· Review ·

# Inflammation-associated hepatocellular carcinoma: a revised comprehensive review from pathogenesis to precision prevention and treatment

Xiaoyun Chen[1], Shan Ji[2*]

[1]Infirmary of Beijing Institute of Graphic Communication, Beijing 100069, China.
[2]Department of Infectious Diseases, Beijing You'an Hospital, Capital Medical University, Beijing 100069, China.

## Abstract

Hepatocellular carcinoma (HCC) develops predominantly on the background of chronic liver inflammation. This revised review focuses on how different etiologies-metabolic dysfunction-associated steatotic liver disease (MASLD, formerly non-alcoholic fatty liver disease), viral hepatitis, alcohol-related liver disease, and cholestatic or autoimmune liver disorders-converge on common inflammatory programs while retaining distinct immuno-metabolic and carcinogenic features. We summarize mechanistic evidence linking persistent hepatocyte injury to activation of NF-κB, IL-6/JAK/STAT3, TLR4/MyD88, COX-2/PGE2, oxidative stress, endoplasmic reticulum stress, ferroptosis, and stromal remodeling, and further discuss how these pathways reprogram macrophages, T lymphocytes, liver sinusoidal endothelial cells, hepatic stellate cells, and hepatic progenitor cells within the tumor microenvironment. Emphasis is placed on the translational bridge from mechanism to clinic, including inflammation-related serum markers, radiomics-clinical nomograms, model development methods, validation metrics, and pathways for clinical implementation. We also critically discuss unresolved issues, including the dual role of regulatory T cells in MASLD/metabolic dysfunction-associated steatohepatitis (MASH), etiology-specific differences in immunotherapy biomarkers, and the challenge of distinguishing causality from association in gut microbiome-HCC studies. Finally, we outline therapeutic strategies that target inflammatory signaling and the immune microenvironment, from immune checkpoint inhibitors and rational local-systemic combinations to pathway-directed small molecules, cell therapy, and nucleic acid delivery platforms. Together, these advances support a precision framework for risk stratification, early detection, and individualized intervention in inflammation-associated HCC.

**Keywords:** hepatocellular carcinoma, chronic liver inflammation, tumor microenvironment, immunotherapy

## Introduction

Hepatocellular carcinoma remains one of the leading causes of cancer-related death worldwide and typically emerges through a long natural history of chronic liver injury, fibrosis, cirrhosis, and malignant transformation.

***Correspondence:**
Shan Ji; Email: jsshjdd@163.com

Inflammation is not merely an accompanying phenomenon; it is a biologically active driver of genomic instability, compensatory proliferation, angiogenesis, immune evasion, and treatment resistance [1,2].

Compared with prior narrative summaries that separately discuss risk factors, signaling pathways, or therapy, the present review is intended to integrate three levels of evidence: (1) etiology-specific inflammatory mechanisms, (2) pathway- and cell-based microenvironmental reprogramming, and (3) translational advances in biomarkers, prediction models, and mechanism-guided intervention. To improve conceptual clarity, we adopt the current consensus nomenclature MASLD (formerly NAFLD) at first mention and use MASLD/metabolic dysfunction-associated steatohepatitis (MASH), consistently throughout the manuscript [3].

A further aim of this revision is to place recent 2025 studies into the context of landmark mechanistic and therapeutic literature that established the modern framework of HCC biology and management, including foundational work on cancer-related inflammation, sorafenib, immune checkpoint inhibition, nomogram construction, and LASSO-based modeling [4–11].

## Inflammatory microenvironment in chronic liver diseases: the soil for HCC initiation and progression

Chronic liver disease provides the ecological soil for HCC development. Across etiologies, repeated hepatocyte injury drives the release of damage-associated molecular patterns, reactive oxygen species, and inflammatory mediators that perpetuate wound-healing responses, fibrogenesis, and selection of transformed clones. However, the composition of this inflammatory soil differs by disease context, which has direct implications for surveillance, biomarker discovery, and treatment response.

### *Immune-inflammatory driving mechanisms in MASLD/MASH*

MASLD and its progressive inflammatory phenotype, MASH, are rapidly becoming dominant etiologies of HCC. Hepatic lipid overload induces lipotoxic stress, organelle injury, hepatocyte death, and the release of damage-associated molecular patterns that recruit and activate monocyte-derived macrophages, neutrophils, and adaptive immune cells [3,12]. Recent work highlights substantial macrophage heterogeneity in MASH, indicating that monocyte-derived populations are not passive bystanders but active organizers of fibrogenic and pro-tumor niches [12].

Dywicki et al. further emphasized that regulatory T cells (Tregs) in MASLD/MASH may not be uniformly protective; in some experimental contexts they acquire inflammatory features, including IL-17-associated programs, and correlate with more severe liver pathology [13]. This observation is important because it challenges the simplistic assumption that Treg expansion is necessarily anti-inflammatory in metabolic liver disease. Liver sinusoidal endothelial cells (LSECs) also amplify MASH progression by responding to macrophage-derived IL-1β through IL-1R1 and producing chemokines that reinforce inflammatory-cell recruitment [14].

At the metabolic-signaling level, the ATG9A-PLA2G6 axis alters phospholipid homeostasis and links defective stress adaptation to inflammation, fibrosis, and hepatocarcinogenesis [15]. These findings support a model in which immunometabolic dysregulation, rather than steatosis alone, drives the transition from fatty liver disease to cancer.

