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Review Article

CircRNAs in hepatocellular carcinoma: emerging roles in protein homeostasis, ferroptosis regulation, and tumor-immune communication

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Abstract: Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide, largely due to the pervasive emergence of resistance to targeted therapies and immune checkpoint blockade. Although circular RNAs (circRNAs) have been increasingly implicated in HCC progression, their roles are often described as isolated competing endogenous RNAs, obscuring their broader functional diversity. In this review, we summarize studies showing that selected circRNAs modulate protein homeostasis, ferroptosis susceptibility, and tumor-immune communication in HCC, and discuss their potential mechanistic relationships. Specifically, circRNA-SORE, CircPIAS1, and CircTTC13 have been linked to protein stabilization or ferroptosis regulation in experimental settings, whereas tumor-derived exosomal circCCAR1 has been shown to impair $CD8^+$ T-cell function and reduce responsiveness to anti-PD-1 treatment in preclinical HCC models. In contrast, effects of other exosomal circRNAs on metastasis and angiogenesis do not, by themselves, establish checkpoint resistance. However, evidence that these mechanisms form a coordinated circRNA-centered network across models or patient cohorts remains limited. We also discuss their potential as candidate biomarkers and therapeutic targets, emphasizing the need for integrated functional studies and prospective clinical validation. This review therefore offers a hypothesis-generating synthesis of circRNA-associated mechanisms rather than an established systems-level model of therapeutic resistance and immune escape in HCC.

Keywords: Circular RNA, hepatocellular carcinoma, ferroptosis, immunotherapy resistance, protein homeostasis

Introduction

Hepatocellular carcinoma (HCC) is a highly lethal malignancy characterized by profound molecular heterogeneity and limited therapeutic options [1, 2]. Over the past decade, systemic treatment for advanced HCC has undergone a paradigm shift from single-agent tyrosine kinase inhibitors (TKIs) toward immune checkpoint inhibitor (ICI)-based regimens and rational combination strategies [3-8]. Agents such as sorafenib and lenvatinib have long served as first-line therapies, while immune checkpoint blockade targeting the PD-1/PD-L1 axis has expanded the therapeutic landscape [9]. More recently, combinations of TKIs with ICIs have demonstrated improved response rates and survival benefits in selected patient populations.

Despite these advances, acquired resistance remains nearly universal. Most patients who initially respond to sorafenib or lenvatinib ultimately experience disease progression, and only a subset derives durable benefit from immune checkpoint blockade. Importantly, resistance to TKIs and failure of immunotherapy frequently coexist rather than occur independently. Tumors that acquire resistance to targeted therapy often exhibit a profoundly immunosuppressive tumor microenvironment (TME), characterized by dysfunctional cytotoxic T lymphocytes, impaired antigen presentation, and enrichment of inhibitory signaling pathways [10-15]. Conversely, immune-refractory tumors frequently display intrinsic resistance programs that blunt the cytotoxic stress imposed by targeted agents. Emerging evidence suggests that classical explanations

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based solely on genetic mutations or pathway reactivation are insufficient to account for this dual resistance phenotype. Instead, cell fate control mechanisms, particularly ferroptosis, and immune regulatory layers, such as $CD8^+$ T-cell exhaustion and resistance to anti-PD-1 therapy, have gained increasing attention as unifying explanatory frameworks [16-21]. Ferroptosis - a form of iron-dependent, lipid peroxidation-driven cell death - has been implicated as a critical vulnerability exploited by TKIs such as sorafenib. However, HCC cells frequently evolve strategies to suppress ferroptotic signaling, thereby blunting therapeutic efficacy. In parallel, sustained immune pressure drives adaptive immune evasion programs, culminating in T-cell dysfunction and immunotherapy failure [22-24]. These observations underscore the need for an integrative framework that can simultaneously explain therapy resistance, altered cell death thresholds, and immune escape.

Circular RNAs (circRNAs) have emerged as a distinct and functionally versatile class of noncoding RNAs generated through back-splicing events. Unlike linear RNAs, circRNAs lack free 5' and 3' ends, rendering them resistant to exonuclease-mediated degradation and conferring exceptional stability. This intrinsic stability, together with their often cell-type- and context-specific expression patterns, positions circRNAs as ideal candidates for sustaining long-term adaptive states in cancer cells under therapeutic and immune pressure. Early studies of circRNAs in cancer predominantly focused on their role as competing endogenous RNAs (ceRNAs), acting as microRNA sponges to modulate downstream gene expression. While this mechanism remains important, it has become increasingly clear that a single-mechanism, single-circRNA view is insufficient to capture the biological complexity observed in HCC [25-29]. Accumulating evidence demonstrates that circRNAs can interact directly with RNA-binding proteins (RBPs), modulate protein stability and localization, influence phase separation and translational control, and even function as transferable signaling molecules via extracellular vesicles such as exosomes [30-33]. These properties allow circRNAs to operate across multiple regulatory layers simultaneously. At the intracellular level, circRNAs can reshape proteostasis networks by stabilizing oncogenic RBPs or shielding key proteins from ubiquitin-mediated degradation. At the level of cell fate determination, circRNAs can tune the threshold for ferroptosis by regulating iron metabolism, antioxidant systems, and lipid peroxidation pathways. Beyond the tumor cell itself, circRNAs packaged into exosomes enable intercellular communication, transmitting resistance and immune-suppressive signals to immune cells within the TME. Together, these features argue strongly for conceptualizing circRNAs not as isolated effectors, but as nodes within interconnected regulatory networks that integrate intrinsic tumor biology with extrinsic immune cues.

In this review, we adopt a network-centric perspective to synthesize recent advances in circular RNA (circRNA) research in hepatocellular carcinoma (HCC). Rather than presenting an exhaustive catalog of circRNAs reported to be dysregulated in HCC, we focus on mechanistic principles that are broadly informative and potentially translatable across therapeutic contexts. Specifically, we organize the current literature around three interrelated axes. First, protein stability control, in which circRNAs function as molecular scaffolds or decoys to stabilize oncogenic proteins and RNA-binding proteins, thereby sustaining malignant signaling and drug-resistant states. Second, ferroptosis evasion, whereby circRNA-mediated regulation of iron metabolism, antioxidant defenses, and system Xc^- activity elevates the threshold for lipid peroxidation-induced cell death. Third, tumor-immune communication, for which exosomal circCCAR1 provides a specific experimental example of circRNA-associated $CD8^+$ T-cell dysfunction and reduced responsiveness to anti-PD-1 treatment. By examining these three axes together, we aim to identify potential mechanistic connections among circRNA-mediated protein regulation, ferroptosis susceptibility, and immune escape, without assuming that they constitute a single experimentally validated network. This framework provides a hypothesis-generating perspective for comparing findings across different therapeutic contexts and identifying potential vulnerabilities that require further experimental validation. Importantly, we distinguish between experimentally established circRNA-specific mechanisms, potential functional associations inferred from independent studies, and con-

ceptual interactions proposed in this review. The latter should be regarded as hypotheses rather than validated components of a unified regulatory network. Ultimately, elucidating circRNA-centered regulatory networks may open new avenues for biomarker development and therapeutic intervention in HCC [34].

The biogenesis layer: how circRNA landscapes are rewired in hepatocellular carcinoma

A defining feature of circRNA-mediated regulation in hepatocellular carcinoma is that circRNA dysregulation can arise from alterations in RNA-processing machinery rather than changes in host gene transcription alone [35]. Indeed, studies of CPSF4 and CPSF3 have demonstrated that RNA 3'-end processing factors can reshape circRNA biogenesis and the balance between circular and linear transcripts in HCC [36, 37]. This biogenesis layer may contribute to the selective dysregulation of specific circRNAs during tumor progression, although its role under therapeutic stress and immune pressure remains insufficiently established. Understanding how circRNA landscapes are regulated at their point of origin may therefore provide insights into their potential contributions to therapeutic resistance and immune escape.

Back-splicing and cyclization machinery: from spliceosome to 3'-end processing factors

CircRNAs are generated through back-splicing, a noncanonical splicing event in which a downstream splice donor is joined to an upstream splice acceptor [37-41]. This process competes directly with canonical linear splicing and is therefore exquisitely sensitive to the activity and composition of the RNA processing machinery. While early models emphasized the role of spliceosomal components and intronic complementary sequences in facilitating circRNA formation, it has become increasingly clear that circRNA biogenesis is governed by a broader regulatory landscape that extends beyond the spliceosome itself.

Pre-mRNA fate is influenced by the coordinated activities of splicing factors, RNA-binding proteins, and 3'-end processing complexes that regulate transcript maturation [42]. Canonical splicing and back-splicing can compete for shared precursor transcripts, and changes in this balance may alter circRNA production without corresponding changes in host gene transcription [43]. Consequently, circRNA dysregulation in cancer cannot always be explained by changes in host gene expression alone but must also be considered in the context of RNA-processing alterations. In HCC, specific RNA-processing factors have been shown to influence circRNA biogenesis. For example, loss of NUDT21 reduces the formation of certain circRNAs, whereas CPSF4 and CPSF3 can suppress circRNA production through mechanisms associated with RNA 3'-end processing and linear transcript formation [35-37]. These findings indicate that alterations in RNA-processing machinery can reshape circRNA expression in a factor- and transcript-dependent manner. However, whether such biogenesis changes directly coordinate circRNA programs involved in therapeutic resistance or immune escape remains to be established.

