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REVIEW

TRIM21 as a Context-Dependent Regulator in Hepatocellular Carcinoma: Integrating Etiological Landscapes (HBV/NASH) with Core Tumor Progression Mechanisms

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Abstract: Tripartite motif-containing protein 21 (TRIM21), an E3 ubiquitin ligase of the TRIM superfamily, modulates critical cellular processes including ubiquitination, autophagy, and oxidative stress response. Accumulating evidence highlights its context-dependent regulatory roles in hepatocellular carcinoma (HCC)—the most prevalent primary liver malignancy with high mortality and limited therapeutic efficacy. This review systematically summarizes the core mechanisms by which TRIM21 orchestrates HCC progression: ① Autophagy regulation: TRIM21 modulates HCC autophagy via multiple axes, including CCR4-NOT complex (TNKS1BP1/CNOT4)-mediated substrate ubiquitination, ATG14-dependent autophagosome initiation, and RETREG1-driven reticulophagy, with context-dependent effects on tumor proliferation. ② Drug resistance: TRIM21 enhances oxaliplatin sensitivity by ubiquitinating and degrading G6PD (the rate-limiting enzyme of the pentose phosphate pathway), while its role in sorafenib resistance involves dual pathways—the MST1/YAP axis and the ApoE/cholesterol/PI3K-AKT cascade. ③ Metastasis suppression: TRIM21 restricts HCC invasion and metastasis by ubiquitinating key oncoproteins, preserving epithelial integrity and inhibiting mesenchymal transition. ④ Reactive oxygen species (ROS) balance: TRIM21 regulates oxidative stress in HCC via the SQSTM1/p62-Keap1-NRF2 axis, coordinating with HIF1α to modulate antioxidant responses and tumor cell survival. Additionally, we discuss the regulatory significance of TRIM21 in HCC associated with hepatitis B virus (HBV) infection (via HBx/DNA polymerase ubiquitination) and nonalcoholic steatohepatitis (NASH) (via suppressing lipogenic enzymes to reduce steatosis-driven carcinogenesis). This review provides a theoretical basis for TRIM21 as a potential diagnostic marker and therapeutic target for HCC.

Keywords: TRIM21, hepatocellular carcinoma, HCC, autophagy, drug resistance, reactive oxygen species, ROS, clinical target

Introduction

Hepatocellular carcinoma (HCC) accounts for 75–80% of primary liver malignancies, ranking sixth in global cancer incidence and third in cancer-related mortality.[1] Despite advances in surgical resection, targeted therapy, and immunotherapy, HCC patients still face formidable challenges—chemoresistance, high metastatic propensity, and post-treatment recurrence—resulting in a 5-year survival rate of <15%.[2] Clarifying the molecular mechanisms underlying HCC progression and identifying novel therapeutic targets are urgent needs for improving clinical outcomes.

