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Review

Nanomedicine-Based Strategies for Regulating Abnormal Amino Acid Metabolism in Liver Diseases

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How To Cite: Yu, L.; Sun, X.; Liu, J.; et al. Nanomedicine-Based Strategies for Regulating Abnormal Amino Acid Metabolism in Liver Diseases. *Sustainable Engineering Novit* **2026**, *2*(1), 1. https://doi.org/10.53941/sen.2026.100001

Received: 30 September 2025
Revised: 5 January 2026
Accepted: 13 January 2026
Published: 23 January 2026

Abstract: Metabolic dysfunction-associated steatotic liver disease (MASLD) has been proposed as a more precise term to characterize steatosis amid metabolic dysregulation and is projected to emerge as the predominant cause of hepatocellular carcinoma (HCC) globally, given the rising prevalence of metabolic comorbidities. Particularly in its inflammatory form, known as metabolic dysfunction-associated steatohepatitis (MASH), hepatic metabolism is profoundly altered. Amino acids are fundamental building blocks that support cellular metabolism and biosynthesis, alongside monosaccharides and fatty acids. Emerging research suggests that aberrant amino acid metabolism in MASLD/MASH and HCC impacts mitochondrial function and redox equilibrium. Nonetheless, the involvement of amino acid metabolism in the progression from MASLD/MASH to HCC is still inadequately comprehended. This review summarizes the aberrant amino acid metabolism in MASLD/MASH and HCC, as well as nanomedicine-based approaches for modulating this metabolism to facilitate the discovery of more effective biomarkers and precision therapeutics for the prevention of MASLD/MASH and HCC.

Keywords: abnormal amino acid metabolism; MASLD; HCC; nanomedicine

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as the leading chronic liver disease worldwide, affecting over one-third of the adult population globally [1,2]. A severe subtype of MASLD is metabolic dysfunction-associated steatohepatitis (MASH), which includes inflammatory clinical features accompanied by hepatic injury [3–5]. Furthermore, MASLD is emerging as the most swiftly escalating contributor to the disease burden associated with detrimental liver outcomes, such as cirrhosis, liver failure, and hepatocellular carcinoma (HCC). MASLD is now recognized as the most rapidly expanding cause of HCC worldwide [6]. Due to the elevated risk of HCC linked to advanced MASLD, there is a critical necessity for rigorous surveillance and preventative measures, particularly in patients with MASLD-related cirrhosis.

Numerous studies have indicated that alterations in amino acid metabolism inside the body are associated with the pathophysiological mechanisms of MASLD. Amino acid biosynthesis and catabolism predominantly occur in the liver, and alterations in circulating amino acid levels can be observed in several chronic liver disorders [7,8]. Regulating abnormal amino acid metabolism may provide a useful technique for the treatment of MASLD

and the prevention of cancer. Moreover, the amino acid is essential in cancer metabolism, facilitating energy production, redox equilibrium, and biosynthesis by supplying nitrogen and carbon sources [7,9]. Cancer cells can modify amino acid metabolism to enhance their survival, unrestricted proliferation, and division in adverse settings, including resistance to treatment drugs [10]. Therefore, it is essential to comprehend how amino acid metabolism is altered to enhance tumor proliferation in a nutrient-scarce environment.

Nanotechnology has emerged as a leading domain in medical detection and therapy due to the unique features associated with the nanoscale. Recently, numerous nanoplatforms have been created, and substantial progress has been achieved in the modulation of amino acid metabolism for the treatment of MASLD and tumor therapy [11,12]. This study seeks to elucidate the diverse functions of amino acid metabolism in the progression of MASLD and tumors while emphasizing nanotechnology-based drug delivery strategies to modulate amino acid metabolism for cancer prevention and treatment.

2. Reprogrammed Amino Acid Metabolism in MASLD

2.1. Essential Amino Acid Metabolism

Essential amino acids (EAAs), indispensable nutrients that must be obtained exclusively from the diet, are integral to hepatic metabolism and are increasingly implicated in the pathogenesis of MASLD. Recent research has elucidated the distinct and often paradoxical roles of specific EAAs in MASLD progression. This review synthesizes current research on the roles of key EAAs—including branched-chain amino acids (BCAAs), aromatic amino acids (AAAs), histidine, and methionine—in MASLD. We will dissect the complex interplay between their metabolic pathways and the mechanisms driving liver disease advancement. A comprehensive understanding of these intricate relationships is paramount for developing targeted dietary and pharmacological strategies to prevent and manage MASLD.

2.1.1. BCAAs Metabolism

BCAAs, comprising leucine, isoleucine, and valine, are characterized by their aliphatic side chains [13]. The catabolism of BCAAs occurs predominantly in skeletal muscle and liver tissues [14]. The catabolic pathway is initiated by branched-chain aminotransferase (BCAT), which exists as cytosolic (BCAT1) and mitochondrial (BCAT2) isozymes, and converts BCAAs into their respective branched-chain α-keto acids (BCKAs) [15]. The BCKAs are then oxidized by the mitochondrial branched-chain α-keto acid dehydrogenase (BCKDH) complex. This reaction commits the BCAAs to catabolism and produces nicotinamide adenine dinucleotide (NADH), CO_2, and acyl-CoA derivatives specific to each amino acid: leucine is catabolized to acetoacetate and acetyl-CoA; isoleucine yields acetyl-CoA and succinyl-CoA; and valine is converted exclusively to succinyl-CoA [16,17].

The catabolism of BCAAs is critically involved in the pathogenesis of MASLD. During the early to moderate stages of the disease, impaired BCAA catabolism leads to their accumulation in the serum and a concomitant weakening of mitochondrial energy metabolism [18]. In stark contrast, circulating BCAA levels decline precipitously with the progression to cirrhosis. This paradoxical decrease is likely attributed to diminished hepatic protein synthesis coupled with a potential resurgence in BCAA catabolism, ultimately resulting in significantly reduced BCAA levels within the liver tissue of patients with end-stage chronic liver disease [16,19].

Recent evidence regarding the impact of a BCAA diet on MASLD is conflicting. A high BCAA diet alleviates MASLD, by inhibiting the tryptophan-indole lactic acid (ILA)- aryl hydrocarbon receptor (AhR) axis and mitogen-activated protein kinase 9 (MAPK9) -mediated *de novo* lipogenesis (DNL), thus activating peroxisome proliferator-activated receptors (PPAR)-retinoid X receptors (RXR) and pexophagy to promote fatty acid β-oxidation [20]. Thus, moderating intake of high BCAA are promising new strategies in MASLD treatment. Moreover, low-dose valine supplementation attenuates MASLD through multiple mechanisms: it downregulates genes related to hepatic lipogenesis and cholesterol biosynthesis, upregulates genes involved in fatty acid oxidation, autophagy, and antioxidant defense, and enhances AMP-activated protein kinase (AMPK) signaling; furthermore, it reduces leptin resistance and inflammation in the liver and hypothalamus, and positively modulates the gut microbiome [21]. Likewise, a low isoleucine diet reprograms liver and adipose metabolism, leading to increased hepatic insulin sensitivity, enhanced ketogenesis, and greater energy expenditure through the activation of the fibroblast growth factor 21 (FGF21)-uncoupling protein 1 (UCP1) axis [22]. Recent research also found that dietary leucine and isoleucine ameliorate hepatic steatosis; they directly bind to and activate Ubr1 E3 ligase, which mediates Plin2 (a lipid droplet-stabilizing protein) ubiquitination and subsequent degradation [23]. However, long-term exposure to high BCAA diets leads to hyperphagia, obesity, and reduced lifespan, which is associated with central serotonin depletion [24]. Thus, preventing hyperphagia might avert the health costs of a high-BCAA diet.

Beyond BCAAs dietary modulation, the therapeutic potential of their derivatives in MASLD is being actively explored. Notably, the synthetic tripeptide DT-109 (Glycine -Glycine-L-Leucine) has demonstrated efficacy in ameliorating MASLD by activating hepatic fatty acid oxidation, mitigating lipotoxicity, and stimulating the *de novo* synthesis of glutathione (GSH) [25]. Similarly, NS-0200, comprising leucine, metformin, and sildenafil, has shown promise in treating MASH. In a clinical trial (NCT 02546609), NS-0200 treatment leads to a significant reduction in metabolically active lipids and an upregulation of fatty acid oxidation [26].

2.1.2. Phenylalanine/Tyrosine Metabolism

AAAs are amino acids that contain aromatic rings, including phenylalanine, tyrosine, and tryptophan. The catabolism of AAAs occurs mainly in the liver. Phenylalanine, obtained primarily from the diet, is metabolized mainly through its hydroxylation to tyrosine, a reaction catalyzed by phenylalanine hydroxylase [27]. Tyrosine is catabolized via transamination to p-hydroxyphenylpyruvate, which is subsequently degraded into acetoacetate and fumarate; this pathway ultimately contributes to the generation of acetyl-CoA, thereby elevating its levels and promoting lipogenesis [28].

It has been identified that phenylalanine and tyrosine are fasting serum metabolites present at higher levels in individuals with MASH compared to those with a normal phenotype [29,30]. The concentrations of phenylalanine/tyrosine are positively correlated with the severity of liver steatosis [27]. Given that the consequences of the dysregulated metabolism of tyrosine are not entirely clear, research has implicated tyrosine and methionine in the assembly of mature very-low-density lipoprotein (VLDL) in hepatocytes [31]. Specifically, the deprivation of methionine and L-tyrosine, induces a phenotype similar to MASLD and disrupts the assembly of triglyceride (TG)-rich mature VLDL in hepatocytes through fumarate metabolism in a nuclear factor erythroid 2-related factor 2 (Nrf2)-dependent manner [31].

It has been found that treatment with Qushi Huayu (QSHY) in MASLD patients with liver dysfunction leads to a significant reduction in circulating phenylalanine and tyrosine levels, coupled with an elevation of the gut microbial metabolite p-Hydroxyphenylacetic acid [32]. Moreover, Hydroxysafflor yellow A (HSYA) administration to high-fat diet (HFD)-fed mice not only decreases serum tyrosine but also induces favorable shifts in the gut microbiota, specifically by increasing the abundance of the beneficial genus *Turicibacter* [33]. A proposed mechanism for this effect is that the proliferation of *Turicibacter* may inhibit host tryptophan (via the kynurenine pathway) and phenylalanine metabolism, leading to a reduction in tyrosine synthesis precursors, thereby lowering the serum tyrosine concentration [33].

Emerging evidence indicates that tyrosine derivatives, in addition to tyrosine, can regulate MASLD. The gut-derived serotonin (GDS)/hepatic serotonin receptor 2a (HTR2A) axis is a critical pathway in the development of MASLD [34]. By targeting this pathway, the tyrosine derivative 14a—a potent 5HTR2A inhibitor—effectively reduces hepatic steatosis, lobular inflammation, and TG levels in mice with HFD-induced steatosis [35].

2.1.3. Tryptophan Metabolism

Tryptophan metabolism proceeds via three primary pathways: the kynurenine (Kyn), the 5-hydroxytryptamine (5-HT, serotonin), and the indole pathways (Figure 1). The Kyn pathway, which accounts for approximately 95% of dietary tryptophan catabolism, is initiated by the enzymes tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO), converting tryptophan into Kyn and its downstream metabolites [36]. The 5-HT pathway is characterized by the synthesis of 5-HT from tryptophan, a reaction catalyzed by the enzyme tryptophan hydroxylase (TPH) [36]. In contrast, indoles and their derivatives are predominantly generated through the catabolism of tryptophan by the gut microbiota [36].

