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Review Article

Omics-based Decoding of Metabolic Dysfunction-associated Fatty Liver Disease: From Pathogenesis to Clinical Translation

Jinyang Zhai[1], Yan Lu[2] and Jian-Gao Fan[1,3*]

[1]Center for Fatty Liver, Department of Gastroenterology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; [2]Institute of Metabolism and Regenerative Medicine, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; [3]Shanghai Key Lab of Pediatric Gastroenterology and Nutrition, Shanghai, China

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Abstract

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a multifactorial disorder driven by complex interactions among genetic, epigenetic, transcriptional, proteomic, metabolic, and microbiome factors. Single-omics technologies have provided valuable insights into disease mechanisms, yet each layer captures only a partial view of MAFLD pathogenesis. Recent advances in multi-omics integration allow systematic dissection of molecular networks, cell differentiation trajectories, intercellular communication, and spatial organization, revealing causal links between molecular alterations and tissue phenotypes. Horizontal integration connects different omic layers within the same biological state, while longitudinal integration captures dynamic changes across disease stages. Emerging spatial transcriptomics, proteomics, and metabolomics techniques further enable in situ mapping of cellular and molecular heterogeneity, uncovering spatially defined pathogenic niches and regulatory hubs. Collectively, these integrated approaches offer a multidimensional framework for understanding MAFLD progression, identifying potential biomarkers, and guiding precision therapeutic strategies. Future efforts should focus on standardized multi-omics pipelines, interdisciplinary collaboration, and functional validation to translate these insights into clinical applications.

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Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD), evolving from non-alcoholic fatty liver disease and recently redefined as metabolic dysfunction-associated steatotic liver disease, represents a shift from exclusion-based nomenclature to a unified, metabolism-driven disease spectrum that has become the most prevalent chronic liver disease worldwide.[1,2] Over the past four decades, it has affected approximately 25% of the global population, with its steadily increasing prevalence imposing a substantial economic and healthcare burden.[3,4] MAFLD ranges from simple steatosis (SS) to metabolic dysfunction-associated steatohepatitis (MASH), a progressive form that can lead to fibrosis, cirrhosis, and even hepatocellular carcinoma (HCC), driving liver-related morbidity and mortality.[5–7] Importantly, all histological stages of MAFLD are associated with increased risk of overall mortality, underscoring the clinical importance of early detection and effective intervention.[8,9]

The pathogenesis of MAFLD remains incompletely understood. Genetic and epigenetic factors, insulin resistance (IR), overnutrition, obesity, ectopic fat deposition, gut microbiota dysbiosis, mitochondrial dysfunction, endoplasmic reticulum stress, oxidative stress, inflammation, and immune responses all contribute to disease initiation and progression.[10,11] Moreover, effective therapeutic options are still lacking, highlighting an urgent need to elucidate the precise molecular mechanisms.

Recent advances in single-cell RNA sequencing (scRNA-seq) and spatial omics have revealed the remarkable cellular and molecular heterogeneity of the liver. Nonetheless, single-omics studies, which examine genes, transcripts, proteins, or metabolites in isolation, provide a fragmented perspective, limiting insights into molecular networks, dynamic disease regulation, biomarker discovery, and the development of precision therapies. However, integrating genomics, transcriptomics, proteomics, metabolomics, and microbiomics provides a systems-level view of MAFLD pathogenesis. Here, we first summarize key single-omics insights into MAFLD pathogenesis and then discuss how integrative multi-omics approaches are advancing mechanistic discovery, biomarker development, molecular subtyping, therapeutic-response prediction, and clinical translation.

Keywords: Metabolic dysfunction-associated fatty liver disease; MAFLD; Multi-omics integration; Molecular mechanisms; Biomarker discovery; Molecular subtyping.

***Correspondence to:** Jian-Gao Fan, Center for Fatty Liver, Department of Gastroenterology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine; Shanghai Key Lab of Pediatric Gastroenterology and Nutrition, Shanghai 200092, China. ORCID: https://orcid.org/0000-0002-8618-6402. Tel & Fax: +86-21-25077340, E-mail: fanjiangao@xinhuamed.com.cn.

Insights from single-omics approaches in MAFLD

A central aim of molecular and cellular biology is to elucidate the dynamic interactions and regulatory mechanisms among biomolecules, including DNA, RNA, proteins, and metabolites. Single-omics approaches, by providing high-dimensional data at distinct molecular layers, have been instrumental in dissecting MAFLD pathogenesis, progression, and heterogeneity, and they serve as a critical basis for subsequent multi-omics integration.

Genomics and epigenetics

Genetic susceptibility loci

Genomic analyses have identified several variants that strongly predispose individuals to MAFLD. Among them, *PNPLA3* (I148M) and *TM6SF2* (E167K) represent the most influential risk loci. The I148M missense variant that impairs PNPLA3 function promotes hepatic lipid accumulation and increases susceptibility to liver injury, whereas the S453I variant is protective and enriched in African American populations.[12,13] The *TM6SF2* E167K variant impairs very-low-density lipoprotein secretion, leading to intrahepatic lipid retention despite reduced circulating lipids.[14–16] Additionally, variants in *MBOAT7* (rs641738) and *GCKR* (rs1260326) have also been implicated in MAFLD pathogenesis.[17,18]

Epigenetic regulation

Epigenetic mechanisms, including DNA methylation, histone modifications, and noncoding RNAs, link environmental and metabolic cues to gene expression, thereby shaping MAFLD progression.[19]

Aberrant DNA methylation alters metabolic and insulin signaling pathways, with partial reversibility after bariatric surgery, underscoring epigenetic plasticity. Circulating methylation signatures (e.g., *SREBF1*, *ABCG1*, *CPT1A*) are also associated with future hepatic fat accumulation, suggesting biomarker potential.[20]

Histone modifications also critically regulate fibrogenic programs. EZH2-mediated H3K27 trimethylation promotes hepatic stellate cell (HSC) activation, whereas its inhibition attenuates fibrosis.[21] In contrast, p300-driven H3K27 acetylation enhances *Ccl2* transcription, driving macrophage recruitment and HSC activation.[22]

Noncoding RNAs further mediate intercellular crosstalk: macrophage- and hepatocyte-derived miRNAs (e.g., miR-155, miR-34a, miR-192-5p) drive HSC activation and inflammatory responses.[23,24] Together, these epigenetic layers integrate metabolic stress with transcriptional reprogramming in MAFLD.