NUDT21 and CPSF4: 3'-end processing factors as regulators of circRNA programs

Among the emerging regulators of circRNA biogenesis in HCC, 3'-end processing factors have attracted increasing attention. NUDT21 and CPSF4, core components of the cleavage and polyadenylation machinery, exemplify how factors traditionally viewed as linear mRNA regulators can exert profound effects on circRNA formation and function [44-47]. NUDT21 plays a pivotal role in alternative polyadenylation by recognizing upstream poly(A) signals and controlling 3'-end site selection. In HCC, NUDT21 has been shown to regulate circRNA cyclization and reshape competing endogenous RNA (ceRNA) crosstalk [35]. Mechanistically, reduced NUDT21 activity favors circRNA production by limiting efficient cleavage and polyadenylation of pre-mRNAs, thereby increasing the availability of back-splicing substrates. Importantly, the consequences of NUDT21 dysregulation extend beyond circRNA abundance. By altering the relative proportions of circular and linear transcripts derived from the same loci, NUDT21 indirectly rewires miRNA-mRNA interaction networks, amplifying or dampening ceRNA effects at a systems level. CPSF4, another essential component of the cleavage and polyadenylation specificity factor complex, further illustrates the functional coupling between circRNA biogenesis and post-tran-

scriptional gene regulation. CPSF4 dysregulation in HCC has been linked to altered circRNA formation and impaired miRNA-mediated gene silencing [36]. Unlike models in which circRNAs act solely as passive miRNA sponges, CPSF4-driven changes in circRNA output modify the efficiency and directionality of miRNA repression across the transcriptome. Thus, CPSF4 operates at a higher hierarchical level, shaping the regulatory environment in which circRNAs exert their downstream effects. Together, these findings establish a conceptual framework in which 3'-end processing factors function as master regulators of circRNA programs, coordinating transcript processing decisions that simultaneously influence circRNA production, ceRNA network arc hitecture, and gene silencing efficacy.

Why biogenesis rewiring matters for therapeutic resistance and immune escape

The relevance of circRNA biogenesis rewiring becomes particularly evident when viewed through the lens of therapeutic resistance and immune failure. Alterations in RNA processing factors, including NUDT21 and CPSF4, can affect circRNA biogenesis. However, whether these factors coordinately regulate circRNAs involved in protein stability, ferroptosis, and immune modulation under therapeutic pressure remains to be established. This coordinated regulation provides a plausible explanation for why resistance phenotypes often involve clusters of functionally related circRNAs, rather than reliance on a single dominant molecule. From this perspective, resistance to TKIs or immunotherapy does not necessarily arise from the activation of one circRNA-mediated pathway, but may reflect the emergence of a broader circRNA program induced by RNA processing reconfiguration [48-53]. Whether distinct circRNAs are coordinately regulated and functionally cooperate to promote therapeutic resistance remains to be determined. This framework has important implications for both biomarker development and therapeutic targeting. Measuring individual circRNAs may capture only a fraction of the underlying biology, whereas profiling circRNA landscapes or their upstream processing regulators may provide a more accurate reflection of tumor adaptive states. Moreover, targeting biogenesis regulators offers the theoretical advantage of disrupting entire circRNA-driven networks rather than single downstream effectors.

Collectively, circRNA dysregulation in hepatocellular carcinoma is rooted in alterations of the RNA processing machinery that governs back-splicing and transcript fate decisions. Factors such as NUDT21 and CPSF4 act at the biogenesis layer to remodel circRNA landscapes, thereby rewiring downstream regulatory networks involved in protein stability, ferroptosis, and immune escape. These findings suggest that alterations in circRNA biogenesis may influence treatment-related phenotypes, although a direct causal link between processing factor reconfiguration and coordinated circRNA-mediated resistance programs has not yet been established. **Figure 1** illustrates how RNA-processing factors regulate circRNA biogenesis in HCC. NUDT21 and CPSF4 influence circular RNA production through distinct mechanisms, providing an upstream regulatory layer for circRNA expression.

CircRNA-mediated protein regulation: direct proteostasis control and indirect signaling

A major conceptual advance in circRNA biology is the recognition that selected circRNAs can directly interact with proteins to regulate their stability, localization, or translational activity, extending their functional repertoire beyond microRNA sequestration [54, 55]. In hepatocellular carcinoma, circRNA-SORE has been shown to stabilize YBX1 by preventing PRP19-mediated ubiquitination and degradation, thereby promoting sorafenib resistance [54]. Similarly, exosomal hsa_circ_0007132 enhances NONO protein stability by inhibiting its ubiquitin-mediated degradation, contributing to lenvatinib resistance [56]. Conversely, circVAMP3 promotes CAPRIN1 phase separation and suppresses c-Myc translation, illustrating a tumor-suppressive mechanism [55]. These findings demonstrate that circRNA-protein interactions can influence protein stability and translational regulation in a context-dependent manner, rather than constituting a universally oncogenic proteostasis network.

Conceptual shift: circRNA-protein interaction as a stability module

Traditional models of circRNA function have largely emphasized ceRNA activity, positioning

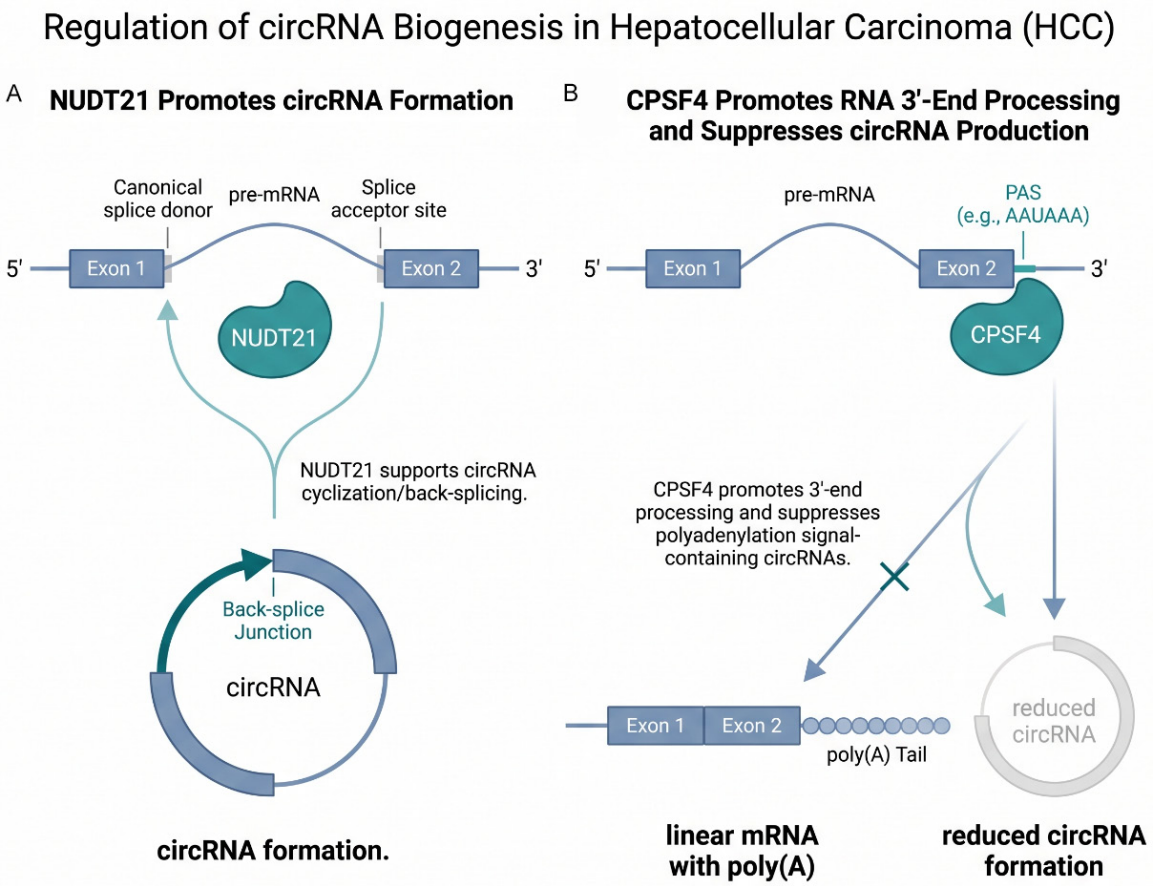


Figure 1. Regulation of circRNA biogenesis in hepatocellular carcinoma. A. NUDT21 promotes UGUA-dependent circRNA cyclization and modulates circRNA-miRNA-mRNA interactions. Loss of NUDT21 reduces circRNA formation and disrupts ceRNA regulation. B. CPSF4 suppresses the formation of circRNAs containing polyadenylation signals, thereby altering miRNA-mediated gene regulation. These mechanisms illustrate how RNA-processing factors influence circRNA abundance in HCC.