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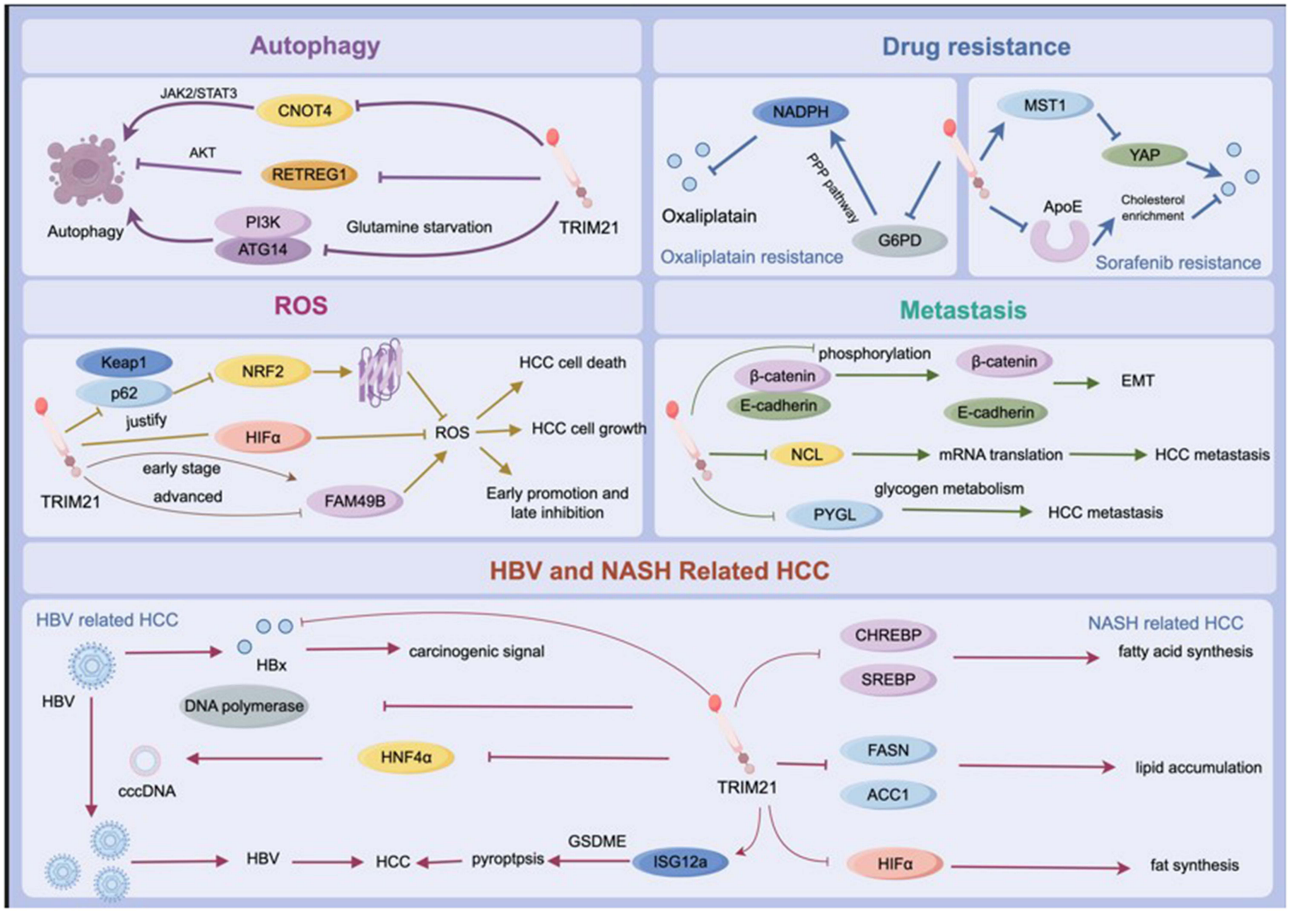
Graphical Abstract



HBV infection (affecting ~300 million people worldwide) and NASH (with a global prevalence of ~5%) are major etiological factors for HCC.[3,4] TRIM21 not only modulates HBV replication via ubiquitination of viral components (for example, HBx, DNA polymerase) but also suppresses NASH-related steatosis by degrading lipogenic enzymes—thereby indirectly influencing HCC initiation.[5,6] Recent advances have begun to delineate the pleiotropic nature of TRIM21, revealing its involvement in proliferation of HCC cells as well as triglyceride metabolism[7] and metabolic reprogramming within the tumor microenvironment.[8] TRIM21, as a downstream effector, also mediates the impact of the N6-methyladenosine epitranscriptome on non-alcoholic hepatocellular carcinoma.[9]

While these findings highlight TRIM21's multifaceted roles in HCC, current knowledge remains fragmented across disparate etiological and mechanistic contexts. A systematic synthesis that unifies these insights is lacking, impeding a holistic understanding of its pathophysiological relevance. A key perspective in oncology highlights that dissecting the context-dependent regulatory networks of pleiotropic molecules like TRIM21 is essential for clinical translation, since fragmented single-target studies often fail to capture the complexity of tumor progression.[9] This underscores the need to integrate discrete findings into a coherent etiological and mechanistic framework. Nevertheless, several important gaps remain in current research: there is no unified regulatory framework explaining TRIM21's dual tumor-suppressive or oncogenic roles in HCC; its etiology-specific regulatory differences between HBV-and NASH-driven HCC are still unclear; and clinical evidence supporting its utility as a diagnostic or therapeutic target remains scarce. To address these gaps, this review pursues three main aims: to systematically integrate TRIM21's ubiquitination-mediated mechanisms in HCC progression (including cell proliferation, invasion, autophagy,