### *Persistent inflammation and carcinogenic processes associated with viral hepatitis (HBV, HCV, and HDV)*

Chronic viral hepatitis remains a major global cause of HCC. In HBV infection, hepatocarcinogenesis results from both indirect inflammatory injury and direct oncogenic events, including viral DNA integration, insertional mutagenesis, and sustained transcriptional perturbation. Recent data suggest that HBV integration near the ORC1 locus may increase circulating ORC1 and improve detection of alpha-fetoprotein-negative HBV-related HCC [16]. In parallel, preS/S single-nucleotide variants can aggravate oxidative stress, mitochondrial dysfunction, and calcium dyshomeostasis, thereby linking viral genetic evolution to inflammatory carcinogenesis [17].

HCV-associated HCC is driven predominantly through chronic necroinflammation, oxidative stress, steatogenic signaling, and cirrhosis rather than genomic integration. High-fitness HCV variants selectively enriched in immunosuppressed hosts have been associated with more severe disease and a higher likelihood of HCC development [18]. HDV coinfection with HBV often produces the most aggressive inflammatory phenotype, with accelerated progression to cirrhosis and HCC, although recent cohort data also underscore heterogeneity in clinical expression [19].

Importantly, antiviral therapy alters the inflammatory field in which carcinogenesis occurs. Long-term nucleos(t)ide analogues reduce HBV-related HCC risk [20], while sustained virologic response after direct-acting antivirals may improve liver reserve and oncologic outcomes in selected patients later treated with systemic therapy [21]. These observations illustrate that etiologic control is itself an anti-inflammatory anticancer strategy.

### *Inflammation and fibrosis induced by bile acid dysregulation, alcohol, and other causes*

Bile acid dysregulation is increasingly recognized as a carcinogenic inflammatory driver. In cholestatic and advanced tumor settings, glycochenodeoxycholic acid may induce hepatic progenitor-cell differentiation toward cancer-associated fibroblasts through sphingosine-1-phosphate receptor 2 (S1PR2) signaling, thereby coupling bile acid stress to fibrosis and tumor expansion [22]. The TBA-MLR score, which combines total bile acid and monocyte-to-lymphocyte ratio, exemplifies how metabolic and inflammatory dimensions can be integrated for prognostic assessment [23].

Alcohol-related liver disease promotes hepatocarcinogenesis through acetaldehyde toxicity, oxidative stress, gut barrier disruption, endotoxemia, and Kupffer-cell activation, with robust induction of TNF-α, IL-1β, and IL-6 [24]. Smoking can further intensify inflammatory and angiogenic programs in cirrhosis [25]. Autoimmune and cholestatic disorders, including autoimmune hepatitis and primary biliary cholangitis, also create chronic injury-fibrosis milieus that increase HCC risk, although absolute risk varies by fibrosis stage and disease control [26].

Across etiologies, despite their distinct, MASLD/MASH, viral hepatitis, alcohol-related liver disease, and cholestatic/autoimmune disorders share several convergent carcinogenic features: persistent hepatocyte injury, cytokine amplification, activation of fibrogenic stromal cells, angiogenic remodeling, and progressive immune dysfunction. Their differences are equally important. MASLD/MASH is characterized by immunometabolic stress and altered lipid handling; HBV uniquely adds direct insertional oncogenesis; HCV relies more heavily on chronic inflammatory-cirrhotic remodeling; alcohol prominently involves

gut-derived endotoxin signaling; and bile acid-related disease accentuates metabolite-receptor crosstalk. Recognizing these shared and disease-specific programs helps explain why biomarkers and therapeutic response are often etiology dependent rather than universally transferable.

## Key inflammatory signaling pathways and cytokine networks in HCC development

Inflammation-associated HCC is orchestrated by interconnected signaling networks rather than isolated pathways. A mechanistic framework is therefore necessary not only to explain tumor initiation but also to identify actionable nodes, biomarkers, and resistance mechanisms.

### *NF-κB, TLR4/MyD88, and TNF-α signaling*

NF-κB is a central signaling hub linking chronic injury to carcinogenesis. Activation of TLR4/MyD88, TNF receptors, and other inflammatory inputs converges on the IKK complex, which phosphorylates IκB and allows nuclear translocation of NF-κB dimers. In hepatocytes, macrophages, and stromal cells, this program induces anti-apoptotic and proliferative mediators including BCL2, BCL-XL, MYC, cyclin D1, VEGF, matrix metalloproteinases, COX-2, and multiple chemokines, thereby supporting cell survival, angiogenesis, extracellular-matrix remodeling, and leukocyte recruitment [1, 2].

Recent experimental work suggests that colon-targeted astragalus polysaccharide nanoparticles suppress MASLD-driven hepatocarcinogenesis partly by reshaping the gut microbiota, increasing acetate, and inhibiting NF-κB through GPR43 signaling [27]. Artemisia rupestris similarly attenuates TLR4/MyD88/NF-κB signaling and macrophage-mediated immune evasion in HCC models [28]. TNF-α, a major upstream activator of NF-κB, also interacts with sex-hormone pathways; Groover et al. reported sex-specific relationships between estrogen receptor beta and TNF-α in HCV-related cirrhosis, suggesting that inflammatory signaling may be modulated by biological sex [29].

### *COX-2/PGE2, IL-1β/IL-1R1, and IL-6/JAK/STAT3 axes*

COX-2/PGE2 signaling is a canonical inflammatory amplifier in solid tumors, including HCC. PGE2 promotes proliferation, angiogenesis, and immune escape, in part through suppression of natural killer (NK) cell function and modulation of myeloid cells. After radiofrequency ablation, residual-tumor microenvironments may show increased COX-2 expression; celecoxib can reverse PGE2-mediated NK-cell suppression and enhance the efficacy of anti-PD-1 therapy in preclinical models [30].

