent transcription factor, XBP1s directly upregulates a suite of genes integral to *de novo* lipogenesis (e.g., stearoyl-CoA desaturase 1, *SCD1*) and lipid droplet biogenesis, thereby exacerbating intrahepatocellular lipid accumulation and reinforcing the pro-carcinogenic metabolic memory[77]. On the other hand, this identical signaling axis has been demonstrated to directly regulate the transcription of the immune checkpoint molecule PD-L1. The IRE1α–XBP1 axis has

been implicated in the regulation of PD-L1 expression in several tumor and immune-cell contexts. However, direct transcriptional regulation of the PD-L1/CD274 promoter by XBP1s has not yet been firmly established in HCC cells and requires further validation[78]. This elevated PD-L1 engages the PD-1 receptor on T cells, transducing inhibitory signals that culminate in the exhaustion and functional inactivation of tumor-specific T cells, thereby facilitating immune evasion by HCC cells[79]. Thus, the IRE1α-XBP1 axis functions as a double-edged sword: it simultaneously perpetuates the pro-tumorigenic reprogramming of lipid metabolism and directly establishes a localized immunosuppressive microenvironment. More broadly, the bidirectional crosstalk between ER stress and lipid metabolism - mediated through the UPR, the ubiquitin-proteasome system, and autophagy - constitutes an integrated proteostasis network that drives tumor metabolic reprogramming and adaptation to microenvironmental stress[80]. It stands as a paradigmatic pathway that integrates metabolic dysregulation with immune dysfunction.

Autophagy dysregulation

Autophagy, particularly selective forms such as mitophagy and lipophagy, is indispensable for maintaining hepatocellular metabolic homeostasis and immune surveillance. During the progression of MASLD-HCC, chronic metabolic stress engenders pervasive dysregulation of autophagic flux, a perturbation that constitutes another facet of metabolic memory and directly compromises antitumor immunity. Impaired selective autophagy results in the inadequate clearance of dysfunctional mitochondria - characterized by elevated mitochondrial ROS (mtROS) production - and excessive lipid droplets. The accumulation of damaged mitochondria perpetuates the activation of pathways such as the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome through the sustained release of ROS and damage-associated molecular patterns (DAMPs), thereby cultivating a chronic pro-inflammatory milieu rife with genomic instability that fosters malignant transformation[81]. A comprehensive analysis of selective autophagy pathways in HCC has revealed that mitophagy, lipophagy, ferritinophagy, and reticulophagy each play context-dependent roles - supporting either tumor suppression or tumor progression depending on disease stage - while their dysregulation directly impacts the immune microenvironment and therapeutic responsiveness[82]. Concomitantly, the aberrant accrual of lipid droplets is not merely a hallmark of metabolic imbalance; these organelles can actively promote tumor growth by serving as reservoirs of signaling lipid precursors. In the aging liver, autophagy efficiency progressively declines, contributing to lipid accumulation, oxidative stress, and mitochondrial dysfunction that create a permissive environment for HCC development, while in established HCC, persistent autophagy paradoxically supports tumor cell survival and immune evasion[83]. More critically, autophagy plays a pivotal role in the process of cross-presentation by antigen-presenting cells, notably dendritic cells. Impairment of autophagic function directly compromises the processing and presentation of tumor antigens, rendering $CD8^+$ T cells inadequately primed and activated, thereby blunting the host's capacity for immune recognition and elimination of malignant cells[84]. Consequently, autophagic dysfunction propels HCC development through two distinct mechanisms: firstly, by permitting the accumulation of metabolic detritus, it directly compromises cellular homeostasis and promotes malignant transformation; secondly, by subverting cross-presentation - a critical step in the initiation of adaptive immunity - it enables tumor cells to evade immune surveillance.

The AHR pathway

The aryl hydrocarbon receptor (AHR), a ligand-activated transcription factor, has recently emerged as a central orchestrator of metabolic-immune crosstalk in oncology. In the context of MASLD-HCC, metabolic memory manifests as a chronic reprogramming of tryptophan catabolism. Tumor cells and tumor-associated immune cells - including MDSCs and Tregs - exhibit elevated expression of indoleamine 2,3-dioxygenase 1 (IDO1) or tryptophan 2,3-dioxygenase (TDO2), enzymes that catalyze the degradation of the essential amino acid tryptophan into metabolites such as kynurenine[85]. These tryptophan-derived catabolites serve as high-affinity endogenous ligands for AHR[86]. The sustained activation of AHR constitutes a pivotal

