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RNA-binding proteins as epithelial transcriptome orchestrators in gastric cancer: Immune-metabolic crosstalk and therapeutic vulnerability (Review)

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Abstract. Among malignant tumors, gastric cancer (GC) ranks fifth in terms of global incidence and third in terms of the number of related deaths, and its high molecular heterogeneity, chemoresistance and lack of targeted therapies remain major clinical challenges. RNA-binding proteins (RBPs), as the core effectors in post-transcriptional regulation, are widely involved in the determination of malignant phenotypes in GC; they act by dynamically regulating RNA splicing, stability, translation and modification, in addition to mediating the crosstalk between metabolism and immunity, and influencing proliferation, metastasis, drug resistance and other malignant phenotypes. However, the functional controversy of RBPs [such as Insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) and YTH N6-methyladenosine RNA binding protein F2 (YTHDF2)] in different GC subtypes and their clinical translatability remain unclear. Notably, RBPs show GC-specific features (such as IGF2BP1/3 regulating metabolic coupling, YTHDF1 modulating dendritic cell recruitment) and clinical value [such as poly (rC)-binding protein predicting peritoneal metastasis, Pumilio 1 guiding anti-programmed cell death protein 1 therapy therapy]. This review highlights the GC-specific mechanisms, controversial scientific issues and latest clinical translation progress of RBPs and proposes personalized treatment strategies based on the molecular characteristics of RBPs, aiming to provide a theoretical and practical basis for overcoming GC chemoresistance and molecular heterogeneity.

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1. Introduction

Gastric cancer (GC) is the fifth most common malignant tumor worldwide and has the third highest mortality rate; its development is strongly associated with chronic infection with *Helicobacter pylori* (*H. pylori*), a high-salt diet and genetic susceptibility (such as a cadherin-1 mutation) (1-3). Although neoadjuvant chemotherapy centered on the fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) regimen and targeted therapies (such as trastuzumab against human epidermal growth factor receptor 2) have significantly improved clinical outcomes, the 5-year survival rate of patients is still <30% and drug resistance-related recurrence and molecular heterogeneity [such as differences in Epstein-Barr virus (EBV)-positive/genome-stable subtypes] limit the efficacy of existing targeted strategies (4,5). Therefore, analysis of the molecular regulatory network of GC progression and exploration of novel targets are urgently needed.

Post-transcriptional regulation of gene expression is a key feature of cancer that precisely shapes the tumor phenotype through the dynamic control of RNA metabolism (6,7). As core effectors in post-transcriptional regulation, RNA-binding proteins (RBPs) bind to single- or double-stranded RNA in a sequence-specific manner and regulate mRNA splicing, polyadenylation, mRNA stabilization and localization (8,9). GC cells are also involved in ribonucleoprotein complex (RNP) synthesis on the basis of their interactions with other biomolecules, especially coding and noncoding RNAs (10). The binding of RBPs to structural motifs or RNA sequences occurs through a set of structurally defined RNA binding domains (RBDs). Depending on the presence or absence of RBDs, they can be categorized as conventional/typical or unconventional/atypical RBPs. Conventional RBPs include RNA recognition motifs, cold shock structural domains, K homology structural domains, DEAD/DEAH deconjugation enzymes and zinc finger structural domains (11,12). Notably, RBPs bind to both DNA and RNA and serve a role in DNA replication and the DNA damage response (13,14).

RBPs are involved in the development of numerous human diseases, including cancer neurodegenerative, renal and cardiovascular diseases (15-17). RBPs can drive stemness maintenance, metabolic reprogramming, immune escape and treatment tolerance in GC (9,18-22). The present review focused on the role of RBPs as post-transcriptional regulatory hubs to integrate cutting-edge advances and provide a theoretical basis for targeted therapeutic strategies (Table I).

2. Coregulatory mechanisms of RBPs in GC

In cancer cells, RBPs serve important roles in regulating the expression of tumor suppressor genes and oncoproteins involved in various cell signaling pathways (9,23). In GC, RBPs are classified into two categories according to their functional properties: i) Oncogenic RBPs, including LIN28A/B, insulin-like growth factor 2 mRNA-binding protein (IGF2BP1/3), human antigen R (HuR) and YTH N6-methyladenosine RNA binding protein F1/2 (YTHDF1/2) (24-28), which primarily drive GC progression by stabilizing oncogenic mRNAs [such as c-MYC and cyclin D1 (CCND1)], mediating N6-methyladenosine (m^6A) modification, activating pro-tumor signaling pathways (including PI3K/AKT and Wnt/β-catenin), and facilitating metabolic reprogramming or immune escape. ii) Tumor-suppressive RBPs, including poly (rC)-binding protein 1 (PCBP1), zinc finger protein 36, RBM5 and QKI (29,30), which inhibit GC malignant phenotypes through mechanisms such as degrading pro-metastatic mRNAs (such as MMP9 and IL-33), regulating alternative splicing to generate tumor-suppressive isoforms (for example, SMAD2ΔE3 and caspase-9a), inducing cell cycle arrest or apoptosis, and suppressing inflammatory niche formation.

RBPs regulate GC cell behavior via m^6A modification. m^6A is the most prevalent and abundant transcriptional modification in eukaryotic RNAs and serves a key role in cellular self-renewal and differentiation (31). m^6A-modified mRNAs can be specifically recognized and bound by m^6A-binding proteins to regulate RNA maturation, splicing, translocation, degradation and translation (32).