and metabolic reprogramming); to dissect its context-dependent roles in HBV-and NASH-related HCC, emphasizing etiology-specific networks; and to evaluate its potential as a diagnostic and therapeutic target. By focusing on these aims, this review will concentrate on the ubiquitination-dependent mechanisms and etiology-driven regulatory networks of TRIM21 in HCC progression. It will not extend to a comparative analysis with other TRIM family proteins or a detailed discussion of its roles in other cancer types, ensuring a focused examination of its context-dependent duality within the HCC landscape.

Given the dismal prognosis of HCC patients due to chemoresistance and recurrence, deciphering TRIM21's context-dependent regulation will provide crucial insights for developing personalized therapeutic strategies—such as context-specific TRIM21 agonists/antagonists or combination therapies targeting its downstream pathways—to improve treatment efficacy and long-term survival. Ultimately, this work aims to bridge the gap between basic research and clinical translation, laying a foundation for advancing HCC precision medicine.

TRIM21 in the Core Mechanisms of HCC Progression

Autophagy Regulation: A Double-Edged Sword in HCC

Autophagy dysregulation is a hallmark of HCC, and TRIM21 modulates HCC autophagy via multiple context-dependent mechanisms, directly influencing tumor cell survival and proliferation.

First, TRIM21 antagonizes tumor-suppressive autophagy by targeting the CCR4-NOT complex. It mediates K48/K6-linked polyubiquitination of CNOT4—a key component of the complex—and promotes its proteasomal degradation. CNOT4 normally induces cytoprotective autophagy via the JAK2/STAT3 pathway; thus, TRIM21-dependent CNOT4 ablation attenuates autophagy, accelerates HCC cell proliferation, and enhances migratory capacity.[10] This process is further regulated by TNKS1BP1, which facilitates TRIM21-mediated CNOT4 ubiquitination, forming a "TNKS1BP1-TRIM21-CNOT4" axis that drives HCC progression.

Second, TRIM21 inhibits autophagosome formation under glutamine starvation—a common microenvironmental feature of advanced HCC. Glutamine scarcity upregulates ER-localized TRIM21, which polyubiquitinates ATG14 (a critical initiator of autophagosome assembly).[11] This modification impairs ATG14's ability to interact with the PI3K complex, blocking autophagosome maturation and enabling HCC cells to adapt to nutrient stress.[11]

Third, TRIM21 targets reticulophagy regulator 1 (RETREG1) to suppress oncogenic autophagy. RETREG1 overexpression in HCC activates the AKT pathway to promote tumorigenesis; TRIM21 specifically catalyzes K247/K252-linked ubiquitination of RETREG1, triggering its degradation.[12] Under ER stress, upregulated TRIM21 further impairs RETREG1-mediated ER homeostasis restoration, limiting HCC cell survival.[12] Collectively, TRIM21 modulates HCC autophagy via distinct axes, with effects dependent on nutrient availability and ER stress status.

Drug Resistance: Modulating Chemotherapeutic Efficacy in HCC

TRIM21 plays a critical role in HCC drug resistance, with pathway-specific effects on oxaliplatin and sorafenib—the two most commonly used chemotherapeutics.

Oxaliplatin Resistance: Targeting the Pentose Phosphate Pathway (PPP)

Oxaliplatin exerts anti-tumor effects by inducing DNA damage, but HCC cells often develop resistance via enhancing antioxidant defense and nucleotide synthesis—processes dependent on the PPP. TRIM21 enhances oxaliplatin sensitivity by ubiquitinating and degrading G6PD, the rate-limiting enzyme of the PPP.[13] G6PD deficiency reduces NADPH production (a key antioxidant cofactor) and depletes nucleotide precursors, impairing HCC cells' ability to repair DNA damage and scavenge reactive oxygen species (ROS).[13,14] This mechanism provides a potential strategy for reversing oxaliplatin resistance by targeting the TRIM21-G6PD axis.

