

Liquid-liquid phase separation and post-transcriptional regulation intersection: A new paradigm of RNA-binding protein condensates in hepatocellular carcinoma malignant phenotypes (Review)

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Abstract. Liquid-liquid phase separation (LLPS) enables RNA-binding proteins (RBPs) to assemble into dynamic biomolecular condensates that influence post-transcriptional regulation. In hepatocellular carcinoma (HCC), these condensates may alter RNA processing and stability. They can also influence transcript localization and translational output. Through these effects, RBP condensates may contribute to tumor growth and metastatic progression. They may further support metabolic adaptation, immune evasion and resistance to therapy. The present review focuses on the intersection between LLPS and post-transcriptional regulation in HCC. In addition, the present review critically assessed current evidence for RBP condensate function and distinguish direct HCC findings from mechanistic extrapolation. Unresolved questions regarding causality and clinical translation were also discussed. This framework may help clarify how condensate biology contributes to HCC and where therapeutic opportunities remain.

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1. Introduction

Hepatocellular carcinoma (HCC) is characterized by extensive dysregulation of gene expression, and post-transcriptional control has emerged as a notable determinant of tumor cell behavior (1). RNA-binding proteins (RBPs) regulate multiple stages of RNA metabolism and thereby influence the abundance and spatial availability of proteins required for tumor growth and adaptation (1). Their dysregulation provides an important regulatory layer beyond transcription alone and contributes to the progression of HCC.

Liquid-liquid phase separation (LLPS) provides a mechanism through which RBPs and RNA molecules can assemble into dynamic biomolecular condensates (2). These condensates concentrate selected molecular components and create spatial environments in which RNA metabolism can be regulated. Emerging evidence supports the functional relevance of this organization in HCC. For example, ataxin 2 like (ATXN2L) undergoes LLPS and forms granules that recruit translation initiation factors, thereby increasing the translation of oncogenic mRNAs in HCC (3). RBP-dependent RNA regulation is also linked to other malignant processes (4). The circLARP1B-heterogeneous nuclear ribonucleoprotein D (HNRNPD) axis contributes to lipid accumulation and metastasis in HCC, whereas enhanced insulin-like growth factor 2 mRNA-binding protein (IGF2BP)1-mediated m6A recognition promotes HCC progression (5,6).

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The specific focus of the present review is the mechanistic connection between condensate organization and post-transcriptional regulation in HCC. The present review proposes a framework in which changes in RBP abundance or molecular interactions first alter condensate assembly and dynamics. Changes in post-translational regulation and RNA binding may further modify these condensates (7). Once condensate behavior is altered, RNA fate can also change. This may affect how transcripts are processed and maintained, while also influencing their subcellular localization and translational output. These molecular effects can subsequently contribute to tumor cell proliferation and survival (8). They may also promote invasion and metastatic progression, while supporting metabolic adaptation, immune escape, and resistance to therapy (9). In this framework, RBP condensates are therefore considered spatial post-transcriptional regulatory nodes that connect molecular organization with the malignant behavior of HCC cells, rather than isolated manifestations of LLPS. This proposed framework is summarized in Fig. 1.

Accordingly, the present review gives priority to evidence obtained directly from HCC or primary liver cancer models. Observations from other experimental systems are used only to provide mechanistic context when HCC-specific evidence remains limited. In addition, how this framework may inform the development of biomarkers and therapeutic strategies was further examined (10). Particular attention is given to interventions that alter pathological condensate formation or interfere with RBP-RNA regulatory networks. By organizing the available evidence along the relationship between condensate behavior, RNA regulation and HCC phenotypes, it was the aim to distinguish established mechanisms from unresolved questions and thereby provide a more focused basis for future translational studies.

2. Basic biological principles of LLPS and RBP condensates

Physical chemistry basis and driving forces of LLPS. LLPS is a reversible demixing process through which biomolecules can form a concentrated phase while remaining dynamically exchangeable with the surrounding environment (11). Phase separation occurs when biomolecular concentration and interaction valency exceed a context-dependent saturation threshold, that is, the concentration above which a homogeneous solution separates into coexisting dense and dilute phases (11,12). In RBP-containing systems, weak multivalent electrostatic, aromatic and hydrophobic interactions provide an important basis for this process (12,13). Intrinsically disordered regions can support these interactions, while RNA concentration, temperature, pH, ionic strength and molecular crowding can shift the saturation threshold and alter condensate properties (14,15). These principles provide the necessary biophysical framework for understanding RBP condensates in HCC and are not reintroduced in the subsequent mechanistic sections.

Overview of major types and functions of RBP condensates. RBP condensates differ substantially in molecular composition and therefore do not produce a uniform effect on RNA fate (16). Stress granules transiently reorganize non-translating mRNAs during cellular stress, whereas P-bodies are associated with

translational repression and RNA turnover (17,18). Nuclear RNA-associated condensates provide spatial organization for RNA processing and related regulatory events (19,20). These examples establish the functional diversity of RBP condensates; the subsequent sections therefore focus on their relevance to HCC rather than repeating their general definitions.

At the molecular level, RBP condensates regulate RNA fate through selective partitioning rather than simple physical enclosure (21). Multivalent interactions allow particular RNAs to partition preferentially into an RBP-rich phase (22). RNA itself can contribute to this process because its modification state can alter RNA-protein interactions and thereby influence phase behavior (23). RNA structure can also affect condensate properties, although the functional consequences depend on the specific RNA-RBP system (24,25). Once a transcript is enriched within a condensate, it encounters a local molecular environment that differs from the surrounding cytoplasm. The resulting effect is determined by the composition of that environment rather than by condensation alone. For example, P-bodies contain RNA-decay machinery and can support transcript repression or degradation, whereas other RBP-rich assemblies can retain transcripts together with factors that favor their persistence or subsequent translation. Condensates should therefore be viewed as dynamic reaction environments that alter molecular access and local interaction probabilities rather than as impermeable compartments.

3. Aberrant expression and altered phase separation capacity of key RBPs in liver cancer

Upregulation of oncogenic RBPs and enhanced condensate formation. Oncogenic RBPs such as members of the IGF2BP family, LIN28B and human antigen R (HuR) are frequently upregulated in HCC (26). Functional studies have linked enhanced IGF2BP1 activity to m6A-dependent oncogenic RNA regulation and HCC progression (6), whereas LIN28B has been shown to increase the translation of an oncofetal RBP regulon required for liver tumor initiation (27). HuR upregulation has also been associated with proliferative, invasive and treatment-resistant phenotypes in hepatobiliary tumors (26). Increased RBP abundance may favor condensate assembly when the relevant molecular interactions are present, while post-translational regulation can further modify condensate dynamics (28). These mechanisms may alter the local organization of oncogenic transcripts. However, these functional consequences should not be attributed to increased condensate formation without direct phase-separation evidence.

Clinical associations support the relevance of RBP dysregulation to HCC but do not by themselves establish a causal role for phase separation. Prognostic models based on RBP expression profiles can distinguish patients with different clinical outcomes (29). However, these associations cannot determine whether altered condensate behavior contributes directly to tumor progression or instead accompanies changes in RBP abundance and tumor state. Therefore these findings are interpreted as evidence of clinical association rather than mechanistic proof of condensate-driven malignancy.