IGF2BP family: m^6A-dependent oncogenic regulation and subtype-specific functions. The IGF2BP family comprises key post-transcriptional regulators (IGF2BP1, IGF2BP2 and IGF2BP3) that regulate tumor-associated gene expression by mediating RNA epigenetic modifications. IGF2BP1 and IGF2BP3, as m^6A reader proteins, both stabilize target mRNAs via m^6A modification mediated by the methyltransferase-like 3 (METTL3), yet exhibit subtype differences in target gene preference (26,33-35).

i) Regulatory mechanism of IGF2BP1 in GC. IGF2BP1 drives GC cell proliferation and metastasis primarily by stabilizing target molecules [such as nuclear factor erythroid 2-related factor 2 (NRF2) and c-MYC] via METTL3-mediated m^6A modification (36,37). At the noncoding RNA level, it also forms complexes with pro-oncogenic long noncoding RNAs (lncRNAs), such as ABL, GLCC1 and GHET1 to promote GC cell migration and chemotherapy resistance, these complexes act by inhibiting cytochrome c/APAF1 interactions (blocking caspase-9/3 activation), stabilizing c-MYC mRNA or activating the PI3K/AKT pathway (37-41). The core innovative mechanism of IGF2BP1 in GC lies in enhancing NRF2 mRNA stability via the methyltransferase-like 5 (METTL5)/m^6A/NRF2 axis. This simultaneously inhibits ferroptosis whilst upregulating the mitochondrial complex protein NDUFA4 to activate the glycolysis-oxidation metabolic coupling. This energy metabolism regulatory pattern remains unreported in colorectal cancer (CRC) and breast cancer (BC), representing a unique strategy for GC cells to sustain their malignant phenotype (42-45).

However, functional controversy persists: A previous small-sample study reported that IGF2BP1 exhibits low expression and tumor-suppressive effects (by downregulating MYC) in EBV-positive GC (46), which is in contrast to its pro-oncogenic role in genomically stable subtypes. Furthermore, IGF2BP1 exerts tumor suppression in hepatocellular carcinoma (HCC) by degrading the lncRNA HULC (47), and the molecular mechanism underlying this tissue-specific functional divergence (such as dependence on distinct RBD targets) remains unclear. Clinically, the specific inhibitor AVJ16 can efficiently reduce the RNA-binding activity of IGF2BP1and the viability of GC cell lines with high IGF2BP1 expression, showing potential for targeted therapy (48).

ii) Regulatory mechanism of IGF2BP3 in GC. IGF2BP3 also relies on METTL3-mediated m^6A modification to stabilize downstream targets [Drp1, lactate dehydrogenase A (LDHA), CCND1 and CD44] and promote GC cell proliferation, migration and metabolic reprogramming (49). At the noncoding RNA level, it binds to circular (circ)-ARID1A and circNFATC3 to enhance the stability of SLC7A5, CCND1 and CD44, while circTNPO3 can competitively bind to IGF2BP3 and block its activation of the MYC-SNAIL axis to inhibit GC progression (50-53). Notably, IGF2BP3 is involved in the metabolic-immune microenvironmental regulatory network, where hypoxia-inducible factor-1α (HIF-1α) disrupts mitochondrial dynamics via upregulation of the METTL3/IGF2BP3/Drp1 axis (54). In the tumor microenvironment (TME), IGF2BP3 participates in metabolic-immune crosstalk: It coordinates with HDGF to activate GLUT4 and ENO2/PKM2, induces the Warburg effect via the OIP5-AS1/heterogeneous nuclear ribonucleoprotein (hnRNP) A1 axis (55-57) and forms a

Table I. Regulatory mechanisms of RBP in GC according to functional type.

A, Oncogenic

RBP family	Mechanism of action	Related signaling pathways/target genes	(Refs.)
IGF2BP1/3	Mediate m^6A modification to stabilize target mRNAs (including c-MYC and LDHA), promoting GC cell proliferation, metastasis and metabolic reprogramming	Wnt/β-catenin, PI3K/AKT, glycolysis (Warburg effect)	(25-60)
YTHDF1	Enhances translation of oncogenic mRNAs (including EGFR and CCND1) and stabilizes PARP1 mRNA (DNA damage repair), thereby maintaining cancer stemness and enhancing chemoresistance.	PI3K/AKT/mTOR, PD-L1/ immune escape	(63-73)
YTHDF2	Regulates RNA stability (degradation/stabilization) of target molecules (including ONECUT2, JAK1), activates JAK/STAT pathway and glycolysis, and modulates cancer stemness, metabolism, and immune escape.	JAK/STAT, AMPK/metabolic adaptation	(74-80)
HuR	Inhibits let-7 miRNA maturation to derepress MYC/ RAS oncogenes, and directly binds target mRNAs (including Oct4 and cyclin B1) to enhance stability/ translation, thereby driving stemness maintenance and glucose/lipid metabolic reprogramming.	VEGF/angiogenesis, BCL-2/ apoptosis resistance, PD-L1/ immune escape	(106-121)
LIN28A/B	Inhibits let-7 miRNA maturation to derepress MYC/ RAS oncogenes, and directly binds target mRNAs (including Oct4, cyclin B1) to enhance stability/ translation, thereby driving stemness maintenance and glucose/lipid metabolic reprogramming.	let-7/MYC/RAS axis, mTOR/ metabolic pathway	(96-105)
hnRNPA1	Stabilizes WISP2 mRNA to activate Wnt/β-catenin signaling (induces EMT) and regulates SCD1/ALOX15/ SLC7A11 expression to inhibit lipid peroxidation, thereby promoting metastasis, ferroptosis resistance and chemoresistance.	Wnt/β-catenin, ferroptosis resistance	(84-89)
hnRNPK	Modulates alternative splicing of CD44 precursor mRNA (promotes CD44v6 isoform) and activates STAT3 pathway (induces TPO secretion), thereby enhancing cancer stemness, thrombocytosis-related metastatic niche formation and glycolysis.	STAT3, CD44v6/stem cell properties	(3,90-95)
FMR1	Stabilizes SOCS2 mRNA to enhance ubiquitination-mediated degradation of SLC7A11 (cystine transporter), thereby inhibiting ferroptosis and promoting GC cell proliferation	SLC7A11/ferroptosis resistance	(129,130)
MSI1/2	Binds to target mRNAs (including HES1, MYC) to enhance their stability/translation, activates Notch/ Wnt pathways, thereby maintaining cancer stemness and mediating chemoresistance.	Notch, Wnt/β-catenin	(125-128)
PUM1	Post-transcriptionally downregulates DEPTOR (mTOR repressor) to activate mTORC1 pathway, thereby promoting glycolysis and lipid synthesis (metabolic reprogramming).	mTORC1/glycolysis, lipid synthesis	(122-124)

B, Tumor-suppressive

RBP family	Mechanism of action	Related signaling pathways/target genes	(Refs.)
QKI	Modulates alternative splicing of SMAD2/3 (TGF-β pathway) to generate anti-EMT splice variants and inhibits aberrant splicing of stemness-related genes (including SOX2), thereby suppressing EMT and metastasis.	TGF-β/SMAD pathway, EMT inhibition	(138-141)

Table I. Continued.