Transcriptomics and epitranscriptomics

Transcriptomics

Transcriptomic profiling defines how hepatic cell types reprogram their gene expression in response to metabolic stress, inflammation, and fibrosis during MAFLD progression.

Bulk RNA sequencing

Bulk transcriptomic analyses have consistently shown dysregulated glucose and lipid metabolism, together with upregulated inflammatory and fibrotic programs in MAFLD.[25,26] However, average signals across heterogeneous cell populations obscure cellular diversity and spatial context.

Single-cell RNA sequencing (scRNA-seq)

Disease-associated cellular reprogramming, rather than uniform changes across cell types, appears to drive MAFLD progression. During MASH regression, a deactivated HSC population emerged, resembling but not identical to quiescent HSCs, highlighting unexpectedly high HSC heterogeneity in both normal and injured livers.[27] Cytokine-enriched HSCs transit into a matrix-producing myofibroblastic state, driving extracellular matrix (ECM) deposition, tissue stiffening, and an increased risk of HCC.[28] Liver endothelial cells (ECs), including sinusoidal ECs, vascular ECs, and lymphatic ECs, maintain homeostasis by regulating vascular tone, immune cell function, and HSC quiescence. Hepatic macrophages also exhibit heterogeneity. $CD68^{+}MARCO^{+}$ resident Kupffer cells (KCs) display immune-tolerant programs, whereas infiltrating $MARCO^{-}$ macrophages exhibit pro-inflammatory phenotypes.[29] Moreover, dual-phenotype populations co-expressing hepatocyte and cholangiocyte markers increase with disease progression and reach their peak in end-stage disease, revealing previously uncharacterized regenerative processes.[30] The pathogenic functions are dictated by localization within fibrotic and lipotoxic niches rather than by cell identity alone.

Spatial transcriptomics (ST)

By integrating gene expression with histological architecture, spatial transcriptomics enables the precise localization of pathogenic cell states within distinct hepatic microdomains rather than assuming their uniform distribution across the liver. The liver is organized into repeating lobular units, with blood flowing from the portal triads toward the central vein, generating gradients of oxygen, nutrients, and hormones that establish metabolic zonation.[31,32] Periportal hepatocytes preferentially support gluconeogenesis and β-oxidation, whereas pericentral hepatocytes specialize in lipogenesis, detoxification, and glycolysis.[33] Midlobular regions serve as the main source of newly generated hepatocytes.[34] In MAFLD, this finely tuned zonation is disrupted, leading to spatially heterogeneous steatosis, inflammation, ballooning, and fibrosis.[35,36]

These spatial analyses further demonstrate that fibrosis develops within highly organized immune-stromal microenvironments. KCs are progressively replaced by monocyte-derived macrophages, which differentiate into $TREM2^{+}$ lipid-associated macrophages (LAMs) and scar-associated macrophages that accumulate within collagen-rich septa and spatially colocalize with activated HSCs.[37–41] In parallel, $IBA1^{+}$ macrophages localize near $CK19^{+}$ ductular cells, defining a spatially restricted macrophage-cholangiocyte-HSC axis that amplifies inflammatory and fibrotic signaling.[33] Spatial analyses further demonstrate that liver sinusoidal ECs of zone 3 preferentially upregulate capillarization- and ECM-related genes, suggesting region-specific basement membrane formation and microvascular remodeling.[42]

In summary, bulk RNA sequencing reveals global transcriptional changes but lacks resolution; scRNA-seq resolves cell states but loses spatial information; and ST integrates gene expression with tissue architecture to characterize metabolic zonation and cell-cell interactions. Applications and comparisons of the three methods are shown in Figure 1 and Table 1.

Epitranscriptomics

Epitranscriptomic RNA modifications, such as N^6-methyladenosine (m^6A), 5-methylcytosine (m^5C), 1-methyladenosine, and N^4-acetylcytidine (ac^4C), modulate hepatic lipid metabolism. The m^6A reader YT521-B homology domain-containing 2 (Ythdc2) destabilizes lipogenic messenger RNAs (mRNAs) (e.g., *Srebp-1c*, *Fasn*, *Scd1*, *Acc1*), suppressing their expres-

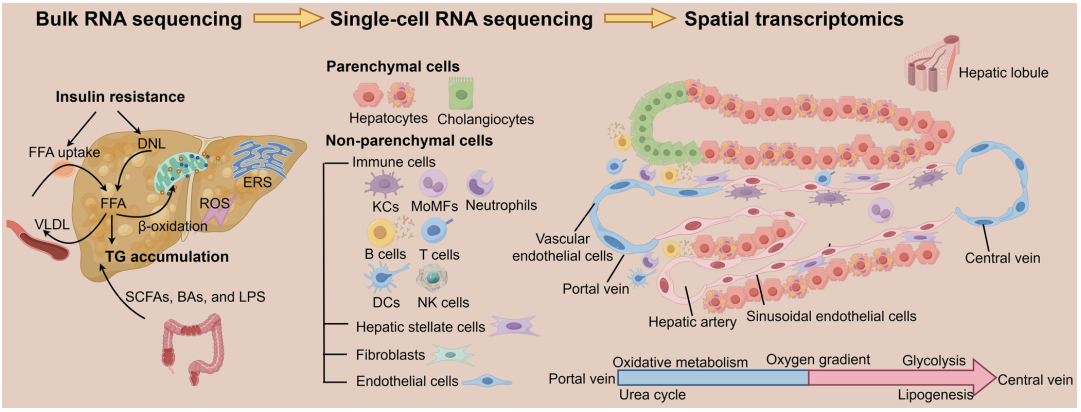

Fig. 1. Multi-dimensional transcriptomic approaches to elucidate MAFLD pathogenesis. Bulk RNA sequencing captures tissue-level transcriptional programs involved in lipid metabolism, inflammation, and fibrosis. Single-cell RNA sequencing identifies disease-associated cellular subpopulations across parenchymal and non-parenchymal compartments, while spatial transcriptomics maps gene expression to histological architecture and zonated metabolic gradients. Together, these approaches provide complementary tissue-level, single-cell, and spatial insights into MAFLD pathogenesis and therapeutic targets. MAFLD, metabolic dysfunction-associated fatty liver disease; FFA, free fatty acids; DNL, de novo lipogenesis; VLDL, very-low-density lipoprotein; TG, triglyceride; ERS, endoplasmic reticulum stress; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; BAs, bile acids; LPS, lipopolysaccharide; KCs, Kupffer cells; MoMFs, monocyte-derived macrophages; DCs, dendritic cells; NK cells, natural killer cells.