Compared to normal subjects, MASH patients exhibit elevated serum tryptophan levels [29]. Despite this elevation, intriguingly, exogenous tryptophan supplementation appears to have therapeutic effects. For instance, Celinski et al. demonstrated that tryptophan administration significantly reduced pro-inflammatory cytokine levels and improved lipid metabolism in MASLD patients [37]. Consistent with these clinical findings, oral administration of tryptophan alleviated the progression of MASLD in mice. The underlying mechanisms remain unclear, but may involve stabilization of the intestinal barrier and restoration of the dysregulated gut 5-HT system [38].

Kyn, a core metabolite of the Kyn pathway, can lead to obesity or related metabolic disorders through AhR activation, which is a transcription factor that becomes active upon binding to ligands like Kyn, indole, and its derivatives [39]. On the contrary, kynurenic acid (KynA), another tryptophan metabolite, ameliorates hepatic steatosis through enhancing AMPK phosphorylation, oxygen regulatory protein 150 (ORP150) expression, and autophagy markers to reduce endoplasmic reticulum stress [40]. Moreover, KynA increases energy utilization by activating G protein-coupled receptor 35 (GPR35), which stimulates the expression of genes related to lipid

metabolism, thermogenesis, and anti-inflammation in adipose tissue, thereby suppressing weight gain and improving glucose tolerance in HFD-fed mice [41]. Likewise, IDO plays a dual role in the regulation of liver inflammation, exhibiting markedly divergent effects. Studies have shown that reduced IDO expression correlates with exacerbated hepatic inflammation and fibrosis in mice [42]. In contrast, IDO-deficient mice on a HFD demonstrated diminished infiltration of inflammatory macrophages. A possible explanation for these differing outcomes may lie in the gut microbiota, which are known to modulate IDO enzymatic activity, thereby influencing the progression of MASLD [43]. Furthermore, TDO2 activates the nuclear factor-kappa B (NF-κB) pathway to promote M1 macrophage polarization representing a crucial event in MASLD progression. Consequently, a bovine serum albumin nanoparticle was fabricated to inhibit TDO2, thereby utilizing its excellent biocompatibility and targeting capacity to robustly alleviate HFD-induced metabolic disorders [44].

The 5-HT system influences MASLD through multiple, sometimes paradoxical, mechanisms. HFD-induced upregulation of hepatic 5-HT/HTR2A signaling promotes insulin resistance and triggers a compensatory increase in plasma FGF21 that precedes overt metabolic dysfunction [45]. However, modulation of this pathway also holds therapeutic promise. Tryptophan supplementation alleviates MASLD by enhancing gut barrier function (via increased Occludin) and altering 5-HT dynamics (via increased 5-HT reuptake transporter and decreased TPH1 expression) [46]. This therapeutic effect is corroborated by clinical data, where long-term co-administration of tryptophan and melatonin (converted from 5-HT) effectively suppressed pro-inflammatory cytokines in MASLD patients [37].

Recent research on tryptophan metabolite produced by intestinal bacteria suggests protective effects against MASLD. Indole derivatives indoleacetic acid (IAA) and indole-3-propionate (IPA) levels are reduced in patients with MASLD compared to those in healthy individuals. Oral indole supplementation mitigates HFD-induced MASLD by counteracting the decline in serum Angiotensin-(1-7) levels and Angiotensin-Converting Enzyme 2 (ACE2) expression, thereby reducing ROS production and preserving mitochondrial membrane potential [47]. It is also demonstrated that administration of IPA and IAA ameliorates hepatic steatosis and liver inflammation by inhibiting the NF-κB pathway via reduced endotoxin levels and macrophage inactivation [48]. In addition, IAA also enhances mitochondrial oxidative phosphorylation via peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) -dependent mechanisms, thereby alleviating diet-induced metabolic disturbances such as glucose dysmetabolism and hepatic steatosis [49]. Similarly, IPA attenuates MASH through a multi-pronged mechanism: it enhances the intestinal barrier (upregulating tight junction proteins, ZO-1 and Occludin) to reduce endotoxemia, suppresses endotoxin-induced macrophage inflammation via NF-κB inhibition, and directly inhibits fibrogenic gene expression [50].

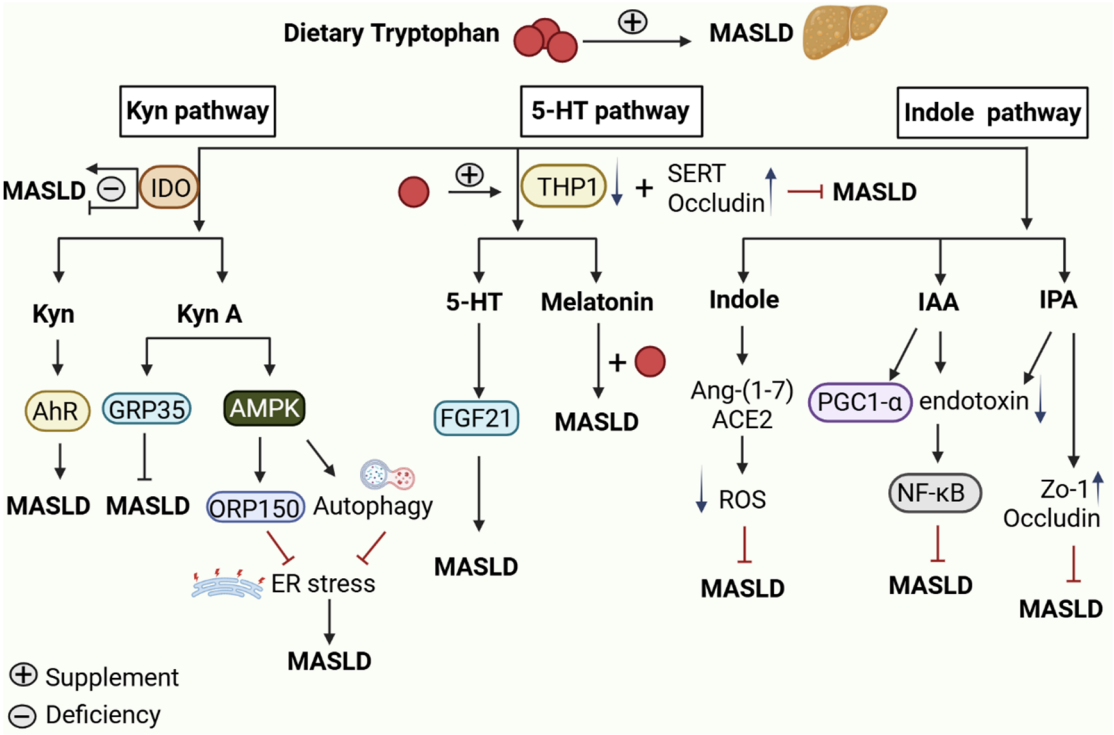

Figure 1. Tryptophan metabolism in MASLD.

2.1.4. Histidine Metabolism

Histidine is decarboxylated to histamine by histidine decarboxylase (HDC), an enzyme present in both mammalian tissues (lung, liver, muscle, gastric mucosa) and gut microbiota [51]. Clinically, serum histidine levels positively correlate with gut microbiota abundance, a parameter that is significantly reduced in metabolic syndrome. Aron-Wisnewsky et al. suggested that gut dysbiosis may disrupt histidine metabolism, potentially linking microbial ecology to the disease pathophysiology [52].

While histidine and its microbial metabolites are established modulators of insulin signaling and diabetes [53–55], their role in MASLD remains incompletely understood. Clinical evidence indicates an inverse relationship between circulating histidine levels and the severity of hepatic steatosis [56]. In contrast, preclinical studies consistently demonstrate that histidine supplementation ameliorates MASLD across various animal models, an effect linked to the suppression of hepatic DNL [56]. This beneficial impact is mediated through the gut-liver axis, as exemplified by the finding that colonization with *Escherichia cloacae* in Drosophila elevates TG and depletes histidine, thereby implicating microbial histidine metabolism in MASLD pathogenesis [56]. It is crucial to note that this relationship is dose-dependent, because excessive histidine intake in rats can paradoxically promote hepatic lipid accumulation, likely by disrupting the equilibrium between hepatic lipid export and free fatty acid uptake [57].

Histamine, a key histidine metabolite, is a biogenic amine critically involved in immune and inflammatory responses, as well as neurotransmission. It has been demonstrated that patients with MASLD and end-stage liver disease exhibit elevated serum histamine levels, alongside upregulated expression of HDC, and histamine-specific membrane receptors (HRs) in liver [58]. While genetic ablation of HDC exacerbates HFD-induced obesity and hepatic steatosis by downregulating the leptin receptor and promoting leptin resistance, it paradoxically exerts a protective effect against fibrosis. Specifically, the loss of HDC appears to shield cholangiocytes from HFD-induced damage, thereby attenuating hepatic fibrosis in the context of MASH [58]. HRs, which are now classified into four subclasses (H1R–H4R). In vivo studies reveal that histamine/H2R signaling alleviates early-stage liver injury in MASLD through two mechanisms: suppressing cholesterol absorption under a high-cholesterol diet (HCD) and modulating bile acid (BA) homeostasis under a high-cholic acid (HCA) diet, resulting in decreased serum BA and increased fecal BA excretion. These effects, mediated via enterohepatic cholesterol and BA metabolism, underscore the protective role of histamine/H2R signaling in MASLD progression [59].

2.1.5. Methionine Metabolism

Methionine metabolism is a pivotal pathway integrating cellular methylation and redox balance (Figure 2). The methionine cycle is initiated by the ATP-dependent conversion of methionine to S-adenosylmethionine (SAM), the universal methyl donor, a reaction catalyzed by methionine adenosyltransferases (MATs) [60,61]. Subsequent methyl transfer reactions, mediated by enzymes like glycine N-methyltransferase (GNMT) and phosphatidylethanolamine N-methyltransferase (PEMT), convert SAM to S-adenosylhomocysteine (SAH), which is then hydrolyzed to homocysteine (Hcy) by S-adenosyl-homocysteine hydrolase (AHCY) [62–64]. At a crucial metabolic crossroads, Hcy can be irreversibly committed to the transsulfuration pathway or remethylated to regenerate methionine via two major routes: the folate/vitamin B12-dependent methionine synthase (MTR) pathway or the betaine-dependent betaine homocysteine methyltransferase (BHMT) pathway [63–65]. In the transsulfuration pathway, Hcy is condensed with serine by cystathionine-β-synthase (CBS) and subsequently cleaved by cystathionine-γ-lyase to produce cysteine, thereby fueling GSH synthesis.

Methionine plays a paradoxical role in MASLD, acting as both a potential therapeutic agent and a factor whose deficiency or dysregulation contributes to disease pathogenesis. On one hand, clinical studies report elevated plasma methionine in MASLD patients [66], and supplementation of L-methionine in rodent models [67] or selenomethionine with antioxidants in human patients [68] has demonstrated beneficial effects on liver pathology and metabolic profiles. On the other hand, a methionine-deficient diet is a well-known trigger for hepatic steatosis in experimental settings [69–71]. This dichotomy may be explained by disturbances in intrahepatic methionine metabolism. Indeed, in advanced disease models featuring significant steatosis and fibrosis, hepatic methionine is depleted despite its high plasma levels. This is associated with an increased SAM/methionine ratio and elevated SAH and Hcy [61], indicating that impaired methionine processing and methylation stress, rather than absolute methionine levels, are central to MASLD progression.