circRNAs as passive competitors for miRNA binding. However, accumulating evidence indicates that circRNAs can interact directly with proteins, particularly RNA-binding proteins (RBPs), to form functional stability modules. In this context, circRNAs serve as molecular scaffolds or decoys that reshape proteostasis without altering protein-coding sequences. Importantly, direct circRNA-mediated proteostasis regulation should be distinguished from indirect changes in protein expression caused by ceRNA activity. Evidence of altered protein stability generally requires direct mechanistic support, such as changes in protein half-life, ubiquitination, or proteasomal degradation, rather than changes in downstream protein abundance alone. Several non-mutually exclusive mechanisms underlie circRNA-mediated protein stabilization. First, circRNAs can physically shield proteins from ubiquitin ligases, thereby preventing E3-mediated recognition and subsequent proteasomal degradation [56-59]. Second, circRNA binding can alter the subcellular localization of target proteins, sequestering them away from degradation-prone compartments or redirecting them toward functionally active niches [60, 61]. Third, circRNAs can influence protein phase behavior, including liquid-liquid phase separation and stress granule dynamics, thereby modulating protein availability and translational control under stress conditions [62]. These mechanisms collectively position circRNAs as post-translational regulators capable of fine-tuning protein abundance and activity in response to environmental cues. Importantly, because circRNAs are highly stable and often induced under stress, they are ideally suited to sustain oncogenic protein pro-

grams during prolonged therapeutic exposure, when linear regulatory mechanisms may be insufficient.

The SORE-YBX1 axis: a paradigmatic protein-stabilizing circRNA in sorafenib resistance

The circRNA-SORE-YBX1 axis represents one of the most compelling examples of circRNA-mediated protein stabilization in HCC and serves as a paradigmatic model for this regulatory logic. circRNA-SORE was identified as a critical mediator of acquired resistance to sorafenib, a first-line TKI for advanced HCC. Mechanistically, circRNA-SORE directly binds to Y-box binding protein 1 (YBX1), a multifunctional RBP and transcriptional regulator implicated in stress adaptation, drug resistance, and malignant progression [54]. Under normal conditions, YBX1 is subject to ubiquitin-mediated degradation, which limits its accumulation and oncogenic activity. circRNA-SORE disrupts this regulatory constraint by acting as a molecular decoy that interferes with the interaction between YBX1 and its cognate E3 ubiquitin ligase, thereby suppressing YBX1 ubiquitination and proteasomal turnover. The resulting stabilization of YBX1 sustains transcriptional and post-transcriptional programs that promote cell survival and drug tolerance [63-65]. This mechanism exemplifies circRNA-driven proteostasis rewiring under drug pressure. Rather than activating new signaling pathways through genetic alteration, HCC cells exploit circRNA-mediated protein protection to reinforce pre-existing resistance programs. The SORE-YBX1 axis thus highlights how circRNAs can function as adaptive stabilizers that convert transient stress responses into durable resistant states, offering a conceptual framework that may extend to other RBPs and therapeutic contexts.

Phase separation and translational control: circVAMP3-CAPRIN1-c-Myc suppression as a tumor-suppressive module

While many circRNA-protein interactions promote oncogenic outcomes, this regulatory logic is not inherently tumor promoting. The circVAMP3-CAPRIN1 axis provides an instructive counterexample, demonstrating that circRNA-mediated protein regulation can also exert tumor-suppressive effects. CircVAMP3 has been shown to bind CAPRIN1, a core component of stress granules and translational control complexes, and to promote CAPRIN1-driven phase separation [66]. This interaction enhances the sequestration of c-Myc mRNA into translationally repressive compartments, thereby suppressing c-Myc protein synthesis. Given the central role of c-Myc in driving proliferation, metabolic reprogramming, and tumor progression, circVAMP3-mediated inhibition of c-Myc translation effectively restrains HCC growth [55]. Importantly, this mechanism operates at the level of translation and phase behavior, rather than protein degradation per se, underscoring the versatility of circRNA-protein interactions. By juxtaposing the circVAMP3-CAPRIN1 module with the SORE-YBX1 axis, a broader principle emerges: circRNAs can shape oncogenic outcomes by modulating distinct dimensions of protein homeostasis, including stability, localization, and translational accessibility. The biological consequence - tumor promotion or suppression - depends on the identity of the target protein and the directionality of regulation. CircRNAs regulate protein homeostasis through mechanisms beyond conventional miRNA sponging. As illustrated in **Figure 2**, circRNA-SORE stabilizes YBX1 to promote sorafenib resistance, whereas circVAMP3 facilitates CAPRIN1-dependent translational suppression of c-Myc.

ceRNA-mediated signaling regulation: distinguishing indirect effects from direct proteostasis control

Beyond the direct circRNA-protein interactions described above, several circRNAs have been reported to regulate oncogenic signaling predominantly through ceRNA-mediated mechanisms. Although these circRNAs can influence downstream protein expression and signaling activity, such effects should not be interpreted as direct evidence of protein stabilization, ubiquitination, subcellular localization, or phase separation. Several circRNAs promote HCC growth by sustaining mitogenic signaling. circRNA_0040705 and hsa_circRNA_103809 enhance tumor progression through activation of the FGFR1/ERK axis, reinforcing MAPK-driven proliferation [67-69]. circRNA 001306 upregulates CDK16, supporting cell cycle progression, while circ-CCND1 promotes HCC tumorigenesis through the miR-497-5p/HMGA2

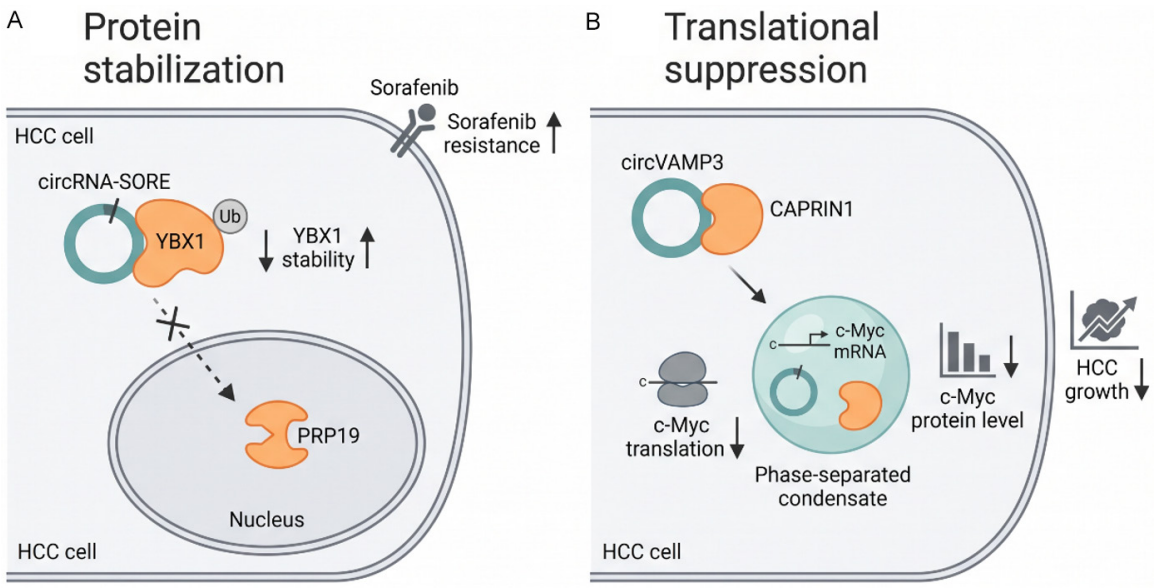


Figure 2. CircRNA-mediated regulation of protein homeostasis in HCC. A. circRNA-SORE binds YBX1 and prevents its ubiquitination and proteasomal degradation, resulting in YBX1 stabilization and sorafenib resistance. B. circVAMP3 interacts with CAPRIN1 and promotes phase separation, facilitating c-Myc mRNA sequestration and translational suppression. These distinct mechanisms demonstrate how circRNAs regulate protein stability and translation to influence HCC progression.

axis [70, 71]. Other circRNAs modulate extracellular matrix remodeling and invasion. circRNA_0001806 promotes MMP16 expression, facilitating matrix degradation, whereas circRNA_0008194 enhances invasion through the AHNAK signaling pathway [72, 73]. circRNA_104348 activates Wnt/β-catenin signaling, and circRNA_104718 regulates TXNDC5, linking redox control to tumor progression [74, 75]. CircRNA GFRA1, through modulation of NAP1L3, further contributes to proliferative and survival signaling [76]. Collectively, these studies illustrate how circRNAs influence oncogenic signaling through indirect regulation of downstream gene and protein expression. However, these ceRNA-mediated effects should be distinguished from direct proteostasis regulation, as changes in protein stability, ubiquitination, or degradation have not been established for these specific mechanisms.