Beyond the more extensively studied RBP families, emerging evidence indicates that additional phase-separating

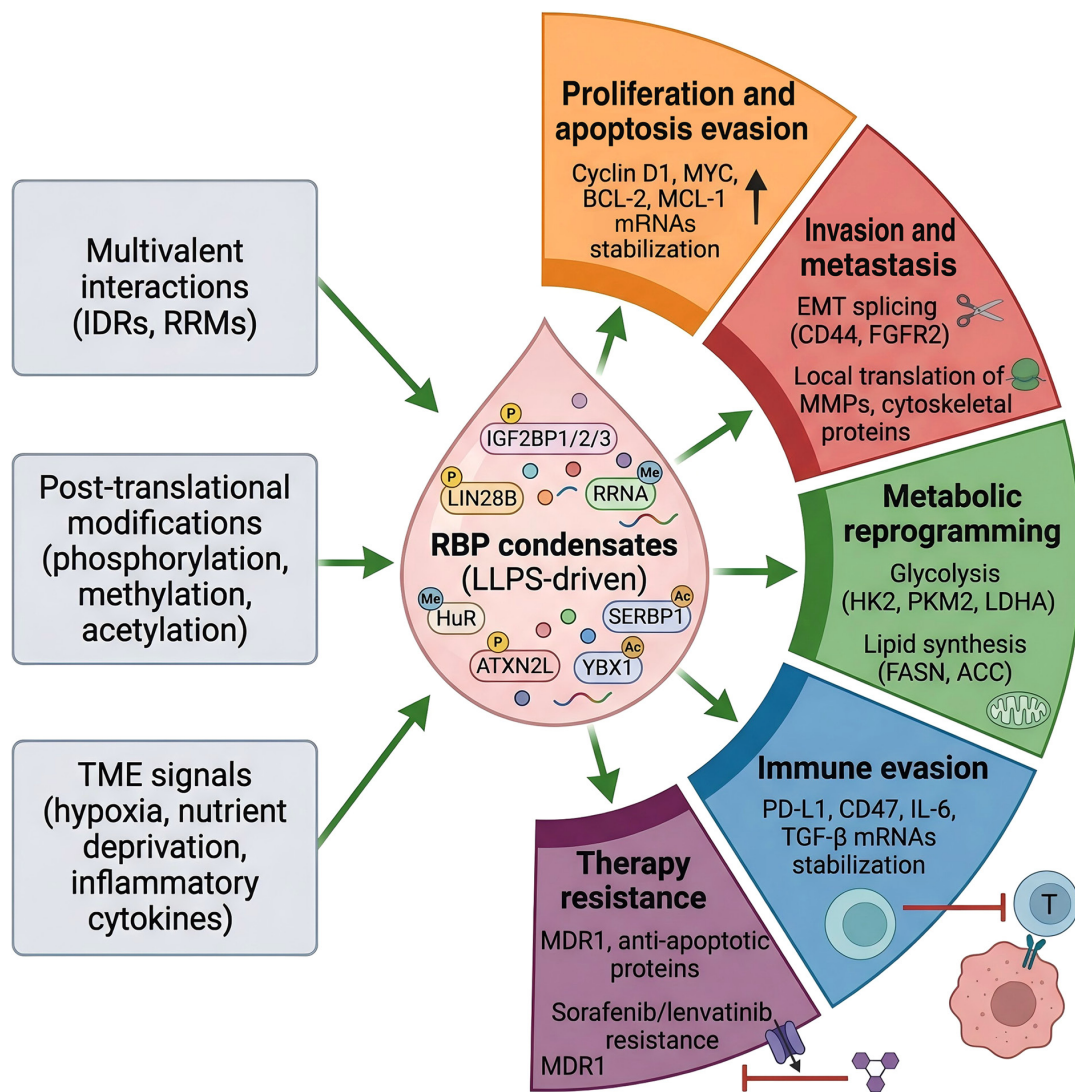


Figure 1. Schematic illustration of the fundamental process by which RBP condensates promote malignant phenotypes in hepatocellular carcinoma through LLPS. Multivalent interactions between IDRs and RRM)s form RBP condensates that are regulated by post-translational modifications and TME cues. These condensates specifically enrich and stabilize important mRNAs and influence six malignant phenotypes: Proliferation, apoptosis evasion, invasion and metastasis, metabolic reprogramming, immune evasion and therapeutic resistance. RBP, RNA-binding protein; RRM)s, RNA recognition motifs; IDR, intrinsically disordered regions; TME, tumor microenvironment; LLPS, liquid-liquid phase separation; IGF2BP, insulin-like growth factor 2 binding protein; HuR, human antigen R; ATXN2L, ataxin-2-like protein; YBX1, Y-box binding protein 1; SERBP1, SERPINE1 mRNA-binding protein 1; EEF1E1, eukaryotic translation elongation factor 1 epsilon 1; rRNA, ribosomal RNA; FGFR2, fibroblast growth factor receptor 2; HK2, hexokinase 2; PKM2, pyruvate kinase isozyme M2; LDHA, lactate dehydrogenase A; FASN, fatty acid synthase; ACC, acetyl-CoA carboxylase.

proteins may contribute to HCC biology; ATXN2L provides one such example. It undergoes LLPS in HCC and forms granules that recruit eukaryotic translation initiation factors and enhance the translation of specific oncogenic targets, including ADAM metalloproteinase domain 9 mRNA (3). Eukaryotic translation elongation factor 1 epsilon 1 represents another emerging condensate-associated protein. Its phase separation has been linked to tumor stemness in HCC and contributes to PTEN/AKT-mediated DNA repair (30). These findings broaden the range of RBP-related condensates implicated in HCC and suggest that the currently characterized regulators represent only part of a larger network (31). However, the available evidence remains uneven across individual RBPs, and the functions established for well-studied proteins should not be assumed to apply to less characterized candidates.

Tumor-suppressive RBP dysfunction and potential alterations in phase separation. Direct evidence that loss of tumor-suppressive RBPs impairs LLPS-dependent condensate function in HCC remains limited; the closest HCC evidence, described in this subsection, involves circASH2-regulated Y-box-binding protein 1 (YBX1) phase separation. Studies in other malignancies provide mechanistic precedents but should not be interpreted as direct HCC evidence. For example, RNA-binding motif protein 10 has tumor-suppressive functions in lung adenocarcinoma, whereas colorectal cancer-associated poly(rC)-binding protein 1 (PCBP1) L100/L102 mutations have been shown to destabilize the protein, increase its cytoplasmic localization and suppress wild-type PCBP1 through a dominant-negative mechanism (32-34). A direct HCC precedent involves circASH2 rather than loss of YBX1 itself: circASH2 is preferentially lost in HCC, and its

restoration enhances nuclear YBX1-mediated phase separation, promotes tropomyosin 4 transcript decay and suppresses metastasis (35). Thus, loss of circASH2 is expected to weaken this antimetastatic condensate axis. However, whether loss of tumor-suppressive RBPs promotes HCC specifically through impaired phase separation remains to be established. Table I summarizes the key RBPs that are dysregulated in HCC and undergo LLPS, the drivers of their phase separation, mRNA targets, biological functions and clinical associations.