sion and thereby alleviating IR and hepatic steatosis.[43] Transcriptome-wide m^5C profiling reveals m^5C changes enriched in lipid metabolic pathways.[44] *Nsun2* knockdown decreases m^5C-modified *Acsl6* mRNA, reducing its expression and improving hepatic steatosis.[45] Similarly, *Nat10*-mediated ac^4C modification stabilizes *Cd36* and *Fatp2* mRNAs, promoting fatty acid uptake, and hepatocyte-specific *Nat10* deletion protects against diet-induced steatosis in male offspring of obese dams.[46] Moreover, zinc finger DHHC-type palmitoyltransferase 23 (ZDHHC23)-mediated palmitoylation promotes N-acetyltransferase 10 (NAT10) nuclear export and exosomal loading, activating fibrogenic signaling in HSCs via enhanced ac^4C modification and *Ddr2* mRNA stabilization.[47] These findings establish RNA chemical modifications as upstream regulators of lipid flux in MAFLD.

Proteomics

Proteomics bridges molecular alterations and phenotypic manifestations by directly quantifying the functional effectors that execute cellular programs. Large-scale aptamer-based platforms have identified circulating protein signatures that outperform conventional noninvasive fibrosis scores, underscoring the clinical potential of proteomics for risk stratification and early detection.[48]

Post-translational modifications, including ubiquitination, palmitoylation, lactylation, glycosylation, methylation, phosphorylation, and acetylation, serve as central metabolic switches in MAFLD. For example, the deubiquitinase RPN11 stabilizes METTL3, enhancing m^6A-dependent acyl-coenzyme A (CoA) synthetase short-chain family member 3 (ACSS3) expression and driving propionyl-CoA-dependent histone propionylation, thereby activating lipogenic transcriptional programs.[49] O-GlcNAcylation of CD36 enhances its transcription, stability, and membrane localization, promoting fatty acid uptake and inflammation, whereas mutation of key sites (S468A and T470A) improves insulin sensitivity and attenuates steatohepatitis.[50] Inhibition of CD36 palmitoylation alleviates intracellular lipid accumulation via AMPK activation and reduces inflammatory responses by suppressing JNK signaling.[51] Moreover, altered protein lactylation, driven by hepatocyte lactate levels, suppresses FASN enzymatic activity, providing a direct metabolic brake on lipogenesis in MPC1-deficient livers.[52]

Emerging spatial omics studies have revealed organized immune-stromal niches in human MAFLD livers, highlighting the potential of spatial proteomics to validate functional effectors and post-transcriptional regulation within these microenvironments.

Metabolomics

Metabolomics provides a direct functional readout of hepatic metabolic stress, capturing the biochemical consequences of genetic, epigenetic, and proteomic reprogramming. Nighttime metabolic dysfunction is a prominent feature of MAFLD, characterized by IR, enhanced de novo lipogenesis, and increased systemic exposure to nonesterified fatty acids.[53]

Dysregulated lipid metabolism is a hallmark of MAFLD. Lipidomics revealed that saturated and monounsaturated triglycerides accumulate in SS but decline in MASH, indicating

Table 1. Evolution of transcriptomic technologies in MAFLD research

Technology	Resolution	Limitations	Applications
Bulk RNA sequencing	Tissue level	Masks cellular heterogeneity and spatial context	Global profiling of gene expression
Single-cell RNA sequencing	Single-cell level	Lacks spatial information	Dissection of cellular heterogeneity and state transitions
Spatial transcriptomics	Spatial tissue resolution	Limited resolution, high cost	Spatial mechanism discovery and therapeutic target identification

MAFLD, metabolic dysfunction-associated fatty liver disease.

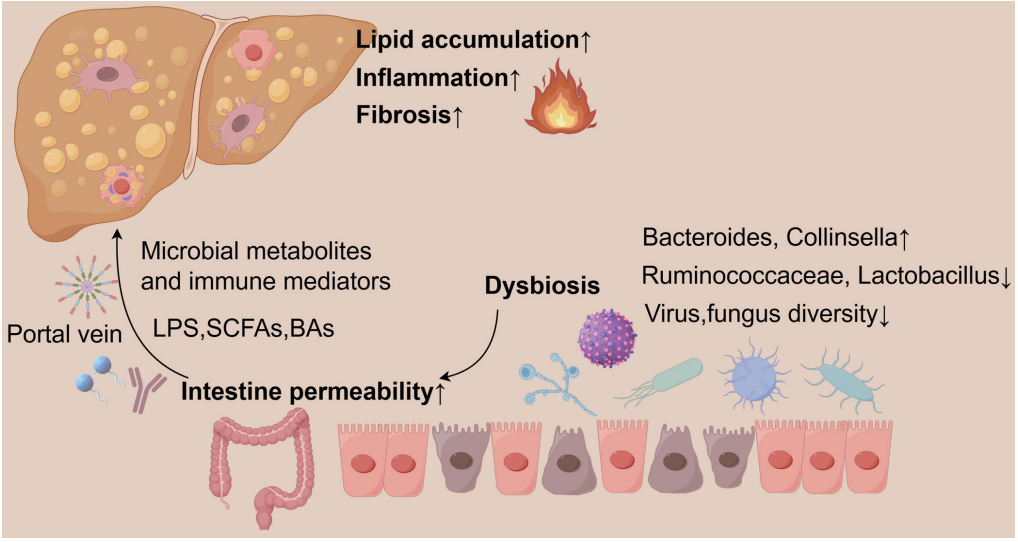

Fig. 2. The gut-liver axis in MAFLD progression. The gut-liver axis links intestinal dysbiosis to MAFLD progression through portal circulation, bile acid signaling, immune pathways, and microbial metabolites. Increased gut permeability allows microbial products, including LPS, SCFAs, and BAs, to enter the portal circulation and reach the liver, where they activate immune responses, induce hepatocellular stress, and promote lipid accumulation, inflammation, and fibrosis. MAFLD, metabolic dysfunction-associated fatty liver disease; LPS, lipopolysaccharide; SCFAs, short-chain fatty acids; BAs, bile acids; ↑, increase; ↓, decrease.