Together, the direct interaction-based studies discussed above support an important role for selected circRNAs in regulating protein stability and other aspects of proteostasis in HCC. By acting as scaffolds, decoys, or phase behavior modulators, circRNAs directly shape the fate of oncogenic proteins and RBPs, enabling sustained signaling and therapeutic resistance. The SORE-YBX1 axis exemplifies how circRNA-mediated protein stabilization drives drug resistance, whereas the circVAMP3-CAPRIN1 module illustrates the context-dependent, tumor-suppressive potential of this regulatory logic. These direct protein-regulatory mechanisms should be distinguished from ceRNA-mediated changes in downstream signaling, which do not necessarily involve alterations in protein stability or degradation.

Ferroptosis evasion: circRNA control of iron handling and system Xc^-

Ferroptosis has emerged as a critical cell death modality in hepatocellular carcinoma and represents a key vulnerability exploited by targeted therapies [22]. Unlike apoptosis, ferroptosis is driven by iron-dependent lipid peroxidation and is tightly coupled to cellular metabolism, redox balance, and iron homeostasis [77]. In recent years, circRNAs have been identified as previously unrecognized regulators of ferroptosis, enabling HCC cells to evade this lethal process and thereby sustain therapeutic resistance [78, 79]. This section highlights ferroptosis evasion as a central axis of circRNA-mediated adaptation, with particular emphasis on iron handling and system Xc^- regulation.

Ferroptosis as a therapeutic vulnerability in hepatocellular carcinoma

Sorafenib, the first approved systemic therapy for advanced HCC, has been shown to induce ferroptosis by disrupting redox homeostasis and promoting lipid peroxidation [80-85]. Beyond its kinase inhibitory activity, sorafenib suppresses cystine uptake and antioxidant capacity, leading to reactive oxygen species (ROS) accumulation and ferroptotic stress [86-89]. Metabolic perturbations inherent to HCC - such as altered lipid metabolism, mitochondrial dysfunction, and chronic oxidative stress - further sensitize tumor cells to ferroptosis. However, ferroptosis is not an inevitable outcome of therapeutic stress. HCC cells frequently activate compensatory mechanisms that elevate the threshold for lipid peroxidation-induced cell death. These mechanisms include reinforcement of iron storage systems, enhancement of glutathione-dependent antioxidant defenses, and rewiring of amino acid transport pathways. As a result, ferroptosis emerges not merely as a binary on-off switch, but as a tunable cell fate decision that can be modulated by adaptive regulatory networks. Within this context, circRNAs represent an ideal regulatory layer for ferroptosis control. These properties make selected circRNAs potential regulators of ferroptosis susceptibility, although their contributions to sustained ferroptosis resistance under prolonged therapeutic pressure require context-specific experimental validation. Importantly, circRNA-mediated ferroptosis regulation should be distinguished from general effects on drug resistance or cell survival. Direct ferroptosis evidence requires appropriate biochemical and functional assessment, including lipid peroxidation, intracellular Fe^{2+} accumulation, ferroptosis-associated molecular changes, and, where feasible, rescue experiments using ferroptosis inhibitors such as ferrostatin-1 or liproxstatin-1.

CircPIAS1-miR-455-3p-NUPR1-FTH1 axis: iron storage as a ferroptosis shield

One of the most compelling examples of circRNA-mediated ferroptosis evasion in HCC is the CircPIAS1-miR-455-3p-NUPR1-FTH1 axis [78]. CircPIAS1 has been shown to promote HCC progression by inhibiting ferroptosis through regulation of iron metabolism. Mechanistically, CircPIAS1 functions as a competing endogenous RNA for miR-455-3p, thereby relieving repression of NUPR1, a stress-responsive transcriptional regulator. NUPR1, in turn, upregulates ferritin heavy chain 1 (FTH1), a core component of intracellular iron storage. FTH1 occupies a pivotal position in ferroptosis regulation [90]. By sequestering labile iron into inert ferritin complexes, FTH1 limits iron-catalyzed lipid peroxidation and suppresses ferroptotic signaling. Thus, CircPIAS1-mediated elevation of FTH1 effectively constructs a metabolic shield against ferroptosis, converting excess iron from a pro-death liability into a buffered resource [91]. Importantly, this axis provides a metabolically coherent explanation for ferroptosis evasion. Rather than acting through abstract signaling intermediates, CircPIAS1 directly rewires iron handling at a fundamental biochemical level. This underscores a broader principle: circRNAs can enforce ferroptosis resistance by stabilizing iron homeostasis, thereby decoupling oxidative stress from cell death execution. Importantly, the original study provided direct ferroptosis-related evidence, including changes in intracellular Fe^{2+}, lipid ROS, and GSH levels, together with functional rescue by ferrostatin-1 and liproxstatin-1. These findings support the involvement of the CircPIAS1-NUPR1-FTH1 axis in ferroptosis regulation rather than merely general tumor cell survival.

CircTTC13-miR-513a-5p-SLC7A11 axis: system Xc^- rewiring links ferroptosis suppression to sorafenib resistance

While iron storage limits the initiation of lipid peroxidation, antioxidant systems determine whether ferroptotic stress is resolved or amplified. The CircTTC13-miR-513a-5p-SLC7A11 axis exemplifies how circRNAs modulate this second line of defense by rewiring system Xc^-, the cysteine-glutamate antiporter essential for glutathione synthesis. CircTTC13 has been identified as a key driver of sorafenib resistance in HCC through its ability to inhibit ferroptosis [79]. In experimental HCC models, circTTC13 silencing increased ferroptosis-associated changes, including elevated Fe^{2+}, 4-HNE, and MDA levels and reduced GPX4 expression. Moreover, ferrostatin-1 partially reversed the inhibitory effects of circTTC13 silencing on tumor growth, providing functional evidence supporting ferroptosis involvement. By sponging miR-513a-5p, CircTTC13 upregulates SLC7A11, the functional subunit of sys-

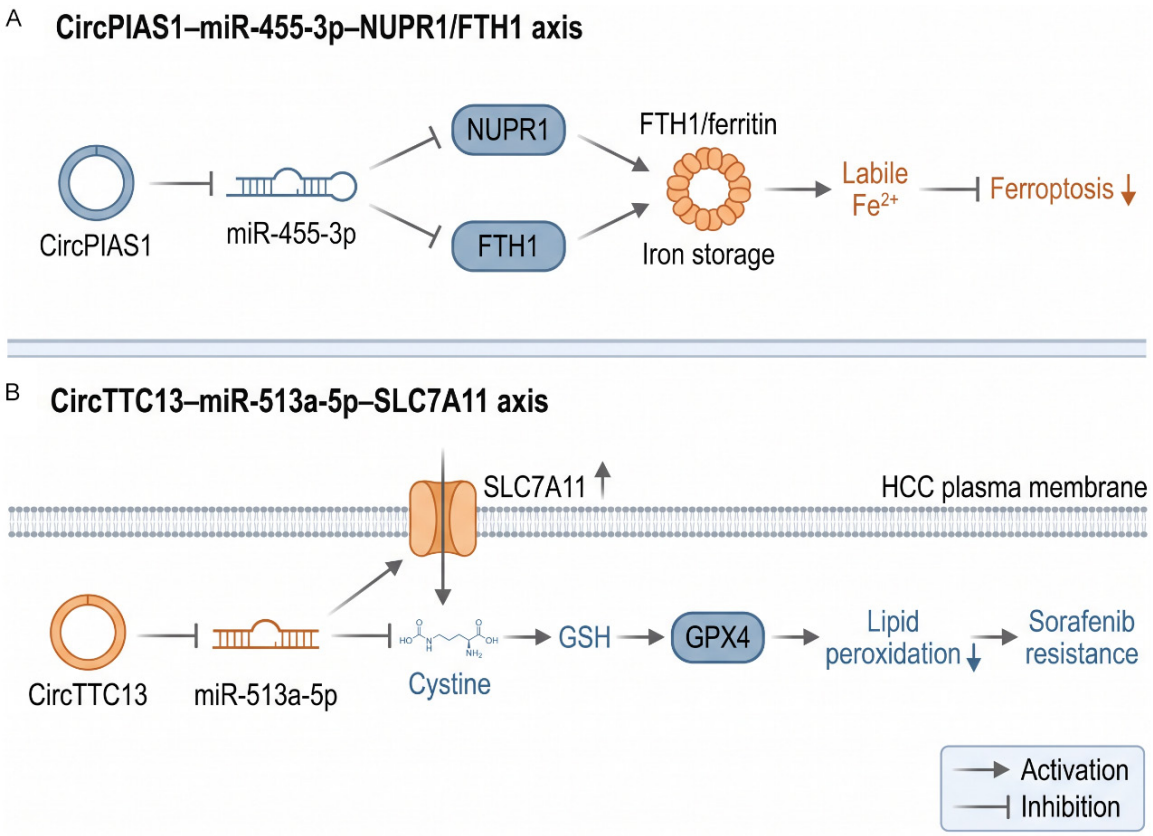


Figure 3. CircRNA-mediated ferroptosis suppression in hepatocellular carcinoma. A. CircPIAS1 sponges miR-455-3p, increasing NUPR1 and FTH1 expression. Enhanced ferritin-mediated iron storage limits labile Fe^{2+} availability and suppresses ferroptosis. B. CircTTC13 inhibits miR-513a-5p, upregulating SLC7A11-mediated cystine uptake and GSH/GPX4-dependent antioxidant defense. Reduced lipid peroxidation promotes ferroptosis resistance and contributes to sorafenib resistance.