Sorafenib Resistance: Dual Pathways Involving YAP and Cholesterol Metabolism

MST1/YAP axis: TRIM21 mediates ubiquitination and degradation of macrophage stimulating 1(MST1), relieving MST1-dependent inhibition of Yes-associated protein (YAP, a key driver of sorafenib resistance).[15] Activated YAP promotes HCC cell survival and proliferation, reducing sorafenib efficacy.[15,16]

ApoE/cholesterol/PI3K-AKT cascade: Conversely, TRIM21 ubiquitinates Apolipoprotein E (ApoE), reducing intracellular cholesterol accumulation.[14] High cholesterol levels activate the PI3K-AKT pathway to enhance sorafenib resistance; thus, TRIM21-dependent ApoE degradation sensitizes HCC cells to sorafenib.[17]

The dual role of TRIM21 in sorafenib resistance may be attributed to the heterogeneity of HCC—for example, MST1 expression is lower in poorly differentiated HCC, while ApoE is highly expressed in lipid-rich tumors—highlighting the need for personalized targeting of TRIM21.

Metastasis Suppression: Preserving Epithelial Integrity and Inhibiting Oncoprotein Activity

HCC metastasis is the leading cause of treatment failure, and TRIM21 restricts this process by ubiquitinating key oncoproteins involved in invasion and epithelial-mesenchymal transition (EMT):

PYGL: TRIM21 ubiquitinates glycogen phosphorylase L (PYGL), an enzyme that promotes HCC invasion by regulating glycogen metabolism.[15] PYGL deficiency reduces glucose availability for tumor cell migration, and TRIM21 overexpression correlates with reduced metastatic potential in HCC cell lines.[18]

β-catenin: TRIM21 inhibits β-catenin phosphorylation and promotes its ubiquitin-dependent degradation.[19] Phosphorylated β-catenin destabilizes E-cadherin/β-catenin complexes, weakening intercellular adhesion and enabling EMT.[19–21] By preserving β-catenin stability, TRIM21 maintains epithelial integrity and suppresses HCC invasion.

Nucleolin (NCL): TRIM21 mediates ubiquitination of NCL—a multifunctional oncoprotein that enhances HCC metastasis by regulating mRNA translation.[22] NCL degradation by TRIM21 reduces the expression of metastasis-related genes (for example, MMP9), limiting HCC cell motility.[22] Furthermore, the ubiquitination of NCL by TRIM21 is potentiated by the silencing of has_circ_0006646, which otherwise competes with TRIM21 for NCL binding, thereby uncovering a novel circRNA-dependent mechanism that fine-tunes TRIM21's metastatic suppressor activity.[22]

In vitro studies confirm that TRIM21 knockdown enhances HCC cell proliferation, clonogenicity, and apoptotic resistance—further supporting its role as a metastasis suppressor.[18,23]

ROS Balance: Coordinating Antioxidant Responses to Modulate Tumor Survival

Oxidative stress is a double-edged sword in HCC: moderate ROS promotes carcinogenesis, while excessive ROS induces tumor cell death. TRIM21 regulates HCC ROS levels via the SQSTM1/p62-Keap1-NRF2 axis and coordination with HIF1α.

SQSTM1/p62-Keap1-NRF2: TRIM21 ubiquitinates SQSTM1/p62 (a selective autophagy receptor), preventing p62 from sequestering Kelch-like ECH-associated protein 1 (Keap1, a repressor of NRF2).[24,25] Unsequestered Keap1 inhibits Nuclear factor erythroid 2-related factor 2(NRF2)—a master regulator of antioxidant genes—reducing the expression of ROS-scavenging enzymes (for example, HO-1) and promoting oxidative stress-induced HCC cell death.[24,26] The interplay between TRIM21 and ROS places it at the nexus of critical HCC pathways, with direct crosstalk to the PI3K/AKT signaling axis—a well-established regulator of liver injury and carcinogenesis that is intrinsically linked to ROS dynamics.[27] For instance, the PI3K/AKT signaling axis, a well-established regulator of liver injury and carcinogenesis, is intrinsically linked to ROS dynamics, and its modulation can influence therapeutic responses.[27] Specifically, ROS imbalance, a key pathogenic mechanism in HCC driven by dysregulated mitophagy, aberrant PI3K/AKT signaling, and enhanced lipid peroxidation,[28,29] can be modulated by TRIM21's regulation of the p62-Keap1-NRF2 axis, creating a reciprocal regulatory loop that influences therapeutic responses.[27] Furthermore, observational evidence from extensive genomic and high-throughput sequencing data supports this interplay, confirming an association between TRIM21 expression, PI3K/AKT pathway activation, and ROS-related hepatocarcinogenesis mechanisms.[30]