4. Regulation of HCC cell proliferation and apoptosis escape by RBP condensates

Concentration and stabilization of pro-proliferative and anti-apoptotic mRNAs. Oncogenic RBP assemblies can alter the stability and translational output of selected transcripts (36,37). However, the term ‘protection’ should not be interpreted as simple physical sequestration. In this context, protection of an mRNA does not imply that the transcript is enclosed within an impermeable structure. A more appropriate mechanistic interpretation is that selective partitioning changes the molecular environment surrounding the transcript. Association with specific RBPs can favor retention of selected mRNAs within an RBP-rich assembly and can alter their exposure to competing regulatory factors. Stress-induced clustering of IGF2BP proteins provides an example of how these RBPs can assemble with mRNA-containing granules (38). The resulting effect on RNA stability depends on which factors are preferentially recruited to, or excluded from, the same molecular environment.

This distinction is important because condensation does not invariably stabilize RNA. Condensates that contain decay-associated factors can instead facilitate transcript turnover. For example, direct interactions between the intrinsically disordered regions of tristetraprolin (TTP) and mRNA-decapping enzyme 2 contribute to the decay of AU-rich element-containing mRNAs (39), illustrating that intrinsically disordered region-mediated recruitment of decay factors can promote, rather than prevent, degradation of the bound transcripts. In HCC, TTP loss during hepatocyte dedifferentiation, which removes this decay activity, increases cancer cell migration and invasion, and is associated with high-grade disease and poor prognosis (40). However, TTP may promote hepatic inflammation and tumor initiation at earlier stages (40). Thus, the relevant mechanism is selective organization of RNA together with particular regulatory proteins rather than a general shielding effect of phase separation. In oncogenic RBP assemblies, enrichment of stabilizing RBPs may shift this balance toward transcript persistence. By contrast, recruitment of decay-promoting proteins can shift the same principle toward RNA degradation.

RNA conformation may provide an additional level of regulation, because RNA structural features can influence condensate phase behavior (41). However, direct evidence that oncogenic mRNAs in HCC are stabilized because condensation imposes a specific protective RNA conformation remains limited. Therefore this possibility is distinguished from the better-supported mechanism of selective molecular partitioning.

Regulation of translation efficiency of cell cycle checkpoint-related mRNAs. Under cellular stress, stress-responsive RBP condensates can reorganize the translational program by changing the local availability of mRNAs and translational machinery (42). Conditions relevant to the HCC microenvironment, including nutrient deprivation and hypoxia, may promote this adaptive remodeling. Therefore, the focus is on how changes in condensate organization affect translational control rather than restating the general principles of LLPS.

Condensates can regulate translation by changing the spatial availability of the translational machinery. Under stress, recruitment of translation initiation factors and ribosomal components into stress-related assemblies can reduce their availability to the bulk cytoplasm and contribute to translational repression (17,42). The opposite effect can occur when a condensate locally enriches factors that support translation. In HCC, ATXN2L undergoes LLPS and forms granules that recruit translation initiation factors, thereby enhancing the translation of oncogenic mRNAs (3). These observations illustrate that the functional consequence of condensation depends on molecular composition; the same general principle of local enrichment can either restrict or promote translation depending on which factors and transcripts partition into the condensate (3,17,42).

Moreover, RNA modifications on target transcripts can provide an additional layer of translational control. Stabilization and amplification of the translation of transcripts related to the metabolism and the cell cycle have been reported to be affected by enzymes such as N-acetyltransferase 10 (NAT10). In HCC, NAT10 catalyzes N4-acetylcytidine (ac4C) modifications within the coding sequence of HMGB2 mRNA. This modification facilitates eukaryotic translation elongation factor 2 binding to the modified sites and thereby increases HMGB2 translation, which promotes HCC proliferation and metastasis (43). Thus, RNA modification can be coupled to translational regulation (43). Direct evidence that this NAT10-ac4C mechanism requires the recruitment of HMGB2 mRNA into an RBP condensate is currently lacking. In addition to facilitating metabolic reprogramming, this axis has been found to play a role in cell cycle progression maintenance in response to stress, facilitating tumor growth and resistance to therapy.

RBP condensates should not be considered to have a fixed function across all HCC cells. Their behavior can change when tumor cells encounter microenvironmental stress (44). Under relatively well-oxygenated conditions, stress-responsive condensation may exert a more limited influence on the translational program. By contrast, hypoxia can increase cellular stress and favor the formation or remodeling of stress-related condensates. These changes may suppress general translation while preserving the expression of transcripts that support cellular adaptation. Thus, the contribution of an RBP condensate may vary across different regions of the same tumor. Direct spatial evidence comparing identical condensates between well-oxygenated and hypoxic regions of HCC remains limited, and this proposed regional difference requires further validation.

5. Molecular mechanisms linking RBP condensates to HCC invasion and metastasis

Regulation of splicing and expression of epithelial-mesenchymal transition-related transcripts. In HCC, direct

Table I. Representative RBP condensates in HCC: Functions, targets and clinical implications.

RBP condensate	Phase separation driver	Major mRNA targets	Biological function	Malignant phenotype	Clinical prognosis	(Refs.)
IGF2BP1/2/3	IDRs, KH domains	MYC, CCND1, BCL-2, MCL-1, PFKL	mRNA stability ↑, translation ↑	Proliferation, metabolism, apoptosis evasion	High expression associates with poor prognosis	(29,38,51,54)
LIN28B	IDRs, CSD	Oncofetal RBP regulon	Translation ↑	Tumor initiation	Supports liver tumor initiation	(27)
HuR (ELAVL1)	RRM, IDR	PD-L1, IL-6, TGF-β, lipogenic enzymes	mRNA stability ↑	Immune evasion, metabolism	High expression associates with metastasis and resistance	(26,63)
ATXN2L	IDRs	ADAM9, oncogenic targets	Translation initiation ↑	Proliferation, therapy resistance	Promotes tumor progression	(3)
YBX1	IDRs, cold-shock domain	TPM4 mRNA	TPM4 mRNA decay	Metastasis suppression	Antimetastatic in liver cancer models	(35)
SERBP1	Intrinsic disorder	RNA binding partners	LLPS-mediated RNA metabolism	Tumor stemness	Promotes cancer-related processes	(28)
ZNF385A/ ZNF346	Zinc finger domains	PD-L1, CD47, cytokine mRNAs	mRNA stability ↑	Immunosuppressive microenvironment	High expression associates with immune evasion	(72)
RALY	RRM	FXYD5, HK2	mRNA stability ↑	Aerobic glycolysis	Promotes progression (in pancreatic cancer; analogous in HCC)	(53)
EEF1E1	IDRs	PTEN/AKT signaling	DNA repair, stemness	Stemness, DNA repair	High expression associates with poor prognosis	(30)

Summary of key RBPs known to undergo LLPS in HCC, their molecular features, mRNA targets, biological functions, associated malignant phenotypes and clinical relevance. RBP, RNA binding protein; HCC, hepatocellular carcinoma; IDR, intrinsically disordered region; RRM, RNA recognition motif; CSD, cold-shock domain; LLPS, liquid-liquid phase separation; PD-L1, programmed death-ligand 1; HK2, hexokinase 2; KH, K homology; BCL-2, B-cell lymphoma 2; MCL-1, myeloid cell leukemia 1; ELAVL1, ELAV-like RNA-binding protein 1; TPM4, tropomyosin 4; ZNF, zinc finger protein; CCND1, cyclin D1; PFKL, phosphofructokinase liver type; ADAM9, ADAM metalloproteinase domain 9; IGF2BP, insulin-like growth factor 2 binding protein; HuR, human antigen R; ATXN2L, ataxin-2-like protein; YBX1, Y-box binding protein 1; SERBP1, SERPINE1 mRNA-binding protein 1; EEF1E1, eukaryotic translation elongation factor 1 epsilon 1.

evidence supports a role for RBP-mediated splicing dysregulation in tumor progression, whereas the specific contribution of LLPS to these splicing events remains less established. Loss of epithelial splicing regulatory protein 2 (ESRP2) activates a fetal RNA-splicing program and TGF- β -activated kinase 1 (TAK1)-MAPK signaling to promote HCC progression (45). In a liver-related but non-tumor model, LINC00663 regulates serine/arginine-rich splicing factor 1 (SF2)-mediated fibronectin splicing in hepatic stellate cells (46). Therefore, the latter finding is considered a mechanistic precedent for liver-associated splicing regulation rather than direct evidence of an HCC condensate mechanism.