Notably, the expression of enzymes involved in methionine cycle is closely associated with the progression of MASLD. In particular, loss of Mat1a markedly reduces hepatic SAM levels, triggering spontaneous hepatic steatosis and its progression to steatohepatitis, fibrosis, and ultimately, HCC. Of note is the observation that SAM treatment of Mat1a-KO mice reverses liver damage [72]. PEMT catalyzes the methylation of

phosphatidylethanolamines (PE) to phosphatidylcholine (PC) with SAM as its substrate and SAH as its product. Pemt-KO mice fed a HFD showed decreased PC/PE molar ratio and developed steatosis due to reduced VLDL-TG secretion, which eventually progressed to MASH [73,74]. Similarly, GNMT catalyzes the conversion of SAM and glycine to SAH and sarcosine. The absence of GNMT in Gnmt-KO mice drives a pathogenic cascade: it elevates hepatic methionine and SAM while reducing SAH [75], which in turn increases the flux from PE to PC, leading to decreased PE, increased PC, and subsequent TG synthesis, steatosis, and eventual progression to steatohepatitis, fibrosis, and hepatocellular carcinoma [70,76]. CBS-deficient mice show elevated hepatic Hcy, SAM, and SAH, reduced GSH, and DNA hypomethylation [77,78], and subsequently develop steatosis and mild liver injury [79]. BHMT, preferentially expressed in the liver, catalyzes the transfer of a methyl group from betaine to Hcy, forming methionine. BHMT disruption in mice increases Hcy levels, reduces SAM, and elevates SAH, leading to fatty liver due to impaired VLDL export and reduced hepatic PC, ultimately progressing to HCC [80]. Thus, targeting enzymes in the methionine cycle represents a promising therapeutic strategy for MASLD.

The metabolic network centered on methionine is intricately linked to numerous other biochemical processes. A pivotal component of this network is one-carbon metabolism, an integrated system formed by the interlocking methionine and folate cycles [81]. A disruption in this system, such as folate deficiency, promotes the utilization of betaine and choline for Hcy remethylation, thereby disrupting choline metabolism and contributing to lipid accumulation [82–84]. One mechanism that is likely involved in this process is folate participation in SAM synthesis, which is subsequently involved in PC synthesis and VLDL secretion. Several recent clinical studies showed that vitamin B12 and folate levels were negatively correlated with MASLD severity [85–88]. Supplementation with vitamins or folate increased the β-oxidation of fatty acids, leading to decreased inflammation and fibrosis, as well as the reversal of hepatic TG and diacylglycerol accumulation in MASH [89]. The observed benefits are attributable, at least in part, to the upregulation of Hcy-to-methionine enzymatic conversion, thereby decreasing Hcy levels and restoring hepatic expression of Hcy-modified syntaxin 17 (Stx17) and autophagy [89].

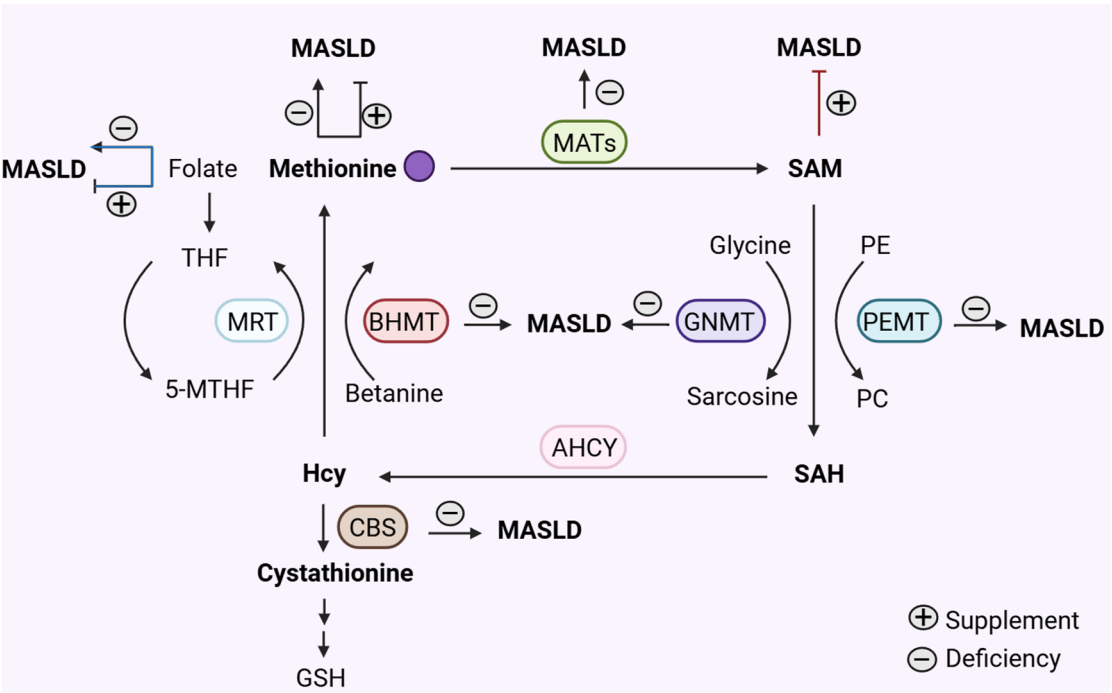

Figure 2. Methionine metabolism in MASLD.

2.2. Nonessential Amino Acid Metabolism

Beyond the EAAs, the metabolism of nonessential amino acids (NEAAs) is critically dysregulated in MASLD, playing a central and complex role in disease pathogenesis. While termed nonessential, the endogenous synthesis and metabolic interconversion of amino acids such as glycine, serine, glutamine, and glutamate are vital for maintaining hepatic redox balance, one-carbon metabolism, and energy homeostasis. In MASLD, the depletion of glycine and serine disrupts glutathione synthesis, exacerbating oxidative stress. Concurrently, glutamine metabolism is reprogrammed across different liver cell types, driving steatosis, inflammation, and fibrosis. Thus,

the intricate and often paradoxical roles of NEAAs metabolism underscore their potential as both biomarkers for disease staging and promising therapeutic targets for intervention.

2.2.1. Glycine and Serine Metabolism

Glycine is a conditionally essential amino acid that is obtained from the diet and synthesized endogenously, primarily from serine. The interconversion between serine and glycine is catalyzed by serine hydroxymethyltransferase (SHMT) isoforms located in either the cytosol (SHMT1) or mitochondria (SHMT2) [90]. In the folate cycle, SHMT utilizes tetrahydrofolate as a coenzyme and serine as a substrate to generate glycine and 5,10-methylenetetrahydrofolate, the latter serving as a key one-carbon unit carrier [90].

Studies indicate that individuals with MASLD and metabolic syndrome tend to have lower levels of serine and glycine in the circulation [91,92]. Consistent with clinical observations, glycine levels are reduced in mice with hepatic steatosis. Further studies indicated that this decline was attributed to enhanced serine production from glycine through reverse SHMT2 activity. Consequently, diminished glycine availability in steatotic livers compromised GSH synthesis under oxidative stress, exacerbating acute hepatotoxicity. Either glycine supplementation or hepatocyte-specific deletion of mitochondrial SHMT2 alleviated hepatotoxicity in steatotic mice by promoting *de novo* GSH synthesis [93]. Contrary to expectations, SHMT2 ablation has been reported to elevate circulating serine and glycine while diminishing hepatic methylation potential, thereby increasing susceptibility to steatosis [94]. Additionally, although SHMT2-deficient mice spontaneously develop fatty liver, they exhibit significantly attenuated inflammation and fibrosis when challenged with a diet high in fat, fructose, and cholesterol [94].

In line with the effects of glycine deficiency, dietary serine deficiency or reduced endogenous serine synthesis in mice leads to excessive hepatic lipid accumulation and inflammation, thereby exacerbating the development of fatty liver [95]. Thus, these two amino acids have been suggested as promising biomarkers for diagnosing MASLD and guiding nutritional interventions [25,92,96,97]. This is exemplified by findings in leptin-deficient mice, where high- glycine, serine, and threonine diet ameliorated pathogenesis of MASLD [98]. Additionally, glycine-based treatment (DT-109) attenuates experimental MASLD by stimulating hepatic fatty acid oxidation and GSH synthesis [25].

2.2.2. Glutamine Metabolism

Hepatic glutamine and glutamate metabolism is zonated, creating a metabolic interplay between the periportal and pericentral regions [99] (Figure 3). Glutamine is converted to glutamate and ammonia in the periportal zone by mitochondrial glutaminase (GLS), mainly the GLS2 isoform in hepatocytes. The ammonia is detoxified by the urea cycle, while the glutamate fuels the TCA cycle for ATP production, gluconeogenesis, and fatty acid oxidation. GLS1, in contrast, is low in hepatocytes but highly expressed in activated hepatic stellate cells (HSCs) and cancer cells. In the pericentral zone, glutamine synthetase (GS) recaptures residual ammonia by synthesizing glutamine, maintaining systemic nitrogen balance [100,101]. This region relies on glycolysis as its main energy source, an adaptation to its hypoxic environment.

A Mendelian randomization study revealed that higher alanine and lower glutamine levels were associated with a higher risk of developing MASLD [102]. In HFD-induced obese mice, glutamine ameliorates liver steatosis by promoting sirtuin 1 (SIRT1) and suppressing acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) expression, while also regulating the protein kinase B (AKT)/forkhead box O1 (FOXO1) signaling pathway to realize glycolipid metabolism [103]. These findings indicate that glutamine serves as a nutritional tool in managing obesity and related disorders. In ob/ob mice, supplementation with L-alanyl-L-glutamine (DIP) effectively reverses the metabolic disturbances seen in controls, restoring depleted plasma and tissue glutamine levels, ameliorating insulin resistance, and concurrently attenuating oxidative stress and inflammation [104].

Glutamine and glutamate serve as major carbon sources fueling the TCA cycle and lipogenesis in hepatocytes [7]. In the context of obesity, this metabolic contribution is underpinned by a dysregulation in glutamine catabolism, characterized by elevated transamination-reductive carboxylation and suppressed oxidative deamination [7]. Consequently, targeted inhibition of broad glutaminolysis (shGls2) or specific suppression of reductive carboxylation (shIdh1) could significantly attenuate hepatic TG accumulation [7]. Moreover, GLS1 is a pivotal mediator of hepatic fibrosis, evidenced by a serum glutamate/glutamine ratio that rises with fibrosis severity and a corresponding upregulation of GLS1 (but downregulation of GLS2) in diseased livers. This pro-fibrotic switch is driven by a hypoxia-activated hypoxia-inducible factor 2α (HIF-2α)/ yes-associated protein 1 (YAP) axis in HSCs. HIF-2α promotes YAP activation by suppressing its phosphorylation, leading to the co-overexpression of GLS1, α-SMA, and Collagen-1, which collectively fuels the progression of MASLD-associated

fibrosis [105]. In addition, Du and colleagues have shown that GLS1 is induced in fibrotic livers, and inhibition of GLS1 blocked the activation of HSCs, halting fibrosis progression [106]. Nonetheless, Jorge Simon et al. demonstrated that GLS1 is overexpressed in MASH, both in the clinical setting and in pre-clinical mouse models, and, more importantly, specific GLS1 inhibition in hepatocytes lowers oxidative stress and restores PC synthesis and VLDL-TG export, thereby reducing liver steatosis [107]. Thus, data regarding the differences in GLS zone-specific expression are not consistent, and these findings require further investigation.

Furthermore, the interplay between glutamate and other amino acid metabolism is a critical factor in MASLD pathogenesis. As a key player of the cystine/glutamate antiporter, the overexpression of solute carrier family 7 member 11(SLC7A11) in hepatocytes paradoxically disrupts redox homeostasis. SLC7A11 hyperactivity depletes intracellular glutamate and serine availability and starves the transsulfuration pathway of its substrates, leading to deficient cysteine synthesis. The resulting cysteine deficiency triggers ferroptosis and accelerates MASLD progression [108]. Consistent with this mechanism, both serine supplementation and pharmacological inhibition of ferroptosis significantly alleviated the disease.

