Acta Pharmaceutica Sinica B 2026;16(3):1292−1335

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

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REVIEW

Targeting RNA binding proteins with small-molecule inhibitors: Advances, challenges, and therapeutic opportunities

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Received 19 May 2025; received in revised form 15 September 2025; accepted 10 November 2025

KEY WORDS

RNA binding proteins;
Post-transcriptional gene expression;
Disease;
Small-molecule modulators;
High-throughput screening;
Chemical biology approaches;
Target identification;
Drug discovery

Abstract RNA-binding proteins (RBPs) constitute central regulators of post-transcriptional gene expression and have been increasingly recognized as critical contributors to the pathogenesis of cancer, neurodegenerative disorders, and autoimmune diseases. However, in contrast to well-established drug targets such as kinases and G protein-coupled receptors, RBPs remain largely underexploited owing to their intrinsic structural heterogeneity, dynamic RNA interactions, and paucity of canonical ligand-binding pockets. In this review, we synthesize current knowledge on the roles of RBPs in disease, outline recent advances in the design of small-molecule modulators, and highlight innovative applications of high-throughput screening and chemical biology approaches for target identification and validation. We further discuss emerging concepts and challenges in translating RBP modulators into therapeutics, providing a forward-looking perspective on how these efforts may reshape small-molecule drug discovery in this evolving field.

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Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2025.12.010

1. Introduction

RNA-binding proteins (RBPs) represent an evolutionarily conserved class of proteins characterized by their ability to recognize and interact with RNA through specialized domains, thereby orchestrating post-transcriptional gene regulation. Foundational works on mRNA identification and nuclear export provided the basis for understanding RBP biochemistry[1]. And subsequent elucidation of RNA splicing mechanisms[2] further expanded their functional repertoire beyond RNA stability to splicing regulation, positioning RBPs as master regulators of RNA metabolism. Mechanistically, these processes are orchestrated through the assembly of diverse ribonucleoprotein (RNP) complexes with RBPs functioning as central scaffolds. Comprehensive profiling has uncovered at least 1542 human RBPs engaging virtually all classes of RNAs[3], underscoring their pervasive roles in shaping RNA regulatory networks and cellular homeostasis. RBPs are predominantly ubiquitously expressed and play direct or indirect roles in protein synthesis, although a considerable proportion of them remain functionally uncharacterized. Advances in molecular biology and genomics have enabled systematic investigations into RBP structures, functions, and interaction networks. Cutting-edge technologies including CLIP-seq, RIP-seq, and quantitative proteomics have revolutionized the mapping of RBP−RNA interactomes, uncovering an unexpected degree of complexity in post-transcriptional regulation. These insights not only broaden our understanding of fundamental cellular processes but also highlight the pivotal roles of RBPs in disease onset and progression.

Dysregulation of RBPs underlies a wide spectrum of pathologies, ranging from neurodegenerative diseases to cancer[4]. Early studies were primarily focused on elucidating the biological functions of RBPs and the mechanisms by which they regulate gene expression. As evidence increasingly linked RBPs to diseases such as cancer, neurological disorders, and viral infections, research emphasis has gradually shifted toward their therapeutic potential. Nevertheless, the majority of RBPs are still considered "undruggable" due to the absence of classical enzymatic pockets or well-defined functional epitopes[5]. Consequently, the most extensively explored drug targets remain conventional enzymes and membrane proteins, reflecting the limitations imposed by the currently chemical space, or so called "accessible doped space"[6].

Notably, although approximately 1.5% of the human genome encodes proteins, only a small fraction about 0.2% are considered traditionally druggable, and fewer than 700 currently addressed by approved drugs, representing just 0.05% of the genome[7]. Expansion of small-molecule drug discovery to encompass a wider array of targets may hold significant promises for addressing unmet medical needs and developing novel therapeutic strategies[8]. The development of small-molecule inhibitors targeting RBPs has emerged as a promising therapeutic strategy. Methods of regulating protein−RNA interactions can be divided into two main approaches: 1) direct RBP modulation through functional domain targeting, and 2) indirect approaches *via* RNA epitope masking or upstream regulator manipulation.

This review will provide an overview of the current research advancements in small-molecule inhibitors targeting RBPs, particularly focusing on developments documented within the preceding five-year period, in the context of various diseases associated with RBP dysregulation. We systematically examined the relevance of RBPs in disease pathogenesis and highlighted the detection and screening strategies employed for identifying small-molecule inhibitors. By summarizing the recent developments in this field, we aim to provide insights into the progress and potential of small-molecule inhibitors as valuable tools for modulating RBPs and addressing the underlying mechanisms of associated diseases.

2. The molecular mechanisms of RBPs

Based on the different binding modalities, RNA−protein interactions can be broadly categorized as conventional and unconventional binding modes (Fig. 1). Conventional binding typically occurs through one or a group of well-defined RNA-binding domains (RBDs), targeting specific RNA sequences and/or RNA structural motifs. To date, a variety of RBDs have been identified, including the RNA recognition motif (RRM) (Fig. 1A), K-homology (KH) domain (Fig. 1B), zinc-finger (ZnF) (Fig. 1C), among others. A comprehensive overview of RBDs has been provided by Yeo and colleagues[9] in their review work. In contrast, unconventional binding involves many noncanonical RBDs and even intrinsically disordered protein regions. These interactions utilize alternative strategies[10]: 1) The intrinsically disordered regions of fragile X mental retardation protein (FMRP) co-folds with its target RNA, forming a tight electrostatic interaction[11] (Fig. 1D); 2) the internal ribosome entry site (IRES) of hepatitis C virus (HCV) interacts directly with the ribosome through shape complementarity between the IRES and the ribosome[10] (Fig. 1E); 3) iron-regulatory protein 1 (IRP1) associates with an iron-sulfur cluster (4Fe−4S), and in low iron levels, the 4Fe−4S cluster is no longer synthesized and IRP1 binds mRNAs that encode cellular factors involved in iron homeostasis[12] (Fig. 1F).

RBPs exhibit evolutionary conservation across species, underscoring their crucial role in maintaining gene expression homeostasis[13,14]. The discovery of RNA splicing sparked significant interest in the role of RBPs in splicing regulation, further highlighting their importance in post-transcriptional gene regulation. Post-transcriptional regulation of gene expression encompasses various processes, including alternative splicing (Fig. 2), modification (Fig. 3), RNA transport and localization (Fig. 4), translation (Fig. 5), and RNA degradation (Fig. 5).

2.1. *Alternative splicing*

RBPs coordinate removal of introns and ligation of exons *via* the spliceosome, a dynamic assembly of U1−U6 small nuclear ribonucleoproteins (snRNPs) and auxiliary factors (Fig. 2)[15,16]. U1 and U2 recognize 5′ splice site (5′ss) and branch point (A), respectively, while U2AF binds the polypyrimidine track (Y) and 3′ splice site (3′ss); subsequent remodeling by the U4/U6−U5 tri-snRNP completes two S_N2-type transesterifications to join exons (Fig. 2A). Alternative splicing precision relies on *cis*-elements (ESE/S, ISE/S)[17] and *trans*-factors; the latter includes serine- and arginine-rich (SR) proteins, which promote splicing by binding enhancers, and heterogeneous nuclear ribonucleoproteins (hnRNPs), which repress splicing *via* silencers (Fig. 2B)[18,19]. Splicing dysregulation of these RBPs underlies diverse pathologies[20], notably cancer, neurodegeneration[21,22] and autoimmunity, by generating aberrant isoforms that alter cellular signaling and stress responses.

2.2. *RNA modification*

RBPs orchestrate post-transcriptional regulation in eukaryotes by mediating dynamic RNA modifications. In addition to 5′ cap/tail

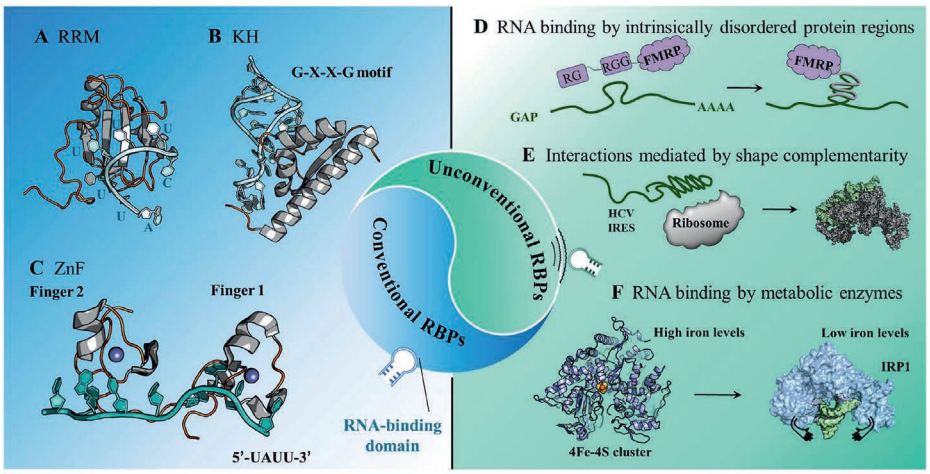

Figure 1 How RNA binds to RBPs. Conventional RBPs: RNA recognition by well-defined RBDs. (A) The RRM of hnRNP C adopts a β-sheet architecture to selectively engage the 5′-AUUUUU-3′ hexamer *via* base-stacking interactions (PDB ID: 2MXY). (B) The hnRNP K homology domain of Nova-2 adopts a winged conformation to recognize the G−X−X−G sequence motif through phosphate backbone coordination (PDB ID: 1EC6). (C) The two zinc fingers of Tis11d include dual zinc ions that stabilize a conformation capable of binding AU-rich elements (PDB ID: 1RGO). In this panel, the RNA nucleotides are in blue; the RBDs are in grey and Zn atom in Tis11d structure is in magenta. Unconventional RBPs: Many noncanonical RBDs and even intrinsically disordered protein regions. (D) FMRP leverages its intrinsically disordered segments to co-fold with target RNAs, generating charge-stabilized complexes. (E) The IRES of HCV interacts directly with the ribosome through shape complementarity between the IRES and the ribosome (PDB ID: 5A2Q). (F) IRP1 associates with a 4Fe−4S to catalyze the interconversion between citrate and isocitrate (PDB ID: 2BSY, 3SNP).