Subcellular localization and local translation control of pro-metastatic mRNAs. RBP-containing transport assemblies can influence the subcellular localization and local translation of transcripts involved in cell migration (47); however, direct evidence for condensate-dependent transport of specific pro-metastatic mRNAs in HCC remains limited. Studies of stress-granule biogenesis at the endoplasmic reticulum provide a mechanistic model for coupling RNA export, transport and local translation, but this model requires direct validation in HCC (48).

In colorectal cancer, LOC101927668 recruits hnRNP D and destabilizes RNA binding motif protein 47 mRNA, thereby modifying p53-related signaling (49). This study provides a mechanistic precedent for RBP-dependent control of metastasis-related transcripts, but it should not be considered direct evidence of an HCC condensate mechanism (50). Future studies should identify the RNA cargos and interaction partners of HCC condensates at invasive fronts and determine whether their spatial regulation is required for metastatic behavior.

6. Role of RBP condensates in metabolic reprogramming of liver cancer

mRNA metabolism of aerobic glycolysis-related enzymes in tissues. Aerobic glycolysis is a common feature of HCC and supports tumor-cell biosynthetic and energetic demands. RBP-dependent post-transcriptional regulation can influence the expression of glycolytic enzymes, although direct evidence for condensate-dependent control varies across individual mechanisms (51).

IGF2BPs and others have been demonstrated to sense the presence of m6A marks on the mRNAs of metabolic enzymes to stabilize these transcripts and facilitate their translation (52). As an example, mRNAs encoding glycolytic enzymes become more stable with the help of IGF2BPs, allowing metabolic reprogramming of tumors. Likewise, the RBP RALY stabilizes FXR1 mRNA, resulting in increased hexokinase 2 (HK2) expression and aerobic glycolysis in pancreatic cancer cells, demonstrating how RBPs can regulate the stability of glycolytic enzyme mRNAs and tumor progression (53). YTH domain-containing family protein (YTHDF)3, an m6A reader protein, facilitates aerobic glycolysis by stabilizing phosphofructokinase liver type (PFKL), a key glycolytic enzyme, via m6A-dependent mechanisms, in HCC. Notably, PFKL also stabilizes the YTHDF3 protein, creating a positive feedback mechanism to increase glycolytic flux and tumor malignancy (54).

The coordination of glycolytic enzyme-coding mRNAs into RBP condensates enables them to be coordinately regulated. Such a spatial colocalization in condensates increases mRNA stability and translation efficiency, thus coordinating the expression of several glycolytic enzymes, including HK2, pyruvate kinase isozyme M2 (PKM2) and lactate dehydrogenase A (LDHA). As an example, circCDKN2B-AS1, a circular RNA (circRNA), can bind the RBP IMP3 to stabilize HK2 mRNA, inducing aerobic glycolysis and malignant phenotypes in cervical cancer (55). Likewise, LDHA mRNA can be stabilized by the long non-coding RNA (lncRNA) DIO3OS, which binds to polypyrimidine tract-binding protein 1, an RBP, to promote glycolytic metabolism and, in part, aromatase inhibitor resistance in breast cancer (56). The results of this study highlight the significance of mRNA stabilization by RBP in the control of enzymes of the glycolytic pathway.

Another notable post-transcriptional regulatory process that depends on the RBPs in the condensates is the alternative splicing of PKM pre-mRNA. The PKM gene encodes two isoforms (PKM1 and PKM2) by mutually exclusive splicing of exons 9 and 10. PKM2 is more biased towards aerobic glycolysis and tumor development. The regulation of this splicing event is by RBPs such as hnRNPs and polypyrimidine tract binding protein (PTB). PTB facilitates PKM1-to-PKM2 transition, which increases glycolytic flux and proliferation of keloid fibroblasts, which is applicable to tumor-like metabolic reprogramming (57). In colorectal cancer, the lncRNA SNHG6 interacts with hnRNP A1 to modulate PKM alternative splicing, increasing the PKM2/PKM1 ratio and promoting aerobic glycolysis (58). Alternatively, hnRNPs create a network of regulation of PKM splicing, which plays a role in tumor development and is a potential therapeutic target.

RBP-dependent control of circRNA formation can also influence PKM2 activity, although a condensate requirement has not been demonstrated. In glioblastoma, zinc finger CCHC-type and RNA-binding motif-containing protein 1 overexpression promotes Alu element-mediated formation of circHEATR5B; this circRNA encodes HEATR5B-881aa, which directly interacts with jumonji domain-containing protein 5 (JMJD5) and reduces its stability through phosphorylation at S361. The resulting loss of JMJD5 increases the pyruvate kinase activity of PKM2, thereby suppressing aerobic glycolysis and tumor growth (59). This highlights the intricate interactions between RBPs, circRNAs and glycolytic enzymes in cancer metabolism.

In HCC, NSUN2 directly modifies PKM2 mRNA at C773 in the 3'untranslated region, increasing its stability and thereby promoting glycolysis, tumor growth and metastasis (60). NSUN2 and PKM2 expression is downregulated with electroacupuncture and moxibustion therapy, which inhibits glycolytic flux and tumor proliferation, indicating that regulating RBP-mediated expression of glycolytic enzymes can be therapeutically advantageous (60). This axis exemplifies the effects of RBP-dependent post-transcriptional regulation, but an LLPS requirement has not been demonstrated, as neither NSUN2 condensate formation nor recruitment of PKM2 mRNA into condensates was examined. In addition, glucose deprivation upregulates sestrin-2 (SESN2) expression through a nuclear factor erythroid 2-related factor 2/activating transcription factor 4-dependent mechanism. SESN2 competes

with IGF2BP3 for binding to the 3'untranslated region of HK2 mRNA, destabilizing the transcript and disrupting IGF2BP3-HK2 mRNA stress granules, thereby suppressing aerobic glycolysis while protecting HCC cells from glucose starvation-induced apoptosis (61).

Collectively, these studies indicate that RBP condensation orchestrates the post-transcriptional regulation of mRNAs encoding the major glycolytic enzymes in liver cancer and other malignancies. RBPs are able to co-localize these mRNAs, increasing their stability and translation, promoting the Warburg effect, and promoting malignant phenotypes. Moreover, RBPs control other splicing events, including PKM-isoform switching, in order to promote aerobic glycolysis (62). Knowledge of these processes sheds new light on the metabolic susceptibility of liver cancer and suggests new avenues of therapeutic intervention to interfere with RBP-mediated mRNA metabolism and inhibit tumor glycolysis and progression.