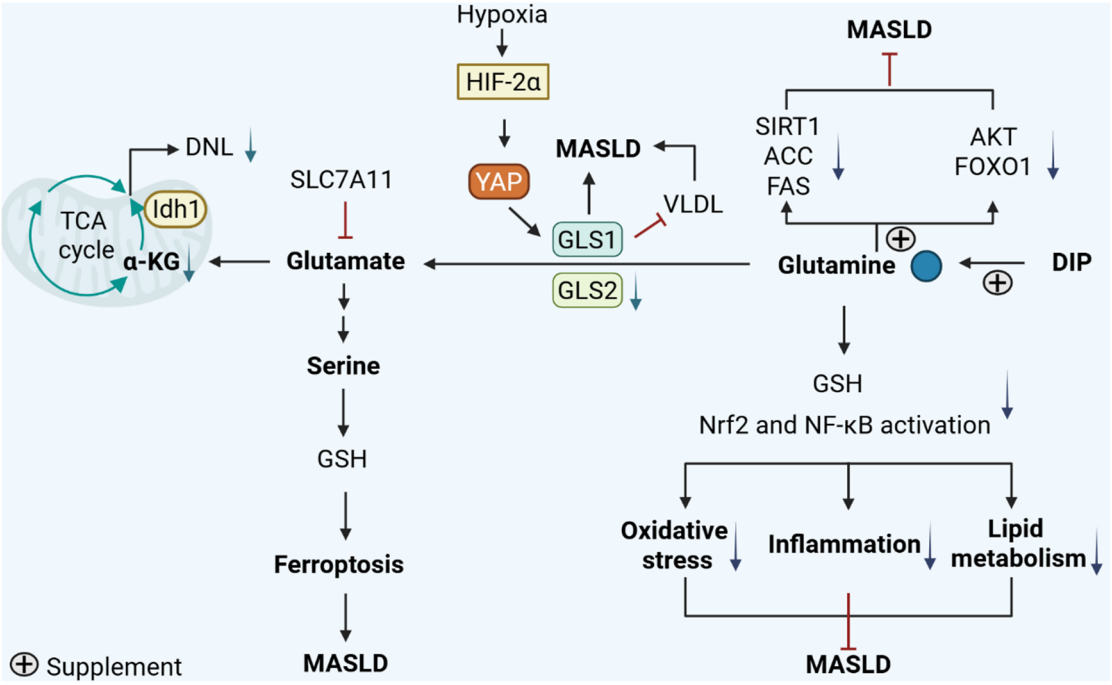

Figure 3. Glutamine metabolism in MASLD.

3. Reprogrammed Amino Acid Metabolism in Liver Cancer

3.1. Essential Amino Acid Metabolism

As the central organ of amino acid metabolism, the liver plays a pivotal role in the uptake, transport, and metabolism of essential amino acids. Studies have demonstrated that various types of HCC exhibit a marked dependence on exogenous essential amino acids, such as tryptophan, arginine, and glutamine, during rapid proliferation [109,110]. These amino acids not only serve as substrates for protein synthesis but, upon catabolism, also promote tumor growth through multiple mechanisms, facilitate immune evasion, and participate in epigenetic modifications, thereby regulating tumor cell survival and self-renewal.

3.1.1. BCAAs Metabolism

BCAT in skeletal muscle converts BCAAs to BCKAs, which are then transferred to the liver and irreversibly decarboxylated by hepatic mitochondrial BCKDH to fuel the TCA cycle. Liver dysfunction alters BCKDH activity, leading to fluctuations in circulating BCAA levels [111]. In contrast to MASLD, plasma concentrations of BCAA are significantly reduced in HCC patients, whereas intratumoral BCAA levels are increased and positively correlate with tumor progression [112–114]. The increased demand for BCAAs in tumor cells is likely associated with their rapid growth and proliferation. The expression of BCAA catabolic enzymes is markedly downregulated in a subset of HCC patients, and elevated BCAA levels can activate rapamycin complex 1 (mTORC1) signaling and promote tumor cell proliferation [115]. It has been demonstrated that in TP53-mutant HCC, the expression of carnitine palmitoyltransferase 1A is significantly downregulated, resulting in suppressed

fatty acid β-oxidation, reduced acetyl-CoA levels, diminished histone acetylation, and inhibited BCAA catabolic gene transcription, which leads to BCAA accumulation and hyperactivation of the mTOR signaling pathway, ultimately driving HCC progression [116]. Specifically, leucine plays a particularly critical role in mTOR pathway activation [117]. Pyruvate dehydrogenase component dihydrolipoamide S-acetyltransferase was found to directly acetylate the leucine catabolic enzyme, RNA-binding methylglutaconyl-CoA hydratase (AUH), at lysine 109, suppressing its activity, causing leucine accumulation, and consequently activating the mTORC1 pathway to promote HCC development [111]. In addition to glucose and glutamine, BCAA catabolism is essential for sustaining HCC cell survival [118]. Under glutamine-deprived conditions, O-GlcNAcylation is upregulated to stabilize the enzyme protein phosphatase 1K (PPM1K), leading to dephosphorylation of the BCKDH α subunit and enhanced BCAA catabolism [118].

3.1.2. Tryptophan Metabolism

Tryptophan is an essential amino acid in humans that contributes to protein synthesis and serves as a precursor for multiple neurotransmitters and neuroactive compounds, thereby regulating central nervous system functions and peripheral neural signaling [119]. In addition, tryptophan and its metabolites modulate immune cell activity and the immune microenvironment, thus maintaining immune homeostasis [120]. Aberrant accumulation of tryptophan metabolites has been closely linked to HCC proliferation, angiogenesis, immune evasion, and drug resistance (Figure 4).

More than 95% of tryptophan metabolism proceeds through the Kyn pathway. Under the catalytic action of the rate-limiting enzymes IDO1, IDO2 or TDO, tryptophan is converted into the intermediate N-formyl-L-kynurenine, which is subsequently transformed into Kyn through a deformylation process [121]. Clinical studies have shown that the ratio of Kyn to tryptophan is elevated in the serum of HCC [122], and high serum Kyn levels are positively correlated with poor prognosis [123]. Moreover, recent findings suggest that the accumulation of Kyn within tumors promotes the formation of an immunosuppressive tumor microenvironment, thereby facilitating HCC immune evasion [124]. Kyn functions as an endogenous ligand of the AhR, directly activating AhR and regulating the transcription of downstream target genes such as cytochrome P450 family 1 subfamily A member 1 (CYP1A1) [125,126]. Studies have demonstrated that the overexpression of zinc finger protein 165 (ZNF165) in HCC facilitates AhR nuclear translocation, thereby enhancing CYP1A1 expression and promoting HCC cell proliferation and migration [127]. Kyn can also be metabolized by Kyn 3-monooxygenase to 3-hydroxykynurenine and subsequently by kynureninase to 3-hydroxyanthranilic acid, yet the impact of this branch remains unsettled, with pro-tumorigenic effects reported in some studies [128,129] and anti-tumor effects in others [130,131]. Differences in enzyme expression, metabolite balance, redox status, and tumor–immune composition likely account for these divergent outcomes and justify further investigation.

The second tryptophan metabolic pathway involves the conversion of tryptophan into 5-hydroxytryptophan (5-HTP) catalyzed by TPH. 5-HTP is subsequently decarboxylated by aromatic L-amino acid decarboxylase (AADC) to form 5-HT, which regulates anxiety, depression, and the sleep-wake cycle, including the synthesis of melatonin [132–134]. A recent study revealed that TPH expression is elevated in HCC tissues, whereas the Kyn pathway of tryptophan metabolism is suppressed, resulting in significantly higher accumulation of 5-HT in tumor tissues compared with adjacent non-tumor tissues [135]. Further experiments demonstrated that transglutaminase 2 mediates covalent modification of the glutamine residue at position 5 of histone H3 (H3) with 5-HT, a process termed serotonylation, which enhances MYC target gene transcription and promotes HCC progression [135]. Moreover, the expression of 5-HT receptors, such as 5-HT1D, 5-HT7, and 5-HT2B, was also significantly upregulated in HCC tissues compared with adjacent tissues. Acting through these receptors, 5-HT can indirectly activate intracellular signaling pathways including Wnt/β-catenin [136], phosphatidylinositol 3-kinase (PI3K)/AKT [137] and YAP [138], thereby promoting cancer cell proliferation, migration, and invasion. Moreover, tryptophan can also be metabolized into indole derivatives independently of microbial enzymes. For example, interleukin-4-induced-1 (IL4I1) converts tryptophan into indole-3-pyruvate (I3P) [139]. In MYC-driven HCC models, tryptophan is preferentially metabolized into I3P while the Kyn pathway is suppressed [140]. I3P induces AhR nuclear translocation and activates downstream target genes such as CYP1A, thereby promoting HCC progression [140].

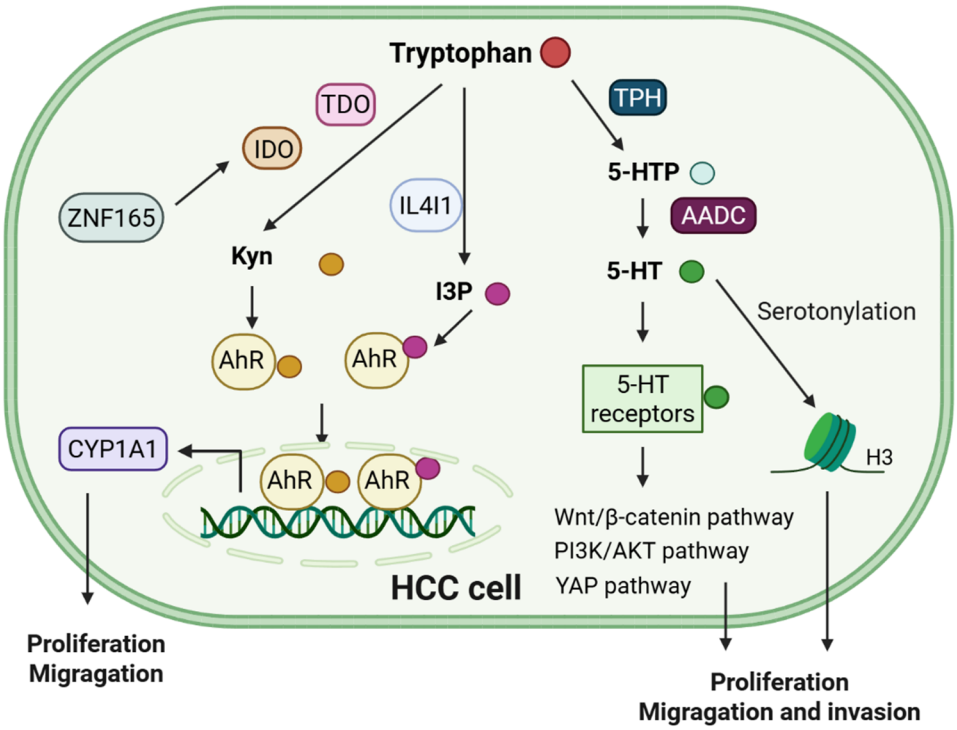

Figure 4. Tryptophan metabolism in HCC.

In the normal intestine, a portion of tryptophan is metabolized by tryptophanase-positive bacteria, particularly *Escherichia coli* and *Lactobacillus*, into various indole derivatives such as IAA, IPA, and ILA [141]. These metabolites enter the portal vein via the gut-liver axis and influence HCC cells as well as the tumor microenvironment. Studies have reported that a reduction in gut microbiota impairs intestinal tryptophan metabolism, leading to decreased levels of 10 tryptophan-derived metabolites, including IAA, indole-3-carboxaldehyde (ICAld), and IPA. This attenuation weakens AhR activation, subsequently upregulates sterol regulatory element-binding protein 2 (SREBP2), and promotes hepatocarcinogenesis [142]. This evidence suggests that AhR may exert a "double-edged sword effect" in HCC: activation by metabolites from the Kyn pathway promotes tumor progression, while activation by indole-derived metabolites suppresses tumor development, likely due to differential gene expression profiles regulated by distinct tryptophan metabolites.