modifications, contemporary investigations emphasize internal modifications on RNA[23], which can target nucleobases and ribose moieties across mRNA[24], lncRNA[25], and other types of RNA[26]. Mirroring chromatin regulation, RNA modifications employ tripartite RBP systems: writers, erasers, and readers[27]. Key modifications include N^6-methyladenosine (m^6A), 5-methylcytosine (m^5C), N^1-methyladenosine (m^1A), N^7-methylguanosine (m^7G), N^4-acetylcytosine (ac4C), pseudouridine (Ψ), uridylation, and adenosine-to-inosine (A-to-I) RNA editing (Fig. 3A).

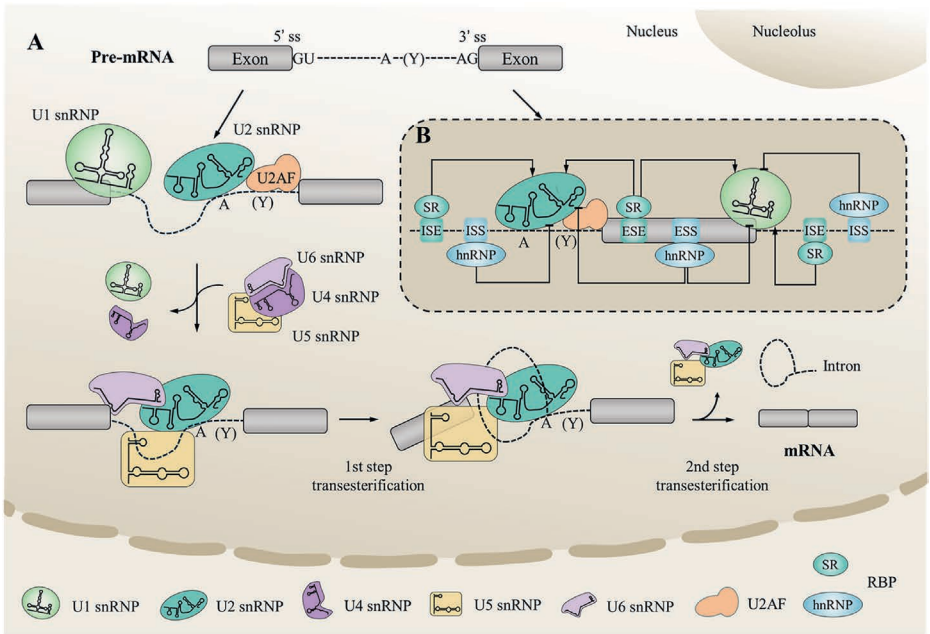

Figure 2 Spliceosome assembly and transcription-coupled splicing. (A) Schematic representation of spliceosome assembly indicating the position of 5′ss, 3′ss, the branch point, and the polypyrimidine tract. The broken lines and rectangles represent introns and exons, respectively. A two-step, S_N2-type transesterification reaction joins the exons and releases an intron lariat, which is subsequently degraded. (B) The regulation of spliceosome assembly involves dynamic interplay between RBPs and specific splicing regulatory elements. Activator RBPs, such as hnRNPs, bind to ESS and ISS, whereas repressor RBPs engage with ESE and ISS to influence spliceosome assembly.

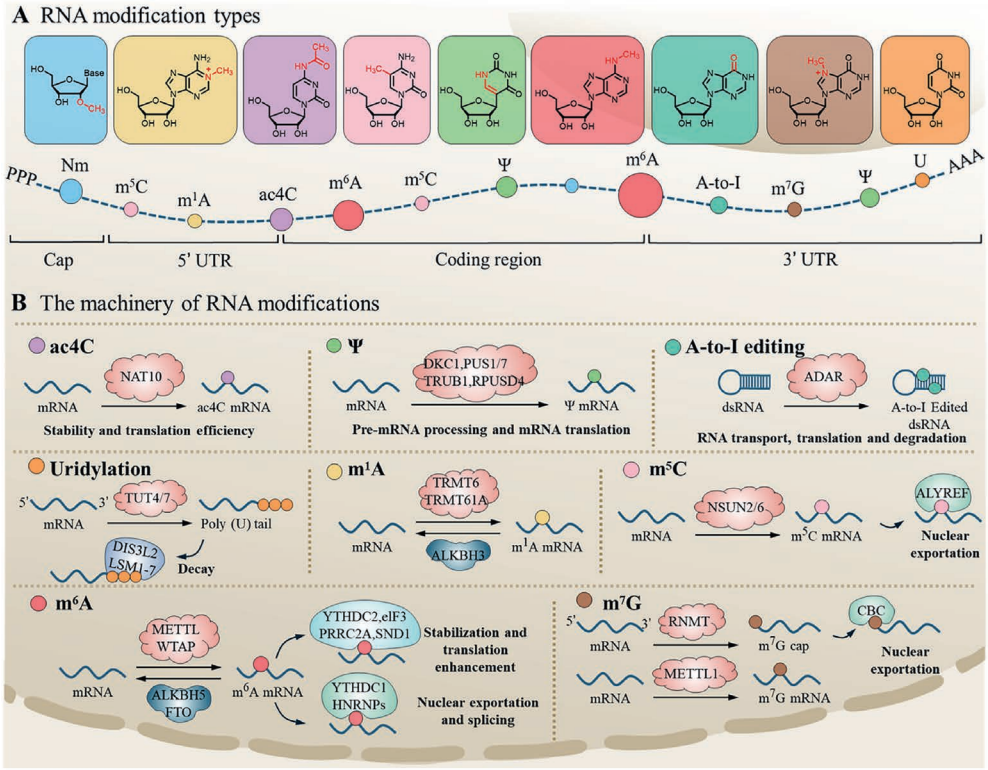

Figure 3 Overview of RNA modifications and their molecular functions. (A) Chemical structures of RNA modifications and their distributions on mRNA. In this panel, the colors of the boxes and circles correspond to different types of RNA modifications. UTR, untranslated region. (B) The machinery of RNA modifications and their molecular functions in mRNA. RNA modifications can be dynamically regulated by writer and eraser proteins, in the case of m^6A and m^1A, removed by erasers. Certain modifications are recognized by reader proteins, influencing RNA fate through regulation of processing, transport, function, and stability.

The m^6A, the most prevalent RNA modification, occurs in mRNAs[28], lncRNAs[29], pri-miRNAs[30] and rRNA[31]. Its writers involve distinct methyltransferase complexes: methyltransferase-like 3 (METTL3)−METTL14 complex for mRNA/lincRNA/miRNA[32], METTL5-TRMT112 for 18S rRNA[33] and ZCCHC4 for 28S rRNA[34]. This modification is enriched near the stop codon and within the 3′ UTR of mRNAs (Fig. 3A), occurring preferentially in the RRACH consensus motif (R = G/A; H = A/C/U)[35]. m^6A demethylases (erasers), essential for dynamic and reversible m^6A modification, include fat-mass and obesity-associated protein (FTO)[10,36] and ALKBH5[37] (Fig. 3B), both implicated in diseases[38], especially oncogenesis[39,40] and are promising pharmacological targets in oncology[40,41]. RNA modified with m^6A is bound by specific readers, which typically contain an m^6A-recognizing YTH domain and regulate RNA fate[42]. YTHDC1, primarily functioning within the nucleus, facilitates exon inclusion by selectively recruiting or inhibiting various splicing factors, including SR proteins[43]. In the cytoplasm, YTHDF1 works in conjunction with YTHDF3 to enhance the translation efficiency of target mRNA[44,45], whereas YTHDF2 regulates RNA degradation[46]. Similarly, YTHDC2 exhibits dual regulatory capacity, enhancing translation while reducing mRNA abundance[47]. Notably, non-YTH domain-containing proteins such as eukaryotic initiation factor 3 (eIF3), hnRNPs (Fig. 3B), and insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs) also function as m^6A readers. HnRNPs bind m^6A-modified pre-mRNAs/pri-miRNAs to regulate splicing and nuclear export[48,49]. IGF2BPs recognize m^6A *via* GG(m^6A) CU motif to enhance stability[50].

The m^5C is an evolutionarily conserved RNA modification catalyzed by the NSUN family (NSUN1-7) and DNMT2. The functionality of m^5C is RNA-type specific: it ensures structural stability in tRNA, while modulating translation in rRNA and directs nuclear export and post-transcriptional regulation in mRNA. The realization of this function is linked to the m^5C reader ALYREF[51] (Fig. 3B). For instance, NSUN2 enhanced ALYREF binding to m^5C-modified *CDKN1A* mRNA, accelerating nuclear export/translation in adipogenesis[52]. Consistent with its role in translation, m^5C is predominantly enriched near the start codon within the coding sequence (CDS) across diverse species, including plants and mammals[53]. Current research indicates that the m^5C modification pathway is associated with the onset and prognosis of diseases such as cancer[54] and cardiovascular diseases[55].