impaired very-low-density lipoprotein assembly and export.[54] Dysregulated sphingolipid metabolism, marked by altered ceramides and sphingosine-1-phosphate and their enzymes (*Cers6, Sptlc2, Sphk2, S1pr1-3*), promotes progression from MASH to cirrhosis and HCC.[55,56] Moreover, amino acid remodeling, particularly elevated branched-chain amino acids, indicates metabolic inflexibility and IR.[57] Surprisingly, high-protein diets are independent risk factors for MAFLD/MASH, particularly in obesity, as amino acids fuel hepatic tricarboxylic acid cycling and de novo lipogenesis more efficiently than glucose.[58] Furthermore, bile acids act as active regulators rather than passive byproducts of liver injury via farnesoid X receptor (FXR) and G protein-coupled bile acid receptor 1 signaling. Specific bile acid species correlate with key histopathological features, with taurocholate associated with steatosis and glycocholate with lobular inflammation.[59] Moreover, genetic susceptibility loci such as *TRIB1* are linked to elevated levels of toxic bile acid species, linking genetic susceptibility to disease severity.[60]

Emerging spatial metabolomics technologies further demonstrate that fibrotic niches exhibit distinct glycan and metabolite signatures, such as fucosylated N-glycans, indicating local metabolic remodeling within scar microenvironments.[61]

Microbiomics

The gut-liver axis integrates microbial composition with hepatic metabolism and immunity. An overview of the gut-liver axis and its role in disease progression is shown in Figure 2.

Across adult and pediatric cohorts, MAFLD and MASH are characterized by reduced microbial diversity and expansion of specific pathogenic taxa, including *Bacteroides*, *Ruminococcus*, *Prevotella copri*, and *Collinsella*, which correlate with fibrosis severity, endotoxin production, and inflammatory signaling.[62–64] Fecal microbiota transplantation restores beneficial taxa such as *Christensenellaceae* and *Lactobacillus*, alleviating steatohepatitis in high-fat diet-fed mice.[65] Interestingly, in a 12-week randomized, double-blind, placebo-controlled trial in 58 overweight or obese participants, *Akkermansia muciniphila* (AKK-WST01) reduced body weight, fat mass, and blood glucose but showed poor colonization and no added benefit in those with high baseline abundance.[66] Beyond bacteria, fungal and viral communities are also remodeled in progressive disease, with increased *Candida* and *Mucor* species and reduced phage diversity linked to immune activation and fibrosis severity.[67,68]

Gut-derived metabolites orchestrate MAFLD progression through multifaceted and context-dependent mechanisms. For example, microbial trimethylamine modulates host inflammation and IR by inhibiting interleukin-1 receptor-associated kinase 4 (IRAK4), while bile acid-FXR signaling coordinates bile acid homeostasis and fibrogenesis.[69,70] Microbiota-modified hyodeoxycholic acid alleviates MAFLD by coordinately reprogramming intestinal FXR activity and hepatic signaling involving peroxisome proliferator-activated receptor (PPAR) α and cytochrome P450 family 7 subfamily A member 1.[71] In contrast, trimethylamine N-oxide and D-lactate have been implicated in promoting hyperglycemia, hepatic oxidative stress, and metabolic impairment.[72,73] Moreover, increased activation of intestinal B cells drives the accumulation of $CD11b^{+}CCR2^{+}F4/80^{+}CD11c^{-}FCGR1^{+}$ hepatic myeloid cells through the IgA-Fc receptor axis, thereby promoting MASH.[74]

In summary, single-omics technologies provide complementary insights into MAFLD across the genomic, transcriptomic, proteomic, metabolic, and microbiome levels. However, these approaches remain constrained by inconsistent cell-type nomenclature, challenges in distinguishing cellular states from bona fide cell types, and limited mechanistic interpretability. These limitations highlight the need for multi-omics integration to systematically decipher complex regulatory networks.

Strategies for multi-omics data integration

Multi-omics integration is essential for resolving MAFLD heterogeneity and identifying causal mechanisms. Conceptually, integration can be divided into horizontal approaches that link molecular layers within the same biological state and longitudinal approaches that reconstruct the temporal evolution of regulatory programs from SS to MASH and then fibro-

Table 2. Overview of multi-omics data integration methods

Strategy	Objective	Methods and Tools
Unsupervised methods	Explore intrinsic structure of data and identify potential patterns and subtypes	Dimensionality reduction techniques (PCA, t-SNE, UMAP)
Network-based approaches	Systematically decode molecular interactions and regulation	WGCNA, PPI networks
Pathway-level analysis	Integrate cross-omics data to reveal functional insights	Pathway enrichment analysis (KEGG, Reactome, GO)
Machine learning and AI	Build predictive models capturing complex nonlinear patterns	Supervised learning: RF, SVMs Deep learning: GNN, Autoencoders

PCA, principal component analysis; t-SNE, t-distributed stochastic neighbor embedding; UMAP, uniform manifold approximation and projection; WGCNA, weighted gene co-expression network analysis; PPI, protein-protein interaction; KEGG, Kyoto Encyclopedia of Genes and Genomes; GO, gene ontology; AI, artificial intelligence; RF, random forest; SVM, support vector machine; GNN, graph neural network.

sis. Together, these strategies define the dynamic landscape of disease progression.

Conceptual frameworks for multi-omics integration

Multi-omics integration strategies can be abstracted into four analytical paradigms, each addressing a distinct layer of biological complexity.

First, unsupervised approaches enable hypothesis-free discovery and molecular stratification by exploring the intrinsic structure of high-dimensional datasets. For example, genome-wide DNA methylation profiling of human liver samples identified hundreds of CpG loci that differed across normal controls, healthy obese individuals, SS, and MASH. Principal component analysis further separated normal and MASH samples along the phenotypic spectrum, with healthy obese and steatotic samples occupying intermediate positions, suggesting a continuum of epigenetic remodeling during MAFLD progression.[75] Similarly, gene set variation analysis followed by non-negative matrix factorization (NMF) has been used to classify MAFLD into four molecular clusters, including an immune-fibrotic subtype distinguished by a fibrosis-associated signature with an area under the receiver operating characteristic curve (AUROC) of approximately 0.95.[25]

Second, network-based methods reconstruct system-level regulatory architecture and intercellular communication. By combining scRNA-seq with secretome ligand-receptor analysis in non-parenchymal liver cells from diet-induced MASH models, Xiong *et al.* identified HSCs, ECs, and macrophages as central signaling hubs. HSCs expressed multiple membrane and secreted factor genes, including 21 predicted HSC-derived "stellakines" that mainly targeted endothelial and immune cells, thereby linking ECM remodeling with vascular and immune crosstalk.[76]