3.1.3. Arginine Metabolism

In the normal liver, arginine metabolism is primarily involved in the urea cycle and nitrogen metabolism (Figure 5), with its central functions being ammonia detoxification and the maintenance of nitrogen balance [143]. Hepatocytes exhibit high expression of arginase 1 (ARG1), which hydrolyzes arginine into urea and ornithine [143]. Urea is transported via the bloodstream to the kidneys for excretion, thereby completing nitrogen elimination. Ornithine can follow three fates: (i) re-entering the ornithine cycle to regenerate arginine, (ii) participating in polyamine synthesis, and (iii) entering the proline synthesis pathway, all of which support normal cell proliferation and collagen production [144].

Studies have shown that arginine levels are significantly elevated in HCC. This increase is not attributed to enhanced endogenous arginine synthesis, as key enzymes in the urea cycle, such as argininosuccinate synthase, are markedly downregulated in HCC, indicating a reduction in endogenous arginine production [145–147]. Instead, the expression of arginine transporters, including members of the solute carrier 7A family (SLC7A1/3/4/6/7/9), is upregulated, suggesting enhanced exogenous arginine uptake by cancer cells [145,148]. Elevated arginine levels regulate metabolic gene expression through interaction with RNA binding motif protein 39 (RBM39), leading to the upregulation of glucose transporter glucose transporter 3 (GLUT3) and hexokinase 2 (HK2), thereby meeting the energy demands of rapid tumor proliferation [145]. Additionally, arginine upregulates nicotinamide N-methyltransferase (NNMT) and amine oxidase 3 (DAO), promoting drug resistance and metastasis [145]. Under conditions of glutamine deficiency, p53 has been reported to upregulate the arginine transporter SLC7A3, thereby increasing intracellular arginine levels, directly activating mTORC1, and enabling tumor cells to sustain growth in a glutamine-deprived state [149]. Moreover, HCC cells optimize lysosomal arginine release and intracellular utilization through the lysosomal arginine sensor transmembrane 4 L six family member 5

(TM4SF5), maintaining elevated arginine levels and promoting persistent mTORC1 pathway activation to support tumor proliferation [150]. In addition, HCC cells can upregulate activating transcription factor 4 (ATF4) by promoting β-catenin degradation under arginine-depleted conditions, thereby avoiding apoptosis [148]. Although the urea cycle is suppressed in HCC, ornithine decarboxylase 1(ODC1) catalyzes the conversion of ornithine into putrescine, which is subsequently processed into spermidine and spermine [151,152]. These polyamine levels in both plasma and tumor tissues of HCC patients are significantly elevated and positively correlated with tumor proliferation and metastasis [151,152]. Furthermore, the accumulation of N1-acetylspermidine (N1-Ac-Spd) within tumors has been shown to act on macrophages in a charge-dependent manner, activating Src kinase signaling and shaping an immunosuppressive tumor microenvironment that attenuates the efficacy of immune checkpoint therapies [153].

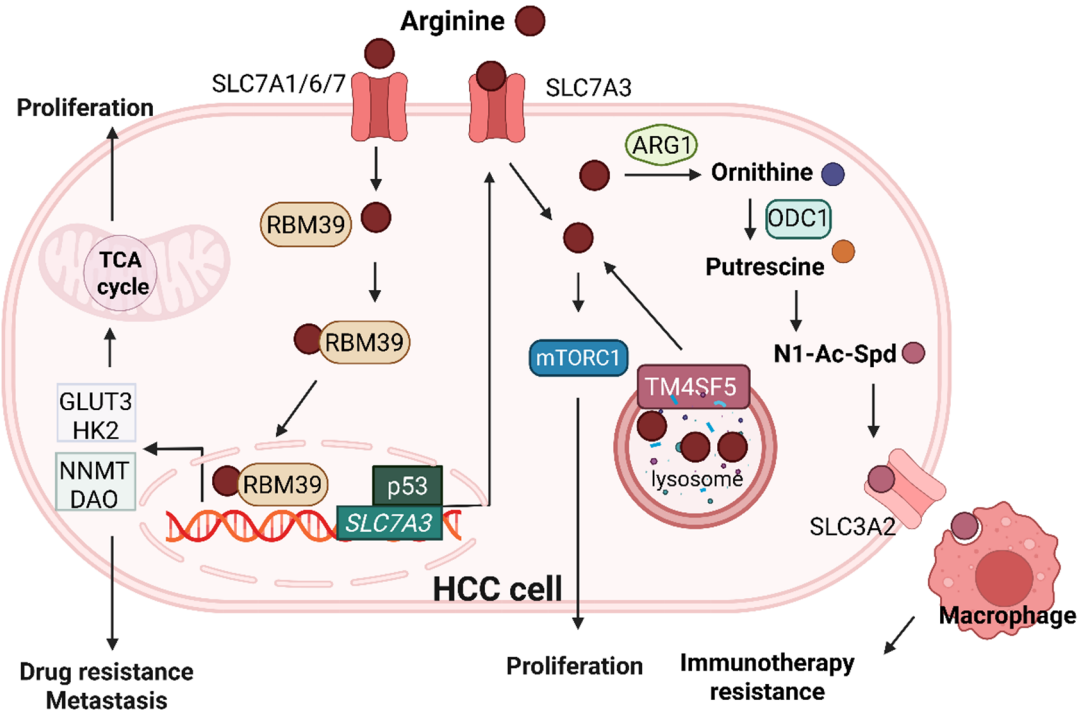

Figure 5. Arginine metabolism in HCC.

3.2. Nonessential Amino Acid Metabolism

In the normal liver, non-essential amino acids play central roles in nitrogen and energy metabolism. Glutamine functions as a nitrogen carrier and an important precursor for the urea cycle and glutathione synthesis [154]. Aspartate donates nitrogen to the urea cycle and contributes to the TCA cycle to maintain energy homeostasis [155]. Serine and glycine support one-carbon metabolism, providing methyl groups for nucleotide synthesis and methylation reactions [156]. Additionally, tyrosine, an aromatic amino acid, participates in the synthesis of catecholamines and thyroid hormones [157]. In HCC, dysregulated metabolism of non-essential amino acid promotes tumor initiation, progression, and therapeutic resistance by supporting nucleotide biosynthesis, fueling the TCA cycle, maintaining redox homeostasis, and activating growth signaling pathways.

3.2.1. Glutamine Metabolism

In HCC, glutamine metabolism undergoes profound reprogramming, characterized by heightened dependence on glutamine [9] (Figure 6). Beyond serving as a substrate for carbon and nitrogen metabolism, glutamine also functions as a critical signaling molecule and redox regulator, playing a central role in tumor initiation, progression, and therapeutic resistance [9].

Clinical data indicate that serum glutamine levels are significantly reduced in HCC patients, whereas glutamate levels are elevated [158]. This metabolic shift is largely attributed to the high expression of glutamine transporters such as solute carrier family 1 member 5 (SLC1A5) and SLC38A1 in HCC cells, which markedly increases glutamine uptake compared to normal hepatocytes [111]. The imported glutamine is subsequently converted into glutamate and then into α-ketoglutarate to fuel the TCA cycle, providing both energy and biosynthetic precursors for tumor growth [111]. In normal hepatocytes, SLC25A15 acts as a tumor suppressor

regulating HCC growth and metastasis, but under hypoxia the suppression of hepatocyte nuclear factor 4α (HNF4α) reduces SLC25A15 expression while upregulating SLC1A5, thereby enhancing glutamine uptake [159]. Furthermore, key enzymes involved in glutamine catabolism, such as GLS1, are aberrantly overexpressed in HCC [160,161], driving the conversion of glutamine into α-ketoglutarate to support the TCA cycle. Normally, α-ketoglutarate promotes hypoxia-inducible factor 1α (HIF-1α) degradation via prolyl hydroxylase (PHD) under normoxic conditions [162]. However, in the hypoxic tumor microenvironment, elevated α-ketoglutarate stabilizes HIF-1α, which subsequently activates transcription of downstream genes involved in angiogenesis (e.g., vascular endothelial growth factor (VEGF)), glycolysis (e.g., glucose transporter 1(GLUT1)), and immune evasion (e.g., programmed death-ligand 1(PD-L1)), thereby promoting tumor proliferation and immune escape [163–166]. In addition, GLS1 activity is regulated by the general control of amino acid synthesis 5-like 1 protein (GCN5L1) mediated acetylation, and the decreased acetylation of GLS1 enhances its enzymatic activity, accelerating glutamine metabolism and supporting rapid tumor cell proliferation [164].

During rapid proliferation, HCC cells upregulate glycolysis and glutamine metabolism to sustain energy and biosynthesis, but this also elevates ROS, whose excessive accumulation leads to lipid peroxidation and ferroptosis [167]. To mitigate oxidative stress, HCC cells adapt by upregulating the cystine/glutamate antiporter system Xc^- (xCT) to facilitate cystine import [168], while concomitantly augmenting glutamine uptake and metabolism, thereby reinforcing GSH biosynthesis and sustaining intracellular redox homeostasis [159]. Glutamate-cysteine ligase (GCL), composed of a catalytic subunit (GCLC) and a modifier subunit (GCLM), is the rate-limiting enzyme for GSH synthesis [169]. In HCC, overexpression of GCL markedly enhances GSH production [170], while Nrf2, frequently overexpressed in tumor cells, further upregulates GCLC and GCLM, thereby boosting GSH biosynthesis [10,171]. Beyond its role in ROS detoxification, GSH contributes to chemoresistance in HCC by conjugating with therapeutic agents through glutathione S-transferases (GST), with the resultant GSH-drug conjugates subsequently exported by multidrug resistance protein 1 [10,172].

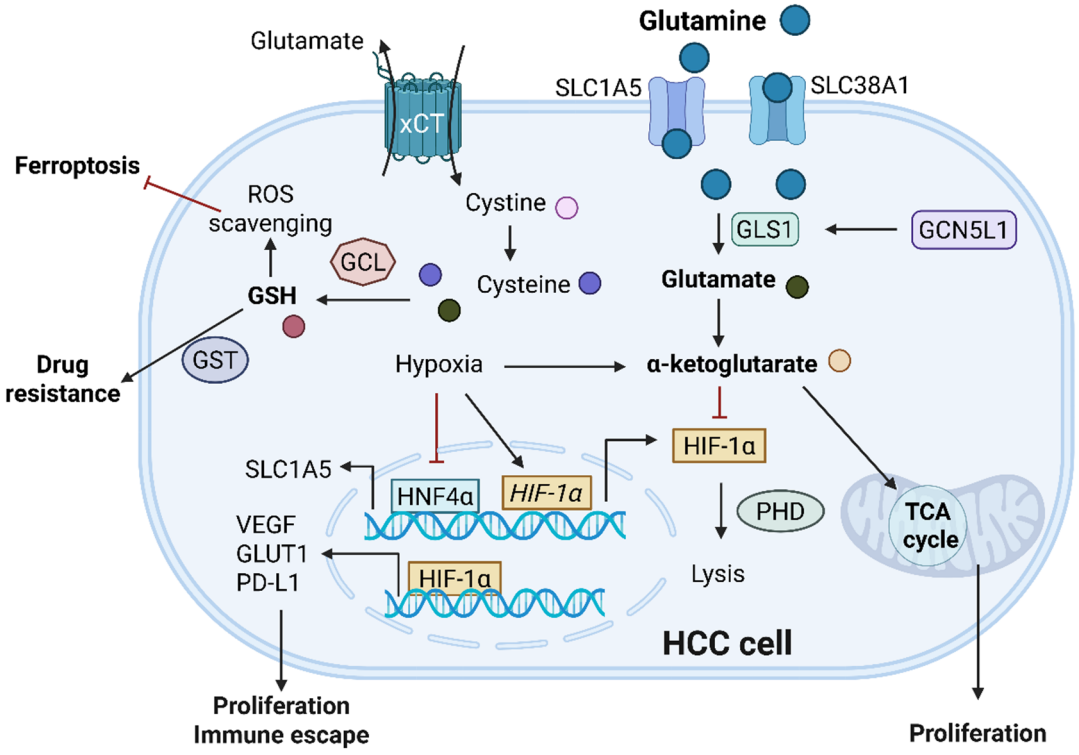

Figure 6. Glutamine metabolism in HCC.