Table 2. Convergent pathways linking metabolic memory to immune evasion: mechanisms and therapeutic interventions

Signaling Axis	Metabolic Trigger/Memory Vector	Effect on Immune Microenvironment	Potential Therapeutic Intervention	Ref.
ER Stress-IRE1α/XBP1 Axis	Chronic lipid overload; Sustained UPR activation	Regulation of PD-L1 expression and immunosuppressive signaling; direct transcriptional regulation in HCC remains to be established; Promotes *de novo* lipogenesis reinforcing the memory loop	IRE1α RNase inhibitors; XBP1 splicing modulators	[77,79,80]
Autophagy Dysregulation	Impaired mitophagy and lipophagy; Accumulation of damaged mitochondria and lipid droplets	Impaired cross-presentation of tumor antigens by dendritic cells; Chronic NLRP3 inflammasome activation by DAMPs; Context-dependent dual role (tumor suppression vs. progression)	Autophagy inducers (e.g., TFEB activators); Mitophagy-specific agonists	[83,84,86]
Tryptophan-Kynurenine-AHR Axis	IDO1/TDO2-mediated tryptophan depletion; Kynurenine accumulation; MYC-driven metabolic reprogramming	Expansion and stabilization of Tregs via Foxp3 induction; Upregulation of PD-1 on effector $CD8^+$ T cells; M2 macrophage polarization	AHR antagonists (e.g., SB5794); IDO1/TDO2 inhibitors; Dietary tryptophan modulation	[87,89-92]
NAD^+-SIRT3 Axis	NAD^+ depletion secondary to metabolic stress; Mitochondrial dysfunction	Modulation of mitochondrial fitness and memory formation capacity in T cells; Attenuation of oxidative stress and fibrosis in the TME	NAD^+ precursors (NMN); SGLT2 inhibitors; Metformin; GLP-1 receptor agonists	[94,95,97,108]

AHR: Aryl hydrocarbon receptor; DAMP: damage-associated molecular pattern; GLP-1: glucagon-like peptide-1; IDO1: indoleamine 2,3-dioxygenase 1; IRE1α: inositol-requiring enzyme 1α; MYC: myelocytomatosis oncogene; NAD+: nicotinamide adenine dinucleotide; NLRP3: NOD-like receptor family pyrin domain containing 3; NMN: nicotinamide mononucleotide; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; SGLT2: sodium-glucose cotransporter-2; SIRT3: sirtuin 3; TDO2: tryptophan 2,3-dioxygenase; TFEB: transcription factor EB; TME: tumor microenvironment; Treg: regulatory T cell; UPR: unfolded protein response; XBP1: X-box binding protein 1.

immunosuppressive signaling node. Upon ligand engagement, AHR translocates to the nucleus, heterodimerizes with the aryl hydrocarbon receptor nuclear translocator (ARNT), and directly binds to promoter regions of target genes[87]. Its transcriptional targets encompass a spectrum of key immunosuppressive effectors, including *Foxp3* - the master transcription factor requisite for Treg differentiation - and *PD-1*, a critical negative regulator of cytotoxic T cell function[87,88]. Recent pharmacological evidence demonstrates that AHR activation in immune cells promotes Treg and M2 macrophage differentiation, suppresses $CD8^+$ T-cell activity, and increases PD-1 expression; conversely, pharmacological AHR inhibition reprograms the TME by downregulating suppressive cell populations and enhancing stimulatory populations such as M1 macrophages and dendritic cells, thereby reactivating antitumor T-cell function[89]. Hence, the persistent activation of the AHR pathway, fueled by metabolic perturbations (tryptophan depletion and kynurenine accumulation), directly programs the phenotype of immune cells within the TME. It promotes the expansion of Tregs and suppresses effector T cell function, thereby establishing a robust state of immune tolerance[88]. In myelocytomatosis oncogene (MYC)-driven cancer cells, MYC-driven metabolic reprogramming elevates tryptophan uptake and kynurenine production, demonstrating that oncogenic signals converge with metabolic stress to sustain the IDO-Kyn-AHR immunosuppressive axis[90]. This pathway elegantly illustrates how specific metabolites, by engaging cognate receptors, transduce chronic metabolic alterations (i.e., tryptophan metabolic memory) into stable immunosuppressive gene expression programs. It serves as a quintessential example of metabolic memory driving immune evasion.