B, Tumor-suppressive

RBP family	Mechanism of action	Related signaling pathways/target genes	(Refs.)
PCBP1	Binds to pro-metastatic mRNAs (including MMP9, CXCR4) to promote their degradation, thereby inhibiting GC cell proliferation, inflammatory niche formation and peritoneal metastasis.	MMP9/CXCR4/metastasis inhibition	(131-137)
TTP	Promotes degradation of IL-33 mRNA (pro-inflammatory cytokine), thereby suppressing inflammatory microenvironment formation and GC progression.	IL-33/inflammatory signaling inhibition	(142)
CELF2	Regulates alternative splicing of caspase-9 precursor mRNA to promote production of pro-apoptotic isoform (caspase-9a), thereby inducing GC apoptosis.	Caspase-9/apoptosis activation	(143)

RBPs, RNA-binding proteins; GC, gastric cancer; m^{6}A, N6-methyladenosine; EMT, epithelial-mesenchymal transition; CCND1, cyclin D1; PD-L1, programmed death-ligand 1; miRNA, microRNA; AMPK, AMP-activated protein kinase; TPO, thrombopoietin; SLC7A11, solute carrier family 7 member 11; SOCS2, suppressor of cytokine signaling 2; TTP, tristetraprolin; CELF2, CUGBP, Elav-like family member 2; mTOR, mechanistic target of rapamycin; mTORC1, mTOR complex 1; LDHA, lactate dehydrogenase A; PCBP1, poly(rC)-binding protein 1

complex with HuR to upregulate glutaminase (GLS) for increased nitrogen and energy supply (58); meanwhile, the IGF2BP3/LDHA axis promotes lactate accumulation, which directly inhibits CD8$^+$ T-cell function via the NFAT1-IRF1 pathway to weaken antitumor immunity (59,60). To summarize, IGF2BP1/3 drive GC progression via m6A-dependent mRNA stabilization and GC-specific immune-metabolic regulation, differing from their roles in other tumors.

The YTHDF family. YTH structural domain family proteins (including YTHDF1-3) are core effector proteins of m^{6}A modification, and YTHDF1 and YTHDF2 serve key roles in gastric carcinogenesis (24,61,62).

i) Regulatory mechanism of YTHDF1 in GC. YTHDF1 drives malignant progression and therapeutic resistance in GC through multidimensional mechanisms. Within tumor-autonomous regulation, YTHDF1 promotes c-MYC translation to activate the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway, upregulates FZD7/TCF7 to maintain tumor stemness, induces SNAIL-mediated epithelial-mesenchymal transition (EMT), while simultaneously stabilizing PARP1 mRNA to preserve CD133$^+$ stem cell properties and enhances SPHK2/USP14 translation to mediate oxaliplatin resistance (63-68). By contrast, within the tumor immune microenvironment, YTHDF1 exerts a dual regulatory role within the immune microenvironment: Suppressing T-cell activity via m^{6}A-dependent programmed death-ligand 1 (PD-L1) translation, whilst simultaneously recruiting mature dendritic cells upon its depletion, upregulates MHC II/IL-12 and activates the JAK/STAT1 pathway to enhance CD4$^+$/CD8$^+$ T cell infiltration and IFN-γ secretion (22,69-71). This regulatory pattern exhibits a more multifaceted phenotype compared to the unidimensional action solely dependent on the circMAP2K4/miR-139-5p axis observed in hepatocellular carcinoma (72).

Furthermore, a clinical study indicated that elevated YTHDF1 expression is significantly associated with oxaliplatin resistance and poor prognosis in patients with GC. Its inhibitor SAC could reverse drug resistance in MGC-803 cells by inhibiting SPHK2/USP14 translation according to preclinical data (73). Patients with high YTHDF1 expression exhibited higher PD-L1 positivity rates and reduced CD8$^+$ T-cell infiltration, suggesting its potential as a predictive biomarker for immunotherapy response. The precision treatment strategy combining SAC with PD-1 antibodies is currently being preclinically validated in GC organoids (69). This suggests that combining SAC with PD-1 antibodies may constitute a precision treatment strategy for YTHDF1-overexpressing GC.

ii) Regulatory mechanism of YTHDF2 in GC. As a core m^{6}A effector protein, YTHDF2 exerts diverse functions in GC. It regulates tumor stemness and oxaliplatin resistance via m^{6}A-dependent stabilization of one-cut homeobox 2 mRNA, activation of tissue factor pathway inhibitor transcription and degradation of lncRNA AC026691.1, which disrupts Ras-related dexamethasone-induced 1 mRNA stability to drive GC proliferation, migration and M2 macrophage polarization (74,75). For metabolic reprogramming, YTHDF2 synergizes with long intergenic non-coding RNA 00659/alkB homolog 5 (LINC00659/ALKBH5) to stabilize JAK1 mRNA. This activates the JAK/STAT pathway and upregulates the glycolytic enzyme phosphoglycerate kinase; additionally, YTHDF2 cooperates with the fat mass and obesity-associated protein, while IGF2BP1 promotes proliferation in BC via the estrogen receptor signaling pathway by stabilizing PRKAA1 (protein kinase AMP-activated catalytic subunit α1) mRNA, thereby enhancing glycolysis and oxidative stress adaptation (76,77). It also impairs CD8$^+$ T-cell activity by JAK1-dependent inhibition of IFN-γ signaling and PD-L1 induction (70), while exerting tumor-suppressive effects via upregulating phosphatase 2 catalytic subunit a (PPP2CA) (blocking cell cycle) and regulating forkhead box C2 (FOXC2) pathway (66,78,79).