3.2.2. Serine/Glycine and One-Carbon Metabolism

One-carbon metabolism, which encompasses the generation and transfer of one-carbon units, is indispensable for nucleotide biosynthesis, methylation reactions, and reductive metabolism, thereby sustaining the high proliferative capacity of cancer cells [173,174]. Notably, in HCC, the activity of the rate-limiting serine biosynthetic enzyme phosphoglycerate dehydrogenase (PHGDH) is markedly elevated, which is further reinforced by protein arginine methyltransferase 1 -mediated methylation and activation of PHGDH, resulting in significantly higher serine levels in tumor tissues relative to adjacent normal counterparts [175]. Mechanistically, serine serves

as a precursor for the transsulfuration pathway to generate cysteine, which, together with glycine, contributes to GSH biosynthesis. Concurrently, serine catabolism couples with the one-carbon metabolic network to produce nicotinamide adenine dinucleotide phosphate (NADPH), and the combined actions of NADPH and GSH are essential for maintaining intracellular redox equilibrium [175]. In addition, mitochondrial SHMT2 is frequently upregulated in HCC, thereby augmenting the conversion of serine into glycine and one-carbon units, ultimately driving nucleotide synthesis and supporting tumor growth [176,177].

3.2.3. Asparagine and Aspartic Acid Metabolism

Asparagine functions as both a storage and transport form of nitrogen, while also participating in protein biosynthesis and N-glycosylation, processes that are critical for the proper function of hepatic secretory proteins [155]. In HCC, tumor transforming gene 1 has been shown to bind to the promoter of asparagine synthetase (ASNS), thereby enhancing ASNS transcription and leading to elevated intracellular asparagine levels [178,179]. Increased asparagine subsequently activates the mTORC1 signaling pathway, which in turn promotes HCC progression [178,180].

Asparagine can be hydrolyzed by asparaginase to yield aspartate, providing an endogenous source of this amino acid. In the liver, aspartate contributes nitrogen through transamination reactions, the urea cycle, and nucleotide biosynthesis, thereby linking the TCA cycle with energy metabolism [181]. In HCC, the urea cycle is often disrupted, primarily owing to the downregulation of argininosuccinate synthase 1, thereby redirecting aspartate utilization from nitrogen disposal toward nucleotide biosynthesis [182,183]. Aspartate serves as both a nitrogen and carbon donor for *de novo* synthesis of purines and pyrimidines, thereby providing essential precursors to sustain the high proliferative capacity of tumor cells [184,185]. In pyrimidine biosynthesis, the rate-limiting step involves the condensation of aspartate with carbamoyl phosphate to form carbamoyl aspartate, a reaction catalyzed by aspartate transcarbamylase [186]. Endogenous aspartate is primarily derived from oxaloacetate in the TCA cycle, which is transaminated with glutamate by mitochondrial glutamic-oxaloacetic transaminase 2 (GOT2) [182]. In HCC, reduced expression of glutamate oxaloacetate transaminase 2 limits aspartate production, forcing cancer cells to reprogram asparagine metabolism to replenish aspartate, a process that concurrently activates the PI3K/AKT/mTOR pathway and thereby drives tumor growth and metastasis [182].

3.2.4. Tyrosine Metabolism

Tyrosine serves as both a structural amino acid and a common site of phosphorylation in intracellular signaling in the liver [187]. Its catabolites also function as precursors for a variety of bioactive compounds and aid in the synthesis of energy and nitrogen metabolism [188]. The canonical pathway of tyrosine degradation proceeds through a series of linear enzymatic reactions involving tyrosine aminotransferase (TAT), 4-hydroxyphenylpyruvate dioxygenase (HPD), homogentisate 1,2-dioxygenase (HGD), glutathione S-transferase zeta 1 (GSTZ1), and fumarylacetoacetate hydrolase (FAH), ultimately yielding fumarate and acetoacetate, which enter the TCA cycle and ketone body metabolism, respectively [188] (Figure 7).

The expression of multiple enzymes involved in tyrosine catabolism is downregulated, contributing to metabolic reprogramming and tumor progression in HCC [189]. Notably, in approximately 70% of HCC patients, loss of heterozygosity at chromosome 16q together with promoter hypermethylation leads to marked suppression of TAT, thereby impairing tyrosine degradation [189,190]. Accumulation of tyrosine in mitochondria attenuates cytochrome c (Cyt-c) release, which in turn prevents apoptosome assembly with apoptotic protease-activating factor 1 (Apaf-1) and subsequent activation of caspase-9, thus enhancing cancer cell survival and proliferation [189]. HPD, the key enzyme responsible for the second step of tyrosine degradation, is also downregulated in HCC [190,191]. Loss of HPD reduces the production of ketone bodies such as β-hydroxybutyrate, thereby suppressing AMPK activation and removing its inhibitory effect on mTOR. This shift permits mTORC1-dependent activation of glutaminase, further promoting tumor cell proliferation and metabolic reprogramming [192].

Another enzyme, GSTZ1, has likewise been reported to be downregulated in HCC and is strongly associated with poor prognosis [52]. GSTZ1 normally catalyzes the isomerization of maleylacetoacetate (MAA) to fumarylacetoacetate (FAA), and its loss leads to MAA accumulation with diversion toward the toxic metabolite succinylacetone (SA). The resulting SA activates the Nrf2/insulin-like growth factor 1 receptor (IGF1R) signaling axis, thereby promoting HCC progression [193]. SA can also compete with prolyl hydroxylase domain protein 2 (PHD2), resulting in stabilization of HIF-1α and subsequent upregulation of VEGFA, which fosters tumor angiogenesis [166]. Furthermore, GSTZ1 has been implicated in the regulation of ferroptosis, whereby its downregulation leads to elevated glutathione peroxidase 4 (GPX4) expression, suppressing sorafenib-induced ferroptosis in HCC cells and thereby contributing to therapeutic resistance [194].

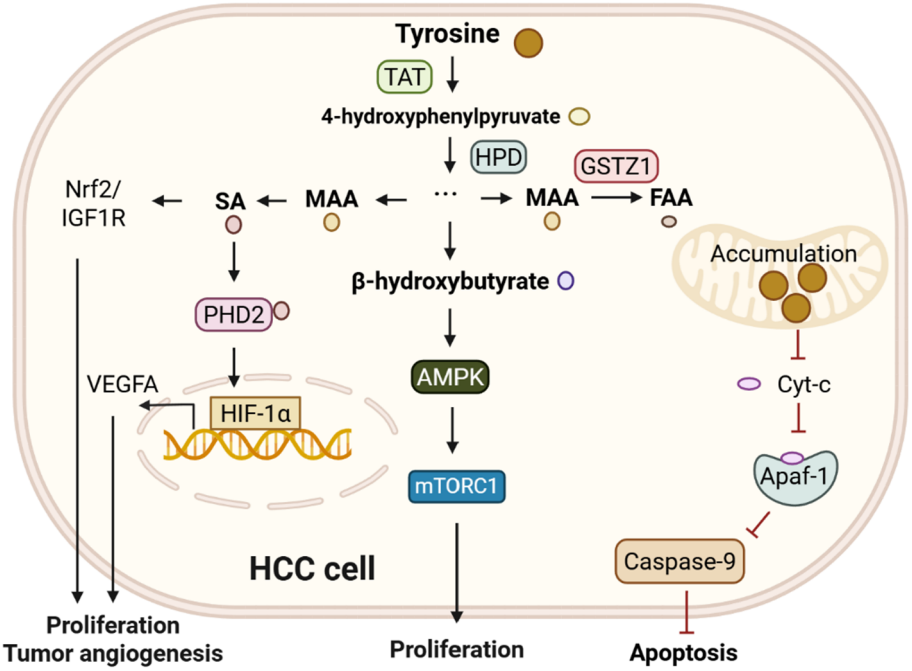

Figure 7. Tyrosine metabolism in HCC.

4. Nanoparticles Regulate Amino Acid Metabolism for HCC Treatment

In HCC, essential amino acids drive anabolic growth and contribute to the establishment of an immunosuppressive tumor microenvironment through enhanced uptake and dysregulated catabolism, whereas non-essential amino acids support tumor proliferation and survival by replenishing the TCA cycle, preserving redox balance, and facilitating nucleotide biosynthesis [109]. These insights highlight amino acid transporters and key metabolic enzymes as promising therapeutic targets to disrupt the metabolic reprogramming that underpins tumor adaptation. Accordingly, recent nanomedicine designs have implemented these concepts through amino-acid restriction/depletion, inhibition of key metabolic nodes and local supplementation; representative examples and their major outcomes are summarized in Table 1.

4.1. Limiting Intracellular Amino Acids Biosynthesis

Recent years, accumulating evidence has established ferroptosis not only as a new form of regulated cell death but also as a prototypical amino acid metabolism-dependent death modality, the execution of which relies on cystine uptake, GSH biosynthesis, and GPX4 activity [195–197]. A widely explored therapeutic strategy involves the design of nanomedicines that restrict amino acid availability, thereby disrupting redox homeostasis and inducing ferroptosis in tumor cells. As cystine is a rate-limiting precursor for GSH synthesis, its intracellular transport is governed by the xCT, a heterodimeric transmembrane protein complex composed of SLC3A2 and SLC7A11 subunits [198]. One study developed an HCC-targeted, long-circulating liposomal system based on the esterase-responsive polymer poly(2-diethylaminoethyl acrylate) (PQDEA) for the delivery of SLC7A11 shRNA (shSLC7A11), designated G-LPQDEA/shSLC7A11 [199]. G-LPQDEA/shSLC7A11 effectively silenced SLC7A11 expression in HCC cells, leading to impaired GSH biosynthesis, GPX4 inactivation, lipid peroxidation accumulation, and ultimately ferroptotic cell death [199]. Similarly, graphene oxide has been employed as a nanocarrier to co-deliver SLC7A11 siRNA, sorafenib, and doxorubicin-Fe^{2+} coordination compound, achieving synergistic induction of ferroptosis in HCC cells [200].

However, sorafenib-induced ferroptosis is frequently attenuated in HCC due to activation of the Nrf2 pathway, which promotes resistance [194,201]. To overcome this limitation, researchers engineered a Fe(III)-based metal-organic framework (MOF) nanocarrier encapsulating sorafenib (Sor@Fe-MOF). This system markedly suppressed GPX4 and SLC7A11 expression, elevated lipid peroxidation, and enhanced ferroptosis, while simultaneously promoting $CD8^+$ T-cell tumor infiltration and augmenting antitumor immunity [202]. Several additional nanotherapeutic platforms have adopted analogous strategies, whereby chemotherapeutic agents were co-delivered with nanocarriers to downregulate GPX4 and SLC7A11, thereby increasing ROS accumulation and reducing GSH levels to potentiate ferroptotic death in HCC cells [203–206].