The m^1A is another prevalent RNA modification, found in tRNA, rRNA and mRNA, albeit with varying abundance (tRNA > rRNA > mRNA)[56]. Recognition by reader proteins such as YTHDC1 and YTHDF1-3[57,58], modulates RNA topology and metabolism[59]. Human tRNA and mRNA m^1A modification is mediated by the TRMT61A and TRMT6 methyltransferase[60] (Fig. 3B). This modification, particularly at sites within the 5′ UTR and mRNA cap, is associated with enhanced translation efficiency (Fig. 3A)[61]. In contrast, m^1A deposition on rRNA requires nucleomethylin (NML)[62]. In addition to differences among writers, distinct RNA species also utilize specific erasers. Nuclear tRNA demethylation is mediated by ALKBH1, ALKBH3, and FTO, whereas mRNA demethylation predominantly involves

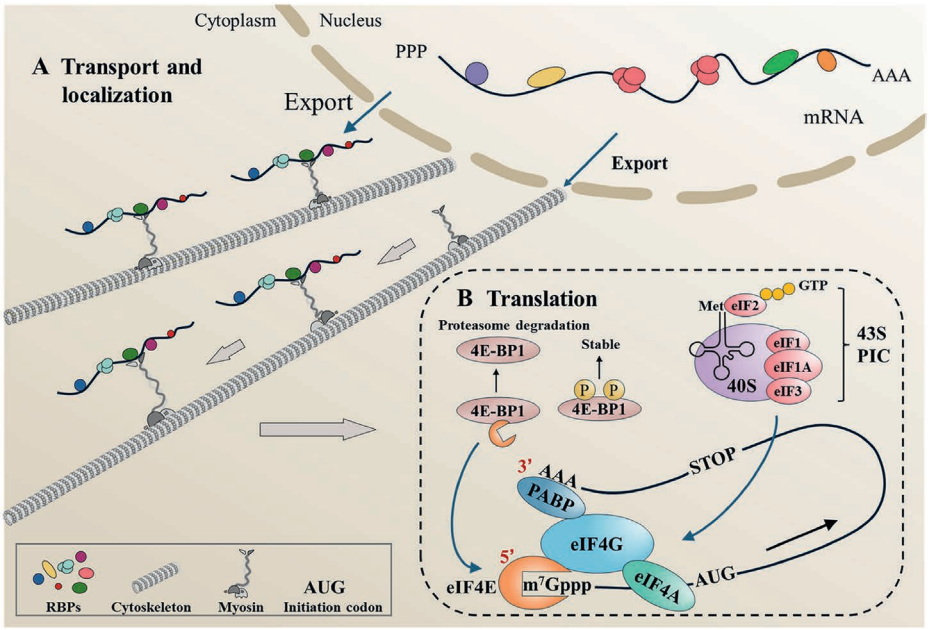

Figure 4 RNA transport, localization and translation. (A) mRNA transport and localization. RBPs facilitate the transport of pre-mRNAs from the nucleus to the cytoplasm. Upon cytoplasmic entry, RNP complexes undergo remodeled, and cytoplasmic factors that couple mRNAs to molecular motors for transport along a polarized cytoskeleton are recruited. Once mRNAs reach their destination, they are anchored, and their translation is activated. (B) Translation initiation mechanism. The ternary complex (eIF2−Met−tRNA−GTP) is associated with the 40S ribosomal subunit to form the 43S PIC, a process facilitated by eIF3, eIF1, and eIF1A. mRNA is activated by eIF4F binding to the m^7G cap and PABP to the poly(A) tail, circularizing the mRNA for 43S PIC attachment at the 5′ end. The ability of eIF4E to join with eIF4G in eIF4F is inhibited by the unphosphorylated isoform of 4E-BP1. When 4E-BP1 is dephosphorylated, it sequesters eIF4E and prevents cap-dependent translation.

ALKBH3. Clinically, dysregulation of m^1A is particularly evident in oncology. The eraser ALKBH3 (Fig. 3B) exhibits pan-cancer relevance[63], and concomitant dysfunction of the TRMT6/TRMT61A complex contributes to tumorigenic progression[64].

Beyond canonical RNA modifications, emerging studies highlight the regulatory significance of non-canonical types. The m^7G modification is catalyzed by three methyltransferase complexes, with METTL1/WDR4 installing internal m^7G in mRNA[65], WBSCR22/TRMT112 modifying rRNA[66], and RNMT/RAM methylating the 5′ cap[67]. The m^7G cap is recognized by readers CBC[68] and eIF4E[69] to modulate RNA stability, localization, and translation[70,71]. Ψ, pseudouridylation, the earliest identified RNA modification, enhances tRNA structural stability[72] and facilitates ribosome biogenesis in rRNA[73], and may influence mRNA stability and translation[74]. Within mRNAs, Ψ is preferentially enriched in CDS and 3′ UTR while being under-represented in 5′ UTR[75]. Notably, pseudouridylation incorporation has been shown to enhance mRNA vaccine efficacy, as demonstrated in COVID-19 vaccine development[76]. Uridylation by TUT4/TUT7 enzymes adds at least four uridines to mRNA 3′ ends[77] (Fig. 3B). This modification is recognized by readers including the LSM1-7 complex, DIS3L2 and La protein. Critically, uridylation facilitates mRNA decay by recruiting deadenylases, decapping enzymes and exonucleases, while concurrently regulating translation efficiency *via* destabilizing transcripts and modulating rRNA/tRNA turnover[78]. A-to-I editing converts adenosine to inosine in dsRNA hairpins formed by inverted Alu repeats[79]. This process is mediated by ADARs, notably in the nervous system[80], and occurs predominantly in introns and untranslated regions[78]. A-to-I editing is implicated in neurological disorders (*e.g.*, ALS[81] and psychiatric disorders[82]), cancer[83] and viral infections[84].

2.3. *RNA transport and localization*

Cellular polarity relies on asymmetric RNA subcellular localization to enable localized protein synthesis and establish protein asymmetry[85]. Among RNA localization mechanisms, motor-driven active transport predominates due to its efficiency[86,87]. RBPs recognize specific RNA motifs to mediate localization[88] by forming RNP complexes[86] (*e.g.*, with hnRNPs) that bind molecular motors for ATP-dependent transport along cytoskeletal scaffolds[89] (Fig. 4A). In yeast, Ash1 mRNA localization requires four stem-loop zip codes (coding region and 3′ UTR), which form RNPs with She2p/She3p enabling Myo4p-driven transport along actin filaments[90]. Subsequent anchoring at the bud tip is mediated by Bni1/Bud6 interactions with actin[91]. Notably, m^6A readers also regulate transport. For example, YTHDC1 recruits SRSF3 for NXF1-mediated nuclear export, while FMRP exports m^6A-transcripts from the nucleus *via* CRM1-or NXF2-dependent pathways[92]. Dysregulation of RBP-mediated RNA localization contributes to oncogenesis[93], as exemplified by Tia1. Tia1 regulates the localization and translation of p53 mRNA[94], and its dysfunction leads to aberrant mRNA redistribution, thereby promoting tumor proliferation, migration, and immune evasion[95].

2.4. *RNA translation*

Protein translation governs cellular homeostasis through precise control of gene expression with mRNA−RBP interactions ensuring translational fidelity. A central regulator of cap-dependent initiation is the eukaryotic initiation factor 4E (eIF4E), which recognizes the 5′ m^7G cap to assemble the eIF4F complex and facilitate ribosomal scanning of structured 5′ UTRs.