Regulation of transcripts related to lipid synthesis and glutamine metabolism. Direct HCC evidence supports RBP-dependent post-transcriptional regulation of lipid metabolism, although direct evidence that these effects require LLPS remains limited. CircLARP1B cooperates with HNRNP D to disrupt liver kinase B1 mRNA and promotes lipid accumulation and metastasis in HCC (5). By contrast, HuR-mediated regulation of H19 in hepatocytes under metabolic stress and TFEB-dependent regulation of glutaminase in pancreatic cancer are retained only as mechanistic precedents (63,64). These findings suggest potential routes for RBP-mediated metabolic regulation, but they do not establish the same condensate-dependent mechanisms in HCC (65-67).

These RBP-regulatory networks also provide a conceptual link between metabolic reprogramming and the immune microenvironment, as summarized in Fig. 2 (68,69). The extent to which this coordination depends directly on condensate formation remains to be established.

7. RBP condensate-mediated regulation of the liver cancer immune microenvironment and therapeutic resistance

Impact on the expression of immune checkpoint molecules and cytokines. RBP-dependent post-transcriptional regulation and the immune microenvironment are likely to influence one another rather than operate as separate processes. Changes in local stress and inflammatory signaling may alter RBP activity and condensate behavior. In turn, altered RNA regulation in tumor cells can modify pathways that affect immune-cell recruitment and immune suppression (70,71). Current HCC evidence supports this reciprocal model at the level of RBP regulation, but direct demonstration of condensate dependence remains incomplete. This distinction is important when interpreting the contribution of RBP condensates to the tumor microenvironment (TME).

The relevance of RBP regulation to the HCC immune environment is also illustrated by the zinc finger proteins (ZNFs) ZNF385A and ZNF346. These RBPs are upregulated in HCC and are associated with poor prognosis, in part because they are linked to an inflamed but immunosuppressive TME. They show positive associations with immune checkpoint

gene expression and infiltration of immunosuppressive cells, including regulatory T cells and myeloid-derived suppressor cells. Knockdown models suggest that their regulatory activities are involved in HCC cell proliferation, migration, tumor progression and immune responses (72); however, current evidence does not establish that these effects require condensate formation. Epithelial splicing regulatory protein 2 (ESRP2) represents an HCC-relevant RBP whose loss has been shown to activate a fetal RNA-splicing program and TAK1-MAPK signaling, thereby promoting HCC progression (45). However, this previous study did not establish whether ESRP2 regulated immune-cell infiltration or required condensate formation.

Induction of chemotherapy resistance and targeted therapy resistance. In HCC, direct evidence links phase-separated RBP-containing assemblies to targeted-therapy adaptation. ATXN2L undergoes LLPS and enhances mRNA translation in HCC (3). In addition, CREB-regulated transcription coactivator 2 (CRTC2) forms co-condensates with YTHDF2 that enhance the translation of m6A-modified mRNAs and drive hepatocarcinogenesis and lenvatinib resistance (73). CAPRIN1 provides a second targeted-therapy example: Through its RGG domain, CAPRIN1 recruits nuclear receptor coactivator 4 (NCOA4) mRNA into stress granules, suppresses NCOA4 translation, attenuates sorafenib-induced ferroptosis and promotes sorafenib resistance (74). Evidence has also supported RBP-dependent chemotherapy resistance, but has not yet clarified whether this extends to condensate-dependence. Parkinson disease protein 7-driven lactylation of IGF2BP3 at K76 has been shown to increase its binding to m6A-modified ferroptosis suppressor protein 1 (FSP1) mRNA, elevate FSP1 expression and promote resistance to oxaliplatin/5-fluorouracil-based hepatic-artery infusion chemotherapy (75). Outside of HCC, uridine diphosphoglucuronic acid has been shown to activate protein kinase R, thereby promoting DNA topoisomerase 2 α phase separation and radioimmunotherapy resistance (76), providing supportive mechanistic context rather than direct HCC-specific evidence.

These mechanistic observations also define potential therapeutic entry points. When condensate function depends on the recruitment of specific molecular partners, disrupting the relevant interaction may provide a more selective strategy than non-specific condensate dissolution (77). CAPRIN1 illustrates this principle because its RGG domain recruits NCOA4 mRNA into stress granules and suppresses NCOA4 translation. CRTC2-YTHDF2 co-condensates provide another example because recruitment of YTHDF2 supports the enhanced translation of m6A-modified mRNAs during hepatocarcinogenesis and lenvatinib resistance. These mechanisms identify potentially targetable interaction steps, although direct inhibitors of these HCC-specific condensate interfaces remain to be established.

8. Targeting RBP condensates: A novel strategy for liver cancer diagnosis and treatment

RBP condensates as potential diagnostic and prognostic biomarkers. Evidence supporting RBP condensates as biomarkers in HCC remains preliminary. Most available clinical observations concern RBP expression or LLPS-related