In sorafenib-resistant HCC, the actin-binding protein cofilin-1 (CFL1) is highly expressed and has been shown to transcriptionally upregulate the rate-limiting serine biosynthetic enzyme PHGDH, thereby enhancing serine metabolism and antioxidant capacity, which enables tumor cells to evade drug-induced oxidative stress [207]. To target this adaptive mechanism, a redox-responsive PEG-S-S-PLGA nanocarrier was designed to co-deliver siCFL1 and sorafenib. This dual-delivery approach effectively silenced CFL1 expression, restricted serine biosynthesis, and attenuated antioxidant defenses, which significantly enhanced sorafenib-induced ROS accumulation and apoptosis. Both in vitro and in vivo studies demonstrated pronounced antitumor activity of this strategy [207].

4.2. Altering Amino Acids Metabolic Enzyme's Function

In a substantial subset of HCC with downregulated or absent argininosuccinate synthase, tumor cells are dependent on exogenous arginine [147]. Consequently, arginine deprivation therapy, which employs arginine-catabolizing enzymes such as arginase or arginine deiminase (ADI) to deplete circulating arginine, has been proposed as a promising strategy to inhibit HCC growth [208]. However, free enzymes including arginase and ADI exhibit an extremely short half-life in circulation, as well as immunogenicity and poor stability, which greatly limit their clinical application [208,209]. To overcome these limitations, polyethylene glycol-modified recombinant human arginase (rhArg-peg) has been developed, demonstrating enhanced stability, favorable pharmacokinetic properties, and potent anti-HCC activity in vivo [208,210]. Notably, rhArg-peg has been evaluated in early-phase trials in advanced HCC (e.g., NCT00988195/NCT01092091; NCT02089763), with clinical studies also exploring combination regimens. Similarly, L-arginase has been encapsulated into poly (lactic-co-glycolic acid) (PLGA) nanoparticles (NPs) using a water-in-oil-in-water (w/o/w) emulsion technique, yielding a formulation with an average particle size of 332.5 ± 3.5 nm (ARGase-PLGA). This nanoplatform exhibited stronger cytotoxicity against HCC cells compared with free L-arginase [211]. *In vivo,* ARGase-PLGA maintained arginine depletion for up to 72 h, while simultaneously reducing nitric oxide levels, hepatic injury markers, and the tumor marker alpha-fetoprotein [211].

As the rate-limiting enzyme of the tryptophan-kyn axis, TDO2 is reported to be upregulated in MASLD and HCC, with higher expression consistently associated with adverse clinicopathological features and disease progression [212,213]. To pharmacologically constrain this pathway, bovine serum albumin-based NPs encapsulating allopurinol (NPs-Allo) have been engineered to afford sustained TDO2 inhibition, exhibiting favorable biocompatibility and targetability [212]. Intravenous administration of NPs-Allo has been shown to markedly attenuate HFD induced metabolic derangements [212].

Intracellular tryptophan can also metabolized by IDO into Kyn, the accumulation of which within tumors fosters an immunosuppressive microenvironment that facilitates immune evasion in HCC [124]. To target this pathway, pH-responsive NPs (HMP1G NPs) were designed for intratumoral delivery by co-loading the IDO1 inhibitor 1-methyl-tryptophan (1-MT) and the nitric oxide donor S-nitrosoglutathione (GSNO) onto PEG-modified $HMnO_2$ (HMP) [12]. In H_2O_2-rich tumors, Mn^{2+} released from HMP1G drives Fenton-like chemistry to generate ROS (hydroxyl radicals) and concurrently catalyzes GSNO decomposition to release NO. NO, together with 1-methyl-tryptophan, suppresses IDO1 and lowers intratumoral Kyn, mitigating metabolic immunosuppression in cold tumors, and ROS confer additional cytotoxicity [12]. Similarly, the IDO inhibitor NLG919, loaded onto thermoresponsive polyimide-coated ferromagnetic vortex-domain iron oxide nanorings (PI-FVIOs), can be precisely released under thermal stimulation. This release triggers antitumor immune responses within the tumor microenvironment and acts synergistically with immunogenic cell death induced by NLG919/PI-FVIOs-mediated magnetothermodynamic therapy, thereby effectively suppressing HCC [214]. Other IDO inhibitors have also been delivered via various nanotechnology platforms for targeted therapy of HCC, in combination with immune checkpoint inhibitors or photothermal therapy, to achieve synergistic antitumor effects [215–217].

GLS1 is one of the rate-limiting enzymes that catalyze the conversion of glutamine to glutamate [161]. Self-assembled, ROS-responsive dissociable nanomicelles fabricated from a sulfur-containing ketone-based gemcitabine prodrug were co-loaded with the GLS1 inhibitor BPTES and the pyruvate dehydrogenase complex inhibitor CPI-613, yielding an integrated therapeutic agent designated as PD-G@BC [218]. This nanoregulator effectively suppresses both glycolysis and glutamine metabolism pathways, thereby disrupting the energy and biosynthetic supply essential for tumor cell survival [218]. Moreover, the remodeling of the tumor metabolic microenvironment by PD-G@BC enhances the infiltration and activity of antitumor immune cells, synergizing with the immunogenic cell death induced by gemcitabine (GEM) to promote antitumor immunity [218]. Metformin (MET)-loaded hyaluronic acid (HA)-derived carbon dots (HA-CD-MET) were designed to target HCC by simultaneously inhibiting GLS1 and GLUT1, thereby depriving tumor cells of essential nutrients including

glutamine and glucose [219]. Although HCC upregulates glutamine and glucose pathways to buffer ROS via the xCT–GSH axis and NADPH regeneration, dual inhibition of GLS1 and GLUT1 collapses these antioxidant defenses, leading to marked ROS accumulation that activates AMPK, suppresses AKT, and triggers apoptosis rather than ferroptosis [219]. Similarly, a hafnium-based metal-organic framework nanoplatform, designated UiO-66-Hf(2OH)-C/B@HA, was engineered to co-deliver the GLS1 inhibitor CB-839 and the GSH synthesis inhibitor BSO. Through HA-mediated CD44 targeting, this system not only enhances radiosensitivity and triggers immunogenic cell death in MYC-amplified HCC, but also achieves superior tumor suppression when used in combination with immune checkpoint blockade therapy [220].

4.3. Replenishing Amino Acids

In normal hepatocytes, NO is generated from arginine and citrulline under the catalysis of endothelial nitric oxide synthase (eNOS) or inducible nitric oxide synthase (iNOS) [221]. High concentrations of NO can induce DNA strand breaks in HCC cells or upregulate the expression of pro-apoptotic proteins such as bcl-2 associated X protein and caspase-3, thereby promoting apoptosis [222–224]. In addition, high NO levels can trigger immunogenic cell death, leading to the release of damage-associated molecular patterns (DAMPs) from tumor cells and eliciting a robust and specific antitumor immune response [225]. Building on this rationale, a polyion complex nanosphere system (Nano^{ARG}s) with an average diameter of ~40 nm was constructed through electrostatic self-assembly of PEG-b-poly(L-arginine) and chondroitin sulfate [226]. Nano^{ARG}s enable localized delivery of L-arginine within the tumor microenvironment inducing NO production by tumor-associated macrophages. When combined with PD-1 antibody therapy, Nano^{ARG}s effectively reprogram the immune microenvironment, enhance T-cell activation, and suppress tumor growth [226].

Regardless of the specific targets and modalities discussed above, in vivo efficacy ultimately hinges on whether the formulation can achieve the required tumor exposure and tissue selectivity with an acceptable safety profile [227]. Carrier choice is not merely a formulation issue but a key determinant of whether amino acid metabolic modulation can be implemented *in vivo*. Lipid-based nanoparticles are a comparatively mature platform that can flexibly encapsulate both small molecules and nucleic acids [228]. Their pharmacokinetics can be tuned by particle size and surface chemistry, and they frequently accumulate in the liver via reticuloendothelial system and mononuclear phagocyte system uptake, making them suitable for liver-directed delivery and co-delivery strategies [229]. However, formulation-dependent immune activation and accelerated clearance upon repeat dosing should be considered [230]. Biodegradable polymeric nanoparticles such as PLGA can protect labile payloads (e.g., enzymes) and provide sustained release, which is advantageous for prolonged metabolic pressure, but careful control of burst release and retention of biological activity is critical [231,232]. In addition, MOF-based platforms offer high loading capacity and stimulus-responsive release, enabling localized modulation and multi-functional combinations, yet their translational development may be constrained by material-dependent long-term biodistribution, clearance, and potential metal-related toxicity [233]. Overall, in amino acid metabolism-guided nanomedicine, carrier selection should be aligned with payload type, desired exposure duration, and safety requirements.

Table 1. Nanomedicine-based strategies targeting amino acid metabolism in HCC.

Strategy	Amino Acid Metabolic Axis	Key Targets	NPs Formulation	Main Effects
Restriction	Glutamate (xCT–GSH–GPX4/ferroptosis)	SLC7A11	SLC7A11 shRNA and PQDEA were encapsulated in lipid bilayers to synthesize G-LPQDEA/shSLC7A11 NPs	SLC7A11 downregulation; GSH restriction and GPX4 attenuation; ferroptosis induction [199]
Restriction	Glutamate (xCT–GSH–GPX4/ferroptosis)	GPX4, SLC7A11	Fe(III) metal-organic framework (MOF) loaded with sorafenib (Sor@Fe-MOF)	GPX4 inhibition; lipid peroxidation accumulation; increased $CD8^+$ T-cell infiltration [202]
Restriction	Serine	PHGDH	Redox-responsive nanocarrier PEG-S-S-PLGA loaded with siCFL1 and sorafenib	PHGDH transcription suppression; reduced serine supply; heightened sorafenib sensitivity [207]
Inhibition	Arginine (ASS1-deficiency dependence)	L-Arginase	Polyethylene glycol-modified human arginase (rhArg-peg)	Systemic arginine depletion; tumor growth inhibition; improved in vivo stability/pharmacokinetics [208,210]

Table 1. *Cont.*

Strategy	Amino Acid Metabolic Axis	Key Targets	NPs Formulation	Main Effects
Inhibition	Arginine (ASS1-deficiency dependence)	L-Arginase	L-arginine enzyme encapsulated in PLGA NPs (ARGase-PLGA)	Sustained arginine depletion; nitric oxide reduction; alpha-fetoprotein reduction [211]
Inhibition	Tryptophan (AhR axis)	IDO1	IDO1 inhibitor 1-MT and NO donor GSNO were added to polyethylene glycol-modified $HMnO_2$ to synthesize HMP1G NPs	Kyn reduction; relief of immunosuppression; increased ROS/NO; conversion to an immunologically "hot" TME [12]
Inhibition	Tryptophan (AhR axis)	IDO1	Pyrolyzable polyimide-coated ferromagnetic vortex domain iron oxide nanorings (PI-FVIOs) loaded with IDO Inhibitor NLG919	IDO1 inhibition; enhanced immunogenic cell death; improved tumor treatment efficacy [124]
Inhibition	Glutamine	GLS1, PDH complex	ROS-responsive nanomicelle-loaded GLS1 inhibitor BPTES and pyruvate dehydrogenase complex inhibitor CPI-613 (PD-G@BC)	Concurrent blockade of glutaminolysis and glycolysis; increased ICD and immune infiltration [218]
Inhibition	Glutamine	GLS1, GLUT1	Metformin (MET)-loaded hyaluronic acid (HA)-derived carbon dots (HA-CD-MET)	GLS1/GLUT1 inhibition; AMPK activation; AKT pathway suppression [219]
Inhibition	Glutamine	GLS1	Hafnium-based metal-organic framework (Hf-MOF) loaded with codeliver telaglenastat (CB-839) and buthionine sulfoximine (BSO) and modified with HA (UiO66-Hf(2OH)-C/B@HA)	Enhanced radiosensitivity; strengthened ICD; synergy with immune checkpoint blockade [220]
Supplementation	Arginine	-	PEG-b-poly(L-arginine) and chondroitin sulfate were prepared into $Nano^{ARG}$s via electrostatic self-assembly	Local L-arginine supply; increased NO production; T-cell activation [226]

5. Conclusions

The prevalence of MASLD is steadily increasing, becoming a global health concern. Simultaneously, instances of HCC linked to MASLD are also rising. The liver functions as a primary metabolic center, coordinating the body's reaction to nutritional consumption and storage. The liver, as the initial organ to absorb nutrient-dense blood from the gastrointestinal tract through the portal vein, regulates glucose, lipid, and amino acid metabolism in response to dietary intake. This study summarizes the aberrant amino acid metabolism in MASLD and the mechanisms for amino acid replenishment in MASLD treatment. The circulating levels of BCAAs, along with tyrosine, tryptophan, methionine, and glutamate, are frequently elevated in MASLD/MASH, although their intrahepatic concentrations are diminished. Conversely, the serum concentrations of amino acids like histidine and glycine are often reduced in MASLD/MASH patients. Direct supplementation of BCAA, glycine, serine, glutamine, tryptophan, and indole metabolites of tryptophan, including IPA and IAA, may successfully alleviate MASLD/MASH. Nonetheless, prolonged use of high BCAA diets results in hyperphagia, obesity, and diminished longevity, while excessive histidine intake in rats can unexpectedly encourage hepatic fat buildup. Therefore, the amount and timing of administration for free amino acids require careful consideration. Low-dose valine supplementation mitigates leptin resistance and inflammation in the liver and hypothalamus while favorably influencing the gut microbiota. Certain herbal formulas, such QSHY and HSYA, may decrease circulating tyrosine levels and promote beneficial alterations in the gut flora to mitigate MASLD.