tem Xc^- [92]. Enhanced SLC7A11 expression increases cystine uptake, replenishes intracellular glutathione pools, and reinforces GPX4-dependent detoxification of lipid peroxides [93-96]. Notably, this mechanism directly couples ferroptosis suppression to therapeutic resistance. Sorafenib-induced oxidative stress is neutralized not by pathway bypass or mutation, but by raising the antioxidant capacity threshold required to trigger ferroptotic death. CircTTC13 thus integrates metabolic adaptation and drug resistance into a single regulatory module, highlighting ferroptosis evasion as a central determinant of sorafenib failure. Taken together with CircPIAS1-mediated iron sequestration, CircTTC13-driven system Xc^- activation illustrates how circRNAs operate at multiple biochemical checkpoints of ferroptosis, collectively transforming a lethal vulnerability into a controllable stress response. **Figure 3** summarizes two distinct circRNA-associated mechanisms of ferroptosis regulation in HCC. CircPIAS1 primarily influences iron sequestration through FTH1, whereas CircTTC13 reinforces SLC7A11-associated antioxidant defenses that limit lipid peroxidation.

Sorafenib resistance-associated circRNAs without established ferroptosis involvement

Not all circRNAs associated with sorafenib resistance have been demonstrated to regulate ferroptosis. For example, circRNA-001241 has been reported to promote sorafenib resistance in HCC through the miR-21-5p/TIMP3 axis [97]. However, the reported findings primarily concern cell proliferation and drug resistance and do not establish ferroptosis as the underlying mechanism. Therefore, circRNA-001241 should be considered a sorafenib resistance-associated circRNA rather than a validated ferroptosis regulator. Further

studies incorporating lipid peroxidation measurements, intracellular iron assessment, and ferroptosis-specific rescue experiments are required to determine whether this axis also influences ferroptosis susceptibility [98].

Ferroptosis represents a potential therapeutic vulnerability in HCC, and selected circRNAs have been shown to regulate ferroptosis susceptibility through distinct molecular mechanisms [22]. CircPIAS1 modulates iron storage through the NUPR1-FTH1 axis, whereas CircTTC13 regulates SLC7A11-associated antioxidant defense and sorafenib resistance [78, 79]. These findings support the involvement of individual circRNAs in ferroptosis regulation but do not establish a unified ferroptosis regulatory network. Importantly, circRNAs associated with general drug resistance should not be classified as ferroptosis regulators without direct biochemical and functional evidence.

Exosomal circRNAs and tumor-immune communication in HCC

Immune checkpoint blockade has reshaped the therapeutic landscape of hepatocellular carcinoma, yet durable responses remain limited to a minority of patients [99]. Primary resistance and rapid adaptive failure are common, highlighting the existence of robust immune evasion programs that operate beyond canonical checkpoint signaling [100]. Increasing evidence indicates that these programs are not solely dictated by immune cell-intrinsic defects, but are actively imposed by tumor cells through multilayered regulatory networks [10, 101]. Among the reported mechanisms, exosomal circCCAR1 provides a specific example of tumor-to-T-cell communication associated with $CD8^+$ T-cell dysfunction and anti-PD-1 resistance in experimental HCC models [102].

Why immune checkpoint blockade fails in HCC: a network perspective

Failure of immune checkpoint blockade in HCC is characterized by a convergence of $CD8^+$ T-cell exhaustion, immunosuppressive stromal and myeloid compartments, and tumor cell-intrinsic tolerance mechanisms. Exhausted $CD8^+$ T cells exhibit diminished cytotoxicity, impaired cytokine production, and sustained expression of inhibitory receptors, rendering them refractory to PD-1 blockade [17, 19, 20, 103-105]. At the same time, tumor cells frequently display intrinsic resistance programs that limit antigen presentation, attenuate interferon signaling, and reshape metabolic competition within the tumor microenvironment (TME). Importantly, these features rarely arise independently. Instead, immune failure in HCC reflects a systems-level state in which tumor cells, immune cells, and stromal elements are dynamically coupled. From this perspective, immune checkpoint resistance is not merely the absence of effective T-cell reinvigoration, but the presence of active tumor-driven mechanisms that enforce immune dysfunction. Identifying the molecular carriers of these mechanisms is therefore essential for understanding why PD-1/PD-L1 blockade fails in most patients. CircRNAs are particularly well suited to fulfill this role. Their stability, stress inducibility, and capacity for intercellular transfer enable circRNAs to function as durable messengers that propagate immune-resistant states from tumor cells to the surrounding immune ecosystem.

Exosome-derived circCCAR1: intercellular transfer of resistance programs

A seminal example of circRNA-mediated immune regulation in HCC is provided by exosome-derived circCCAR1. circCCAR1 has been shown to promote $CD8^+$ T-cell dysfunction and confer resistance to anti-PD-1 therapy, positioning it as a central node linking tumor-intrinsic regulatory circuits to extrinsic immune failure [102]. Mechanistically, circCCAR1 is selectively packaged into tumor-derived exosomes and transferred to immune cells within the TME. Following uptake by $CD8^+$ T cells, exosomal circCCAR1 stabilizes PD-1 protein by reducing its ubiquitination and proteasomal degradation, thereby impairing T-cell function and promoting resistance to anti-PD-1 treatment in experimental HCC models. This process exemplifies a critical conceptual advance: circRNAs can act as transferable information units, exporting tumor-adaptive programs beyond the boundaries of the cancer cell. Further reinforcing its impact, circCCAR1 participates in regulatory feedback loops involving miRNAs and epitranscriptomic regulators such as WTAP [106]. These loops stabilize circCCAR1 expression and function, ensuring persistence of the immunosuppressive state even under therapeutic pressure. Rather than inducing transient

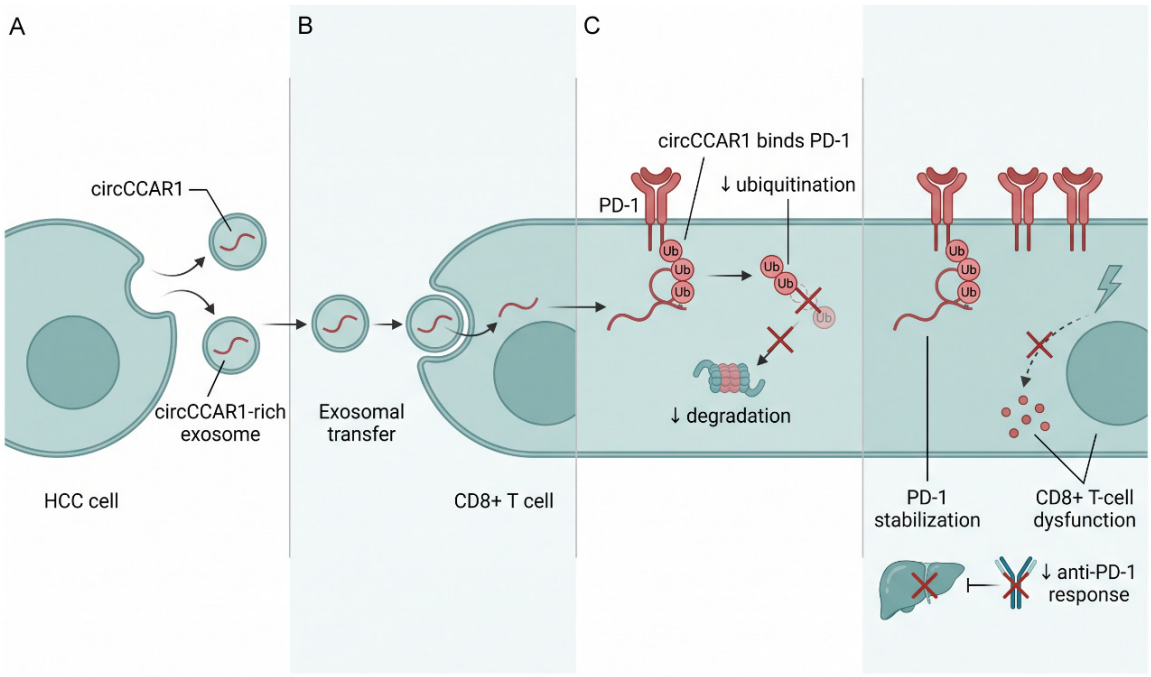


Figure 4. Exosomal circCCAR1-mediated CD8⁺ T-cell dysfunction in HCC. A. HCC cells package circCCAR1 into exosomes and release them into the tumor microenvironment. B. Following exosomal uptake by CD8⁺ T cells, circCCAR1 binds PD-1 and reduces its ubiquitination and proteasomal degradation. C. Increased PD-1 stability impairs CD8⁺ T-cell activity and contributes to resistance to anti-PD-1 therapy in preclinical HCC models.

immune suppression, circCCAR1 establishes a self-reinforcing circuit that locks CD8⁺ T cells into a dysfunctional phenotype. This mechanism highlights how immune resistance can be actively imposed by tumor cells through circRNA-dependent intercellular communication, rather than emerging passively from immune exhaustion alone. In doing so, circCCAR1 bridges intracellular regulatory networks and the multicellular architecture of immune escape. Nevertheless, these findings are specific to the circCCAR1-associated mechanism and should not be generalized to other exosomal circRNAs without direct functional evidence. **Figure 4** illustrates a tumor-to-immune-cell communication mechanism mediated by exosomal circCCAR1. Following transfer into CD8⁺ T cells, circCCAR1 stabilizes PD-1 protein and contributes to T-cell dysfunction and resistance to anti-PD-1 treatment in experimental HCC models.