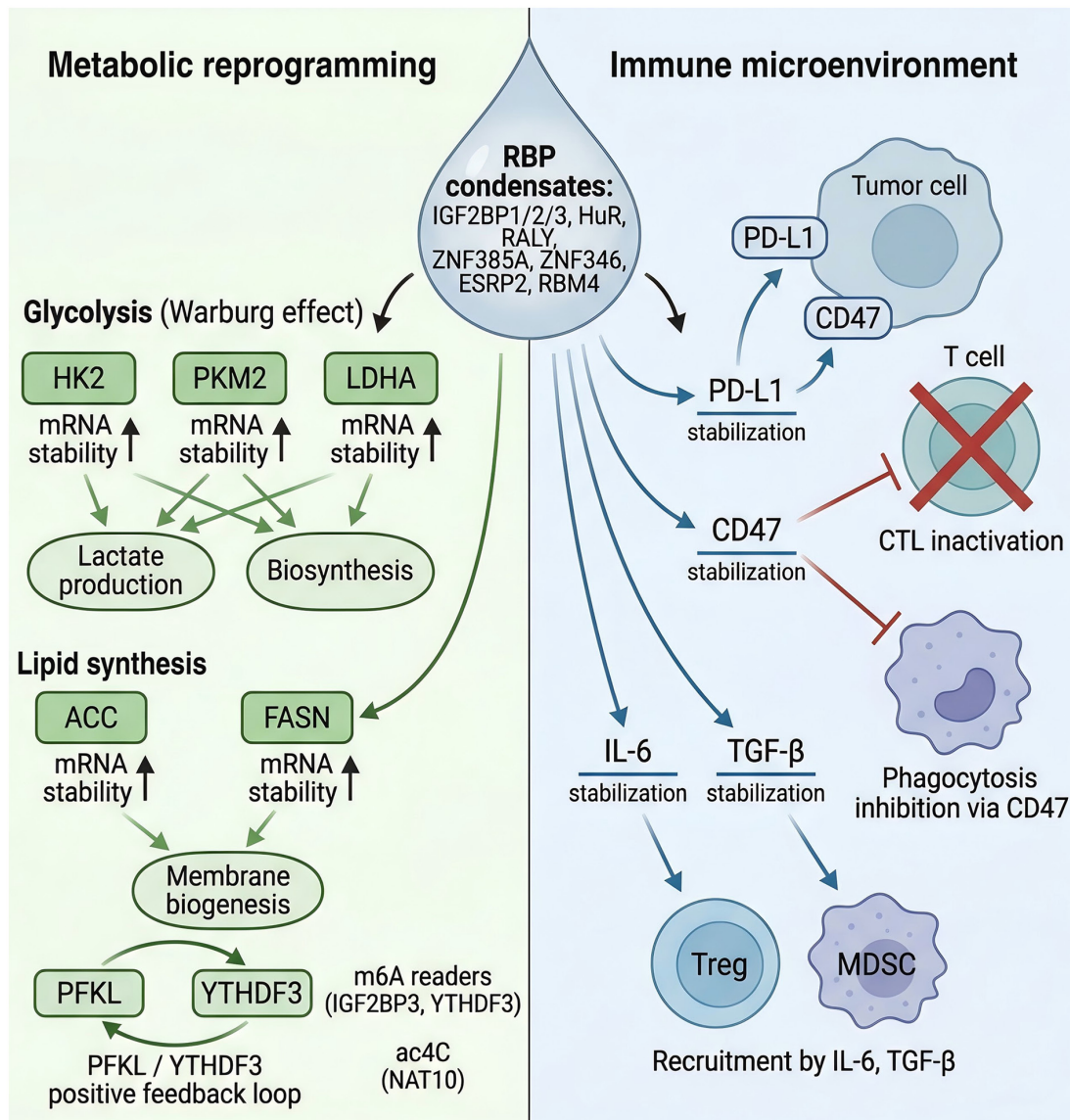


Figure 2. Proposed roles of RBP condensates in hepatocellular carcinoma metabolic reprogramming and immune microenvironment regulation. The left side illustrates how RBP condensates enhance aerobic glycolysis and fatty acid synthesis by stabilizing mRNAs encoding glycolytic enzymes (HK2, PKM2 and LDHA) and lipid-metabolizing enzymes (FASN and ACC). The right side illustrates how RBP condensates may promote CD8⁺ T-cell inactivation and Treg/MDSC recruitment by stabilizing mRNAs encoding immune checkpoints (PD-L1 and CD47) and immunosuppressive cytokines (IL-6 and TGF- β), thereby creating an immunosuppressive microenvironment. RBP, RNA-binding protein; HK2, hexokinase 2; PKM2, pyruvate kinase isozyme M2; LDHA, lactate dehydrogenase A; FASN, fatty acid synthase; ACC, acetyl-CoA carboxylase; Treg, regulatory T cells; MDSC, myeloid-derived suppressor cells; PD-L1, programmed death-ligand 1; CTL, cytotoxic T lymphocyte; IGF2BP, insulin-like growth factor 2 binding protein; HuR, human antigen R.

molecular signatures rather than direct measurements of condensate properties in patient tumors (78). For example, ZNF385A and ZNF346 are associated with prognosis and an immunosuppressive TME in HCC. An LLPS-related lncRNA signature that includes ZNF32-AS2 has also been proposed for prognostic stratification (79). These findings support further biomarker investigation, but they do not establish that condensate abundance or behavior independently predicts clinical outcome.

Studies in other malignancies provide additional biological precedent but should not be considered validation in HCC. In bladder cancer, higher T-cell-restricted intracellular antigen-1 (TIA1) expression and condensate-competent TIA1 are associated with a more favorable treatment response: TIA1 condensates suppress LDHA, PKM2 and HK2 expression,

reduce lactate production and enhance CD8⁺ T-cell activation, thereby supporting intravesical Bacillus Calmette-Guérin efficacy (80). In acute myeloid leukemia, homoharringtonine promotes EWS RNA binding protein 1 phase separation through an m6A-YTHDF2-dependent mechanism and suppresses leukemia progression (81). These observations provide mechanistic precedent but not validation for RBPs as biomarkers in HCC.

Another challenge is the measurement of condensate properties in clinical specimens (82). Experimental methods can assess condensate dynamics and phase behavior under controlled conditions, while resources such as PRALINE facilitate the identification of protein and RNA variants associated with condensates (83-85). These approaches are valuable for mechanistic investigation, but they are not yet standardized

clinical assays. Before condensate-based measurements can be considered for routine use, reproducible analytical methods will be required. Their prognostic or predictive value should then be tested in independent HCC cohorts and compared with information obtained from RBP expression and established clinicopathological variables.

Non-invasive imaging and liquid-biopsy approaches should likewise be regarded as exploratory. Detecting circulating RBP-RNA complexes or imaging condensate-associated features may eventually provide information about tumor biology, but it remains uncertain whether these measurements accurately reflect condensate states within HCC tissue (86). Their analytical reproducibility and clinical performance also require systematic evaluation. Therefore, current evidence supports RBP condensates as candidate biomarkers for further investigation rather than clinically established diagnostic or prognostic markers.

Therapeutic strategies targeting phase separation processes. Therapeutic targeting of condensates is most logically considered in relation to the mechanism that sustains each assembly. When condensate formation depends on a defined protein-protein interaction, competitive disruption of that interface provides a direct intervention strategy. This principle has been demonstrated in primary liver cancer using TEAD1-derived peptides, which interfere with YAP condensate formation and suppress tumor progression (87). Although YAP is not an RBP, this study provides a liver cancer proof of principle that a defined condensate-forming interaction can be translated into an interface-directed therapeutic strategy. A similar approach may become applicable to RBP condensates once the interactions required for their assembly have been identified.

A different intervention point arises when condensate function depends on selective recruitment of RNA or regulatory proteins. In this setting, the therapeutic objective need not be complete condensate dissolution. Instead, disrupting a critical recruitment step may be sufficient to reduce the pathological output of the assembly. The aforementioned ATXN2L and CRTC2-YTHDF2 mechanisms illustrate this possibility in HCC. Their biological effects depend on the local recruitment of factors that modify translational output. These findings therefore suggest that future inhibitors could be designed against the molecular interfaces responsible for functional recruitment (88). However, this remains a therapeutic hypothesis until selective inhibitors of these HCC-specific interactions are experimentally validated.

Condensate material state and localization provide another mechanism-based therapeutic opportunity (89). Treatment does not necessarily need to prevent phase separation. In some settings, deliberately redirecting phase behavior may suppress oncogenic signaling (90). In liver cancer, a small molecule has been shown to induce β -catenin phase separation and retain β -catenin in cytoplasmic condensates, thereby reducing its nuclear oncogenic activity (91). Although β -catenin is not an RBP, this finding demonstrates that therapeutic modulation can either inhibit a pathological condensate or induce a nonproductive condensate, depending on the underlying mechanism.

Evidence from other systems is retained as mechanistic precedent rather than direct HCC evidence. For example, BBA disrupts an intrinsically disordered region-mediated interaction

required for c-Maf phase separation, whereas G3Ia and G3Ib bind G3BP1/2 and interfere with stress-granule co-condensation (92,93). These studies support the feasibility of targeting defined condensate-forming interfaces. Their application to HCC-related RBP condensates, however, requires direct validation. Taken together, these observations support a mechanism-guided therapeutic framework in which the intervention is selected according to the molecular process that is required for the pathological condensate to assemble or function. These mechanism-guided strategies are summarized in Fig. 3.

Although pharmacological modulation of condensates is a promising strategy, selectivity remains a major limitation. An inhibitor that binds an RBP or alters its phase-separation behavior may also affect functions of the same protein outside the pathological condensate. In addition, physiological RBP assemblies participate in normal RNA regulation and cellular stress responses. Stress granules and P-bodies provide examples of such functional condensates. Therefore, broad interference with condensate formation may produce effects that extend beyond the intended tumor-associated pathway (94).