Additionally, we describe the dysregulated amino acid metabolism in HCC and the nanomedicine-based approaches for HCC treatment by reprogramming amino acid metabolism: In contrast to MASLD, plasma levels of BCAA are markedly decreased in HCC patients, although intratumoral BCAA concentrations are elevated due to the tumor's rapid growth and proliferation requirements. The principal tryptophan metabolic pathway in HCC shifted from Kyn to 5-HT, with elevated levels of 5-HT activating intracellular signaling pathways such as Wnt/β-

catenin, PI3K/AKT, and YAP, thereby enhancing cancer cell proliferation, migration, and invasion. Due to glutamine and glutamate acting as primary carbon sources for the TCA cycle and lipogenesis in hepatocytes, serum levels of glutamine fell while glutamate levels increased in MASLD and HCC with metabolic dysregulation. In addition to direct supplementation of free amino acids, the modulation of amino acid transporters and essential metabolic enzymes using nanomaterials presents promising therapeutic strategies for HCC. These strategies include restricting intracellular amino acid biosynthesis, regulating the function of amino acid metabolic enzymes, and replenishing amino acids through nanosystems.

From a clinical translation perspective, most nanomedicine strategies aimed at reprogramming amino acid metabolism remain at the preclinical stage, and robust clinical evidence is still limited. In oncology, clinically advanced nanoformulations are largely built on carrier families with established regulatory and manufacturing precedence, particularly lipid nanoparticles/liposomes and biodegradable polymers (e.g., PLGA). Therefore, near-term translational progress in amino acid-modulating nanomedicine is more likely to be achieved by leveraging these mature delivery backbones and optimizing liver/tumor exposure and safety, rather than introducing entirely new material classes. Key priorities include scalable and reproducible manufacturing (CMC), batch-to-batch quality control, biodistribution and clearance in diseased livers, repeat-dosing tolerability and immunogenicity, and biomarker-guided patient stratification to identify metabolic dependencies most likely to respond.

Current literature indicates a significant disparity, where amino acid-targeting nanotherapies are predominantly reported in the context of HCC, leaving the MASLD/MASH landscape nearly empty. We identify this as a critical knowledge gap, highlighting the unmet need for developing nanomaterials that can specifically modulate amino acid metabolism. For instance, future strategies could focus on intervening in methionine cycles, correcting BCAA imbalances, or restoring tryptophan catabolism to effectively ameliorate hepatic steatosis and inflammation. Future translational research should focus on bridging this gap by designing precision nanomedicines tailored for the early metabolic disturbances of MASLD/MASH, potentially offering novel strategies to halt disease progression before carcinogenesis.

Despite the increasing investigation of aberrant amino acid metabolism in MASLD/MASH and HCC, some problems persist in comprehending the progression from MASLD/MASH to HCC from an amino acid perspective:(1) The mechanism of reverse amino acid metabolism in MASLD/MASH and HCC remains unexamined; (2) in contrast to normal humans and mice, circulating serine levels fell in humans while they increased in mice with MASLD. Moreover, SHMT2 ablation demonstrated reduced hepatotoxicity in steatotic mice, although it may potentially heighten vulnerability to steatosis; (3) The regulation of amino acid metabolism in MASLD/MASH mostly emphasizes free amino acid supplementation. The regulation of amino acid metabolism, governed by specific metabolic enzymes and transporters, necessitates a diversification of regulatory approaches for enhanced therapy of MASLD/MASH.

To identify the optimal approach for MASLD/MASH alleviation and HCC suppression, various promising methodologies may be explored: Additional metabolic study must be conducted to clarify the entire evolutionary trajectory from MASLD/MASH to HCC. Strategies for regulating amino acid metabolism through nanomedicine could be developed for the alleviation of MASLD/MASH and the prevention of HCC. Investigate certain amino acids as biomarkers for prompt diagnosis, facilitating interventions at earlier stages when therapy alternatives are accessible. In conclusion, elucidating the molecular processes of MASLD/MASH-HCC offers a framework for the creation of novel targeted, customized, and innovative therapeutics. These findings not only augment our comprehension of the disease but also provide more effective and customized strategies to increase patient outcomes.

Author Contributions

L.Y., M.W..: conceptualization, methodology, software; L.Y., L.Z., M.W.: data curation, writing—original draft preparation; L.Y., M.W.: visualization, investigation; J.L., X.S.: supervision; L.Y., M.W.: software, validation; J.L., X.S., L.Z.: writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (32201078, 82404498, 32571600), the funding for the Distinguished Professorship Program of Jiangsu Province, and Distinguished Professorship Program of Yangzhou University (137012765), and the Natural Science Foundation of the Jiangsu Higher Education Institutions (23KJB310032).

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable

Data Availability Statement

No new data were generated or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

Abbreviation

MASLD	metabolic dysfunction-associated steatotic liver disease
MASH	metabolic dysfunction-associated steatohepatitis
HCC	hepatocellular carcinoma
EAAs	essential amino acids
BCAAs	branched-chain amino acids
AAAs	aromatic amino acids
BCAT	branched-chain aminotransferase
BCKAs	branched-chain α-keto acids
BCKDH	branched-chain α-keto acid dehydrogenase
NADH	nicotinamide adenine dinucleotide
ILA	indole lactic acid
AhR	aryl hydrocarbon receptor
MAPK9	mitogen-activated protein kinase 9
DNL	*de novo* lipogenesis
PPAR	peroxisome proliferator-activated receptors
RXR	retinoid X receptors
AMPK	AMP-activated protein kinase
FGF21	fibroblast growth factor 21
UCP1	uncoupling protein 1
GSH	glutathione
VLDL	very-low-density lipoprotein
TG	triglyceride
Nrf2	nuclear factor erythroid 2-related factor 2
QSHY	Qushi Huayu
HSYA	Hydroxysafflor yellow A
HFD	high-fat diet
GDS	gut-derived serotonin
HTR2A	hepatic serotonin receptor 2a
Kyn	kynurenine
5-HT	5-hydroxytryptamine
TDO	tryptophan 2,3-dioxygenase
IDO	indoleamine 2,3-dioxygenase
TPH	tryptophan hydroxylase
KynA	kynurenic acid
ORP150	oxygen regulatory protein 150
GPR35	G protein-coupled receptor 35
IAA	indoleacetic acid
IPA	indole-3-propionate
ACE2	Angiotensin-Converting Enzyme 2
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
HDC	histidine decarboxylase
HRs	histamine-specific membrane receptors
HCD	high-cholesterol diet
BA	bile acid
HCA	high-cholic acid
SAM	S-adenosylmethionine
MATs	methionine adenosyltransferases

GNMT	glycine N-methyltransferase
PEMT	phosphatidylethanolamine N-methyltransferase
SAH	S-adenosylhomocysteine
Hcy	homocysteine
AHCY	S-adenosyl-homocysteine hydrolase
MTR	methionine synthase
BHMT	betaine homocysteine methyltransferase
CBS	cystathionine-β-synthase
PE	phosphatidylethanolamines
PC	phosphatidylcholine
Stx17	syntaxin 17
NEAAs	nonessential amino acids
SHMT	serine hydroxymethyltransferase
GLS	glutaminase
HSCs	hepatic stellate cells
GS	glutamine synthetase
SIRT1	sirtuin 1
ACC	acetyl-CoA carboxylase
FAS	fatty acid synthase
SLC7A11	solute carrier family 7 member 11
mTORC1	mammalian target of rapamycin complex 1
AUH	RNA-binding methylglutaconyl-CoA hydratase
PPM1K	protein phosphatase 1K
CYP1A1	cytochrome P450 family 1 subfamily A member 1
ZNF165	zinc finger protein 165
5-HTP	5-hydroxytryptophan
AADC	L-amino acid decarboxylase
PI3K	phosphatidylinositol 3-kinase
AKT	protein kinase B
IL4I1	interleukin-4-induced-1
I3P	indole-3-pyruvate
ICAld	indole-3-carboxaldehyde
SREBP2	sterol regulatory element-binding protein 2
ARG1	arginase 1
RBM39	RNA binding motif protein 39
GLUT3	glucose transporter glucose transporter 3
HK2	hexokinase 2
NNMT	nicotinamide N-methyltransferase
DAO	amine oxidase 3
TM4SF5	transmembrane 4 L six family member 5
ATF4	activating transcription factor 4
ODC1	ornithine decarboxylase 1
N1-Ac-Spd	N1-acetylspermidine
SLC1A5	solute carrier family 1 member 5
HNF4α	hepatocyte nuclear factor 4α
HIF-1α	hypoxia-inducible factor 1α
PHD	prolyl hydroxylase
VEGF	vascular endothelial growth factor
GLUT1	glucose transporter 1
PD-L1	programmed death-ligand 1
GCN5L1	general control of amino acid synthesis 5-like 1 protein
xCT	cystine/glutamate antiporter system Xc^-
GCL	glutamate-cysteine ligase
GST	glutathione S-transferases
PHGDH	phosphoglycerate dehydrogenase
NADPH	nicotinamide adenine dinucleotide phosphate
ASNS	asparagine synthetase
GOT2	glutamic-oxaloacetic transaminase 2
TAT	tyrosine aminotransferase
HPD	4-hydroxyphenylpyruvate dioxygenase
HGD	homogentisate 1,2-dioxygenase
GSTZ1	glutathione S-transferase zeta 1
FAH	fumarylacetoacetate hydrolase
Cyt-c	cytochrome c
Apaf-1	apoptotic protease-activating factor 1
MAA	maleylacetoacetate
FAA	fumarylacetoacetate
SA	succinylacetone
IGF1R	insulin-like growth factor 1 receptor
PHD2	prolyl hydroxylase domain protein 2

GPX4	glutathione peroxidase 4
MOF	metal-organic framework
CFL1	actin-binding protein cofilin-1
ADI	arginine deiminase
PLGA	poly (lactic-co-glycolic acid)
NPs	nanoparticles
1-MT	1-methyl-tryptophan
GSNO	S-nitrosoglutathione
GEM	gemcitabine
MET	metformin
HA	hyaluronic acid
eNOS	endothelial nitric oxide synthase
iNOS	inducible nitric oxide synthase
DAMPs	damage-associated molecular patterns

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