Exosomal circRNAs in metastasis and angiogenesis: potential implications for tumor immunity

Beyond circCCAR1, several exosomal circRNAs have been implicated in HCC metastasis and angiogenesis, processes that may influence the tumor immune microenvironment but are not necessarily associated with demonstrated resistance to immune checkpoint blockade. Exosomal circRNA-100338 has been reported to promote HCC metastasis by enhancing tumor cell invasiveness and angiogenesis [107]. Whether circRNA-100338-associated changes in metastasis and angiogenesis directly affect immune-cell infiltration or responsiveness to immune checkpoint blockade has not been established. Enhanced angiogenesis can promote immune exclusion by generating aberrant, dysfunctional vasculature that limits T-cell infiltration. Similarly, increased invasiveness and metastatic dissemination are associated with stromal remodeling, hypoxia, and accumulation of immunosuppressive metabolites, all of which impair CD8⁺ T-cell function. These observations raise the possibility that exosomal circRNAs may indirectly influence antitumor immunity through tumor microenvironment remodeling, although direct functional evidence linking these effects to immune checkpoint resistance remains limited. These observations broaden the scope of circRNA-mediated immune regulation. Accordingly, the potential immunological consequences

of these exosomal circRNAs should be distinguished from their established roles in tumor progression and vascular remodeling.

Collectively, these findings illustrate distinct functions of exosomal circRNAs in HCC. Exosomal circCCAR1 has been experimentally associated with $CD8^+$ T-cell dysfunction and resistance to anti-PD-1 treatment, whereas evidence for other exosomal circRNAs discussed here mainly concerns metastasis, angiogenesis, or tumor progression. Whether these effects converge to influence immunotherapy outcomes requires further investigation.

Metastasis and metabolic adaptation as network amplifiers

While protein stability control, ferroptosis evasion, and immune dysfunction constitute the core functional axes of circRNA-mediated adaptation in hepatocellular carcinoma, these processes do not operate in isolation. Metastatic dissemination and metabolic reprogramming profoundly reshape the tumor ecosystem, amplifying circRNA-driven regulatory networks and stabilizing malignant phenotypes. In this context, circRNAs may participate in metabolic and metastatic adaptation, although their proposed roles as amplifiers of interconnected resistance and immune escape pathways require further investigation.

CircLARP1B: lipid metabolism as a metastatic engine

CircLARP1B represents a compelling example of how circRNA-mediated metabolic regulation fuels metastatic progression in HCC. CircLARP1B has been shown to regulate HCC metastasis by modulating lipid metabolism-associated transcriptional and post-transcriptional programs [108]. Rather than simply supporting tumor growth, this circRNA promotes phenotypic plasticity that enables tumor cells to adapt to the energetic and structural demands of dissemination.

Lipid metabolism plays a multifaceted role in metastatic competence. Alterations in lipid synthesis, storage, and remodeling influence membrane composition, fluidity, and signaling capacity, thereby facilitating cell migration and invasion. Moreover, lipid metabolic rewiring intersects with ferroptosis sensitivity, as polyunsaturated fatty acids constitute the substrates for lipid peroxidation. By reshaping lipid pools and redox balance, circLARP1B-associated programs may indirectly elevate ferroptosis thresholds, reinforcing cell survival during metastatic stress.

Beyond intrinsic tumor cell effects, lipid metabolism also impacts the immune microenvironment [109-111]. Accumulation of lipid-derived metabolites can suppress cytotoxic T-cell function and promote immunosuppressive myeloid populations [112]. Although lipid metabolic reprogramming can influence antitumor immunity, direct evidence linking circLARP1B to $CD8^+$ T-cell dysfunction or immunotherapy resistance in HCC is currently lacking. Collectively, CircLARP1B illustrates how circRNAs can couple metabolic reprogramming to metastatic behavior, acting as amplifiers that sustain adaptive networks across spatial and environmental transitions.

Viral circRNAs: HBV-encoded circRNA-5 and pathway hijacking

Hepatocellular carcinoma frequently arises in the context of chronic hepatitis B virus (HBV) infection, introducing an additional layer of regulatory complexity. Viral circRNAs have recently emerged as novel contributors to HCC pathogenesis, exemplified by HBV-encoded circRNA-5 [113]. This viral circRNA has been shown to promote HCC progression by modulating the Hippo signaling pathway, a central regulator of organ size, cell proliferation, and tumor suppression. The existence of HBV-derived circRNAs highlights a pathogen-specific circRNA network, distinct from but intersecting with host circRNA programs. By hijacking conserved signaling pathways such as Hippo, viral circRNAs can reinforce oncogenic transcriptional programs and promote tumor cell survival. Importantly, these effects are superimposed on host circRNA-mediated adaptation, potentially exacerbating resistance and immune evasion in HBV-associated HCC [114-118]. This phenomenon underscores an important principle: circRNA networks in HCC are not uniform across etiological subtypes. Instead, they are shaped by disease context, with viral circRNAs acting as additional nodes that amplify malignant signaling. Recognizing such etiology-spe-

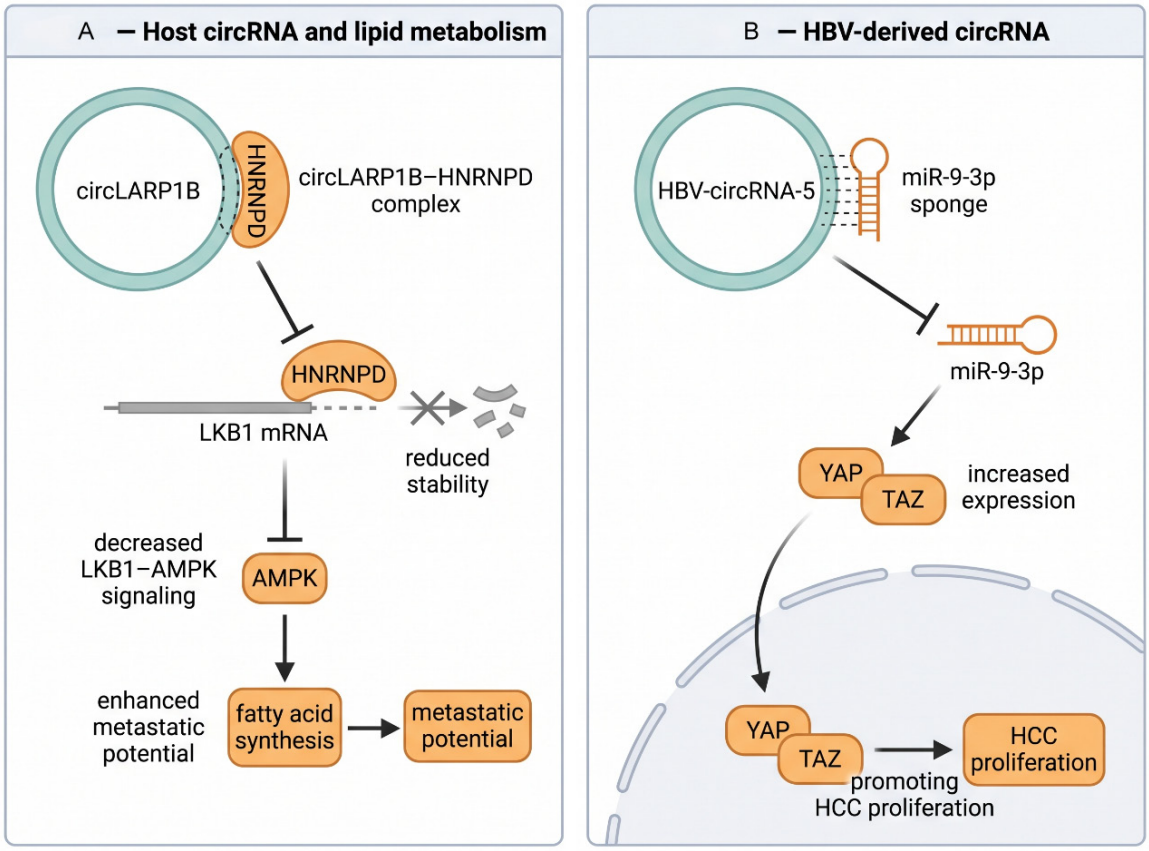


Figure 5. Metabolic and viral circRNA-associated mechanisms in HCC progression. A. circLARP1B regulates HNRNPD-dependent LKB1 mRNA stability and downstream AMPK signaling, promoting lipid accumulation and metastatic progression. B. HBV-derived circRNA-5 sponges miR-9-3p, enhancing YAP/TAZ expression and promoting tumor cell proliferation. These mechanisms illustrate distinct contributions of host-derived and viral circRNAs to HCC progression without implying direct interactions between the two pathways.

cific circRNA contributions may be critical for patient stratification and precision therapy. **Figure 5** highlights two context-specific circRNA mechanisms associated with HCC progression. CircLARP1B regulates lipid metabolism through the HNRNPD-LKB1-AMPK pathway, whereas HBV-derived circRNA-5 promotes oncogenic YAP/TAZ signaling through miR-9-3p regulation.