Stress-granule inhibitors illustrate this challenge. G3Ia and G3Ib bind G3BP1/2 and interfere with their co-condensation with RNA and other proteins, thereby suppressing stress-granule formation (93). These findings establish the feasibility of pharmacologically perturbing a defined condensate-forming process. However, inhibition of stress-granule assembly should not be assumed to be selective for malignant cells, because stress granules also participate in physiological adaptation to cellular stress.

A more selective therapeutic strategy would therefore target a molecular dependency that is particularly important for the pathological condensate. If disease-associated assembly requires a defined interaction interface, disruption of that interface may preserve more of the normal function of the RBP than global inhibition of phase separation (95). A similar principle applies when pathological activity depends on recruitment of a specific molecular partner. In that setting, interfering with partner recruitment may reduce the pathological output without requiring complete condensate dissolution. The feasibility and safety of this approach will require direct experimental validation, because the therapeutic window depends on separating pathological condensate activity from physiological RBP function.

The interventions summarized in Table II should be interpreted as preclinical strategies rather than condensate-specific therapies (96). Several approaches may affect broader RBP functions or physiological condensates in addition to the intended pathological assembly. Their potential therapeutic value must therefore be considered together with molecular specificity and preservation of normal RBP-dependent cellular functions. Table II provides an overview of preclinical interventions targeting RBP condensates, including small-molecule inhibitors, peptide-based competitors, and modulation of condensate physicochemical properties.

9. Challenges and future prospects

Current technical bottlenecks and complexities in studying RBP condensates in liver cancer. Studying RBP condensates in HCC remains technically difficult because live-cell

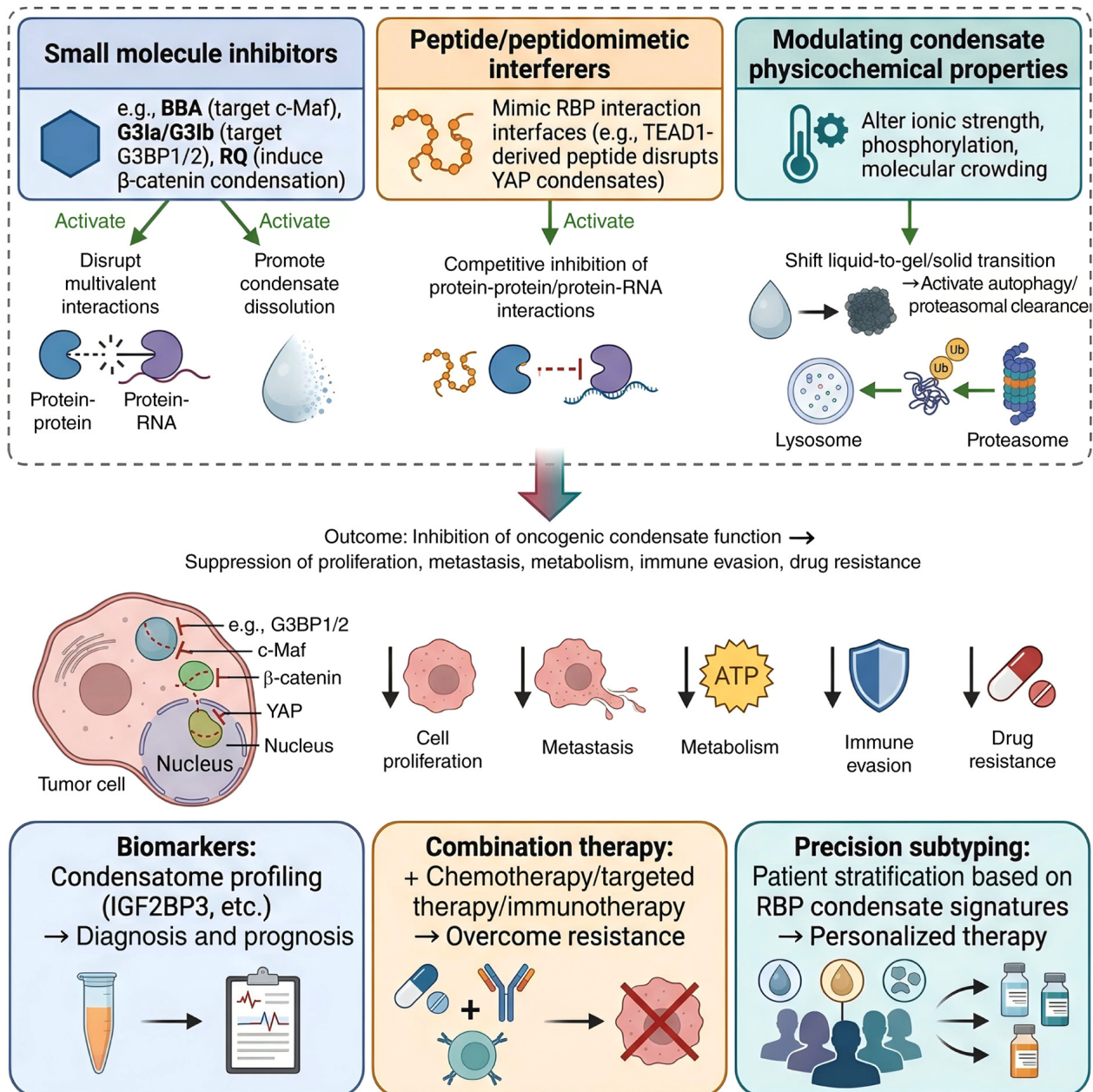


Figure 3. Potential three major intervention strategies: i) Small molecule inhibitors disrupt multivalent interactions or cause aggregates to dissolve; ii) competitive inhibition at the interface of RBP interaction by peptides/peptide mimetics; and iii) alteration of the physical and chemical properties of condensation (such as ion strength phosphorylation) triggers the liquid-solid phase transition and cell quality control clearance mechanism. The proposed directions of clinical application in the future include diagnostic/prognostic markers according to condensate characteristics, combination therapy to overcome drug resistance, specific typing and personal treatment.

measurements often require fluorescent labeling and may not capture condensate composition or material properties (97). Label-free methods provide complementary information, but they are not yet sufficient for resolving all dynamic molecular processes in living tumor cells (98).

A notable unresolved question is whether altered RBP condensation acts upstream of malignant transformation or develops downstream as part of tumor-associated adaptation. Evidence from HCC supports a functional contribution in some settings (99). ATXN2L undergoes LLPS and enhances oncogenic mRNA translation in HCC. CRTC2 also forms co-condensates with YTHDF2, and this process contributes to hepatocarcinogenesis and lenvatinib resistance. These findings

support a functional role for condensate formation, but they do not establish that condensation is a universal initiating event in HCC.

An alternative interpretation is that some condensates arise after the cellular environment has already been altered. Stress-responsive condensates are particularly relevant to this possibility because their assembly and dissolution can change with metabolic conditions. For example, SESN2-mediated stress-granule disassembly occurs during glucose starvation and is accompanied by changes in glycolytic regulation (61). The TME may likewise influence the propensity of RBPs to undergo phase separation. Under these conditions, condensate formation may represent an adaptive response to the malignant

Table II. Preclinical interventions targeting RBP condensates: Small molecules, peptides, and modulators of physicochemical properties.