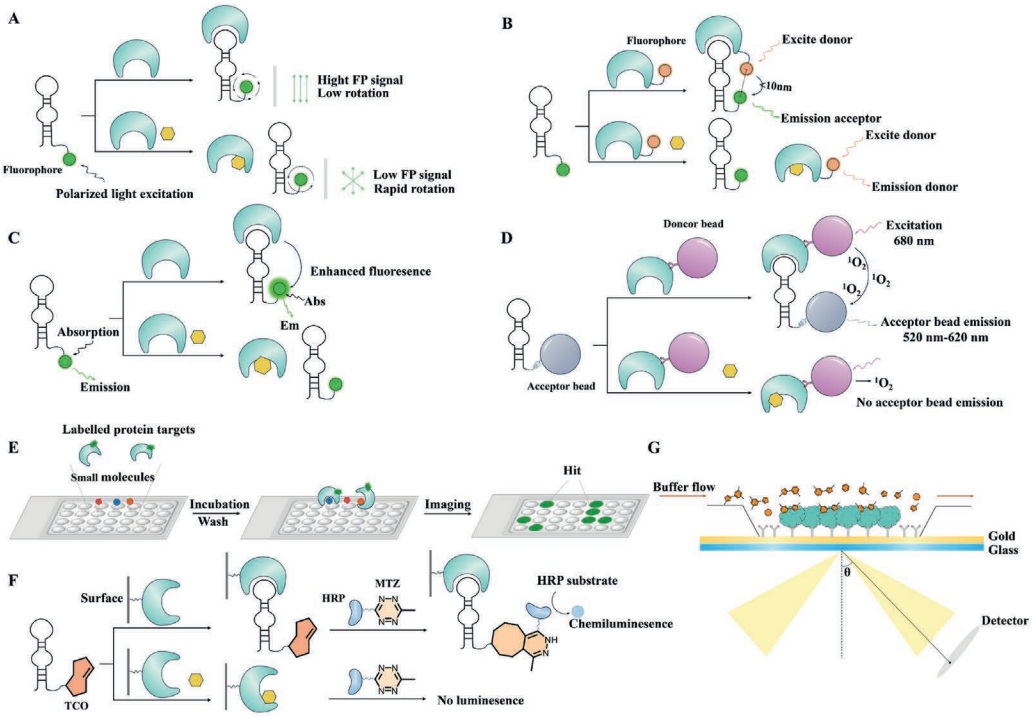

Figure 5 Biochemical assays. (A) Fluorescence polarization (FP) assay. RNA is labeled with a fluorophore that rapidly rotates in its free state, leading to low emission of depolarized light when excited with polarized light. Binding of RBPs slows fluorophore rotation, enhancing polarized light emission. Small-molecule inhibitors disrupt the RBP-RNA interaction, leading to RNA dissociation and a return to depolarized fluorescence emission. (B) Förster resonance energy transfer (FRET) assay. Both RNA and RBP are tagged with fluorophores possessing overlapping spectra. FRET occurs upon their interaction and is abolished upon inhibition. (C) Fluorescence intensity (FI)-based assay. The intensity of the RNA-labeled fluorophore is enhanced upon protein binding. Weak fluorescence indicates inhibition of interaction. (D) AlphaScreen. RBP and RNA are attached to donor and acceptor beads, respectively. Donor bead excitation generates singlet oxygen, which reacts with the acceptor bead to produce a chemiluminescent signal. This signal then excites a fluorophore, resulting in fluorescence emission. Small-molecule inhibition prevents emission. (E) Small-molecule microarrays (SMMs). Small molecules are immobilized on a glass slide, followed by incubation with fluorescently labeled RBPs and subsequent imaging to identify hit compounds. (F) Catalytic enzyme-linked click-chemistry assay (cat-ELCCA). Proteins immobilized on a microplate bind 5′-*trans*-cyclooctene (TCO)-labelled RNAs. The captured RNAs are then ligated to methyl-tetrazine (MTZ)-labelled horseradish peroxidase (HRP) *via* a click reaction and generate chemiluminescence upon an HRP substrate addition. Small molecule disruption of this interaction is indicated by a decrease in chemiluminescence. (G) Surface plasmon resonance (SPR). Binding small molecules to their targets alters the refractive index at the interface of a metal or other material, resulting in a change in the prism. In all panels, small molecules are yellow hexagon and protein is aqua green.

This process is dynamically suppressed by dephosphorylated eIF4E-binding protein-1 (4E-BP1) (Fig. 4B). Concurrently, the poly(A)-binding protein (PABP) binds mRNA poly(A) tails and recruits the eukaryotic initiation factor 4 complex (eIF4G), mediating 5′−3′ circularization to enhance ribosomal recruitment efficiency[96,97] (Fig. 4B). Furthermore, RNA modification-related proteins contribute to translational control. Experimental evidence corroborates that YTHDF1 bound to 3′ UTR m^{6}A sites promotes translation *via* eIF3 interaction[45], whereas YTHDF2 stabilizes 5′ UTR m^{6}A modifications during heat shock, enabling selective eIF3-dependent translation initiation[98].

3. Emerging roles of RBPs in disorders

Generally, RBPs mediate biological processes through a wide range of mechanisms, including alternative splicing, modification, localization and translation. This indicates that RBPs establish highly intricate regulatory networks that can simultaneously coordinate multiple disease traits. The various mechanisms of RBP regulation have been extensively reviewed recently. Herein, we summarize in Table 1[34,39,40,44,51,58,76,78,94,95,99-120,121-141,142-162,163-183,184-205] selected examples of RBP implicated in cancer, neurodegenerative disorders and autoimmune diseases, providing a reference for readers. Subsequently, we will focus primarily on the emerging roles of RBPs.

3.1. *Metabolic reprogramming*

RBPs were thought to regulate the expression of metabolic enzymes. For example, hnRNPA1 Ser6 phosphorylation mediated PKM splicing to modulate glycolysis[206]. IGF2BP2 supports oxidative phosphorylation by delivering mRNA encoding the subunit of the respiratory chain to mitochondria and promoting complex I and complex IV assembly, thereby fueling tumor growth and chemoresistance through metabolic alterations in contexts such as CSC[207] and gliomas[208]. ALKBH5 phosphorylation triggers its cytosolic translocation in obesity, driving hyperglycemia *via* GCGR signaling (in a demethylase-dependent

Table 1 The role of RBPs in cancer, neurodegenerative disorders and autoimmune diseases.

Disease category	Mechanistic basis	RBPs	Specific disease/ model	Biological functions	Ref.
Cancer	Alternative splicing	SRSF, hnRNPs (A1, A1/A2, C1, E1, L, U, H1, M), PTBP1, KHSRP, QKI, RBM39, SAM68, TIA1/ TIAR, SF3B, U2AF, NONO, ESRP	Colorectal cancer, glioma, prostate cancer, gastric cancer, NSCLC, breast, renal, melanoma, neuroblastoma	Aberrant splicing leads to expression of pro-oncogene (*e.g.*, BCL-xS) or loss of cancer suppressor genes (*e.g.*, TP53), driving tumorigenesis, invasion and drug resistance.	99-103,112-128
	RNA modification	METTL3, METTL14, FTO/ ALKBH5, ADAR, ZCCHC4, YTH (C1, F), IGF2BPs, NSUN, ALYREF, CPEB1	AML, GSCs, NSCLC, prostate cancer, renal damage, glioblastoma, multiple cancers and viral infections	Abnormalities in RNA modification drive tumorigenesis, metastasis, and drug resistance by rewriting the "RNA epigenetic code".	34,39,40,44,51, 58,76,129-131
	RNA localization	HnRNPs (E1, K, U), Tia1, HuR, IMP1, YTHDC1, XPO1	Colorectal cancer, lymphoma, glioma, AML, multiple myeloma, brain tumor, breast, liver	By targeting specific mRNA to specific regions in the cell (such as cell front, pseudopod, stress granule, etc.), local translation or functional regulation can be achieved to promote tumor invasion and microenvironment adaptation.	94,95,99,132-137
	RNA translation	eIF4A, eIF4E, eIF4EBP1, HuR, IGF2BP, YTHDF2, CPEB1, MUSASHI, GRSF1(hnRBP (F, H)), CESF1, YB-1, LARP1, ESRP, LIN28, PUF, PTBP1, NELFE	Breast cancer, renal cell carcinoma, hepatocellular carcinoma, gastric cancer, esophageal squamous cell carcinoma, endometrial cancer, HCC, colorectal cancer, ovarian cancer, prostate cancer, bladder cancer, lung cancer, AML	By controlling translational efficiency, selectively translating specific mRNA and regulating translational-coupled RNA stability, RBPs can drive tumor proliferation, metabolic reprogramming and drug resistance.	138-154
Neurodegenerative disorders	Alternative splicing	SRSF1/3/6, hnRNPs, RBFOX1, RBFOX2, FUS, TDP-43, PTBP	SMA, ALS, FTLD, AD, PD, HD	Disruption of the neuronal splicing program results in a frameshift that generates isoforms susceptible to nonsense-mediated mRNA decay, thereby leading to functional protein depletion and severe phenotypic outcomes.	155-162
	RNA modification	METTL3, METTL14, NSUN2, ADAR1, ADAR2, hnRNPA1,	AD, PD, DM2, ALS, HD, BSN	It regulates mRNA metabolism, ultimately disrupting protein homeostasis, triggering	104,163-170

Table 1 (*continued*)

Disease category	Mechanistic basis	RBPs	Specific disease/ model	Biological functions	Ref.
		YTHDF2		neuroinflammation, and mediating aberrant phase separation.	
	RNA localization	FUS, TDP-43, hnRNPs (A1, A2/ B1, K), FMRP, ZBP1/IGF2BP1, XPO1, NXF1, SFPQ	SMA, ALS/FTD, FXS, AD, HD, PD	Abnormal aggregation of RBP leads to RNA transport as well as dynamic imbalance of contingency granules.	105,185,171-176
	RNA translation	FMRP, SFPQ, TDP-43, ZBP1, SMN, HuD, TDP-43/DISC1, FUS, eIF2A	FXTAS, ALS/ FTD, AD, PD, SMA, FTLD	RBP dysfunction impairs mRNA translation and promotes toxic protein production, leading to synaptic failure, mitochondrial defects, and neurodegeneration.	105,106,177-183
Autoimmune diseases	Alternative splicing	HnRNP A1, hnRNP A2/B1, SRSF, hnRNP I (PTB1), PTB2, PCBP, QKI, KHSRP, SAM68, CELF1, NOVA1/ 2, RBFOX1/2, HuD	MS, SLE, LN, RA, T1D	The generation of aberrant splice variants exposes autoantigens or dysregulates immune cell function, thereby driving autoimmune responses and inflammatory damage.	107,184-190
	RNA modification	ADAR1, Tet2, hnRNP UL1, hnRNP M, METTL3	AGS, LN, RA	By dynamically regulating immune-related RNA metabolism and function, RBPs orchestrate intricate immune response.	78,108,109,191-194
	RNA localization	HuR, hnRNPA1, TDP-43, Ro60, SAM68	RA, MS, SLE, T1D	Aberrant transport of immune-related RNA molecules results in nuclear RNA leakage, uncontrolled immune signaling pathways, and local enrichment of inflammatory molecules.	110,111,195-198
	RNA translation	HuR, TTP, ZPF6L1, TIS11B, YTHDF1, CPEB, Roquin-1, Regnase-1, Arid5a, NF90, CIRP, HuD	RA, SLE, LN, EAE, MS, T1D	Through aberrant promotion of inflammatory factors, it induces breakdown of immune tolerance and autoantigen generation, driving autoimmune tissue attack.	199-205