Third, pathway-level integration enhances biological interpretability by linking molecular alterations to disease-relevant pathways. In leptin receptor-deficient mice, integrated RNA-seq and RNA bisulfite sequencing identified 156 genes with concurrent changes in mRNA expression and m^5C modification, highlighting fatty acid metabolism, pyruvate metabolism, peroxisome function, and PPAR signaling.[44] In arsenic-exposed rats, integrated proteomics and metabolomics implicated cholesterol metabolism, linoleic acid metabolism, arachidonic acid metabolism, purine metabolism, and PPAR signaling in arsenic-induced MAFLD. A three-metabolite model composed of adenosine monophosphate (AMP), 13-hydroxyoctadecadienoic acid (13-HODE), and hippuric acid distinguished arsenic-induced MAFLD in rats with an AUC of 0.94 and human MAFLD with an AUC of 0.86.[77]

Finally, machine learning frameworks support prediction and nonlinear pattern discovery from high-dimensional omics data. In serum proteomic studies of biopsy-confirmed MASH, SomaScan-based profiling combined with Elastic Net generated fibrosis-stage classifiers with AUROCs generally ranging from 0.74 to 0.83 across discovery and validation cohorts.[78] In parallel, aptamer-based plasma/serum proteomics combined with generalized linear modeling identified soluble protein classifiers for at-risk MASH, with AUROCs ranging from 0.83 to 0.90.[48] These examples show that effective integrative studies increasingly combine unsupervised stratification, network analysis, pathway interpretation, and predictive modeling to balance mechanistic insight, statistical robustness, and translational relevance. Representative tools are summarized in Table 2.

Horizontal integration

Horizontal integration links multilayer omics data derived from the same tissue or individual, enabling reconstruction of causal chains from genetic and epigenetic variation to cellular states and tissue phenotypes in MAFLD.

Across integrative studies, HSCs consistently emerge as central regulatory hubs coordinating fibrogenesis. Joint single-nucleus RNA sequencing and single-nucleusassay for transposase-accessible chromatin using sequencing (snATAC-seq) were performed on 18 human liver samples, which identified activated HSCs as the dominant source of ECM and revealed conserved regulatory modules (*GAS7*, *SPON1*, and *SERPINE1*) controlled by *JUNB/AP1*, *RUNX*, and *FOXA* factors.[79] A cross-species analysis integrating multiple technologies, including cellular indexing of transcriptomes and epitomes by sequencing (CITE-seq) , single-nucleus sequencing, ST, and spatial proteomics, revealed that LAMs occupy the cholangiocyte niche and are specified by HSC-KC interactions via the conserved ALK1-BMP9/10 axis.[80] In line with this, integration of paired liver-plasma data from 306 patients with biopsy-proven MAFLD linked HSC activation to circulating biomarkers, enabling MASH stratification and fibrosis assessment.[81] Beyond fibrosis, horizontal integration uncovered a role for HSCs in maintaining hepatocyte metabolic zonation. ST analyses demonstrated that HSC-derived RSPO3 sustains Wnt-dependent zonation, which expands from perivenous to periportal regions in MASH.[32]

Longitudinal integration

Longitudinal integration captures the temporal ordering of immune, metabolic, and stromal programs that drive the transition from SS through MASH to fibrosis, facilitating a deeper understanding of the molecular mechanisms underly-

ing disease progression.[82]

The immune system exerts a context-dependent role in maintaining hepatic homeostasis during both disease progression and recovery. In early disease stages, inflammatory activation can accelerate tissue injury and metabolic dysfunction, whereas concomitant anti-inflammatory and reparative programs are engaged to limit damage and preserve tissue integrity. Biliary reactions, characterized by cholangiocyte proliferation or hypertrophy, are tightly linked to periportal inflammation, MASH activity, and fibrosis severity, and are therefore considered histological hallmarks of ongoing liver repair and remodeling.[83] Importantly, disease reversal processes, including clearance of cellular debris and fibrosis regression, also rely on coordinated immune regulation. Macrophages release Wnt3a after engulfing necrotic hepatocytes, thereby activating Wnt signaling in hepatic progenitor cells and sustaining Numb expression, which promotes their differentiation toward hepatocytes.[84]

These studies highlight how integrative multi-omics approaches move beyond descriptive associations to reconstruct causal and dynamic regulatory programs. However, horizontal and longitudinal integration are not mutually exclusive. The integrated analysis highlights the advantage of multi-omics approaches in identifying functionally relevant targets. Ahrens *et al.* performed an integrative analysis of DNA methylation and transcriptomic data using liver samples from individuals across the full disease spectrum, identifying a series of CpG sites that may act as a "molecular clock" during MAFLD progression.[75] A human liver atlas constructed from 10 control, 17 MAFLD, and 34 MASH samples by integrating single-cell transcriptomic, ST, and spatial metabolomic data revealed a hepatoprotective role of LAMs mediated via the axis of microphthalmia-associated transcription factor (MITF) and hepatocyte growth factor (HGF) and defined a spatial fibrosis-associated gene program in at-risk MASH, together with an immune-metabolic-fibrotic coupled network driven by lipid metabolic reprogramming.[85]

Multi-omics integration driving clinical translation in MAFLD

These advances establish a conceptual framework in which integrative multi-omics links disease mechanisms with biomarker discovery, molecular subtyping, therapeutic-response prediction, and clinical outcome assessment in MAFLD, as summarized in the graphical abstract.

Elucidating novel pathogenic mechanisms

Multi-omics integration provides a systematic perspective for uncovering previously unrecognized molecular circuits in MAFLD. For example, a combined analysis of NHANES epidemiological data and serum metabolomics revealed that arsenic exposure is an independent risk factor for MAFLD. Mechanistically, arsenic induces hepatic lipid accumulation and inflammation by inhibiting pyruvate dehydrogenase and activating the lactate-H3K18 lactylation-CD36-NLRP3 inflammasome axis.[86] The "environmental toxin-metabolite-epigenetic modification" axis illustrates how integrative omics approaches can delineate novel mechanistic pathways linking environmental exposure and hepatic metabolic inflammation.