Intervention strategy	Compound/molecule	Target RBP/condensate	Mechanism of action	<i>In vivo</i> model	Effect	(Refs.)
Small molecule inhibitor	BBA	c-Maf (IDR-IDR interaction)	Inhibits LLPS, blocks transcriptional activation	Multiple myeloma model	Suppresses tumor growth	(92)
Small molecule inhibitor	G3Ia/G3Ib	G3BPI/2	Disrupts stress granule assembly, dissolves condensates	Cell models	Inhibits SG formation	(93)
Small molecule inhibitor	RQ	β -catenin	Induces LLPS, sequesters β -catenin in cytoplasm	HCC mouse model	Suppresses tumor growth, overcomes immune evasion	(91)
Peptide interferer	TEAD1-derived peptide	YAP condensates	Disrupts YAP condensate formation, activates AMPK α	Primary liver cancer mouse model	Inhibits tumor progression	(87)
Physicochemical modulator	Methylene blue	Tau condensates	Accelerates liquid-to-gel transition, inhibits fibrillization	Neurodegeneration model	Reduces cytotoxicity	(90)
Other (aptamer)	Anti-MEX3C aptamer	MEX3C	Disrupts MEX3C-mediated mRNA destabilization	HCC cells	Restores immune recognition	(77)
Other (small molecule)	TRBP-Dicer inhibitor	TRBP	Modulates miRNA biogenesis	HCC cells/mouse model	Suppresses tumor growth	(88)

Summary of preclinical approaches to RBP condensates, such as small molecule inhibitors, peptide-based competitors, modulators of condensate physicochemical properties, and other tools (aptamers). The mechanism of action, experimental models, and observed anti-tumor effects are listed. RBP, RNA binding protein; IDR, intrinsically disordered region; LLPS, liquid-liquid phase separation; SG, stress granule; miRNA, microRNA; HCC, hepatocellular carcinoma.

state and may subsequently reinforce tumor-associated RNA regulation. The relationship between condensate formation and malignant transformation may therefore be context dependent and potentially bidirectional rather than uniformly causal.

Establishing causality remains experimentally challenging because numerous perturbations that alter phase separation also modify other functions of the same protein (100). Changes in low-complexity regions may affect molecular interactions in addition to condensate formation, while manipulation of post-translational regulatory sites can produce similarly pleiotropic effects (101–103). Changes in RBP abundance create an additional difficulty because protein concentration can influence phase behavior while also altering functions that do not require condensation. Therefore, a change in malignant phenotype after RBP perturbation cannot automatically be attributed to altered condensate formation. Future studies will require more selective approaches that modify condensate assembly while minimizing changes in other RBP functions. Such experiments will be required to distinguish condensate-dependent effects from broader consequences of RBP dysregulation.

The relationship between RBP condensates and the TME should be considered bidirectional. On one side, local environmental stress can change condensate behavior. Hypoxia and nutrient deprivation increase cellular stress and can alter the assembly or remodeling of stress-responsive RBP condensates (104). Metabolic state can also determine whether a condensate persists. During glucose deprivation, SESN2-mediated stress-granule disassembly is accompanied by changes in glycolytic mRNA regulation. These observations indicate that condensate behavior is not determined solely by RBP expression but can change as local metabolic conditions change.

Inflammatory and disease-associated signals provide another layer of regulation. Stress granules are dynamically regulated during liver disease and respond to changes in the cellular stress state. In liver cancer, HBx-associated upregulation of cellular prion protein enhances NF- κ B signaling through an LLPS-dependent process (105). Although this example is not an RBP-specific condensate mechanism, it provides liver cancer evidence that inflammatory or viral signaling and phase separation can be mechanistically connected. Together, these observations support the view that the TME can reshape phase-separation-dependent regulation rather than simply acting as a passive background.

The reverse direction is also relevant but is less firmly established for RBP condensates in HCC. RBP-mediated post-transcriptional regulation can alter pathways that shape the immune environment. For example, the poly(A) binding protein nuclear 1-C5 axis promotes HCC progression through NF- κ B activation and is associated with the recruitment of immunosuppressive cells (106). ZNF385A and ZNF346 are also associated with an immunosuppressive TME in HCC. However, current evidence does not establish that these effects are specifically dependent on condensate formation. These studies therefore support a connection between RBP regulation and the TME, while the contribution of LLPS requires further experimental separation.

Several components of this reciprocal relationship remain poorly characterized. The acidic extracellular environment

that can accompany tumor metabolism may be relevant to condensate behavior, but direct evidence linking acidosis to specific RBP condensates in HCC is currently insufficient. Stromal regulation is similarly underexplored (107). LINC00663-dependent regulation of SF2-mediated fibronectin splicing has been demonstrated in hepatic stellate cells, showing that RBP-dependent RNA regulation occurs in a liver stromal context; however, this study does not establish an LLPS-dependent mechanism. Future work should therefore examine tumor cells together with stromal and immune compartments and determine how local environmental states alter condensate behavior across these cell populations.

Future research directions and clinical translation prospects.

A systematic HCC condensatome remains an important goal. Spatial proteomic and transcriptomic approaches may help identify stage-specific or cell-state-specific assemblies, but candidate discovery must be followed by direct functional validation (108). An important future direction is to identify RBP regulators that have not yet been examined systematically for condensate behavior in HCC. Some proteins already have established roles in HCC RNA regulation but lack direct evidence for an LLPS-dependent mechanism (109). For example, ESRP2 regulates an RNA-splicing program that contributes to HCC progression. ZNF385A and ZNF346 have also been associated with prognosis and the immune microenvironment in HCC. At present, these observations do not demonstrate that their HCC-related functions require condensate formation. Therefore, these RBPs should be regarded as candidates for future investigation rather than established condensate regulators. Expanding this candidate space will be important because the current literature is likely biased toward a limited number of well-studied proteins. Future studies should determine which additional RBPs undergo functionally relevant phase separation in HCC and then test whether their condensate-dependent activities can be separated from their broader RNA-binding functions.

Clinical application of RBP condensate profiling will require substantial validation. Future studies should first establish reproducible measurements in clinical specimens and confirm their association with relevant outcomes in independent patient cohorts (110). It will also be important to determine whether condensate-based information provides additional value beyond RBP expression and conventional clinical variables. Until these requirements are met, condensate profiling should be considered an investigational approach rather than a component of routine HCC management.

10. Conclusion

Current evidence supports a functional role for RBP condensates in selected aspects of HCC biology. However, their causal position is not uniform across experimental systems. In some settings, condensate formation contributes to oncogenic RNA regulation or therapeutic adaptation (111). In others, condensates may arise after cellular stress or malignant transformation and then reinforce an altered regulatory state. Therefore, future studies should distinguish condensate-dependent effects from the broader molecular functions of individual RBPs before these assemblies are considered therapeutic targets.

Clinical translation will also require selective interventions that preserve physiological RBP functions and validated assays that demonstrate added value beyond conventional biomarkers. Until these requirements are met, RBP condensates should be viewed as a mechanistically informative and investigational framework rather than established clinical targets (112).

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XL conceptualized the review, performed literature search and screening, drafted the main manuscript and prepared the figures. YH supervised the study, revised the manuscript critically for intellectual content and approved the final version for submission. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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