manner) and promoting MAFLD/hyperlipidemia *via* EGFR−PI3K−AKT−mTORC1 signaling (in a demethylase-independent manner, through direct enhancer binding). Therapeutic hepatic knockdown of ALKBH5 has been shown to reverse type 2 diabetes mellitus (T2DM) and metabolic dysfunction-associated fatty liver disease (MAFLD) *in vivo*[209]. Metabolic reprogramming not only reshapes cellular bioenergetics but also profoundly influences RNA metabolism through metabolite signaling and the RNA-binding activities of metabolic enzymes. For instance, serine synthase PHGDH functions as an RBP *via* a novel RNA-binding domain (125−166 aa) to stabilize PRKCD mRNA, thereby driving HCC progression through mitophagy

activation[210]. The study found YTHDF2 operates as a dual-function reader. It recognizes m^5C-modified transcripts and stabilizes target mRNAs (*e.g.*, those encoding ATP synthase subunits) by recruiting PABPC1, thereby enhancing ATP synthesis. Concomitantly, as an m^6A reader, it degrades immunogenic mRNAs (*e.g.*, CD19/MHC-II), facilitating immune evasion. This strategy overcame antigen-escape relapses while allowing for a substantially lower CAR-T cell dose, thus mitigating treatment-related toxicity[211]. Similarly, YTHDF2 exhibits synthetic lethality with Myc in triple-negative breast cancer (TNBC). It promotes tumor growth by stabilizing MAPK pathway mRNAs, facilitating epithelial-mesenchymal transition (EMT) and enhancing global translation rates. Depletion of YTHDF2 induces proteomic heterogeneity and leads to selective endoplasmic reticulum stress-mediated apoptosis thereby disrupting Myc-driven mRNA synthesis compensation[212]. In addition, evidence suggests that YTHDF2 exacerbates ischemic neuroinflammation by promoting M1 microglial polarization *via* m^6A-dependent degradation of PARP14[213]. Conversely, YTHDF2 may alleviate neuroinflammation-associated metabolic disturbances by destabilizing NLRP3 mRNA[214]. RBPs also critically regulate the initiation and resolution of inflammation. A deeper understanding of RBP−RNA interactions and their crosstalk with metabolism may thus provide alternative therapeutic targets for inflammation control. Specifically, RRP1 suppresses inflammation by bridging one-carbon metabolism through its Nop52 domain-mediated targeting of TYMS mRNA, establishing an integrated epi-metabo-inflammatory therapeutic paradigm[215].

3.2. *Liquid−liquid phase separation*

RBPs drive liquid−liquid phase separation (LLPS) through multivalent weak interactions mediated by their low-complexity domains (LCDs) and RNA-binding domains, forming dynamic membraneless condensates[216] (*e.g.*, stress granules, nucleoli, Cajal bodies). Physiologically, these condensates facilitate RNA processing and translation; pathologically, however, dysregulated LLPS kinetics can induce a liquid-to-solid transition into insoluble pathological aggregates. Although TDP-43 cytosolic aggregation drives neurodegeneration, such as ALS and FTD, its triggers remain unresolved. Recent studies demonstrate that synergy between up-concentration within condensates and oxidative stress promotes intra-condensate demixing, forming dynamic TDP-43-rich phases within SGs that ultimately transition into pathological aggregates[217]. Clinical observations reveal heterogeneity in TDP-43 inclusion morphology and distribution among ALS/FTLD patients: high-aggregation mutants (*e.g.*, TDP-43C173/175S) cause focal neuronal injury through intracellular retention (limiting spread), whereas low-aggregation mutants (*e.g.*, TDP-43G298S) exhibit high toxicity and greater spreading potential[218]. Notably, G3BP1 serves as the central node for the protein−protein and protein−RNA interactions within stress granules (SGs)[219,220]. Its impaired assembly and disassembly are associated with multiple diseases, including cancer. Endoplasmic reticulum stress triggers cytosolic UTX condensation into SG-co-localized puncta. Subsequent recruitment of UTX to SGs destabilizes granule networks *via* TPR-NTF2L domain interactions with G3BP1, accelerating disassembly and inhibiting neoplastic growth[221]. Pathogens exploit phase-separated condensates to support their life cycles, remodel membrane-bound organelles, regulate host cell death, and modulate innate immunity. For instance, *Mycobacterium tuberculosis* effector EsxB subverts host immunity by inhibiting p38-mediated METTL14 phosphorylation, thereby suppressing the formation of METTL14 nuclear condensates in macrophages[222]. This destabilizes Nox2 transcripts, suppresses ROS production, and promotes bacterial immune evasion. Additionally, upon binding viral RNA, RIG-I undergoes disulfide-linked (C864−C869) oligomerization, enabling LLPS and resisting MIB2-mediated degradation, thereby amplifying type I interferon and interferon-stimulated gene (ISG) responses. Wang et al.[223] proposed a bidirectional modulation strategy—using peptides to either block the C864−C869 disulfide bond or mimic its structure—to regulate RIG-I phase separation with potential applications in managing infections and autoimmune disorders.

4. Strategies to identify small-molecule RBPs inhibitors

The choice of screening technique depends on the target's screenability and chemical susceptibility, and understanding the different screening techniques can facilitate the selection[224]. High-throughput screening represents a widely used strategy in small-molecule drug discovery for identifying hit compounds. Diverse methodological approaches can be employed to screen different small molecules targeting RBPs[225], which are generally categorized into biochemical and cell-based screening approaches.

4.1. *Biochemical assays*

Biochemical screens such as fluorescence anisotropy/polarization (FA/FP) and Förster resonance energy transfer (FRET) represent target-centric approaches suitable for small molecule screening for RBPs[226]. FA and FP measure the change in the rotation correlation time, or tumble time, of a fluorescent dye[227,228], which reflect changes in the apparent molecular weight of the labeled species. When fluorescently labelled RNA binds to RBP, the resulting larger molecular complex rotates more slowly and emits polarized light. Small-molecule inhibitors disrupt the RBP−RNA interaction, leading to RNA dissociation and emission depolarized fluorescence (Fig. 5A). FA and FP are robust and straightforward techniques for probing weak interactions, particularly between molecules of markedly different mass, although their sensitivity decreases for very low-molecular-weight ligands.

In FRET, energy from a fluorescent donor is transferred to an acceptor through dipole−dipole interactions. The efficiency of this energy transfer depends on several factors, including the spectral overlap between the donor and acceptor, the distance between them (typically <10 nm), and their relative orientations, as described by Forster's equation[227,229]. When RNA and proteins are labeled as FRET pairs, disruption or inhibition of the complex reduces the observed FRET signals, reflecting the loss of interaction between the protein and RNA[230] (Fig. 5B). FRET enables high-precision, real-time detection of molecular interactions between molecules; however, it requires sophisticated instrumentation and is highly susceptible to environmental interference. Despite these limitations, these techniques have been effectively applied to identify small-molecule inhibitors targeting spliceosomal proteins, Lin28[231,232], HuR[233], MSUT2[234], the MUSASHI[235] family of proteins, and the EIF4[236] family of proteins.

In a similar format, fluorescence-intensity (FI)-based screening has been employed to identify LIN28 inhibitors, such as pyrazolyl thiazolidinediones. In this assay, the FI of an environment-sensitive fluorophore-labelled RNA is enhanced upon LIN28 binding[237] (Fig. 5C); conversely, inhibitors of this interaction lead

to a decrease in FI[7]. Compared with the aforementioned techniques, FI provides a technically undemanding, high-throughput-compatible approach for rapid interaction screening. However, it is limited to monitoring macroscopic changes in total fluorescence and cannot resolve molecular conformational rearrangements or dynamic interaction parameters. In contrast, AlphaScreen (PerkinElmer's Amplified Luminescence Proximity Homogeneous Analysis) is a non-radioactive, proximity-based technique that does not require fluorescence labeling, thereby avoiding fluorescence-related artifacts. In this method, the proximity of "donor" and "acceptor" microbeads is mediated by the presence and co-recognition of the analyte of interest[238] (Fig. 5D). Within sufficient distance, acceptor microbeads receive a chemiluminescent signal generated upon excitation at 680 nm. Recently, AlphaScreen was employed to identify the HuR inhibitor CMLD-2, which disrupts the interaction between HuR and ARE-containing mRNA[133].

Small-molecule microarrays (SMMs), originally developed for discovering inhibitors of undruggable proteins, have later been adapted to identify RNA-binding ligands. SMMs consist of small-molecule libraries spatially arrayed on a slide, which are screened through co-incubation with either a radioactively labelled or a fluorescently tagged RNA. Following stringent washing to eliminate off-target or low-affinity binding, the array is fluorescently imaged[239] (Fig. 5E). SMMs combine high throughput, minimal sample consumption, and compatibility with diverse libraries, making them ideal for early target−ligand interaction discovery. A major challenge is that the small molecules identified through *in vitro* screening often exhibit poor cell permeability and limited bioactivity[225]. Validation and modification are therefore needed for further drug development.