Discovery of diagnostic and molecular subtyping biomarkers

Noninvasive diagnostic models

To address the critical need for noninvasive diagnostics, various blood- and imaging-based biomarkers have been proposed to identify at-risk MAFLD/MASH. For instance, Govaere *et al.* integrated plasma proteomics with paired liver transcriptomics in 306 patients with histologically characterized MAFLD. Using the SomaScan platform, they profiled 4,730 circulating proteins and derived a 31-marker proteo-transcriptomic signature associated with steatohepatitis activity and advanced fibrosis. Through backward elimination binary logistic regression, they developed a composite model incorporating four circulating proteins (ADAMTSL2, AKR1B10, CFHR4, and TREM2), body mass index, and type 2 diabetes (T2DM) status. This model identified at-risk MASH with an AUROC of 0.878 in the discovery cohort (n = 191) and maintained diagnostic performance in an independent validation cohort (n = 115), with an AUROC of 0.80.[81] These findings illustrate that integrating circulating proteomic signatures with hepatic transcriptomic data can enhance biomarker interpretability, but the modest validation AUROC (0.80) and tissue dependence underscore its current limitation to mechanistic discovery and trial enrichment rather than routine diagnostics.

The NIS4® score, composed of miR-34a-5p, α2-macroglobulin, YKL-40, and HbA1c, was developed in a discovery cohort of 239 patients and externally validated in a pooled cohort of 702 patients with MAFLD. It achieved an AUROC of 0.80 (95% confidence interval [CI], 0.73–0.85) for identifying at-risk MASH, with prespecified rule-out and rule-in cutoffs showing clinically useful sensitivity, specificity, and predictive values.[87] To improve subgroup robustness and reduce potential confounding related to HbA1c and T2DM status, the optimized blood-based NIS2+™ model was subsequently developed using miR-34a-5p, YKL-40, and sex-specific correction parameters. In the independent RESOLVE-IT test cohort (n = 2,035), NIS2+™ achieved an AUROC of 0.813 (95% CI, 0.795–0.832), outperforming NIS4® (0.792, $P = 0.0002$), FIB-4 (0.653, $P < 0.0001$), and alanine aminotransferase (ALT) (0.699, $P < 0.0001$), while maintaining stable performance across age, sex, body mass index, and T2DM subgroups.[88] Together, these findings support the potential clinical utility of blood-based multi-analyte models for MASH risk stratification, although further validation is required to define their role in routine clinical practice.

In contrast to these validated diagnostic panels, arachidonoyl-taurine (ARA-T) represents an exploratory metabolite biomarker. In the Copenhagen Cohort, plasma N-acyl taurine profiling in 65 controls and 56 MAFLD participants showed that ARA-T increased with hepatic steatosis severity. In a 14-day overfeeding study involving 20 healthy male adults, participants with serum ALT levels above 57 IU/L showed a 52% increase in circulating ARA-T from baseline, whereas no significant change was observed in those with normal-range ALT. In a separate dietary intervention study, 19 healthy men received 1.5 g/d arachidonic acid or placebo for 4 weeks, which increased plasma ARA-T levels without increasing inflammation.[89] However, without AUROC-based validation against histological endpoints, its clinical utility remains uncertain, distinguishing it from the validated diagnostic panels discussed above, which have undergone rigorous performance evaluation in large cohorts.

Together, these studies indicate that noninvasive biomarker discovery has transitioned from single biochemical indices toward multi-analyte and multi-omics-informed composite models. However, diagnostic performance varies according to endpoint definition, cohort composition, and validation strategy. Therefore, to ensure clinical merit, future studies should consistently report sample size, target endpoint, AUROC with 95% CI, sensitivity, specificity, predictive values,

Table 3. Quantitative evidence for diagnostic, subtyping, therapeutic, and prognostic models in MAFLD/MASH

Ref.	Endpoint/state	Cohort/model and sample size	Core quantitative metrics/ statistical performance	Key molecular/ cellular drivers
81	At-risk steatohepatitis; advanced fibrosis	Discovery n = 191; validation n = 115	Discovery AUROC 0.878 ± 0.025; validation AUROC 0.80 ± 0.04	ADAMTSL2, AKR1B10, CFHR4, TREM2 + BMI + T2DM
87	At-risk MASH	Discovery n = 239; pooled validation n = 702	AUROC 0.80 (95% CI, 0.73–0.85); rule-out <0.36: sensitivity 80.8%, NPV 81.5%; rule-in ≥0.63: specificity 90.4%, PPV 78.3%	miR-34a-5p, α2-macroglobulin, YKL-40, HbA1c
88	At-risk MASH; optimized panel	Training n = 198; validation n = 684; test n = 2,035	Test AUROC 0.813 (95% CI, 0.795–0.832); superior to NIS4® (0.792, $P = 0.0002$), FIB-4 (0.653, $P < 0.0001$), and ALT (0.699, $P < 0.0001$); indeterminate zone 23%	miR-34a-5p + YKL-40 with sex-specific correction
89	Exploratory metabolic stress biomarker; steatosis severity	Controls n = 65; MAFLD n = 56; overfeeding n = 20; ARA supplementation n = 19	ARA-T increased with steatosis; ALT >57 IU/L subgroup: 52% increase after 14-day overfeeding; normal ALT: no significant change	Plasma N-acyl taurine profiling; hepatic steatosis/acute liver injury marker
90	Molecular subtypes of biopsy-proven MAFLD	Internal n = 120 (17 controls, 103 MAFLD); external validation n = 92	7,205 hepatic proteins; NMF of 1,346 proteins identified 3 subtypes; 3-protein IF panel: 92.98% accuracy, AUROC 0.991	mSI: CYP1A2/CYP3A4; mSII: ECM/TGF-β-SMAD2/3/macrophages; mSIII: CEBPB/ERCC3 oncogenic programs
25	Molecular phenotypes; fibrosis progression	14 transcriptomic datasets; 2 scRNA-seq datasets; clustering n = 206	Four clusters; Cluster 4 AUROC approx. 0.95; MacC2 vs. fibrosis $r = 0.52$, $P < 0.0001$; MacC2 vs. TGF-β $r = 0.44$, $P < 0.0001$	Cluster 4: fibrosis/ TGF-β/activated HSC/ liver aging; profibrotic macrophage programs
91	Preclinical OCA responsiveness	Western diet-induced MAFLD mice: OCA n = 19; vehicle n = 8	Overall response rate 36.8%; response increased to 80% when Cyp7b1/Cyp8b1 ≥5.0	Alternative bile acid pathway activation; CYP7B1 silencing validation
55	MASH-to-HCC progression; survival	DIAMOND MASH-HCC model; TCGA-LIHC n = 365	MASH vs. control: 1,042 DEGs; HCC vs. control: 2,412 DEGs; survival stratification $P = 1.081 \times 10^{-3}$	Sphingolipid remodeling; risk genes *CERS6/ SPTLC2* and protective gene *S1PR1*