However, the bidirectional regulatory function of YTHDF2 remains a subject of core controversy. Within the same GC cell line, the spatiotemporal coexistence of progression-promoting mechanisms (stabilizing JAK1/PRKAA1) and tumor growth-inhibiting mechanisms (upregulating PPP2CA, regulating FOXC2) remains unclarified. The molecular switches governing this functional switch (such as m^{6}A modification levels or differential interactions with long non-coding RNAs) remain unidentified. Furthermore, YTHDF2 exhibits tissue-specific functionality; whilst it induces PD-L1 expression via JAK1-dependent pathways in GC, YTHDF2 primarily regulates ARHGEF2 translation in CRC (80). The tissue-specific variations in its immunomodulatory functions remain under-explored, potentially limiting the universality of targeted therapies.

Regulation of RBPs in GC by stabilizing mRNA expression. In GC, RBPs can specifically recognize and bind to conserved sequences or structural elements of target mRNAs, significantly enhancing the stability of these mRNAs and thereby regulating the expression levels and translation efficiency of downstream genes. The regulatory effects of these RBPs permeate key stages of GC initiation and progression, covering multiple dimensions including the maintenance of cancer stem cell stemness, EMT, metabolic reprogramming, chemoresistance and immune escape (81-83).

hnRNP family regulates GC progression by stabilizing mRNA expression. The hnRNP family serves as a key participant in the post-transcriptional regulatory network of GC. As core members of this family, hnRNPA1 and hnRNPK, regulate the initiation and progression of GC in a multidimensional manner by stabilizing the expression of target mRNAs. Although both proteins exert their functions relying on mRNA stabilization, there are significant differences in their regulatory focuses and functional characteristics (81,82).

i) Regulatory mechanism of hnRNPA1 in GC. Among hnRNPs, hnRNPA1, which serves a central role in hnRNPA1, promotes GC metastasis by stabilizing WNT1 inducible signaling pathway protein 2 mRNA to activate Wnt/β-catenin signaling, upregulate SNAIL/Vimentin expression and induce EMT (84). Furthermore, hnRNPA1 regulates ferroptosis inhibition and chemoresistance in GC. hnRNPA1 binds downstream arachidonate 15-lipoxygenase and inhibits lipid peroxidation; levels of reactive oxygen species (ROS) increase in metastatic GC cells compared with that in primary tumor cells, ultimately contributing to ferroptosis resistance and chemoresistance (85); it also upregulates stearoyl coenzyme A desaturase 1, which maintains the oncogenicity of GC stem cells (86) and enhances solute carrier family 7 member 11 (SLC7A11) and glutathione peroxidase 4 (GPX4, an antioxidant enzyme) expression, thus inhibiting lipid peroxidation and promoting GC progression (87). Additionally, in the regulation of metabolic reprogramming in GC, the lncRNA OIP5-AS1 drives glycolysis-dependent proliferation and metastasis by inhibiting Trim21-mediated ubiquitination degradation of hnRNPA1, which promotes the expression of LDHA and PKM2 (57).

Notably, cancer-associated fibroblasts (CAFs) serve as a core stromal component within the TME. Through multiple pathways, CAFs interact with hnRNPA1, IGF2BP3, YTHDF2 and other RBPs to form an interactive network that reinforces the malignant phenotype of GC epithelial cells: i) miR-522 from CAF-derived exosomes targets the ubiquitination site of hnRNPA1, inhibiting its degradation to enhance the stabilization of SLC7A11 and GPX4 (87); ii) paracrine TGF-β activates epithelial SMAD2/3 signaling to directly upregulate IGF2BP3 transcription (88,89); and iii) secreted hepatocyte growth factor activates epithelial c-MET signaling, inducing YTHDF2 expression. This protein stabilizes JAK1 mRNA via m^{6}A modification, activates the JAK/STAT pathway and upregulates PD-L1. It also forms a positive feedback loop with CAF-secreted IL-6 to suppress CD8$^+$ T-cell infiltration (70). Such regulatory circuits involving CAFs-TGF-β-IGF2BP3-epithelial cells not only expand the functional dimensions of RBPs within the microenvironment but also demonstrate their pivotal role as epithelial transcriptome coordinators linking stromal signals to epithelial malignant transformation.

ii) Regulatory mechanisms of hnRNPK in GC. hnRNPK exhibits functional dynamics in GC and its role is regulated by microenvironmental signals and genetic background, such as p53 status. First, hnRNPK is involved in the maintenance of cancer stem cell properties. hnRNPK increases β-catenin stability and synergistically activates Wnt signaling to drive GCSC self-renewal and chemoresistance (90), promotes the expression of the prometastatic isoform CD44v6 and enhances invasiveness and stemness through the modulation of the selective splicing of CD44 precursor mRNAs (91). Binding to the lncRNA ELF3-AS1 activates the signal transducer and STAT3 pathway and induces the release of thrombopoietin, promoting tumor-associated thrombocytosis and the formation of a metastatic microenvironment (92). hnRNPK upregulates key enzymes involved in glycolysis, hexokinase 2 (HK2) and LDHA, which drive abnormal energy metabolism (93). Furthermore, hnRNPK promotes the TPT1-OCT1/CDX2 transcriptional axis and induces gastrointestinal epithelial chemotaxis, a precancerous stage of GC (94). However, the functional controversy surrounding hnRNPK poses challenges for clinical targeted therapies; in p53-mutant gastric carcinomas (GC), hnRNPK exhibits significant oncogenic effects (stabilizing β-catenin and driving glycolysis), whereas in p53-wild-type GC, hnRNPK exerts tumor-suppressing effects by stabilizing p53 (95). Currently, p53 mutations account for 40-60% of clinical gastric carcinoma cases (3). The primary controversy and technical challenge in current research lies in designing conditionally active inhibitors based on p53 status, such as those selectively blocking hnRNPK-β-catenin interactions only in mutant p53 contexts, to avoid compromising its tumor-suppressing function.