Other methods, such as catalytic enzyme-linked click chemistry assay (cat-ELCCA), demonstrate enhanced sensitivity and generalizability compared to fluorescence-based assays[226] (Fig. 5F). Cat-ELCCA was designed as a click chemistry-based amplification assay that combines copper-catalyzed azidoalkane cycloaddition (CuACC) with enzyme-linked immunoassay (ELISA). It has been successfully applied cat-ELCCA to discover pre-miRNA-selective small molecule probes[240], as well as to study acyltransferases and protein−protein interactions (PPIs) and pre-let-7−Lin28 interactions[241,242].

In addition, binding-based assays also belong to this category. A prominent example is surface plasmon resonance (SPR), a highly sensitive analytical tool that allows real-time monitoring of biomolecular interactions[243]. SPR detects binding events between small molecules and target biomolecules by measuring changes in the refractive index at a metal or other material[244] (Fig. 5G). Although highly sensitive, SPR is relatively expensive, offers limited throughput, and requires strict control of buffers, temperature and particulate matter[224].

4.2. Cell-based assays

By definition, cell-based screening assesses the effects of small molecules in an intracellular environment, avoiding the limitations of *in vitro* reconstitution systems. This strategy aims to identify compounds that affect pathways associated with specific phenotypes[230], such as changes in cell viability, enzyme activity, or other biomarkers, thereby offering greater potential for drug discovery than target-based strategies[245]. Assays done in mammalian cells typically use luciferase or fluorescent protein production as readouts[230].

In reporter gene assays, a reporter gene is transfected into a given cell line, incubated with compounds of interest, and analyzed by plate reader or cytometry for alterations in fluorescence or luminescence, in that it reflects the degree of activation or inhibition of the promoter[224] (Fig. 6A and B). The most commonly used reporter genes are luciferase and GFP, and others include chloramphenicol acetyltransferase (CAT), β-galactosidase (GAL), β-lactamase (LAC) and secreted alkaline phos-phatase (SEAP)[246]. A notable constraint of reporter gene assays is that they typically require long incubation times for transcription and translation, suggesting that the observed signals are products of the entire pathway and that the compounds being screened can interact at any point, thus increasing the likelihood of indirect effects[247].

Protein-fragment complementation assays (PCA, alternatively termed bimolecular fluorescence complementation) and two-hybrid screening, splits a single detection protein into two parts that are conjugated to the biomolecules of interest, such that a luminescent signal is detected upon their interaction (Fig. 6C). GFP is less frequently employed in such applications owing to its irreversible binding characteristics[248], whereas the NanoLuc Binary Technology (NanoBiT) system comprising two engineered luciferase subunits[249], SmBiT (13 kDa) and LgBiT (18 kDa), offers a more versatile split-luciferase platform. For example, cells stably expressing SmBiT-HaloTag are transfected with RBP-LgBiT and a chloroalkane-modified RNA probe for covalent labeling. RNA−RBP interaction then drives NanoLuc reconstitution, triggering a quantifiable chemiluminescent signal. RiPCA (RNA-based protein-fragment complementation assay)[250], which reports splicing events through recombinant enzyme complementation fragments, has been used to discover small-molecule inhibitors of spliceosomal proteins and microRNA-binding proteins. Unlike *in vitro* approaches, these cell-based assays do not identify the direct targets or precise mechanisms of active compounds[239], as these may act at any points within the cellular network[224].

A variant on luciferase assays is Triple Exon Skipping Luciferase Reporter (TESLR) assay[251], which is a novel assay that specifically activates luciferase in cells exposed to SF3B1 targeted compounds[226,252] (Fig. 6D).

4.3. Other techniques

Advancing beyond conventional methodologies, novel technological platforms have demonstrated significant potential in facilitating the identification of RNA-binding protein ligands. Chemoproteomic methods, such as photo-crosslinked probes[253] and proximity labelling techniques[254], are generally employed for characterizing RBP−RNA interactions but are expected to be used for RBP probe development given their widespread adoption and flexible design. Integrative computational strategies—encompassing *in silico* screening and machine learning-driven predictive modeling are revolutionizing the discovery of RBP probe through advanced bioinformatics frameworks. Illustratively, the recent study identified RBP probe targeting the stress granule-associated protein TDP-43[255,256]. Notably, machine learning-driven approaches integrating ligand-based virtual screening and RBP structural dynamics modeling are accelerating the discovery of small molecules targeting RBPs[239]. Additionally, Disney's Labs have pioneered the Inforna[257] computational framework, an RNA structure-centric platform, which enables dual-space screening of RNA motif-ligand interactions.

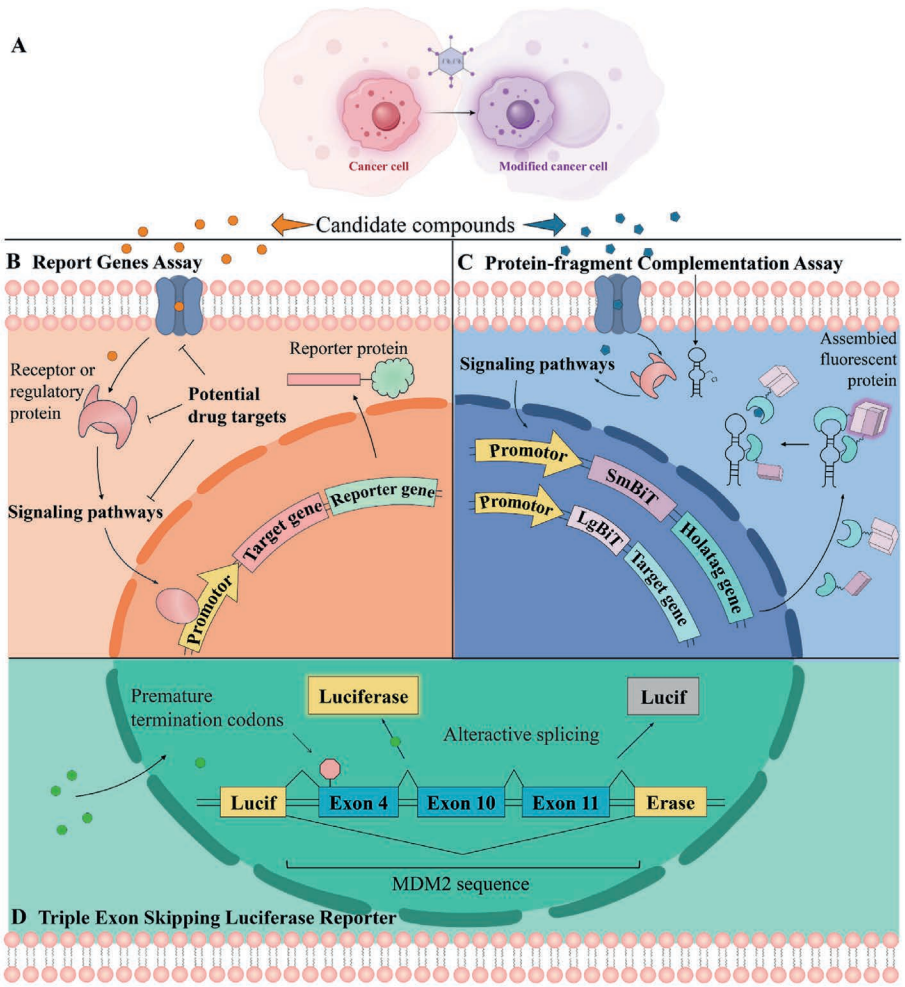

Figure 6 Cell-based assays. (A) Schematic diagram of transfection. (B) Reporter genes assay. The expression of the reporter is monitored by a luminescent, fluorescent, or optical readout that reflects the degree of promoter activation or inhibition. (C) Protein-fragment complementation assay. This assay uses a hybrid RNA and two fusion proteins, in which the target RBP and RNA-binding domain are each fused to non-fluorescent fragments of fluorescent protein. RNA binding promotes the assembly of a ternary complex, resulting in reconstituted fluorescence that can be detected through imaging. Small-molecule inhibition of RNA-RBP binding prevents this fluorescence. (D) Triple exon skipping luciferase reporter. Cellular luminescence occurs only when a splicing modulator drug induces skipping of MDM2 cassette exons 4, 10, and 11, enabling production of a correctly spliced, full-length luciferase transcript. In the absence of the small molecule, these exons disrupt the luciferase gene, preventing proper expression.

The cell-type specificity of RBPs complicates the identification of biologically relevant targets, particularly *in vivo*. To address this, Rosbash group[258] developed TRIBE (Targets of RBPs Identified by Editing), fusing RBPs to the catalytic domain of Drosophila ADAR (dADARcd). It maps RBP targets by introducing sequencing-detectable editing events. TRIBE successfully identified targets of Hrp48, dFMR1, and NonA in *Drosophila*, outperforming CLIP with single-neuron resolution (≥150 cells) without requiring antibodies. Further, they engineered Hyper TRIBE[259] by incorporating a hyperactive mutation (ADARcd-E488Q), which enhanced editing efficiency, reduced bias, and improved sensitivity while maintaining specificity. This cost-effective protocol has been extended to mammals (human ADAR2cd-E488Q) and yeast. Hyper TRIBE addresses limitations of CLIP-seq, such as low UV transmittance by fusing yeast RBPs (KHD1, BFR1) to hADAR2. The above work established a robust cross-species platform for discovering RBP target[260].

The biophysical characteristics of a target RBP, such as its RNA-binding domain topology and aggregation propensity, dictate the choice of the optimal method. Consequently, the selected assay approach must be precisely aligned with the mechanistic profile of the RBP under investigation[261].