HIF1α coordination: Under hypoxic conditions (common in HCC tumors), TRIM21 interacts with HIF1α to balance ROS levels.[24] HIF1α normally upregulates glycolysis to reduce ROS production; TRIM21 modulates HIF1α activity by regulating its ubiquitination, ensuring that ROS levels remain within a range that supports tumor survival but avoids excessive damage.[24]

Additionally, TRIM21 regulates ROS via FAM49B: in early HCC, TRIM21-dependent FAM49B upregulation increases ROS production to disrupt hepatocyte homeostasis, while in established HCC, FAM49B inhibition by TRIM21 reduces ROS to suppress tumor growth.[31] This context-dependent role reflects TRIM21's adaptability to different HCC stages.

TRIM21 in HBV/NASH-Related HCC

HBV-Related HCC: Balancing Viral Suppression and Hepatocyte Injury

Chronic HBV infection is the leading cause of HCC, and TRIM21 modulates HBV-related HCC via dual effects on viral replication and hepatocyte damage:

Viral suppression: TRIM21 inhibits HBV replication by ubiquitinating viral components: ① It mediates K48-linked polyubiquitination of HBx (a viral oncoprotein), promoting its proteasomal degradation to reduce HBV-induced oncogenic signaling.[5] ② TRIM21 ubiquitinates HBV DNA polymerase at conserved Lys260/Lys283 residues, impairing viral DNA synthesis.[32] ③ It enhances innate immunity by catalyzing K27-linked polyubiquitination of Mitochondrial Antiviral Signaling Protein (MAVS), amplifying interferon-mediated antiviral responses.[32] ④ Furthermore, TRIM21 targets host hepatocyte nuclear factor 4α (HNF4α) for ubiquitin-mediated degradation, thereby suppressing HBV cccDNA transcription and replication, which unveils a novel host-directed antiviral mechanism of TRIM21.[33]

Hepatocyte injury: Paradoxically, TRIM21 exacerbates HBV-related liver injury by promoting hepatocyte pyroptosis. It scaffolds the interaction between ISG12a (an interferon-stimulated gene) and mitochondria, inducing ISG12a's mitochondrial translocation via ubiquitination.[34] This complex triggers caspase-3-dependent cleavage of Gasdermin E (GSDME), releasing its pore-forming N-terminal domain to induce pyroptosis.[34] Persistent pyroptosis promotes chronic inflammation, a key driver of HBV-related HCC.[34,35]

Notably, TRIM21 interacts with the PD-1/PD-L1 axis in HBV-related HCC: it modulates AKT/β-catenin signaling to upregulate PD-L1 expression, promoting immune evasion.[35] Conversely, the interferon-stimulated gene ISG12a has been shown to antagonize this pathway by promoting TRIM21 degradation, thereby disrupting the TRIM21/AKT/β-catenin /PD-L1 axis and enhancing the antitumor activity of natural killer (NK) cells against HBV-HCC.[35] Targeting TRIM21 may therefore simultaneously inhibit HBV replication and restore anti-tumor immunity.