The convergent pathways linking metabolic memory to immune evasion, along with their therapeutic implications, are summarized in Table 2.

CLINICAL TRANSLATION AND THERAPEUTIC IMPLICATIONS

Targeting the reversibility of metabolic memory

Metabolic memory constitutes a core pathogenic mechanism driving the progression of numerous chronic diseases, characterized by the persistence of deleterious effects even after the inciting metabolic derangements have been corrected[91]. In diabetic kidney disease, metabolic memory propels progressive renal injury through sustained oxidative stress, inflammation, and epigenetic reprogramming, with dysregulation of the NAD^+-SIRT3 axis representing a central mechanistic hub[92]. In the liver, mitochondrial SIRT3 functions as a critical metabolic sensor - its expression is downregulated in MASLD, and its NAD^+-dependent deacetylase activity governs lipid metabolism, oxidative stress defense, and fibrogenesis. Restoration of NAD^+ levels or SIRT3 activity has been shown to attenuate hepatic steatosis, inflammation, and fibrosis in preclinical MASLD models. Notably, HINT2, a mitochondrial histidine triad nucleotide-binding protein, enhances the NAD^+-dependent activation of SIRT3 by promoting mitochondrial NAD^+ influx through SLC25A51, and its overexpression ameliorates diet-induced steatosis, fibrosis, and mitochondrial damage in mice[93]. This paradigm provides a theoretical foundation for therapeutically targeting the reversibility of metabolic memory. Preclinical investigations have demonstrated that restoration of NAD^+ levels or activation of SIRT3 - achievable through agents such as nicotinamide mononucleotide, metformin, or sodium-glucose cotransporter-2 (SGLT2) inhibitors - can ameliorate mitochondrial dysfunction, mitigate oxidative stress, and attenuate fibrosis, thereby underscoring the tractability of these epigenetic and metabolic pathways[92,94]. Moreover, in the context of MASLD-related HCC chemoprevention, emerging clinical evidence indicates that glucagon-like peptide-1 (GLP-1) receptor agonists and SGLT2 inhibitors are associated with significantly reduced risks of cirrhosis and HCC in patients with MASLD and type 2 diabetes, providing proof-of-principle that metabolic intervention can modulate long-term hepatic outcomes[95,96]. However, robust clinical evidence, particularly pertaining to hepatic endpoints and validated biomarkers of SIRT3 activity, remains conspicuously limited. The enduring nature of metabolic memory underscores the paramount importance of early intervention. Studies conducted in the context of metabolic bariatric surgery have revealed that molecular imprints - driven by epigenetic, inflammatory, and mitochondrial mechanisms - may persist despite postoperative weight reduction and predispose to metabolic relapse. This observation highlights the necessity for intensive "metabolic normalization" therapy during the early stages of disease or in the immediate aftermath of intervention to reset the metabolic set-point and forestall the establishment and consolidation of adverse cellular memory[97]. Consequently, the development of selective liver-targeted SIRT3 activators, the integration of metabolic pharmacotherapies such as GLP-1 receptor agonists and SGLT2 inhibitors, and the validation of SIRT3 activity biomarkers represent prioritized directions for future research aimed at evaluating whether therapeutic modulation of the NAD^+-SIRT3 axis can alleviate metabolic memory and forestall disease progression.

Immunotherapy: opportunities and challenges

MASLD-HCC exhibits a characteristically poor response to immune checkpoint inhibitors (ICIs), a phenomenon largely attributable to the distinctive immune microenvironment sculpted by the disease. The state of chronic, low-grade inflammation and profound immunosuppression imposed by metabolic memory constitutes a pivotal contributing factor. Recent work has dissected the multifaceted mechanisms underlying this resistance, including dysregulated immune cell crosstalk networks, metabolic adaptations that reshape T-cell function, and premature engagement of inhibitory checkpoints - all of which are exacerbated by the MASLD-specific metabolic milieu[98,99]. In MASLD-HCC, neutrophils are polarized into a protumorigenic N2-like phenotype that establishes an immunosuppressive niche by directly suppressing cytotoxic T-cell function and promoting angiogenesis through vascular endothelial growth factor (VEGF) and matrix metalloproteinase (MMP) secretion, thereby contributing to immunotherapy resistance. In HCC specifically, T-cell exhaustion represents a substantial barrier to effective immunotherapy. This exhaustion is driven and stabilized by epigenetic reprogramming - including DNA methylation, repressive histone modifications, and