The IL-1β/IL-1R1 axis is especially relevant in MASH, where lipotoxic macrophages with defective autophagy overproduce IL-1β. LSECs receiving this signal activate JNK and induce chemokines such as CCL2 and CXCL10, thereby recruiting additional inflammatory cells and accelerating fibrosis [14].

IL-6/JAK/STAT3 is another core hepatocarcinogenic circuit. Persistent IL-6 signaling activates JAK kinases and STAT3, which transactivates genes involved in proliferation and survival, including MYC, cyclin D1, survivin, BCL-XL, and VEGF, while also promoting stemness, angiogenesis, and resistance to apoptosis [1,24]. Negative regulation by SOCS proteins, particularly SOCS3, is frequently inadequate in chronic inflammatory states, allowing sustained STAT3 activity. Mechanistically, NF-κB and STAT3 can cooperate at shared

promoters and enhancers, creating feed-forward transcriptional programs that intensify inflammatory tumor promotion [1,2]. Following tissue ablation, cytokine panels incorporating IL-7, IL-6, IL-1alpha, and CXCL1 may predict radiologic response, suggesting that transient inflammatory surges can be mined for clinically useful biomarkers [31].

***Oxidative stress, endoplasmic reticulum stress, autophagy, and ferroptosis cross-talk***

Oxidative stress and endoplasmic reticulum stress are integral to chronic liver injury and interact bidirectionally with inflammatory signaling. Mitochondrial dysfunction, lipid peroxidation, and reactive oxygen species formation promote DNA damage and genomic instability, while inflammatory cytokines further aggravate organelle stress [17, 24].

Autophagy normally constrains these processes by clearing damaged organelles and limiting inflammasome activation. Oroxyloside has been reported to restore autophagic flux through AMPK-ULK1 signaling, thereby reducing oxidative stress, DNA damage, IL-6 production, stellate-cell activation, and fibrosis [32]. Conversely, inhibition of the autophagy-repressive hormone DBI/ACBP can enhance anti-tumor immunity and increase the expression of ferroptosis-related genes, sensitizing HCC cells to iron-dependent cell death [33].

The NOTCH1-KEAP1-NRF2 axis adds another layer of complexity. NOTCH1 intracellular signaling may destabilize KEAP1-NRF2 interactions, promoting oxidative injury and ferroptosis-related vulnerability in chronic liver disease and HCC [34]. Together, these data suggest that stress-adaptation pathways are not peripheral phenomena but central determinants of inflammation-driven malignant evolution.

## Immune cell heterogeneity and functional reprogramming in the tumor microenvironment

The HCC microenvironment is a dynamic immune ecosystem in which macrophages, lymphocytes, endothelial cells, stellate cells, and progenitor populations are reprogrammed by chronic inflammation. Single-cell and spatial technologies increasingly show that functional states in HCC cannot be reduced to simple binary categories.

***Tumor-associated macrophages: heterogeneity, accumulation of TREM2-positive subsets, and pro-carcinogenic functions***

Tumor-associated macrophages (TAMs) are among the dominant leukocyte populations in HCC and are major mediators of tumor-promoting inflammation [35,36]. Single-cell studies have identified a conserved FABP5-positive macrophage subset that persists across advanced fibrosis and hepatocarcinogenesis, supporting both extracellular-matrix remodeling and malignant progression [37].

The manuscript was revised to avoid conceptual imprecision regarding TREM2. TREM2 is best understood as a marker of a distinct macrophage subset rather than a classical polarization state. Accordingly, it is more accurate to describe the accumulation or metabolic reprogramming of TREM2-expressing TAMs than the “polarization of TREM2-positive TAMs.” Metabolism-archetype HCC cells may increase oxidized low-density lipoprotein through squalene epoxidase upregulation, which in turn promotes the accumulation and reprogramming of TREM2-positive TAMs via the TREM2-SYK-CEBPα axis [38]. These macrophages contribute to invasion, cytokine resistance, CD8-positive T-cell dysfunction, and poor

immunotherapy response.

Myeloid TGF-β signaling further shapes macrophage composition in MASH-associated HCC; loss of myeloid TGF-β signaling reduces Trem2-positive macrophages while expanding Fcrl5-positive subsets and favoring effector T-cell exhaustion [39]. Additional mechanisms, such as RNASEH2C-driven impairment of antigen presentation, demonstrate that TAMs regulate both inflammatory tone and antigenic visibility of the tumor [40].

### *T lymphocytes, Treg plasticity, and the problem of context-dependent immune suppression*

CD4-positive and CD8-positive T lymphocytes are central effectors of anti-tumor immunity, yet chronic inflammatory liver disease frequently drives them into dysfunctional, exhausted, or skewed states. In MASH, increased intrahepatic CD4-positive PD-1-positive populations may help identify patients at future risk of HCC, and integration with routine clinical parameters improves predictive performance [41].

Ajith et al. reported striking Treg enrichment in a DEN/$CCl_4$ mouse model of fibrosis-to-HCC progression, including approximately 125-fold and 80-fold higher infiltration in the tumor margin and surrounding non-tumor liver, respectively [42]. Because these values appear to reflect relative cell-count enrichment in defined tissue compartments rather than a direct percentage increase in total hepatic immune cells, they should be interpreted cautiously to avoid overstatement. This revision therefore preserves the biological message—prominent Treg accumulation—while clarify the likely quantitative meaning.