AUROC, area under the receiver operating characteristic curve; BMI, body mass index; T2DM, type 2 diabetes mellitus; CI, confidence interval; MASH, metabolic dysfunction-associated steatohepatitis; NPV, negative predictive value; PPV, positive predictive value; FIB-4, fibrosis-4 index; ALT, alanine aminotransferase; ARA, arachidonic acid; ARA-T, arachidonoyl-taurine; MAFLD, metabolic dysfunction-associated fatty liver disease; NMF, non-negative matrix factorization; IF, immunofluorescence; ECM, extracellular matrix; scRNA-seq, single-cell RNA sequencing; HSC, hepatic stellate cell; OCA, obeticholic acid; HCC, hepatocellular carcinoma; DEGs, differentially expressed genes.

indeterminate-zone proportion, and robustness across clinically relevant subgroups. Representative quantitative metrics are summarized in Table 3.[25,55,81,87–91]

Molecular subtyping

Integrative multi-omics has also enabled molecular subtyping of MAFLD beyond conventional histological categories. Ding *et al.* quantified 7,205 hepatic proteins from 17 non-MAFLD controls and 103 patients with biopsy-proven MAFLD. NMF of 1,346 highly variable hepatic proteins identified three distinct molecular subtypes: MAFLD-mSI, MAFLD-mSII, and MAFLD-mSIII. MAFLD-mSI was characterized by higher CYP1A2 and CYP3A4 abundance and lower steatosis activity; MAFLD-mSII showed enrichment of ECM remodeling, TGF-β-SMAD2/3 signaling, and macrophage infiltration, indicating a fibrosis-prone phenotype; and MAFLD-mSIII exhibited activation of oncogenic programs involving CEBPB and ERCC3, suggesting a potential HCC-prone state. A three-protein multiplex immunofluorescence panel classified these subtypes with an accuracy of 92.98% and an AUROC of 0.991, with further validation in an external cohort (n = 92).[90] These findings suggest that multi-omics-based molecular classification may complement conventional histological assessment by identifying biologically distinct MAFLD subtypes with potential implications for personalized disease management.

Complementarily, He *et al.* integrated 14 liver transcriptomic datasets and two scRNA-seq datasets to construct molecular and cell-type-specific signatures. In a cohort of 206 MAFLD liver samples, gene set variation analysis-based enrichment followed by NMF identified four molecular clusters. Cluster 4 was characterized by enriched fibrosis, TGF-β, activated HSC, and liver aging signatures, and was distinguished by the fibrosis subset signature with an AUROC of approximately 0.95 (95% CI, 0.92–0.97). Macrophage-related signatures were also quantitatively associated with profibrotic programs, including significant correlations between the MacC2 signature and the fibrosis signature ($r = 0.52$, $P < 0.0001$) and TGF-β signature ($r = 0.44$, $P < 0.0001$).[25] These findings link fibrosis-associated molecular subtypes with macrophage-related programs, although further validation is required to establish their causal role in fibrosis progression.

Together, these studies indicate that molecular subtyping can refine risk stratification by identifying steatosis-related,

fibrosis-prone, immune-fibrotic, and potential HCC-prone molecular states. However, most subtype definitions remain based on retrospective datasets or tissue-based assays. Therefore, prospective validation across diverse populations, standardized clinical endpoints, and treatment-response cohorts is still required before clinical implementation in precision therapy.

Predicting therapeutic response and clinical outcomes

Integrative omics has increasingly been deployed to establish molecular predictors of therapeutic response and long-term prognosis. Nuclear receptor pathways, including PPAR and FXR signaling, remain core therapeutic targets in MAFLD/MASH. However, heterogeneous therapeutic responses, as illustrated by the failure of the phase III RESOLVE-IT trial of elafibranor to meet its primary endpoint of MASH resolution without worsening of fibrosis, underscore the need for drug-specific predictive biomarkers rather than assuming uniform efficacy across all patients.[92–94] In this context, integrative omics offers a strategy for biomarker-guided patient selection, shifting therapeutic development from a one-size-fits-all model toward molecularly informed precision medicine.

As a preclinical multi-omics example, Lee *et al.* used a Western diet-induced MAFLD mouse model to investigate obeticholic acid (OCA) responsiveness. The overall response rate to OCA was 36.8%, but increased to 80% in mice with a hepatic *Cyp7b1/Cyp8b1* expression ratio ≥ 5.0. *CYP7B1* silencing in LX-2 cells abolished the antifibrotic effect of OCA, suggesting that the balance between alternative and classical bile acid synthesis pathways may represent a tissue-based candidate biomarker of FXR agonist response.[91] These findings provide a proof of concept that multi-omics approaches can identify molecular determinants of therapeutic response and support biomarker-guided patient selection.

For outcome prediction, Zeng *et al.* integrated transcriptomics, targeted lipidomics, NanoString profiling, and single-nucleus RNA-seq in a DIAMOND mouse model of MASH-HCC progression. RNA-seq identified 1,042 differentially expressed genes during MASH progression and 2,412 differentially expressed genes in HCC. Targeted lipidomics revealed pronounced serum and hepatic sphingolipid remodeling. Subsequent multivariate Cox regression analysis using The Cancer Genome Atlas liver hepatocellular carcinoma cohort identified a sphingolipid metabolism-related prognostic model involving *CERS6* and *SPTLC2* as risk-associated genes and *S1PR1* as a protective gene, which stratified patients by overall survival ($P = 1.081 \times 10^{-3}$).[55] Importantly, this study shifts the application of multi-omics from describing molecular alterations toward capturing disease trajectories, demonstrating that metabolic remodeling signatures can provide prognostic information during MASH progression toward HCC.

Together, these examples show that integrative omics can support drug-specific response prediction, pharmacodynamic monitoring, and prognosis assessment in MAFLD/MASH. Representative therapeutic-response and prognostic readouts are summarized in Table 3. Nevertheless, most current evidence remains preclinical, retrospective, or tissue-based, and prospective validation in well-characterized human cohorts is required before these biomarkers can be incorporated into precision therapeutic decision-making.