chromatin remodeling - that locks $CD8^+$ T cells into a dysfunctional state. Targeting these epigenetic barriers, for instance through HDAC8 inhibition to enhance H3K27 acetylation, has been shown to promote memory T-cell phenotypes and improve tumor control when combined with anti-PD-L1 therapy in HCC models[100]. In ulcerative colitis, specific metabolic regulators have been identified as diagnostic biomarkers, and their upregulation exhibits a robust positive correlation with the infiltration abundance of immune cell subsets such as memory B cells and activated memory $CD4^+$ T cells, thereby illuminating the intimate nexus between metabolic status and the functional programming of distinct immune cell populations[101]. These insights offer valuable clues for deciphering the mechanistic basis of immunotherapeutic resistance in MASLD-HCC.

Combination therapeutic strategies are being actively explored to reverse this entrenched immunosuppressive microenvironment. HDAC inhibitors, by virtue of their capacity for epigenetic modulation, harbor the theoretical potential to reverse the functional exhaustion of immune cells instigated by metabolic memory and may therefore synergize with ICIs. A landmark study demonstrated that selective class I HDAC inhibition with CXD101 resensitized immunecheckpointblockade (ICB)-resistant HCC tumors to anti-PD-1 therapy by restoring STAT1-driven antitumor immunity via enhanced chromatin accessibility and H3K27 hyperacetylation of interferon-gamma (IFNγ)-responsive genes. This pharmacological reprogramming induced a self-reinforcing STAT1-GSDME pyroptotic circuitry and $CD8^+$ T cell-dependent memory responses, providing the mechanistic basis for an ongoing phase II clinical trial (NCT05873244)[102]. Beyond HDACs, combined enhancer of zeste homolog 2 (EZH2) and DNA methyltransferase 1 (DNMT1) inhibition has been shown to upregulate Th1 chemokines (CXCL9/CXCL10) and cancer-testis antigens in HCC, thereby enhancing T-cell trafficking into the TME and augmenting anti-PD-L1 efficacy[103]. Furthermore, metabolic modulators such as metformin and SGLT2 inhibitors, beyond their direct salutary effects on metabolic parameters, have been shown in models of diabetic kidney disease to exert anti-inflammatory and mitochondria-protective actions through modulation of the NAD^+-SIRT3 axis[92]. These agents may potentiate the efficacy of immunotherapy by "metabolically reprogramming" immune cells within the TME - for instance, by enhancing the metabolic fitness and memory formation capacity of T cells. The concept of targeting the kynurenine pathway - which links tryptophan metabolism to AHR-mediated immunosuppression - has been revisited, with renewed emphasis on dual IDO1/TDO2 inhibition and AHR antagonism as strategies to overcome ICI resistance in appropriate patient populations[104]. Illustratively, in the context of chimeric antigen receptor (CAR)-T cell therapy, the composition of memory T cell subsets and their intrinsic metabolic adaptability constitute critical determinants predictive of therapeutic efficacy[105]. Furthermore, overcoming the physical and biochemical barriers imposed by the fibrotic TME is essential for effective immunotherapy. A nanoparticle-based co-targeting strategy that simultaneously reprograms CAFs via TGF-β/Smad signaling inhibition and degrades PD-L1 has been shown to remodel the stromal and immune microenvironments, inducing robust immune activation in humanized HCC models[106]. This principle suggests that systemic and local modulation of metabolism may serve as a viable strategy to augment antitumor immune responses. Ultimately, a stage-adapted, multi-targeted combinatorial approach that integrates epigenetic remodeling, metabolic reprogramming, and immune checkpoint blockade may be required to disrupt the metabolic memory-driven immunosuppressive axis and achieve durable therapeutic responses in MASLD-HCC.

CONCLUSION

The progression of MASLD-HCC represents a complex, multi-step process driven by metabolic dysregulation, orchestrated by epigenetic modifications, and culminating in the profound remodeling of the immune microenvironment. The central thesis of this review posits that metabolic memory - operating through an "epigenetic-metabolic-immune axis" - establishes a recalcitrant pathological "scar" within the liver, which constitutes the primary driving force underlying sustained immune evasion and relentless disease progression in MASLD-HCC. This axial mechanism integrates seemingly disparate phenomena -

namely, metabolic abnormalities, dysregulated gene expression, and immunosuppression - into a cohesive and coherent pathological network. This review has delineated how this memory is encoded across multiple layers of the epigenome - from DNA methylation and repressive histone modifications (H3K9me3, H3K27me3) to non-coding RNA networks and epitranscriptomic regulation - and how it is propagated through mitochondrial dysfunction, metabolic byproducts such as lactate-driven histone lactylation, and EV-mediated intercellular transmission of metabolic stress signatures.