LIN28A/B regulates GC progression by stabilizing mRNA expression. LIN28A/B is a class of RBPs that regulate stem cell properties and tumorigenesis. LIN28A/B drives the malignant progression of GC by inhibiting lethal-7 (let-7) microRNA (miRNA) family biosynthesis and directly binding to target mRNAs (82). Blocking let-7 maturation and deregulating its inhibitory effects on proto-oncogenes (such as MYC and RAS) by LIN28A/B maintains stem cell pluripotency and promotes gastric carcinogenesis (82,96,97). In GC, the NF-κB/LIN28A/let-7a axis accelerates carcinogenesis by activating telomerase human telomerase

reverse transcriptase (98). LIN28A is also involved in stem cell and proliferation regulation, binding Oct4 (a stem cell factor), insulin-like growth factor 2 and cell cycle-related mRNAs (such as cyclin B1) to increase their stability or translational efficiency and drive proliferation and dedifferentiation (96,99-102). In addition, the lin28A/B/let-7 axis regulates cellular metabolic reprogramming and enhances glucose uptake and glycolysis through inhibition of the insulin-PI3K-mTOR pathway (103,104). Components of this axis bind to sterol-regulatory element binding proteins (SREBP-1)/SREBP cleavage-activating protein mRNAs, which promotes fatty acid ab initio synthesis and desaturation (saturated to unsaturated fatty acid conversion), providing raw materials and energy for membrane synthesis (105). Therefore, targeting the LIN28A/B-let-7 axis may reverse GC stemness and drug resistance.

HuR (ELAVL1) regulates GC progression by stabilizing mRNA expression. HuR, also known as ELAVL1, is an RNA-binding protein. It regulates the stability and translation of target mRNAs by recognizing their AU-rich regions (AREs) and exerts pro-cancer effects in GC via multiple mechanisms (83). HuR stabilizes VEGF mRNA, induces tumor neovascularization, enhances the expression of the antiapoptotic protein Bcl-2, ubiquitin-specific protease 1 (USP1) and autophagy-related gene 4B, and mediates resistance to chemotherapy (5-FU/cisplatin) (106-108). HuR also upregulates SNAIL and vimentin at the mRNA level, and promotes EMT and metastasis (109). HuR activates pro-oncogenic signaling pathways by forming complexes with multiple lncRNAs. The LINC00707/LINC00324 complex stabilizes vav guanine nucleotide exchange factor 3/F11 receptor (VAV3/F11R) mRNA and activates β-catenin. The small nucleolar RNA host gene 12 complex stabilizes catenin b 1/tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein ζ (CTNNB1/YWHAZ) mRNA and synergistically activates the Wnt and AKT/GSK-3β pathways, in addition to the VCAN-AS1/RP11-138J23.1 complex, which upregulates FAM83B (a metastasis-associated protein) expression (110-116). Furthermore, in synergy with IGF2BP3, GLS drives glutamine catabolism (58) and activates the p38 MAPK-COX-2/IL-8 axis, promoting gastrin-dependent inflammation-associated tumor progression (119). In addition, HuR inhibits CD8 T-cell activity and promotes immune escape by stabilizing PD-L1 mRNA (118,119).

The HuR inhibitor CMLD-2 combined with oxaliplatin achieved a tumor suppression rate of 62% in patient-derived xenograft (PDX) models of GC, significantly outperforming monotherapy (120). Furthermore, a nanoparticle-mediated CRISPR/Cas9-HuR knockout system achieved tumor-specific delivery in head and neck cancer models (121). This system has been adapted for GC cell lines (SGC-7901), with *in vitro* experiments confirming it significantly reduces VEGF and PD-L1 expression, potentially providing a viable delivery strategy for subsequent GC clinical trials.

Other oncogenic RBPs: Key participants in immune-metabolic regulatory networks. i) Pumilio 1 (PUM1). A mammalian target of rapamycin complex 1 (mTORC1) pathway-dependent immunosuppressive factor. PUM1 drives tumor progression in GC through multidimensional mechanisms: It activates the DEPTOR-mediated glycolytic pathway; and promotes GC cell development via circGMPS carried by exosomes through the miR-144-3p/PUM1 axis, while simultaneously regulating the NPM3/NPM1 axis to facilitate PD-L1-mediated immune evasion (122-124). Furthermore, PUM1 activates the mTORC1-HIF-1α axis by inhibiting the mRNA translation of the mTORC1 inhibitor DEPTOR. This not only upregulates glycolytic enzymes such as HK2 and LDHA but also directly binds to the PD-L1 promoter to promote its transcription, thereby regulating the GC immune microenvironment (122).

ii) MSI1/2: Notch/Wnt pathway-mediated hub of immune suppression. MSI1/2 regulates the GC immunosuppressive microenvironment by stabilizing Notch1 and Wnt3a mRNA: It binds to the 3'-UTR regions of Notch1 and Wnt3a mRNA, prolonging their half-lives (from 8.7 and 7.9 h to 14.2 and 13.5 h, respectively). The activated Notch1 pathway promotes Treg cell differentiation (increasing IL-10 secretion by 2.3-fold), while the Wnt3a pathway upregulates CCL2 to recruit M2 macrophages. Single-cell sequencing demonstrated that in MSI1/2-high GC tissues, the proportion of Treg cells ($FOXP3^+CD4^+$) and M2 macrophages ($CD206^+CD68^+$) was significantly higher compared with that in the low-expression group (Treg cells: 15.7% vs. 6.2%; M2 macrophages: Not specified vs. 8.3%, respectively; P<0.001) (125,126). Clinically, patients with high MSI1/2 expression demonstrated significantly shorter progression-free survival (4.2 months) following anti-PD-1 therapy compared with those with low expression (9.5 months; P=0.008) (127,128).

iii) Fragile X mental retardation protein (FMR)1: A potential target for ferroptosis regulation and immune remodeling. FMR1 inhibits GC ferroptosis by stabilizing suppressor of cytokine signaling 2 (SOCS2) mRNA. SOCS2 promotes the ubiquitin-mediated degradation of the cystine transporter SLC7A11, thereby reducing glutathione synthesis. FMR1 deficiency is reported to cause a 40% reduction in SLC7A11 expression, significantly increasing GC cell susceptibility to ferroptosis (129). A preclinical study demonstrated that the FMR1 inhibitor Sc1-VHLL, by degrading FMR1, increases $CD8^+$ T cell infiltration in GC tumor tissue by 2.4-fold and reduces cell proportions of Tregs by 35%, thereby converting 'cold tumors' to 'hot tumors', which achieved a tumor growth inhibition rate of 58.7% (P<0.01) (130). In summary, oncogenic RBPs promote GC progression by regulating the epithelial-immune-metabolic axis, thereby providing novel targets for GC prevention and treatment (Fig. 1).