NASH-Related HCC: Suppressing Steatosis-Driven Carcinogenesis

NASH progresses to HCC via steatosis, inflammation, and fibrosis, and TRIM21 inhibits NASH-related HCC by targeting lipogenic pathways:

TRIM21 mediates ubiquitin-dependent degradation of key lipogenic enzymes and transcription factors, including ChREBP, SREBP1, A1CF, FASN, and ACC1.[6] ChREBP and SREBP1 are master regulators of de novo lipogenesis; their degradation by TRIM21 reduces fatty acid synthesis, while degradation of FASN (fatty acid synthase) and ACC1 (acetyl-CoA carboxylase 1) further inhibits lipid accumulation.[6] A1CF (a splicing regulator) normally promotes lipogenic gene expression; TRIM21-dependent A1CF degradation suppresses this effect.[6]

By reducing hepatic steatosis, TRIM21 alleviates NASH-related inflammation and fibrosis—key precursors of HCC. In NASH mouse models, TRIM21 overexpression reduces lipid accumulation by ~40% and decreases HCC incidence by ~35%,[6] highlighting its potential as a NASH-related HCC chemopreventive target.

Discussion

The accumulating evidence solidifies TRIM21 as a pivotal, yet complex, regulator in HCC pathogenesis. Rather than exhibiting a purely tumor-promoting or suppressive function, TRIM21 operates as a "context-dependent signaling hub", whose output is decisively shaped by the tumor microenvironment (TME), disease etiology, and therapeutic pressures. This review synthesizes how TRIM21 orchestrates HCC progression through core mechanisms—autophagy, drug resistance, metastasis, and ROS homeostasis—and underscores its potential as a therapeutic target. The central challenge and opportunity lie in deciphering the rules governing its functional duality.

The Paradigm of Context-Dependency: TRIM21 as a Microenvironment Sensor

To resolve the apparent contradictions and establish a predictive framework for TRIM21's function, we propose a classification based on two cardinal criteria: Tumor Microenvironment (TME) Cues and Disease Ontogeny and Stage.

TME Cues (Metabolic and Nutrient Sensing): TRIM21 acts as a metabolic sensor, with its output dictated by local nutrient availability and metabolic stress. Under glutamine scarcity, its ER-localized upregulation and subsequent inhibition of autophagosome formation via ATG14 ubiquitination represent an adaptive survival strategy.[11] Conversely, in lipid-rich environments characteristic of NASH, TRIM21 suppresses lipogenesis by degrading key enzymes, thereby antagonizing steatosis-driven tumorigenesis.[6]

Disease Ontogeny and Stage: The functional impact of TRIM21 is inextricably linked to the etiological background and the temporal stage of hepatocarcino genesis. Its regulation of ROS exhibits a stage-specific switch: facilitating redox homeostasis disruption in early transformation versus protecting established tumors from lethal oxidative damage.[24,31] Also, in HBV-related HCC, its role is bifurcated, encompassing both antiviral defense and the promotion of pyroptotic injury.[5,34] Notably, recent studies have further delineated the molecular basis of this duality: TRIM21's antiviral activity is mediated by ubiquitinating viral HBx protein for proteasomal degradation, while its pro-carcinogenic effect is driven by STAT3 pathway activation—induced by interferon signaling in HBV-infected hepatocytes—which upregulates pro-inflammatory cytokines to fuel chronic inflammation.[36] This finding highlights that etiological context-specific signaling crosstalk refines TRIM21's functional output, reinforcing the necessity of our classification framework.

This dichotomous classification provides a foundational schema for deconvoluting TRIM21's context-dependency, emphasizing that its role cannot be defined in absolute terms but must be interpreted through the prism of specific pathological contexts.

Clinical Translation: From Mechanism to Biomarker and Therapeutic Target

The intricate involvement of TRIM21 in key HCC pathways positions it as a attractive candidate for clinical translation.

Diagnostic and Prognostic Biomarker: Clinical evidence suggests TRIM21's prognostic value is context-dependent. Studies associate high TRIM21 levels with advanced TNM stage and inferior sorafenib response, implicating it in aggressive disease.[15,17] This is supported by cohort data showing that TRIM21 expression is significantly elevated in HCC tissues compared to adjacent non-tumor tissues, and its high expression correlates with advanced disease stage and poorer overall survival (OS) and progression-free survival (PFS) in patients. Furthermore, its regulatory network holds diagnostic promise; for instance, the oncogenic circRNA has_circ_0006646, which inhibits TRIM21-mediated ubiquitination of NCL, is upregulated in HCC tissues and correlates with poor prognosis.[22] Notably, circ0006646 expression is also associated with higher TNM staging and serves as an independent risk factor for survival in HCC cohorts. Validating TRIM21 and its interactors as stratified biomarkers in defined etiological contexts remains a critical future direction.