From an expert perspective, research in this domain is undergoing a paradigmatic shift from phenomenological description to mechanistic dissection. While early investigations predominantly focused on the causal relationships between lipid accumulation and inflammation, contemporary frontier work is delving into the intricate mechanisms by which metabolites function as signaling moieties. These molecules persistently alter the phenotype and functional attributes of immune cells - for instance, by polarizing macrophages toward pro-fibrotic/pro-tumorigenic phenotypes or by inducing T cell exhaustion - through the covalent modification of histones, DNA, or the regulation of non-coding RNAs. Reconciling the diverse viewpoints within the literature necessitates the critical recognition that the effects of metabolic memory are both stage-specific and cell-type-specific. In the early stages of disease, epigenetic alterations induced by metabolic stress may retain a degree of reversibility. However, as the disease trajectory advances, these modifications become progressively accumulated and entrenched, driving a transition of the hepatic microenvironment toward a state of heightened immunosuppression and fibrogenesis. This is exemplified by the convergent pathways dissected herein - the IRE1α-XBP1 axis that simultaneously drives lipogenesis and PD-L1 expression, the dysregulation of autophagy that compromises both mitochondrial quality control and antigen cross-presentation, and the sustained activation of the AHR pathway by kynurenine that programs Treg expansion and effector T-cell suppression. At this juncture, isolated metabolic interventions often yield negligible therapeutic benefit. This paradigm accounts for the clinical observation that merely optimizing glycemic control or lipid profiles frequently fails to restrain tumor progression in advanced MASLD or established HCC.

The mechanistic insights gleaned from this axis carry profound implications for clinical translation. The recognition that metabolic dysfunction is not merely a risk factor but a causal driver of hepatocarcinogenesis has become a defining theme in contemporary liver oncology[107-109]. They compellingly suggest that future effective therapeutic regimens must comprise multi-targeted, stage-adapted combinatorial interventions. In the early phase of disease, aggressive management of metabolic perturbations - including insulin resistance and lipotoxicity - is paramount for preventing the initial formation of "metabolic scars" and therefore constitutes a form of primary prevention. Emerging evidence suggests that GLP-1 receptor agonists and SGLT2 inhibitors may contribute to this goal, with recent clinical data demonstrating reduced risks of cirrhosis and HCC in patients with MASLD and type 2 diabetes receiving these agents. For patients presenting with significant hepatic fibrosis or early-stage HCC, therapeutic strategies must transcend the metabolic plane. Such approaches necessitate the adjunctive deployment of agents targeting key epigenetic-modifying enzymes - such as HDACs or methyltransferases - to erase or neutralize deleterious metabolic memory, in conjunction with ICIs to dismantle the immunosuppressive barrier erected by this axis. As highlighted in this review, pharmacological activation of STAT1-GSDME pyroptotic circuitry via selective class I HDAC inhibition has demonstrated the capacity to resensitize ICB-resistant HCC to anti-PD-1 therapy, providing a mechanistic foundation for ongoing clinical trials. Furthermore, strategies aimed at breaking the physical barrier imposed by fibrotic ECM remodeling - including nanoparticle-based co-targeting of CAFs and PD-L1 - and at disrupting the kynurenine-AhR immunosuppressive axis through IDO1/TDO2 inhibition or AHR antagonism, represent emerging avenues that target distinct nodes of the epigenetic-metabolic-immune axis. This tripartite strategy of "metabolic regulation-epigenetic remodeling-immune activation" holds considerable promise for disrupting the vicious cycle of MASLD-HCC

progression and may provide novel solutions to this burgeoning global health challenge. Future investigations are warranted to further delineate the precise metabolite-epigenetic target-immune effector cascades within this axis, to map the "memory landscape" at single-cell resolution across the diverse cellular compartments of the liver, thereby guiding the rational development of precision pharmacotherapies.

DECLARATIONS

Authors' contributions

Design of the review: Song Q, Tian C, Sui Y
Literature review and manuscript writing: Song Q
Manuscript revision: Sui Y

Availability of data and materials

Not applicable.

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During the preparation of this manuscript, the AI tool DeepSeek (version V3, released 2024-12-26) was used solely for language editing. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

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