The role of Tregs in MASH remains controversial rather than uniform. Dywicki et al. highlighted settings in which Tregs display pro-inflammatory features and fail to protect against disease progression [13], whereas other conceptual frameworks still support an immunosuppressive, tissue-protective role for Tregs under specific metabolic and temporal conditions. This apparent contradiction may reflect disease stage, tissue compartment, antigenic context, and phenotypic plasticity rather than true incompatibility. Such complexity is clinically relevant because it may partly explain why immunotherapy biomarkers derived from viral HCC do not always transfer to MASH-related HCC. In addition, checkpoint molecules such as PD-1 and CTLA-4 mark functionally constrained T-cell states that may be altered by locoregional therapy [43].

### *Stromal and endothelial partners: hepatic stellate cells, LSECs, and hepatic progenitor cells*

Inflammation-associated HCC is not created by leukocytes alone. Hepatic stellate cells, the principal fibrogenic effectors of the liver, respond to inflammatory cues and in turn regulate extracellular matrix, angiogenesis, and tumor permissiveness. Hydroxysafflor yellow A has been shown to upregulate miR-29a-3p in stellate-cell-derived exosomes and suppress extracellular matrix-receptor and PI3K/AKT signaling, thereby reducing angiogenesis in fibrosis-related HCC [44].

LSECs function as gatekeepers of hepatic immune trafficking and become active inflammatory participants in MASH by responding to IL-1β and generating chemotactic gradients [14]. Hepatic progenitor cells also contribute to tumor-promoting stromal remodeling; bile-acid stress can redirect these cells toward cancer-associated fibroblast-like phenotypes via S1PR2 [22]. Endothelial circadian-regulatory programs have additionally been linked to adverse prognosis and altered immune interactions in HCC [45].

## Gut-liver axis: microbiota dysbiosis and systemic/hepatic inflammation

The portal circulation makes the liver uniquely vulnerable to intestinal barrier failure and microbial translocation. As a result, the gut-liver axis is increasingly viewed as an upstream regulator of chronic hepatic inflammation and a potential source of biomarkers and therapeutic targets.

### *Gut microbiota dysbiosis, barrier disruption, and pathogen-associated molecular pattern translocation*

In chronic liver disease, loss of epithelial tight-junction integrity permits bacterial products such as lipopolysaccharide to enter the portal circulation, where they activate pattern-recognition receptors including TLR4 on Kupffer cells and other myeloid populations. Microbiome studies have identified recurring compositional shifts across the spectrum of hepatitis, cirrhosis, and HCC; for example, reduced Ruminococcaceae/Lachnospiraceae and enrichment of Enterococcaceae, Enterobacteriaceae, Streptococcus, and Veillonella have been associated with HCC-related states [46]. Pathobionts such as Fusobacterium nucleatum, Helicobacter pylori, and Enterococcus faecalis may contribute through barrier disruption, genotoxicity, altered bile-acid signaling, and inflammatory pathway activation [47].

### *Regulatory effects of microbial metabolites*

Short-chain fatty acids generally support epithelial integrity and anti-inflammatory signaling, whereas trimethylamine N-oxide and dysregulated secondary bile-acid pools have been linked to oxidative stress, insulin resistance, and carcinogenic signaling [27,48]. These metabolites provide plausible mechanistic bridges between diet, microbiome configuration, and liver cancer risk.

### *Potential strategies for targeting the gut microbiota*

Preclinical strategies include probiotics, prebiotics, fecal microbiota transplantation, bacterium-directed interventions, and microbiota-remodeling nanocarriers [27,47]. Nevertheless, most approaches remain exploratory, and few have progressed to standardized clinical protocols in HCC.

### *Translational perspective: from association to clinically usable diagnostics*

A major unresolved issue is causality versus association. Many human microbiome studies in HCC are cross-sectional and cannot easily distinguish whether dysbiosis is a driver, a consequence of cirrhosis/HCC, or simply a correlate of confounders such as proton-pump inhibitors, antibiotics, diet, or portal hypertension. For translation, candidate microbiome biomarkers must proceed through analytical validation, external cohort replication, and demonstration of incremental value over existing clinical models. Standardized sampling, prespecified classifier thresholds, and etiology-aware study design will be essential before gut microbiome signatures can become reliable diagnostic tools.

## Inflammation-related biomarkers and prognostic prediction models

Inflammation-related biomarkers are clinically meaningful only when they move beyond biological plausibility to reproducible prediction, calibration, and implementation. This revised section therefore expands both the marker layer and the methodological considerations underlying model development.

### *Traditional and novel serum inflammatory markers*

C-reactive protein, IL-6, neutrophil-related indices,

and albumin-based inflammation-nutrition markers have long been associated with HCC risk and prognosis. More recent composite indicators show stronger discrimination than single analytes alone. The CALLY index integrates C-reactive protein, albumin, and lymphocyte count, thereby jointly reflecting systemic inflammation, nutritional reserve, and host immunity [49].

The TBA-MLR score combines total bile acid with the monocyte-to-lymphocyte ratio and may identify occult high-risk patients after curative-intent resection, including some individuals considered low risk by conventional staging or alpha-fetoprotein [23]. Circulating hPG80, a Wnt-related peptide secreted by malignant cells, has shown promising diagnostic performance in prospective studies [50]. Cytokine signatures after tissue ablation and serum proteomic panels linked to the TGF-beta pathway likewise suggest that inflammatory biology can be translated into blood-based risk tools [31,51].

### *Nomograms and prediction models based on radiomics, clinical features, and inflammatory parameters*

Nomograms are graphical prediction tools that translate multivariable regression models into individualized probability estimates. Their appropriate use requires rigorous methodology, including candidate-variable selection, handling of collinearity, transparent modeling assumptions, internal and external validation, and clinically interpretable end points [5]. When survival is the outcome, the correct terminology is usually LASSO Cox regression rather than generic "LASSO regression" [4,5].