Therapeutic Targeting Strategies: Targeting TRIM21 requires precision. Broad inhibition or activation is unlikely to be beneficial. Instead, several sophisticated strategies emerge:

1. Exploiting Synthetic Lethality: In oxaliplatin-resistant HCC, pharmacological activation of TRIM21 could degrade G6PD and cripple the PPP, effectively re-sensitizing tumors to chemotherapy.[13] Notably, G6PD is also a core component of the PPAR signaling pathway-related prognostic model, whose risk stratification can assist in identifying chemotherapy-sensitive subgroups to synergize with TRIM21-targeted strategies.[37]

2. Pathway-Specific Intervention: For tumors relying on the TRIM21-MST1-YAP axis for sorafenib resistance, direct YAP inhibitors or MST1 mimetics could be deployed to bypass TRIM21's effect.[15] Alternatively, targeting upstream regulators of TRIM21 stability is a viable approach. For example, the natural compound Sophoricoside (Sop) has been identified as a potential inhibitor of METTL21A, which methylates and stabilizes BAG3, thereby inhibiting TRIM21-mediated ubiquitination of BAG3 and suppressing HCC progression.[38]

3. Etiology-Specific Modulation: In HBV-related HCC, the ideal intervention would harness TRIM21's antiviral activity (for example, by enhancing its E3 ligase activity toward viral proteins) while mitigating its pro-pyroptotic function (for example, using caspase-3 or GSDME inhibitors).[34] Notably, the interferon-stimulated gene ISG12a has been shown to interact with TRIM21, blocking the TRIM21/AKT/β-catenin/PD-L1 axis and enhancing the antitumor

activity of NK cells, presenting a novel immunotherapeutic strategy for HBV-HCC.[35] Supporting this notion, a preclinical study confirmed that TRIM21 knockdown sensitizes HBV-HCC to anti-PD-1 therapy by reducing tumor cell PD-L1 expression and enhancing CD8+ T cell infiltration, providing direct evidence for this combination strategy.[36] In NASH-driven HCC, TRIM21 activators could serve as a chemopreventive strategy by reducing hepatic steatosis and subsequent inflammation.[6]

Future Perspectives and Concluding Remarks

Despite significant progress, critical questions remain. A central unresolved issue is the upstream regulation of TRIM21 itself. What specific signals control its expression, ligase activity, and substrate specificity in different contexts? For instance, the deubiquitinase OTUB1 has been identified as a critical upstream regulator that antagonizes TRIM21-mediated ubiquitination and degradation of SPHK1, thereby promoting HCC progression.[39] Furthermore, its role in HCC stemness and the tumor immune microenvironment is largely uncharted. Does TRIM21 modulate cancer stem cell self-renewal through autophagy or ROS pathways? Given its known interaction with PD-L1,[35] does it influence the response to immune checkpoint inhibitors? The efficacy of emerging dual-immune checkpoint inhibitor therapies (for example, tremelimumab + durvalumab) in advanced HCC may be influenced by such regulatory networks, warranting investigation into whether TRIM21 status can predict immunotherapy response.[40,41]

In conclusion, TRIM21 emerges not as a conventional oncogene or tumor suppressor, but as a "master regulator of cellular adaptability" in HCC. Its ability to fine-tune critical processes like autophagy, metabolism, and stress response makes it a central node in HCC progression and therapy resistance. This review integrates TRIM21's context-dependent regulatory roles in HCC with etiological landscapes (HBV/NASH) and core progression mechanisms, providing a unified framework for understanding its dual functions. The findings underscore TRIM21's potential as a subgroup-specific biomarker and therapeutic target, offering new insights for personalized HCC management. Future research must focus on defining these contextual cues, and TRIM21-focused interventions hold immense promise for improving patient outcomes in hepatocellular carcinoma.

Data Sharing Statement

The data used and/or analyzed during the current study are available from the corresponding author (Yanru Chen or Ruihong Zhang) upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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