Oncogenic signaling hubs as convergent endpoints of circRNA networks

Despite the diversity of circRNA species and upstream regulatory mechanisms, their downstream effects frequently converge on a limited set of oncogenic signaling hubs. Pathways such as ERK/MAPK, Wnt/β-catenin, and Hippo/YAP signaling repeatedly emerge as terminal effectors of circRNA-mediated regulation in HCC [114-118]. CircRNAs targeting these pathways do so through multiple mechanisms, including miRNA sequestration, protein stabilization, and modulation of transcriptional co-regulators. Activation of ERK signaling sustains proliferative and survival cues, Wnt/β-catenin signaling promotes stemness and immune exclusion, and Hippo pathway dysregulation enables unchecked growth and metastatic competence [119-121]. The recurrence of common downstream signaling pathways across individual circRNA studies suggests potential points of functional convergence, although direct evidence for compensatory regulation or functional redundancy among these circRNAs remains limited. From a systems perspective, these signaling hubs serve as integration points where metabolic adaptation, cell death regulation, and immune modulation intersect. CircRNA-driven amplification of these hubs stabilizes malignant network states, rendering them

resistant to therapeutic intervention and immune surveillance. Metastasis and metabolic adaptation amplify circRNA-mediated regulatory networks in hepatocellular carcinoma, reinforcing malignant phenotypes across spatial and environmental contexts. CircLARP1B exemplifies how lipid metabolic reprogramming fuels metastatic progression while intersecting with ferroptosis resistance and immune suppression. Viral circRNAs, such as HBV-encoded circRNA-5, further intensify these networks in etiologically defined HCC subsets by hijacking core oncogenic pathways. Ultimately, diverse circRNA programs converge on shared signaling hubs, including ERK, Wnt/β-catenin, and Hippo pathways, stabilizing adaptive tumor states and promoting therapy resistance.

Translational implications

Emerging evidence that individual circRNAs regulate several resistance-associated pathways in HCC suggests potential opportunities for biomarker development and therapeutic investigation. By integrating protein stability control, ferroptosis evasion, and immune escape, circRNA-centered networks offer new opportunities for biomarker development, therapeutic intervention, and rational combination strategies. At the same time, their clinical application poses distinct technical and conceptual challenges that must be addressed to enable translation.

circRNAs as biomarkers: tissue, plasma, and exosomal signatures

The intrinsic stability of circRNAs, coupled with their cell-type specificity and presence in extracellular vesicles, makes them particularly attractive as biomarkers for HCC. Unlike many linear RNAs, circRNAs are resistant to exonuclease degradation and can be reliably detected in tumor tissues, plasma, and exosome fractions. Several circRNAs highlighted in this review show promise as predictors of therapeutic response. CircRNA-SORE, CircTTC13, and CircRNA-001241 are closely linked to resistance to TKIs such as sorafenib and lenvatinib, suggesting their potential utility in stratifying patients who are unlikely to benefit from first-line targeted therapy [122, 123]. Monitoring these circRNAs could enable early identification of emerging resistance and guide treatment adjustment. In the context of immunotherapy, exosome-derived circCCAR1 represents a particularly compelling biomarker candidate. Its association with $CD8^+$ T-cell dysfunction and resistance to anti-PD-1 therapy positions circCCAR1 as a surrogate marker of immune-refractory tumor states. Because circCCAR1 is detectable in tumor-derived exosomes, it may provide a minimally invasive means to predict or monitor immunotherapy failure. CircRNAs linked to metastasis and metabolic adaptation, such as CircLARP1B and exosomal circRNA-100338, may further inform prognosis and risk of dissemination. Collectively, these observations support the development of circRNA panels, rather than single markers, to capture the network-level states that underlie resistance, immune escape, and aggressive behavior in HCC.

Therapeutic strategies: how to target a circRNA network

Beyond biomarker applications, circRNA networks present novel therapeutic opportunities. Multiple strategies can be envisioned to directly or indirectly target circRNAs and their downstream effects. Direct targeting approaches include antisense oligonucleotides (ASOs) and siRNAs designed to specifically degrade circRNAs or disrupt their functional interactions [124-129]. Emerging RNA-editing technologies, such as CRISPR-Cas13 systems, offer the possibility of selectively targeting circRNA sequences with high specificity. Advances in nanoparticle- and lipid-based delivery systems further enhance the feasibility of these approaches in vivo.

Given the prominent role of exosome-mediated circRNA transfer in immune regulation, strategies aimed at inhibiting exosome biogenesis, release, or uptake may provide an indirect means to disrupt circRNA-driven immune suppression [130]. Such approaches could be particularly relevant for targeting the circCCAR1 module implicated in immunotherapy resistance [102]. Importantly, circRNA-targeted interventions are unlikely to be used as monotherapies. At present, circRNA-targeted approaches should be regarded as experimental strategies whose potential to enhance existing HCC treatments requires further preclinical and clinical validation [131]. For example, combin-

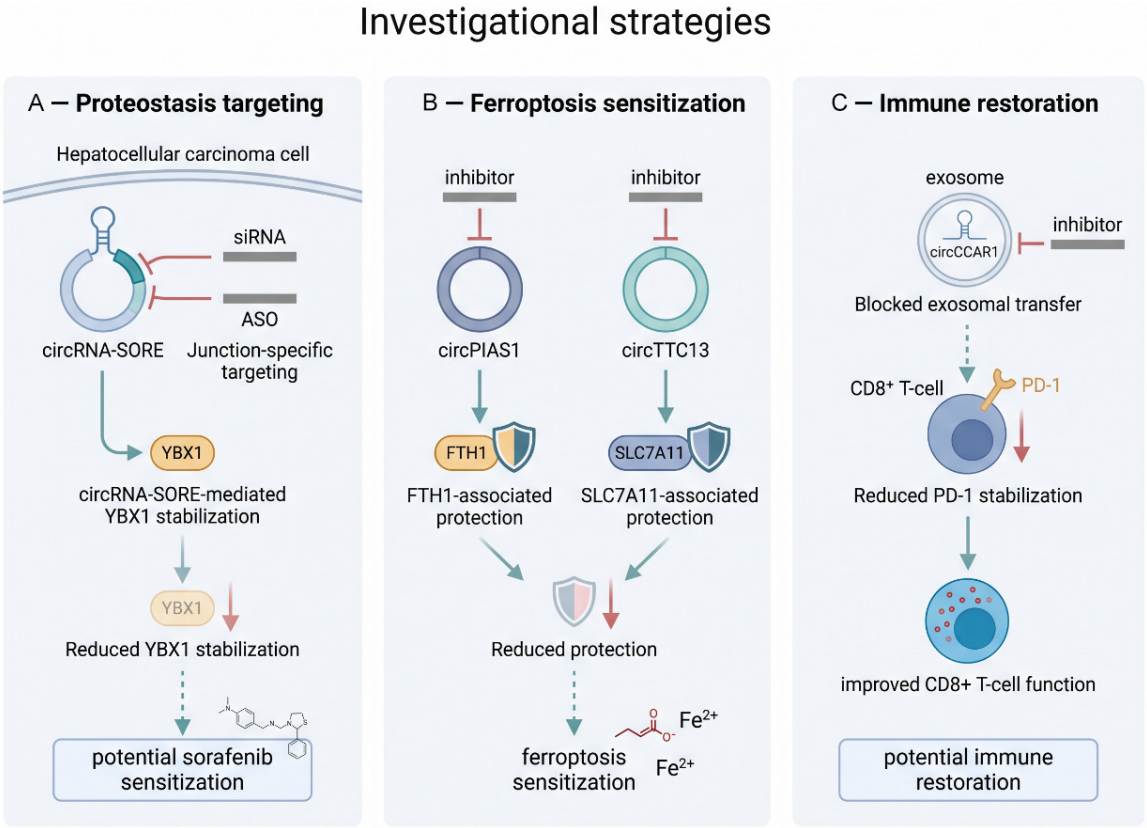


Figure 6. Potential therapeutic strategies targeting circRNA-associated resistance in HCC. A. CircRNA-SORE inhibition may reduce YBX1 stabilization and enhance sorafenib sensitivity. B. Targeting CircPIAS1 or CircTTC13 may impair FTH1-dependent iron storage or SLC7A11-mediated antioxidant defense, increasing ferroptosis susceptibility. C. Inhibiting exosomal circCCAR1 transfer may restore $CD8^+$ T-cell function and improve anti-PD-1 responsiveness. Dashed arrows represent proposed therapeutic effects requiring further validation.

ing TKIs with ferroptosis inducers may counteract circRNA-mediated reinforcement of iron storage and system Xc^- activity, particularly in tumors with elevated FTH1 or SLC7A11 expression [78, 79]. Similarly, combining immune checkpoint blockade with exosome inhibition or disruption of circCCAR1-associated regulatory loops may enhance $CD8^+$ T-cell reinvigoration. Protein stability circuits represent another promising point of convergence. CircRNAs that stabilize oncogenic RBPs and proteins, such as the SORE-YBX1 axis, could be therapeutically targeted in combination with modulators of ubiquitination and deubiquitination [54]. Such strategies would integrate circRNA biology with proteostasis-targeting approaches, providing a conceptual bridge to broader efforts aimed at exploiting ubiquitin signaling in cancer therapy [132]. **Figure 6** outlines potential interventions targeting distinct circRNA-associated resistance mechanisms in HCC. Combining circRNA-directed strategies with existing targeted therapies or immune checkpoint blockade may provide therapeutic opportunities, although clinical efficacy remains to be established.