5. Small-molecule inhibitors

Small-molecule-based approaches remain a cornerstone in pharmaceutical development. This is primarily because they allow researchers to systematically modulate drug potency and selectivity *via* structure−activity relationship (SAR) profiling, while enabling precision engineering of physicochemical properties through rational molecular design. Current strategies for modulating protein−RNA interactions can be stratified into two principal modalities: direct targeting and indirect targeting. The direct

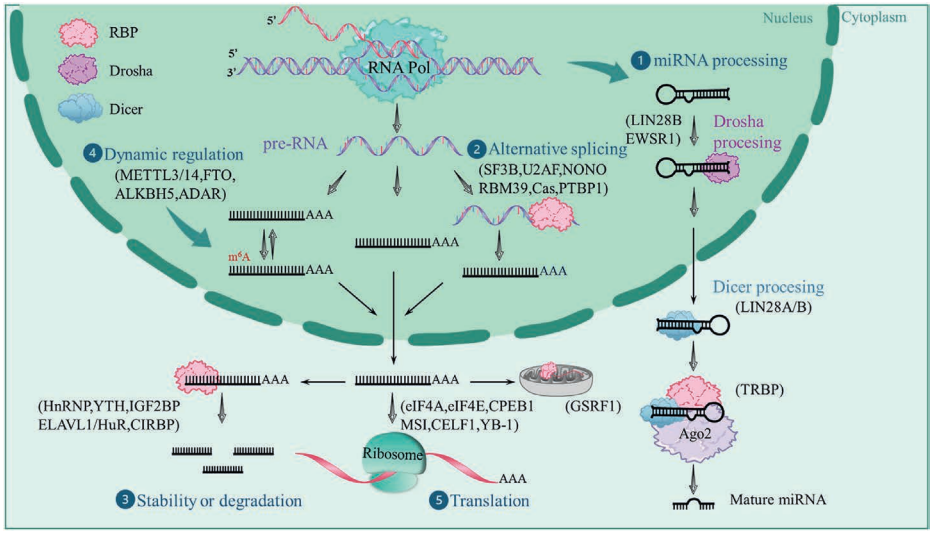

Figure 7 RNA-binding proteins mechanisms of post-transcriptional regulation. Gene expression begins with the transcription of DNA into pre-mRNA, followed by multiple RNA processing steps, many of which occur concurrently with transcription. In parallel, primary transcripts encoding microRNAs (miRNAs) undergo a separate pathway. The figure describes the RBPs involved in five processes during post-transcriptional RNA, each of which is regulated by related small molecules.

targeting paradigm focuses on RBPs through competitive inhibition of RNA−protein binding interfaces. Conversely, indirect approach encompasses RNA-targeting strategies and targeting upstream regulators for which direct RBP modulators remain elusive. Additionally, the modularity and combinatorial potential of small molecules are overcoming the historical limitation of target space, enabling drug discovery against once undruggable targets. Herein, in the subsequent section, we present a comprehensive overview of these two categories, and summarize the collected drug information spanning small molecules, antisense oligonucleotides (AOS), and ncRNA—with detailed compendium presented in Supporting Information Table S1.

5.1. Targeted RBPs directly

Direct target engagement is critical for elucidating a compound's mechanism of action. RBPs regulate all aspects of RNA life[4], encompassing both nuclear (transcription, splicing and modification) and cytoplasmic processes (transport, localization, translation and degradation) of mRNA metabolism, as depicted in Fig. 7. Notably, recent advancements have demonstrated an encouraging trend of identifying small-molecule inhibitors of RBPs[99]. Consequently, increasing attention has been directed toward how these small molecules can be used to regulate the multiple functions of RBP in RNA life, such as miRNA biogenesis, alternative splicing, modification, localization and translation. The following is a classified overview of the drug molecules that regulate these five types of functions.

5.1.1. Small molecules affecting the regulation of miRNA biosynthesis

In miRNA biosynthesis, LIN28, TRBP and EWSR1 are three key RBPs. They fulfill distinct roles in the processing of miRNA from primary transcripts to mature miRNA. These RBPs provide multiple potential targets for small molecule design, and disrupting their interactions with miRNA enables precise regulation of miRNA expression levels. The following sections will explore the functions of these RBPs and how small molecules can modulate miRNA biogenesis.

5.1.1.1. LIN28. In the strategy of directly targeting RBPs, important progress has been made in the development of LIN28 inhibitors. LIN28, a highly conserved RBP, plays a pivotal role in stem cell self-renewal and cancer progression. It was originally identified in the *Caenorhabditis elegans*, where it regulates heterochronic development[262]. Its expression is mainly restricted to embryonic stem cells (ESCs) and certain transformed cell lines but is typically absent in differentiated cells; it is therefore considered a biomarker for cancer stem cells[263]. The interaction between LIN28 and the let-7 miRNA is one of the most extensively studied protein−RNA interactions and has considerable therapeutic significance[7]. Mechanistically, LIN28 regulates stem cell self-renewal and pluripotency by inhibiting let-7 miRNA maturation. Additionally, it directly binds to and regulates a wide range of mRNAs, thereby affecting cellular metabolism and growth[264,265]. Specifically, LIN28 consists of two homologues, LIN28A and LIN28B (Fig. 7). LIN28A acts in the cytoplasm, where it recruits terminal uridylyl transferase (TUTase) to pre-let-7 miRNAs, prompting their uridylation and thereby blocking Dicer processing[266]. Conversely, LIN28B accumulates predominantly in the nucleolus where it binds pri-let-7 miRNAs to block processing by the Microprocessor (DROSHA/DGCR8 complex)[267,268]. This Bistable Switch depends on two important functional domains, the cold shock domain (CSD) and the zinc knuckle domain (ZKD). These domains recognize distinct sequence motifs in the terminal loop of pri-let-7—the ZKD binds with high specificity to GGAG-like motifs, whereas the CSD preferentially recognizes (U)GAU sequences[269].

Recent studies have revealed that LIN28 can synergistically bind mRNAs with another RNA-binding protein, YB-1, and this interaction may potentially underlie the LIN28-mediated reprogramming of translation, which plays a role in development and tumor adaptation[270]. In tumor biology, overexpression of LIN28 is associated with a variety of cancer types, and it promotes tumor

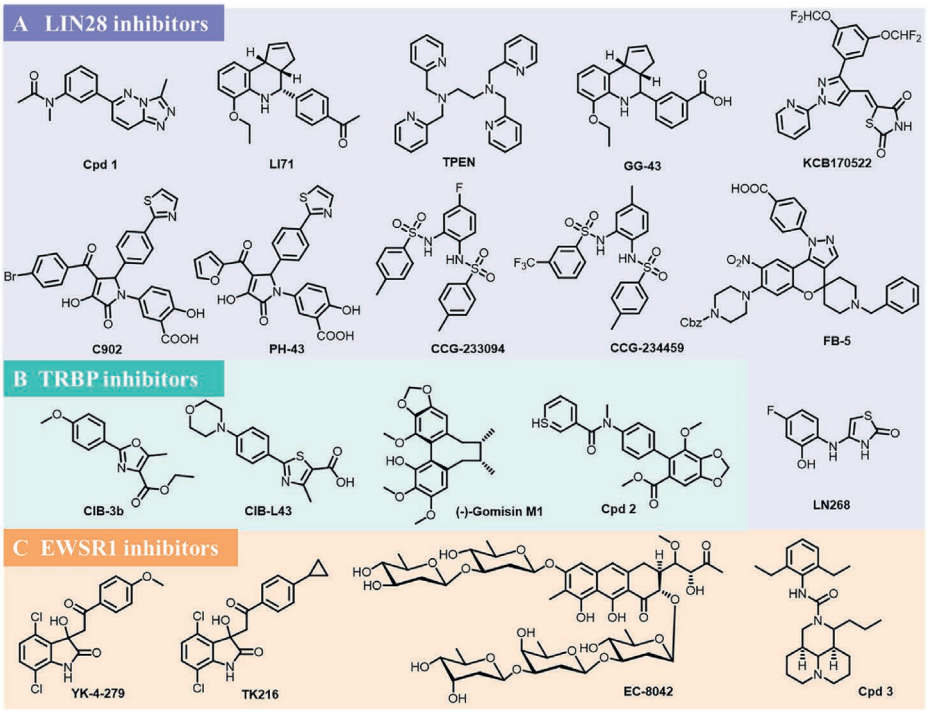

Figure 8 Small-molecule inhibitors of the biogenesis of miRNA related to RBPs.

development and adaptation by modulating of let-7 target genes (*e.g.*, RAS, Myc and HMGA2), thereby facilitating cancer stem cell maintenance and tumor progression[265,271]. In addition, LIN28 is involved in the regulation of glucose homeostasis and insulin sensitivity, playing an important role in metabolic regulation. Given its critical roles in these diverse biological processes, the development of LIN28 inhibitors has emerged as a vital research direction. Several small-molecule inhibitors have been reported (see Fig. 8A), providing new strategies for the treating LIN28-related diseases.