Recent HCC nomograms illustrate the translational potential of inflammation-informed modeling. Hu et al. developed a large retrospective model for patients receiving PD-1/PD-L1 inhibitors by integrating tumor burden, nutritional indicators, and inflammatory variables selected through LASSO Cox procedures; the model showed good discrimination in validation cohorts [52]. Xu et al. constructed a recurrence-oriented nomogram for initially unresectable HCC after successful conversion therapy, outperforming conventional CNLC and BCLC staging in their dataset [53]. In microvascular invasion-negative HCC, a model combining Ki-67, AFP-L3, and neutrophil-to-lymphocyte ratio improved postoperative recurrence stratification, thereby addressing the lack of dedicated tools for this ostensibly lower-risk subgroup [54].

From a methodological standpoint, model reporting should include at least three domains. First, discrimination—commonly quantified by the concordance index time-dependent area under the curve, or receiver operating characteristic analysis-indicates whether the model can correctly rank patients by risk. Second, calibration curves evaluate agreement between predicted and observed outcomes across risk strata. Third, clinical utility can be explored through decision-curve analysis, risk reclassification, and comparison with existing staging systems. These components are essential because a model with statistically significant predictors may still be poorly calibrated or clinically unhelpful.

Radiomics-based models add another layer by extracting quantitative texture and shape features from ultrasound, CT, or MRI, then integrating them with inflammatory and clinical variables. For real-world deployment, however, radiomics pipelines must contend with scanner heterogeneity, segmentation reproducibility, feature stability, and external-site transportability. Therefore, future HCC nomograms should ideally combine interpretable clinicobiological variables with robust imaging features, and they should undergo prospective, multicenter validation before clinical adoption.

Finally, implementation pathways deserve emphasis. A clinically useful prediction model should define intended use (screening, recurrence surveillance, treatment selection, or toxicity prediction), specify cutoff-based action thresholds, and be deliverable through electronic calculators, radiology reporting systems, or electronic health records. Without these practical steps, even technically strong models rarely change care.

### *Integrated strategies for risk stratification and early diagnosis*

Integrated risk stratification increasingly combines serum biomarkers, imaging, pathology, and clinical variables. The GALAD score, for example, merges sex, age, alpha-fetoprotein, AFP-L3, and PIVKA-II and continues to show utility for HCC detection in selected populations [55]. Artificial intelligence can further support image-based phenotyping, automated lesion characterization, and multimodal fusion of radiomics with laboratory and clinical data [56,57].

In high-risk disease contexts such as MASH, combining intrahepatic immune signatures with routine parameters may refine surveillance strategies [41]. Yet integration should remain etiology aware: biomarkers predicting immunotherapy responsiveness or tumor emergence in viral HCC may not perform equivalently in metabolic HCC, where immune exhaustion, steatotic stress, and T-cell dysfunction can differ qualitatively. This variability should be acknowledged explicitly when proposing generalized models.

### *Translational perspective: mechanism-based biomarkers and development pipeline*

Mechanism-based biomarker development in inflammation-associated HCC can be viewed as a staged pipeline: discovery in mechanistic or omics studies; analytical validation in blood, tissue, or imaging platforms; clinical validation in retrospective and prospective cohorts; and finally assessment of clinical utility. Serum ORC1, hPG80, TGF-β-related proteomic signatures, cytokine panels, and microbiome-derived classifiers are currently positioned at different phases of this pipeline rather than being equally mature [16,31,50,51].

Translational gaps remain substantial. Many biomarkers are derived from single-center datasets, use non-standardized assays, or lack head-to-head comparison against established tools such as alpha-fetoprotein, GALAD, and staging systems. For therapeutic targets, the preclinical-to-clinical pipeline is similarly uneven: some pathways have clear druggable nodes and early translational readouts (for example, COX-2/PGE2, checkpoint signaling, and S1PR2), whereas others remain biologically intriguing but clinically immature (for example, DBI/ACBP or niche-specific macrophage programs). Clarifying developmental phase prevents overstatement and improves the scholarly rigor of translational discussion.

## Therapeutic strategies and challenges targeting inflammation and the immune microenvironment

### *Immune checkpoint inhibitors and management of immune-related adverse events*

The modern systemic-treatment era of HCC was established by the SHARP trial, which demonstrated survival benefit with sorafenib [6], and subsequently broadened by immune checkpoint blockade, including nivolumab in CheckMate 040 [7] and pembrolizumab in KEYNOTE-224 [9]. More recently, immunotherapy-based combinations have reshaped first-line standards [10,11].

Immune checkpoint inhibitors reactivate anti-tumor

T-cell responses but also expose patients to immune-related adverse events (irAEs). Predictive nomograms incorporating tumor burden, nutritional status, and inflammatory variables may improve selection of patients for PD-1/PD-L1-based therapy [39]. However, predictive biomarkers remain inconsistent across etiologies; viral-inflammation-rich tumors may show different immune responsiveness from MASH-driven tumors, an issue that warrants continued prospective study.

Rare but clinically important irAEs have been described in HCC [58,59]. Early identification, multidisciplinary assessment, and guideline-based immunosuppression remain central to safe immunotherapy delivery [60].