Practical challenges and limitations

Despite their promise, several challenges must be overcome before circRNA-based strategies can be widely translated into clinical practice. One major issue is the structural complexity of circRNAs. Many genes generate multiple circRNA isoforms with overlapping sequences, complicating accurate detection and selective targeting. Standardization of circRNA annotation, quantification, and validation methods will be essential for reproducibility and clinical deployment. Tissue specificity and off-target effects represent additional concerns. CircRNAs often exhibit context-dependent functions, and perturbing circRNA networks in non-

tumor tissues may have unintended consequences. Achieving tumor-selective delivery and minimizing systemic toxicity remain critical hurdles. For exosomal circRNAs, technical challenges include reliable isolation of tumor-derived exosomes, discrimination from exosomes of non-malignant origin, and accurate quantification of circRNA cargo [133-136]. Without standardized protocols, variability in exosome preparation and analysis could limit clinical applicability. Finally, circRNA networks are inherently dynamic. Their expression and function may evolve during disease progression and under therapeutic pressure, necessitating longitudinal monitoring and adaptive treatment strategies. Addressing these challenges will require close integration of molecular biology, bioinformatics, and clinical research.

The circRNAs discussed in this review represent potential candidates for biomarker development and therapeutic investigation, although their clinical utility remains to be established. Tissue and exosomal circRNA signatures have the potential to predict therapeutic resistance, immunotherapy failure, and metastatic risk, while emerging targeting strategies may enable disruption of circRNA-driven adaptive programs. However, translating these insights into clinical practice will require overcoming technical challenges related to circRNA heterogeneity, specificity, and delivery, as well as a deeper understanding of network dynamics under treatment pressure.

Open questions and future directions

Despite rapid advances in our understanding of circRNA-mediated regulation in hepatocellular carcinoma, many fundamental questions remain unresolved. Addressing these issues will be essential for translating circRNA biology from descriptive studies into mechanistic insight and clinical application. Below, we highlight several key open questions that define important directions for future research.

Selective amplification of circRNAs under therapeutic pressure

One of the most intriguing observations in HCC is that sorafenib resistance is associated with selective increases and decreases in circRNA expression rather than a uniform global increase [137]. The mechanisms underlying this selectivity remain poorly understood. Potential determinants include alterations in RNA processing factors, such as splicing regulators and 3'-end processing components [35, 36], as well as changes in transcriptional dynamics and chromatin-associated regulation that may influence back-splicing efficiency [138]. Changes in circRNA stability may also contribute, as illustrated by circRNA-SORE in sorafenib-resistant HCC cells [123]. Future studies should investigate how drug-induced signaling pathways, metabolic stress, and inflammatory cues converge on the RNA processing machinery to bias circRNA production. Integrative analyses combining chromatin accessibility, transcription dynamics, and circRNA biogenesis profiling may be required to uncover the upstream logic governing circRNA selectivity.

Quantifying the contribution of non-ceRNA mechanisms

Although miRNA sponging remains a prominent theme in circRNA research [139], accumulating evidence indicates that non-ceRNA mechanisms - such as protein stabilization [54], modulation of phase separation, and translational control [55] - play critical roles in shaping tumor behavior. However, the relative contribution of these mechanisms in HCC remains unclear. A key challenge for the field is to move beyond binary classifications of circRNA function and develop quantitative frameworks that assess how frequently and under what conditions circRNAs exert protein-centric versus RNA-centric effects. Systematic mapping of circRNA-protein interactomes, coupled with functional perturbation studies, will be necessary to determine the true prevalence and impact of these noncanonical mechanisms.

Coupling between ferroptosis regulation and antitumor immunity

Ferroptosis and antitumor immunity have traditionally been studied as distinct processes, yet emerging evidence suggests they are functionally intertwined. Changes in ferroptosis sensitivity may influence the immunogenicity of dying tumor cells, the release of danger-associated molecular patterns, and the metabolic landscape of the tumor microenvironment. Conversely, immune-derived cytokines and metabolic competition can modulate ferroptosis

thresholds in tumor cells. How circRNA-mediated control of ferroptosis affects $CD8^+$ T-cell function and responsiveness to immune checkpoint blockade remains an open question [140-142]. Elucidating this coupling may reveal new opportunities to coordinate ferroptosis induction with immunotherapy, thereby overcoming resistance rooted in both metabolic and immune adaptation. Importantly, most available studies investigate circRNA-mediated ferroptosis regulation and immune modulation in separate experimental systems, making it difficult to establish direct mechanistic interactions between these processes. Future studies should determine whether perturbation of a specific circRNA simultaneously alters ferroptosis sensitivity and $CD8^+$ T-cell function within the same HCC model. Such investigations would be essential for distinguishing genuine cross-pathway regulation from parallel but independent circRNA-associated mechanisms.

Origin and targeting specificity of exosomal circRNAs

The discovery that circRNAs can be selectively packaged into exosomes and transferred to immune cells raises important questions about their cellular origin and targeting specificity. It remains unclear whether all tumor cells contribute equally to the exosomal circRNA pool or whether distinct tumor subpopulations preferentially export circRNAs associated with immune suppression or metastasis. Single-cell and spatial transcriptomic approaches, combined with exosome tracing technologies, may help resolve whether circRNA-loaded exosomes originate from specific niches within the tumor. Understanding the determinants of exosome uptake by immune cells could further inform strategies to disrupt circRNA-mediated intercellular communication.

Prevalence and functional relevance of viral circRNAs in HCC

HBV-encoded circRNAs represent a newly recognized layer of regulation in hepatocellular carcinoma, yet their prevalence and functional diversity remain largely unexplored. Whether additional viral circRNAs exist and contribute to therapy resistance or immune evasion is an open question with significant implications for HBV-associated HCC [143-148]. Future research should systematically characterize viral circRNA repertoires and investigate how they interact with host circRNA networks. Such studies may reveal pathogen-specific vulnerabilities and inform tailored therapeutic strategies for virally driven HCC.

Clinical stratification and rational combination strategies

Finally, translating circRNA biology into clinical benefit will require precise patient stratification. Identifying which patients are most likely to benefit from combinations such as TKI plus ferroptosis induction or immune checkpoint blockade plus exosome inhibition remains a major challenge [149-151]. Integrating circRNA expression profiles with clinical parameters, genomic features, and immune phenotypes may enable the development of predictive models that guide treatment selection. Prospective studies incorporating circRNA biomarkers into clinical trial design will be essential to validate these approaches and establish their clinical utility.

Collectively, these open questions underscore the complexity and promise of circRNA-mediated regulation in hepatocellular carcinoma. Addressing issues of selectivity, mechanism, intercellular communication, viral contribution, and clinical stratification will be critical for advancing circRNA research from mechanistic insight to therapeutic innovation. Continued interdisciplinary efforts integrating molecular biology, systems analysis, and clinical investigation are poised to define the next phase of circRNA-driven cancer research.

Conclusion

Collectively, the studies reviewed here demonstrate that selected circRNAs participate in distinct regulatory processes associated with hepatocellular carcinoma progression and therapeutic resistance, including protein homeostasis, ferroptosis regulation, and tumor-immune communication. Mechanistic investigations of circRNA-SORE, CircPIAS1, CircTTC13, and exosomal circCCAR1 provide evidence for their context-dependent roles in protein stability, ferroptosis susceptibility, and immune dysfunction. However, these findings largely originate from independent experimental studies and do not yet establish a unified circRNA-centered regulatory network linking these process-

es. Accordingly, the integrative framework proposed in this review should be regarded as a conceptual model that highlights potential mechanistic connections and future research priorities. Further studies integrating multi-omics profiling, functional perturbation, and clinically relevant models are needed to determine whether these pathways interact and whether their combined targeting can improve therapeutic responses in HCC.

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Disclosure of conflict of interest

None.

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