Tumor-suppressing RBPs: Inhibiting GC progression through RNA metabolic regulation. In GC, oncogenic RBPs inhibit tumor progression by regulating key nodes of RNA metabolism (stability, splicing and translation) (29,30), which regulate the malignant phenotype of GC through different mechanisms of action.

PCBP1: A key regulator suppressing GC peritoneal metastasis. PCBP1(αCP1), as a tumor suppressor RBPs, inhibits the malignant progression of GC through multidimensional mechanisms. Its functional abnormalities are closely associated with GC metastasis, drug resistance and prognosis (131,132). C12orf48 depletion also inhibits metastasis by upregulating PCBP1 to suppress MMP9/CXCR4 regulation (133). In hypoxic microenvironments, circPRELID2 binds to PCBP1 and

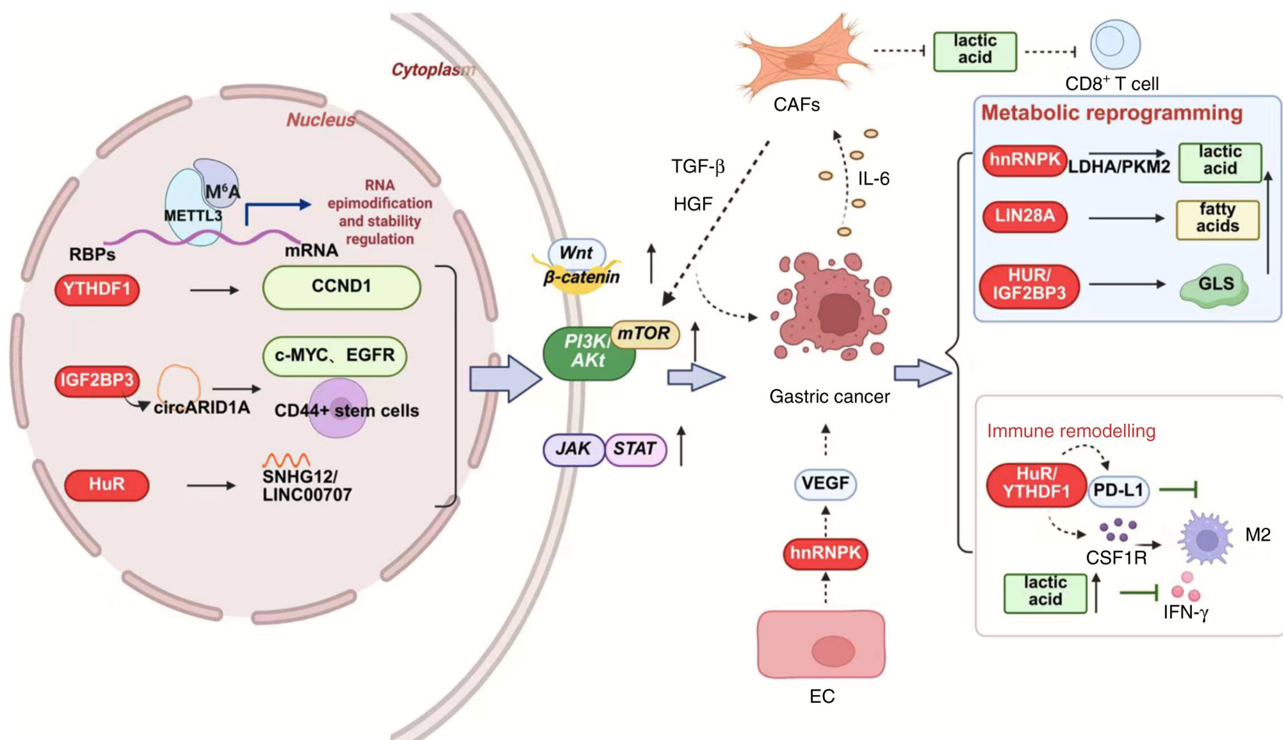

Figure 1. Carcinogenic RBPs mediate multidimensional interactions in GC. In the nucleus, RBPs (YTHDF1, IGF2BP3 and HuR) regulate mRNA stability and translation (such as CCND1, c-MYC, EGFR) via mechanisms such as m^6A modification (mediated by METTL3). In the cytoplasm, activated signaling pathways (PI3K/AKT, Wnt/β-catenin and JAK/STAT) drive GC cell progression and crosstalk with CAFs and EC. RBPs also mediate metabolic reprogramming (for example, hnRNPK regulates LDHA/PKM2, LIN28A regulates fatty acid synthesis and HuR/IGF2BP3 regulate GLS) and immune remodeling (HuR/YTHDF1 regulates PD-L1, CSF1R and influences M2 macrophages and IFN-γ). Created with BioRender. RBPs, RNA-binding proteins; m^6A, N^6-methyladenosine; METTL3, methyltransferase-like 3; YTHDF1, YTH domain family protein 1; IGF2BP3, insulin-like growth factor 2 mRNA-binding protein 3; HuR, human antigen R; CCND1, cyclin D1;circARID1A, circular RNA AT-rich interaction domain 1A; SNHG12, small nucleolar RNA host gene 12; mTOR, mechanistic target of rapamycin; HGF, hepatocyte growth factor; CAFs, cancer-associated fibroblasts; EC, endothelial cells; hnRNPK, heterogeneous nuclear ribonucleoprotein K; LDHA, lactate dehydrogenase A; GLS, glutaminase; PD-L1, programmed death-ligand 1; CSF1R, colony stimulating factor 1 receptor; M2, M2-type macrophages; GC, gastric cancer.

promotes its O-GlcNAcylation modification, thereby reducing its RNA-binding activity and releasing its inhibition on GC transfer (134). Regarding chemotherapy resistance, PCBP1 forms a complex with Siva-1 to enhance BCL-2 mRNA degradation, thereby increasing cisplatin sensitivity. Inhibition of Siva-1 leads to its inactivation and subsequent resistance development, which can be reversed by PCBP1 supplementation (135,136).