### *Immune regulatory effects of local therapies and rationale for combination strategies*

Locoregional therapies do more than debulk tumors; they also reshape inflammatory and immune landscapes by releasing tumor antigens, damage-associated molecular patterns, and cytokines. Radiofrequency ablation can induce COX-2/PGE2-mediated suppression of NK-cell function in residual disease, a mechanism that may be counteracted by celecoxib plus anti-PD-1 therapy [30]. Transarterial chemoembolization induces dynamic changes in myeloid cells, NK cells, CD8-positive T cells, and CTLA-4 expression, indicating that post-treatment immune states may be exploitable for sequencing or combination design [43].

Histotripsy and proton-beam therapy further illustrate that local therapies can serve as immunologic primers rather than purely local interventions [31,61]. The clinical challenge is to identify the optimal timing, patient subset, and immunologic window in which local-systemic combinations are synergistic rather than merely additive.

### *Small-molecule inhibitors and natural products targeting inflammatory circuits*

Pathway-focused small molecules remain attractive because they can modulate defined inflammatory nodes. Examples include S1PR2 inhibition to block bile-acid-driven progenitor-to-fibroblast conversion [22], direct AMPK activation to attenuate steatosis and fibrosis [62], and COX-2 inhibition to reverse PGE2-mediated immune suppression [30].

Natural products are notable for multi-target effects but should be interpreted carefully because mechanistic richness does not automatically translate into clinical efficacy. Pien Tze Huang, Artemisia rupestris, alisol A 24-acetate, and butein all show anti-inflammatory or anti-fibrotic activity in preclinical systems [28,63–65]. The next translational step is not additional descriptive network pharmacology alone, but rigorous pharmacokinetic characterization, target engagement, safety testing, and biomarker-linked early clinical trials.

### *Cell therapy, gene therapy, and nanoparticle delivery platforms*

Next-generation cell therapies aim to overcome the immune paralysis of HCC. NKG2D-directed CAR-macrophages can directly phagocytose tumor cells, promote M1-like inflammatory activation, engage cGAS-STING signaling, and augment T-cell recruitment in preclinical models [66]. Bacterial outer-membrane-vesicle-based neoantigen mRNA delivery and nucleic-acid strategies targeting genetic drivers such as PNPLA3 variants likewise illustrate the breadth of emerging liver-directed immunogenetic therapies [67–69].

Nevertheless, these approaches remain mostly preclinical or early translational. Key barriers include liver-

specific delivery, on-target/off-tumor toxicity, manufacturing complexity, immune-related toxicity, and the need for biomarkers that identify patients most likely to benefit. Their promise is substantial, but their current developmental phase should be stated transparently.

## Conclusion and outlook

Inflammation is the central biological thread linking chronic liver injury to HCC across diverse etiologies. This revised review emphasizes that the inflammatory basis of hepatocarcinogenesis is both convergent and context specific: multiple diseases activate overlapping pathways such as NF-κB and IL-6/STAT3, yet each etiology imprints a distinct immunometabolic microenvironment with implications for surveillance, biomarker selection, and therapy.

Equally important, the field is moving from descriptive inflammation biology toward clinically actionable translation. Serum markers, cytokine panels, radiomics-clinical nomograms, and microbiome-derived signatures are expanding the toolbox for early detection and risk stratification, but only those supported by rigorous validation, calibration, and implementation pathways will influence practice. Therapeutically, progress now spans established systemic agents, checkpoint-based combinations, locoregional-immunologic synergy, pathway-specific inhibitors, and next-generation cellular and nucleic-acid interventions.

Future work should prioritize etiology-stratified biomarker validation, multicenter prospective model testing, standardized translational pipelines, and explicit integration of mechanistic insights with real-world clinical workflows. Through this precision-oriented approach, inflammation-associated HCC may increasingly become a disease that is not only treatable but also more predictable, preventable, and interceptable.

## Acknowledgments

None.

## Author contributions

Xiaoyun Chen and Shan Ji contributed to the conception, design, literature review, manuscript drafting, and critical revision of the manuscript. Both authors read and approved the final manuscript.

## Conflicts of interest

All authors declare no conflicts of interest.

## References

[1] Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002 (420):860-867.

[2] Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008 (454): 436-444.

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

[4] Tibshirani R. Regression shrinkage and selection-via the lasso. J R Stat Soc Series B Stat Methodol. 1996 (58):267-288.

[5] Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. J Clin Oncol. 2008 (26):1364-1370.

[6] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008 (359):378-390.

[7] El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017 (389):2492-2502.

[8] EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018 (69): 182-236.

[9] Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 2018 (19):940-952.

[10] Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 (382):1894-1905.

[11] Bruix J, Chan SL, Galle PR, Rimassa L, Sangro B. Systemic treatment of hepatocellular carcinoma: An EASL position paper. J Hepatol. 2021 (75):960-974.

[12] Zhang M, Xia E, Li C, Ma S, Yang F, Tian S, et al. The heterogeneity of monocyte-derived macrophages in MASH pathogenesis. Cell Commun Signal. 2025 (24):5.

[13] Dywicki J, Buitrago-Molina LE, Baumann AK, Davalos-Misslitz AC, Hendriks CM, Hupa-Breier KL, et al. From model to man: Understanding Tregs' dual role in MASLD. JHEP Rep. 2025 (7): 101619.

[14] Fukumoto K, Hikita H, Saito Y, Makino Y, Soma K, Kato S, et al. Liver Sinusoidal Endothelial Cells Promote Metabolic Dysfunction-associated Steatohepatitis Progression via Interleukin-1R1-mediated Chemokine Production Induced by Macrophage-derived Interleukin-1β. Cell Mol Gastroenterol Hepatol. 2026 (20):101698.

[15] Zhu Q, Gu Y, Gao Y, Zhao X, Zhang L. ATG9A-PLA2G6 axis reprograms phospholipid metabolism to drive metabolic liver disease and hepatocellular carcinoma. Autophagy. 2026 (22):409-426.