Clinical interpretability, strengths, and limitations of omics-based studies

The clinical merit of omics-based studies should be interpreted not only by statistical performance but also by endpoint definition, validation design, assay feasibility, and whether the results can change patient management. Blood-based multi-analyte panels currently have the clearest route toward clinical use because they can be incorporated into risk stratification, referral decisions, and trial enrichment. Several proteomic and composite biomarker models, including proteo-transcriptomic signatures and NIS-based panels, have demonstrated clinically relevant performance in independent cohorts—yet their integration into routine practice will require further validation as well as prospective demonstration of incremental benefit over existing clinical assessment tools.[81,87,88]

However, AUROC values alone do not guarantee clinical utility. Predictive performance depends on disease prevalence, endpoint definition, validation strategy, and implementation context. Future biomarker studies should report calibration, decision-curve analysis, rule-in/rule-out performance, indeterminate-zone proportions, and comparisons with current clinical standards. These metrics collectively determine whether a test can meaningfully influence clinical decision-making beyond statistical significance.

Tissue-based omics and molecular subtyping studies provide strong mechanistic insight but remain limited by invasiveness, retrospective design, sample size, and difficulty in longitudinal clinical application. Proteomic- and transcriptomic-based molecular classification studies have challenged the traditional histological classification of MAFLD by identifying biologically distinct subtypes associated with fibrosis progression, metabolic alterations, and oncogenic risk; however, most signatures remain dependent on liver tissue and require prospective validation before routine clinical implementation.[25,90]

Therapeutic-response and prognostic models are promising for precision medicine, but most current evidence remains preclinical or retrospective and requires prospective validation before clinical implementation. For example, biomarker-guided prediction of OCA responsiveness and sphingolipid-based prognostic models illustrate how omics approaches may shift therapeutic strategies from empirical treatment toward biomarker-guided patient selection, but their clinical utility remains to be confirmed in prospective human studies.[55,91] A structured summary of the current clinical applications, strengths, and remaining translational barriers of representative omics-based approaches is provided in Table 4.

Future perspectives

Future research should aim to bridge the gap between multi-omics discovery and clinical translation in MAFLD. Although multi-omics integration has substantially advanced the understanding of disease pathogenesis, current liver tissue-based omics studies often involve relatively small sample sizes or single-center cohorts, limiting statistical power and the generalizability of findings.[95] Data heterogeneity, platform-specific technical variability, batch effects, and the lack of standardized protocols across platforms and cohorts further impede reproducibility, cross-study comparison, and meta-analysis.[29] In addition, studies comprehensively covering the full pathological spectrum of MAFLD remain limited, restricting the applicability of current conclusions across different disease stages. Because most findings are still derived from correlation-based analyses, experimental validation, longitudinal cohorts, and perturbation-based studies are needed to establish causal relationships among genomic susceptibility, transcriptional regulation, proteomic function, metabolic remodeling, and disease progression.

Clinical translation also faces several barriers. The high cost of multi-omics profiling limits routine clinical application, while

Table 4. Clinical strengths and translational limitations of representative omics-based approaches in MAFLD/MASH

Application type	Current clinical strength	Major limitation
Blood-based biomarker models (diagnostic)	Noninvasive and clinically accessible; validated in independent cohorts with test cohort sizes up to 2,035. Multi-analyte models achieved AUROC values of 0.80–0.878 in discovery cohorts and 0.80–0.813 in validation cohorts, with improved performance compared with conventional markers such as FIB-4 and ALT	Moderate discrimination (AUROC generally <0.90); further cost-effectiveness evaluation and real-world validation required; performance which may vary across cohorts and clinical endpoints
Molecular subtyping (tissue-based)	Reveals fibrosis-associated, immune-fibrotic, and oncogenic-risk molecular states. Proteomic and transcriptomic classifiers demonstrated high performance, including a 3-protein IF panel with 92.98% accuracy (AUROC 0.991, external n = 92) and a fibrosis signature with AUROC ~0.95	Tissue-dependent (requiring liver biopsy); mainly based on retrospective discovery cohorts; limited external validation; unsuitable for routine monitoring or population screening
Therapeutic-response biomarkers	Provide proof-of-concept for biomarker-guided treatment selection; OCA response increased from 36.8% to 80% in biomarker-defined mice with mechanistic validation	Mostly supported by preclinical evidence; prospective human validation required; no established clinical thresholds or regulatory qualification
Prognostic models	Integrate multi-omics features for outcome prediction; sphingolipid-based models stratified survival in TCGA-LIHC cohorts ($P = 1.081\times10^{-3}$)	Primarily retrospective discovery; limited comparison with established prognostic models; prospective validation required to determine clinical utility

AUROC, area under the receiver operating characteristic curve; FIB-4, fibrosis-4 index; ALT, alanine aminotransferase; IF, immunofluorescence; OCA, obeticholic acid; TCGA-LIHC, The Cancer Genome Atlas liver hepatocellular carcinoma cohort.

the lack of standardized analytical pipelines and the complexity of multi-omics data integration further complicate practical implementation.[54] Moreover, most candidate biomarkers identified through omics studies remain at the discovery or early validation stage, with only a limited number having progressed to clinical application. Future large-scale, longitudinal, and multicenter studies are therefore needed to bridge the gap between multi-omics discoveries and clinical translation.[95]

To overcome these hurdles, future research should prioritize three directions. First, integrating ST with time-resolved metabolomics will help clarify metabolic zonation and microenvironmental drivers of disease progression. Second, artificial intelligence-driven frameworks, including graph neural networks and transformer-based models, may improve the interpretation of high-dimensional gene–metabolite–phenotype networks and disease trajectory prediction. Third, multi-omics signatures should be further integrated into clinical workflows for patient stratification, adaptive trial design, and noninvasive diagnosis and monitoring.

Conclusions

Multi-omics integration has transformed MAFLD research from histology-centered description into a systems-level field linking molecular mechanisms with clinical phenotypes. By integrating genomic, transcriptomic, proteomic, metabolomic, spatial, and computational layers, these approaches reveal that MAFLD progression is driven by coordinated interactions among genetic susceptibility, cellular reprogramming, immune-metabolic remodeling, and microenvironmental heterogeneity. With further standardization, validation, and clinical implementation, multi-omics research may facilitate clinically useful strategies for MAFLD, including molecular subtyping, individualized risk prediction, noninvasive monitoring, and tailored therapeutic intervention.

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Conflict of interest

JGF has been an Associate Editor of the *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflicts of interest related to this publication.

Author contributions

Writing—original draft (JZ), writing—review and editing (YL), funding acquisition, and conceptualization (JGF). All authors have made significant contributions to this study and have approved the final manuscript.

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