In a clinical cohort of 128 patients with GC (including 43 with peritoneal metastasis), PCBP1 exhibited a lower positive rate in metastatic sites (23.3%) than that in primary tumors (68.5%). As aforementioned, the oncogenic lncRNAs ABL, GLCC1 and GHET1 are closely associated with GC metastasis via interacting with IGF2BP1, with a median overall survival (14.2 months) shorter in low-expression patients compared with high-expression patients (28.6 months; P<0.001). Low expression of PCBP1 was also an independent prognostic risk factor for peritoneal metastasis (hazard ratio=2.87; P=0.003) (132). Furthermore, EGCG-lys fibrils silence circMAP2K2 to upregulate PCBP1 and inhibit GC proliferation, providing a direction for targeted therapy (137). In summary, PCBP1 exerts its effects through the pathway of mRNA degradation-protein modification-drug sensitivity regulation. PCBP1 expression serves as a potential biomarker for predicting GC metastasis, assessing prognosis and determining treatment response, thereby providing a target for precision medicine.

QKI: A core molecule in EMT inhibition via splicing regulation. QKI inhibits GC metastasis by regulating the alternative splicing of key molecules in the TGF-β pathway. QKI specifically binds to splicing sites on SMAD2/3 precursor mRNA, promoting the generation of the tumor-suppressor subtypes SMAD2ΔE3 and SMAD3ΔE4 while reducing expression of the pro-metastatic subtypes SMAD2-FL and SMAD3-FL, thereby blocking TGF-β-mediated EMT. Analysis of clinical samples demonstrated that QKI expression levels in GC tissue were negatively correlated with lymph node metastasis (r=-0.42; P<0.01). Patients with low QKI expression levels exhibited a significantly higher lymph node metastasis rate (62.7%) compared with those with high expression (28.3%) (138-141).

Tristetraprolin (TTP) and CUGBP, Elav-like family member 2 (CELF2): Regulating the inflammatory microenvironment and apoptotic pathways respectively. TTP inhibits the formation of the GC inflammatory microenvironment by targeting IL-33 mRNA degradation. As a pro-cancer cytokine, reduced IL-33 expression diminishes M2 macrophage recruitment. Clinically, patients with high TTP expression demonstrated significantly longer median overall survival (31.5 months) compared with those with low expression (18.2 months; P<0.01), indicating its prognostic value (142). CELF2 promotes the generation of the pro-apoptotic subtype caspase-9a, by regulating the alternative splicing

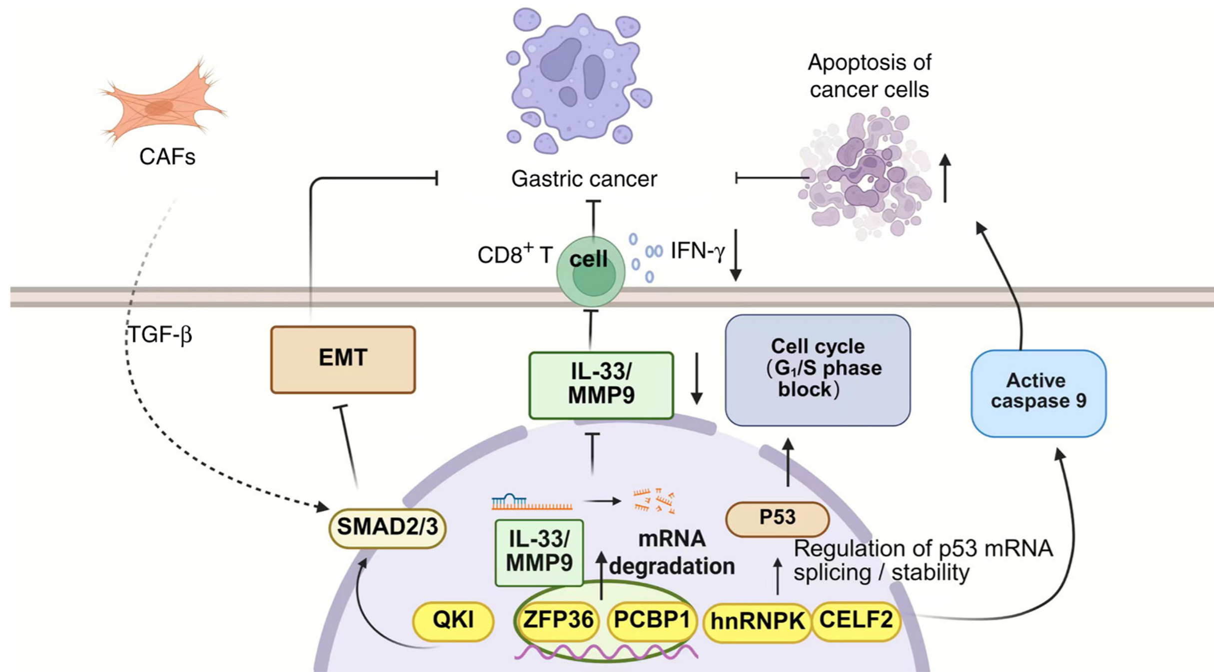

Figure 2. Regulatory mechanisms of tumor-suppressive RBPs in GC. Tumor-suppressive RBPs (QKI, ZFP36, PCBP1, hnRNPK and CELF2) inhibit GC progression through multiple pathways: QKI regulates SMAD2/3 splicing to block EMT; ZFP36 and PCBP1 promote degradation of pro-metastatic mRNAs (IL-33 and MMP9); hnRNPK and CELF2 regulate p53 mRNA and caspase 9 activation to induce cell cycle arrest and apoptosis; and $CD8^+$ T cells secrete IFN-γ to enhance antitumor immunity. Created with BioRender. RBP, RNA-binding protein; CAFs, cancer-associated fibroblasts; EMT, epithelial-mesenchymal transition; ZFP36, zinc finger protein 36; PCBP1, poly(rC)-binding protein 1; hnRNPK, heterogeneous nuclear ribonucleoprotein K; CELF2, CUGBP, Elav-like family member 2; GC, gastric cancer.