[16] Feng YF, Su TM, Hu BB, Wang H, Li QM, Yin QB, et al. Diagnostic performance of serum origin recognition complex subunit 1 protein for hepatitis B virus-related hepatocellular carcinoma. World J Gastroenterol. 2025 (31):112481.

[17] Teng W, Chang TT, Su CW, Xu JH, Hsu CC, Chang YC, et al. The impact of single-nucleotide variants of hepatitis B virus and antiviral on liver cancer in gray zone patients. J Biomed Sci. 2025 (32):101.

[18] Rothhaar P, Arand T, Seong HG, Heuss C, Tulessin M, Wang Z, et al. Highly replicating hepatitis C virus variants emerge in immunosuppressed patients causing severe disease. Nat Commun. 2025 (16):10948.

[19] Caviglia GP, Dileo E, Olivero A, Mengozzi G, Ciancio A, Loglio A, et al. The Medical Impact of Hepatitis D Virus Infection in Natives and Immigrants: The Italian Paradigm. Liver Int. 2025 (45): e70242.

[20] Yang J, Lim J, Kim Y-J, Kim HJ, Choi J. Hepatocellular Carcinoma Risk in Chronic Hepatitis B Patients Treated With Tenofovir Alafenamide or Tenofovir Disoproxil Fumarate. Liver International. 2025 (45):e70357.

[21] Stella L, Cabibbo G, Celsa C, Ciccia R, Sparacino A, Piscaglia F, et al. Hepatitis C Eradication Improves Oncologic and Clinical Outcomes in Patients Treated With Atezolizumab Plus Bevacizumab. Liver Int. 2025 (45):e70362.

[22] Gao L, Lv G, Huang Y, Xue M, Zhang Z, Weng J, et al. Glycochenodeoxycholic acid promotes hepatocarcinogenesis by inducing hepatic progenitor cell differentiation into cancer-associated fibroblasts via sphingosine-1-phosphate receptor 2 signalling. Biomark Res. 2025 (13):157.

[23] Zhao Y, Huang W, Deng X, Li P, Yao S, Yang Y, et al. TBA-MLR score: a metabolic-immune prognostic biomarker for postoperative hepatocellular carcinoma. Front Immunol. 2025 (16): 1628571.

[24] Li L, Li X, Zhang F. The pivotal role of cytokines in liver disease pathogenesis and therapeutic potential. Front Immunol. 2025 (16):1694582.

[25] Dominik N, Simbrunner B, Scheiner B, Schwarz M, Hartl L, Jachs M, et al. Smoking Aggravates Inflammation, Fibrogenesis, Angiogenesis and Cancer Risk in Patients With Cirrhosis. Liver Int. 2025 (45):e70314.

[26] Lytvyak E, Hirschfield G, Shreekumar D, Wong YJ, Montano-Loza AJ. Pathogenesis, Non-Invasive Assessments and Treatment of Hepatic Fibrosis in Autoimmune Liver Diseases. Liver Int. 2025 (45):e70190.

[27] Liu D, Li R, Li M, Liang Y, Wang Z, Sun Y, et al. Colon-Targeted astragalus polysaccharide nanoparticles prevent NAFLD-Driven hepatocarcinogenesis via microbiota remodeling and NF-κB Inhibition. J Exp Clin Cancer Res. 2025 (44):330.

[28] Zhang S, Li J, Ding M, Khan GJ, Abuduaini A, Chang Y, et al. Dual targeting by Artemisia rupestris L. disrupting TLR4/NF-κB signaling and macrophage driven immune evasion in hepatocellular carcinoma. J Ethnopharmacol. 2026 (358):121028.

[29] Groover S, Addison S, Nicks S, Mwangi M, Brooks A, Kaul A, et al. Sex based relative expression of estrogen receptors and tumor necrosis factor-alpha in liver affects hepatitis C virus viral pathogenesis. World J Gastroenterol. 2025 (31): 104277.

[30] Lei Y, Bai Y, Bai X, Sun B, Zhu L, Wu W, et al. COX-2/PGE(2) axis blockade with celecoxib enhances anti-PD-1 efficacy by activating natural killer cells for residual hepatocellular carcinoma after radiofrequency ablation. J Exp Clin Cancer Res. 2025 (44):321.

[31] Chan ACY, Lau VWH, Wong GTC, Chan YW, Man K, Ng LY, et al. Prospective analysis on the outcomes of histotripsy for primary and metastatic liver tumors. Int J Surg. 2026 (112):3287-3296.

[32] Liu Y, Chen L, Liu X, Tao R, Dong R, Wang X, et al. Oroxyloside inhibits liver fibrosis and hepatocarcinogenesis dependent on hepatocyte-specific knockout of Atg5. Phytomedicine. 2025 (145):157053.

[33] Li S, Lambertucci F, Martins I, Pol J, Maiuri MC, Kroemer G. Neutralization of the autophagy-repressive tissue hormone DBI/ACBP (diazepam binding inhibitor, acyl-CoA binding protein) for the treatment of hepatocellular carcinoma. Autophagy. 2025 (21):2301-2303.

[34] Chang C, Wang M, Li J, Qi S, Yu X, Xu J, et al. Targeting NOTCH1-KEAP1 axis retards chronic liver injury and liver cancer progression via regulating stabilization of NRF2. J Exp Clin Cancer Res. 2025 (44):232.

[35] Mantovani A, Sica A, Allavena P, Garlanda C, Locati M. Tumor-associated macrophages and the related myeloid-derived suppressor cells as a paradigm of the diversity of macrophage activation. Hum Immunol. 2009 (70):325-330.

[36] Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P. Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol. 2017 (14):399-416.

[37] Ge W, Ma L, Huang Y, E W, Lai S, Cui B, et al. A Conserved FABP5(high) Macrophage Subset Promotes Fibrosis and Carcinogenesis in Advanced Liver Disease. Liver Int. 2025 (45):e70262.

[38] Chu T, Zhu G, Tang Z, Qu W, Yang R, Pan H, et al. Metabolism archetype cancer cells induce protumor TREM2(+ ) macrophages via oxLDL-mediated metabolic interplay in hepatocellular carcinoma. Nat Commun. 2025 (16):6770.

[39] Meng Z, Qiu X, Chen Z, Lee YT, Zhou L, Lu Y, et al. Myeloid TGF-β signaling shapes liver macrophage heterogeneity and metabolic liver disease pathogenesis. JHEP Rep. 2025 (7):101488.

[40] Pan B, Yu H, Lin Z, Liu M, Liu J, Xu Y, et al. RNASEH2C enhances TRAF3IP1 to degrade RAI14 in lysosomes thus hindering macrophage antigen presentation and advancing liver cancer. Cell Death Dis. 2025 (17):92.

[41] Rodriguez E, Simon P, Dhooge S, Fernandez M, Calafat P, Kurpis M, et al. Hepatic CD4 T Cells Predict Hepatocellular Carcinoma Risk on Metabolic Dysfunction-Associated Steatohepatitis Patients. United European Gastroenterol J. 2026 (14):e70159.

[42] Ajith A, Evraerts J, Bouzin C, Brusa D, Merimi M, Najar M, et al. Progression to fibrosis and hepatocellular carcinoma in DEN CCl(4) liver mice, is associated with macrophage and striking regulatory T cells infiltration. Front Immunol. 2025 (16):1601215.

[43] Schmidt R, Gebauer B, Akbari N, Roderburg C, Torsello GF, Fehrenbach U, et al. Immunologic effects of locoregional therapies for unresectable hepatocellular carcinoma. JHEP Rep. 2025 (7): 101555.

[44] Xue X, Fu K, Zhou M, Li Y, Dai S, Zhang C, et al. Hydroxylsafflower yellow A modulates tumor vascularization in liver cancer through intercellular communication and extracellular matrix-receptor interactions. Phytomedicine. 2025 (148):157455.

[45] Qin H, Wang Y, Yan YF, Liu J, Li YY, Xu YL. Endothelial circadian rhythm genes as prognostic modulators of tumor progression and immune interactions: insights from pan-cancer single-cell RNA sequencing. Int J Surg. 2026 (112):4291-4306.

[46] Sun X, Zhou Z, Chi X, Cheng D, Zhang Y, Xu Y, et al. Featured intestinal microbiota associated with hepatocellular carcinoma in various liver disease states. Front Immunol. 2025 (16):1674838.

[47] Ramesh A, Subbarayan R, Srinivasan D, Balakrishnan R, Shrestha R, Chauhan A. Gut microbiota-mediated oncogenesis in hepatocellular carcinoma: a new avenue for therapeutic intervention. Int J Surg. 2026 (112):4725-4750.

[48] Saha B, Banerjee A, Pathak R, Duttaroy AK, Pathak S. Trimethylamine N-Oxide (TMAO) and cancer risk: Insights into a possible link. Biomed Pharmacother. 2025 (192):118592.

[49] Zhang L, Wang K, E H, Jiang W, Chen C, Zhao K, et al. Integrative prognostic value of the CALLY index in cancer patients undergoing surgical resection. Int J Surg. 2026 (112):4047-4058.

[50] You B, Couraud S, Ceruse P, Badet L, Paparel P, Durand A, et al. Diagnostic value of the wnt target and cancer-associated blood biomarker hPG80: ONCOPRO case-control prospective study. Biomark Res. 2025 (13):91.

[51] Xiang X, Shetty K, Yu H, Mishra B, Wong LL, Zhou XJ, et al. Serum Proteomic Profile Based on the TGF-β Pathway Stratifies Risk of Hepatocellular Carcinoma. Liver Int. 2025 (45):e70325.

[52] Hu S, Xu M, Li S, Chen W, Peng Z. LASSO-empowered nomogram integrating nutritional-inflammatory-tumor characteristics predicts immunotherapy outcomes in advanced HCC: Large retrospective cohort. Front Immunol. 2025 (16): 1626940.

[53] Xu C, Tang Z, Wei M, Liu D, Pang Q, Huang B, et al. Predicting recurrence and recurrence-free survival in initially unresectable hepatocellular carcinoma: a novel nomogram for patients undergoing conversion hepatectomy with lenvatinib, PD-1 inhibitor, and interventional therapy. Front Immunol. 2025 (16):1602327.

[54] Ye Q, Yu Y, Pang S, Zhao D, Li D, Ma Y, et al. Nomogram for predicting postoperative recurrence in patients with microvascular invasion-negative hepatocellular carcinoma: development and validation. Front Immunol. 2025 (16):1614392.

[55] Villa E, Donghia R, Coletta S, Bonfiglio C, Critelli RM, Ancona A, et al. Insights into the GALAD score: A new optimal cut-off for hepatocellular carcinoma. World J Gastroenterol. 2025 (31): 111727.

[56] Ren SQ, Chen JM, Cai C. Translational artificial intelligence in gastrointestinal and hepatic disorders: Advancing intelligent clinical decision-making for diagnosis, treatment, and prognosis. World J Gastroenterol. 2025 (31):110742.

(Continued on page 69)