of the caspase-9 precursor mRNA, thereby increasing GC apoptosis by 2.3-fold ($P<0.05$) (143). In summary, in GC, tumor suppressor RBPs inhibit tumor progression through differential RNA metabolic regulatory mechanisms (Fig. 2).

3. Differences in the molecular mechanisms of RBPs in GC and other tumors

In cancer research, RBPs serve crucial roles in post-transcriptional regulation. A comparison of their functions in GC with those in other common tumors, such as lung cancer, BC and CRC, demonstrated both similarities and differences. In terms of similarity, the IGF2BP family (such as IGF2BP1/3) stabilizes target mRNAs through m^6A modification across multiple tumors, thereby promoting malignant behaviors including tumor cell proliferation and migration (18,27). In GC, BC, HCC and CRC, IGF2BPs bind to and stabilize the mRNA of key target molecules such as c-MYC, activating downstream oncogenic pathways to confer a growth advantage to tumors (40,144-149). HuR promotes PD-L1 expression in both BC and GC, thereby inducing tumor metastasis and immune evasion (106,150). LIN28A/B promotes tumorigenesis in both CRC and GC by inhibiting let-7 miRNA synthesis (25,151).

In terms of differences, IGF2BP1 promotes proliferation in BC via the estrogen receptor signaling pathway and influences endocrine therapy sensitivity in cancer cells; this mechanism has not been reported in GC (152). The function of HuR in BC is also regulated by estrogen receptor signaling, unlike in GC (153). Furthermore, YTHDF1 maintains tumor stemness and EMT in GC by enhancing c-MYC translation and activating the PI3K/AKT/mTOR pathway, whilst exerting bidirectional regulation on the immune microenvironment (its deletion enhances antitumor immunity). In BC, YTHDF1 expression correlates with estrogen receptor status and influences tumor progression by regulating the translation of proliferation- and invasion-related genes, lacking the immune regulatory function observed in GC (154-156).

In summary, the specificity of RBPs in GC manifests in three aspects: i) IGF2BP1/3 maintains an energy advantage by regulating ferroptosis and glycolysis-oxidation metabolic coupling, an immune-metabolic crosstalk mechanism rarely observed in other gastrointestinal tumors; ii) YTHDF1 regulates dendritic cell recruitment and the MHC II/IL-12 axis, representing an immune regulatory feature unique to GC; and iii) HuR synergizes with the gastrin-dependent p38 MAPK-COX-2/IL-8 axis, distinctly differing from the estrogen receptor-mediated regulatory pathways observed in BC. These GC-specific mechanisms provide core targets for developing tumor-specific targeted therapeutic strategies.

4. Multidimensional exploration of RBPs in GC therapy and clinical translation

RBPs serve a pivotal role in post-transcriptional regulation of GC and its progression, with their therapeutic and clinical translational value attracting significant attention. Cui *et al* (157) demonstrated that RBPs and miRNAs jointly constitute the core mechanism of cancer drug resistance, confirming that targeting their complexes represents a potential strategy to overcome treatment failure in GC. Furthermore, the nanomedicine delivery systems reviewed by Molinaro *et al* (158) and Li *et al* (159) enhance targeting through surface modification

and combination with phototherapy, nano-drug delivery systems, chemotherapy and immunotherapy. Notably, it was recently reported that differentially expressed circRNAs in GC promote carcinogenesis by inhibiting the ubiquitination pathway of RBPs such as G3BP1 (160). This uncovered circRNA-RBP interaction provides novel directions for post-transcriptional regulatory mechanisms and therapeutic target development (160). Furthermore, gastrointestinal organoid models provide a physiologically relevant research platform for investigating RBP function, evaluating RBP-related pathways and detecting drug responses preclinically (161,162). In summary, integrating RBP-targeting strategies with nanomedicine, molecular diagnostics and organoid technologies holds promise for enhancing the precision of GC treatment, overcoming drug resistance and advancing the clinical translation of novel RBP-related interventions.

5. Conclusion

RBPs have GC-specific regulatory features (such as the metabolic coupling of IGF2BP1/3, DC-MHC II/IL-12 regulation of YTHDF1 and gastrin pathway synergy of HuR) and clinical utility (such as PCBP1 for metastasis/prognosis and PUM1 for immunotherapy prediction). RBPs act as molecular switches for GC development through a multilevel and multidimensional post-transcriptional regulatory network. Intervention strategies targeting cancer-promoting RBPs (such as inhibitor development and combination therapies) have demonstrated translational potential, whereas the activation or restoration of cancer-suppressing RBPs has provided new ideas for reversing drug resistance. Under the framework of precision medicine, future studies may combine multi-omics technology and preclinical models to resolve the spatial and temporal specificity of RBP regulatory networks and facilitate the development of individualized treatment options. The study of RBPs in GC not only deepens the understanding of tumor biology but also provides hope for overcoming existing therapeutic challenges.

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Availability of data and materials

Not applicable.

Authors' contributions

XL and TL conceived and designed the review, and supervised the entire research process. SL drafted the initial manuscript and organized the core literature. BJ contributed to topic selection, participated in the design of the review framework, and provided critical insights into the immune-metabolic crosstalk section. JZ performed the literature review. ZM constructed figures. SY and ST performed the literature review. BT, TL and XL revised the manuscript critically for important intellectual content, including mechanism validation and clinical significance discussion. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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