The targeted inhibition of RNA−protein interactions has long been a major challenge in drug development. For this purpose, Roos et al.[232] developed a FRET-based screening method using GFP-Lin28 as the donor and pre-let-7 miRNA with black hole quencher (BHQ) as the acceptor. They identified **Cpd 1** (IC_{50} = 8 μmol/L) from a screen targeting the LIN28/let-7 interaction. This compound, an anxiolytic agent, suppressed stemness and induced differentiation in mouse embryonic stem cells, in addition to inhibiting proliferation and stem-like properties in 22Rv1 and Huh7 cells. Moreover, Wang's team[272] conducted high-throughput screening using FP assays on a commercial compound library, successfully identifying small-molecule inhibitors targeting both the CSD and ZKD domains of LIN28 involved in let-7 interactions. To balance RNA-binding activities between these functional domains, they engineered a truncated LIN28 mutant, which reduced CSD-RNA binding affinity, while increasing the sensitivity for detecting compounds that target the ZKD. In a further step, six compounds including TPEN and L171 completely inhibited LIN28-mediated oligouridylation at 40 mmol/L[272]. L171 directly binds to LIN28's CSD domain (IC_{50} = 7 μmol/L), whereas TPEN selectively targets the ZKD (IC_{50} = 2.5 μmol/L), inducing significant structural changes of the zinc knuckles and RNA-binding residues in the ZKD. However, the technical limitations of FRET and FP hinder their universal application. To address this, Byun's team[237] developed an alternative simple fluorescence intensity based binding assay to facilitate precise measurement of PRIs. Changes in the microenvironment caused by protein binding can significantly alter the fluorescence intensity of organic fluorophores conjugated to nucleic acids. Based on this method, four pyrazolyl thiazolidinediones-type molecules were identified, one of which was KCB170522, further verified to inhibit the binding interaction between Lin28A and let-7g in a dose-dependent manner, as confirmed by EMSA. In recent years, Borgelt et al.[273] screened the novel LIN28 backbone, the trisubstituted pyrrolidone C902 (IC_{50} = 5 μmol/L). This is the first report of a dual PRI and PPI modulating scaffold, whose PRI inhibitory and PPI stabilizing activities can be tuned by carefully choosing different substituents attached to its core. Through high-throughput cat-ELCCA screening of 127,000 compounds, Lorenz groups[241] identified aryl bis-sulfonamides as novel LIN28 inhibitors. The RNA−protein interaction was quantified using a click chemistry approach, which employed Halo-tagged mouse LIN28A (biotin-labeled) and *trans*-cyclooctene-modified pre-let-7d with methyltetrazine-HRP conjugation. Two lead compounds (CCG-233094 and CCG-234459) exhibited dose-responsive inhibition in both cat-ELCCA and EMSA (IC_{50} values of 8.3 and 10.3 μmol/L, respectively). After systematic analyses of tricyclic tetrahydroquinoline (THQ)-containing scaffold[274], Wu et al.[275] identified novel spirocyclic chromenopyrazoles FB-5[276] as potent LIN28/let-7 interaction inhibitors with single-digit micromolar potency. This work overcomes the limitations of moderate potency and flat SAR plaguing existing LIN28/let-7 disruptors, providing next-generation inhibitors for further evaluation. While several compounds have been identified, they exhibit low potency and, more importantly, often lack a clearly defined mode of action (MOA). Recent studies have employed CADD-based rational drug design to develop novel Lin28 inhibitors LN268[277], which disturbs the

conformation of the ZKD of Lin28 suppressing Lin28-mediated cancer cell proliferation and spheroid growth. Furthermore, LN268 synergizes with chemotherapeutic agents (*e.g.*, cisplatin, etoposide) and cellular stress inducers such as arsenite to suppress tumor growth. This synergy highlights a promising combinatorial strategy that target Lin28-mediated stress granule formation alongside conventional chemotherapy.

5.1.1.2. TRBP. TRBP has previously been identified as an RNA-binding protein involved in HIV viral replication and regulating the stability of mRNAs related to tumor metastasis and angiogenesis. Recent studies have shown that TRBP serves as a key component of the miRNA-induced silencing complex (RISC) (Fig. 7). Joo's team[278] developed a single-molecule, two-color fluorescence technique combined with single-molecule immunoprecipitation to study the dynamic process of pre-miRNA processing by the human Dicer−TRBP protein complex. This complex ensures efficient Dicer processing of microRNAs in an RNA-dense environment and regulates RISC assembly and Ago2-induced miRNA stability. Mutations in TRBP disrupt miRNA biogenesis, leading to aberrant miRNA expression and promoting cancer development[279]. Through phenotypic high-throughput screening, Peng and colleagues identified CIB-3b[280] (IC_{50} = 3.1 μmol/L), a phenyl oxazole-based small molecule, that targets TRBP to inhibit HCC proliferation and EMT-mediated metastasis. This compound disrupts TRBP−Dicer interaction, altering the expression of a subset of miRNAs (*e.g.*, miR-21) and cancer-associated pathway proteins (*e.g.*, PDCD4 and PTEN). Furthermore, they designed a potent novel 2-phenylthiazole-5-carboxylic acid derivative, CIB-L43[281], which demonstrated a 4500-fold increase in inhibitory activity and oral bioavailability increased from less than 2.0% to 53.9%. This is different from the mechanism of action of two TRBP modulators previously identified by the team ((−)-gomisin M1 and its analogue **Cpd 2**)[278]. (−)-Gomisin M1 modulates TRBP-mediated miRNA biogenesis by specifically enhancing the TRBP−Dicer interaction without affecting Ago2. This mechanism occurs independently of the EMT pathway. Furthermore, (−)-gomisin M1 exhibits potent anti-hepatoma effects both *in vitro* and *in vivo* through the reconstitution of tumor-related proteins and signaling pathways. Small molecules are shown in Fig. 8B.

5.1.1.3. EWSR1. EWSR1 is a multifunctional protein that is ubiquitously expressed in most cell types. Extensive studies have shown that EWSR1 is involved in the development of a wide range of benign and malignant tumors with mesenchymal, neural ectodermal, and epithelial/myoepithelial features[282]. The Ewing sarcoma family of tumors (ESFT) is characterized by chromosomal translocations that produce the Ewing sarcoma breakpoint region 1 and Friend leukemia virus integrating 1 (EWS−FLI1) fusion transcription factor, which is an oncogenic fusion transcription factor that contributes to the highly malignant phenotype of this tumor, and its continued expression is thought to be critical for the survival of ESFT cells. *In vitro* and *in vivo* studies have demonstrated that inhibition of the binding of the oncoprotein EWS−FLI1 to RNA helicase A (RHA) leads to a reduction in the proliferation of the ESFT cell line and a reduction in tumor size. EWS−FLI1 lacks enzymatic activity, however, PPIs between RHA and EWS−FLI1 regulate oncogenesis and are therefore necessary to maintain tumor growth. Toretsky's team[283] used SPR screening to identify NSC635437, an indolone structural backbone compound. And optimized it into YK-4-279, which blocks RHA−EWS−FLI1 interaction, induces apoptosis *via* caspase activation, and suppresses ESFT xenograft growth. In DLBCL, YK-4-279 enhances antitumor effects when combined with lenalidomide by targeting subtype-specific transcription factors[284]. Structural modification of YK-4-279 yielded TK216, a metabolically stable analogue now in phase II clinical trials for Ewing sarcoma[285]. In addition to the above molecules with an indolone backbone, Mithramycin (MMA) was initially thought to inhibit EWS−FLI1, but failed to enter the clinic due to its unforeseen toxicity[286]. To tackle this problem, the team generated a panel of more than 20 MMA analogues for their ability to reverse EWS−FLI1 activity. The MMA chemical space was expanded by genetic engineering of its biosynthesis pathway and enzymatic biocatalysis to generate mithramycin analogs with improved therapeutic profiles. Among these, EC-8105 exhibited significantly higher inhibitory activity (IC_{50} = 2 nmol/L, MMA IC_{50} = 17 nmol/L) yet maintained comparable toxicity (MTD <4 mg/kg, MMA MTD = 2 mg/kg). In contrast, EC8042 demonstrated both lower toxicity and higher biologic activity than the parent compound[287]. In addition, EWSR1 contains a putative RNA-binding domain, which plays an important role in the maintenance of cellular senescence and regulates the expression of collagen IV α 1 (Col4a1) and CTGF mRNA by targeting microRNAs. Bao et al.[288] obtained a new tricyclic matrinane derivative, **Cpd 3**, *via* fragment-based structural optimization, which may regulate the process of hepatic fibrosis by inhibiting CTGF mRNA degradation through direct binding to EWSR1 or interfering with the EWSR1-Drosha interaction. Small molecules are shown in Fig. 8C.

5.1.2. *Small molecules inhibiting splicing regulators*

Alternative splicing is a mechanism that regulates the diversity of gene expression, wherein RBPs play an important regulatory role by recognizing specific splice sites on pre-mRNAs to control intron splicing and exon retention. Here, we highlight how RBPs contribute to the enhanced translation of pathogenic mRNAs and discuss the development of small-molecule inhibitors that modulate the activity of splicing regulatory RBPs[289].

5.1.2.1. SF3B1. SF3B1, a core component of the SF3b complex (a subunit of the U2 snRNP), mediates branch point adenosine (BPA) recognition and selection *via* pre-mRNA splicing[6]. SF3B1 associates with PHD finger protein 5A (PHF5A), SF3B3, and SF3B5 to form an approximately 250 kDa scaffolding complex that recruits additional splicing factors. The HEAT repeats domain of SF3B1 form a superhelical structure that confers structural flexibility to the complex. This helix wraps around PHF5A while establishing contact regions with pre-mRNA and the polypyrimidine channel of BPA[290,291]. This interaction with PHF5A in turn stabilizes SF3B1's conformation and promotes spliceosome activation. In its apo state, SF3B1 assumes an open conformation, which undergoes RNA-induced closure upon binding[6].

Although target identification remains a persistent challenge in chemical biology, cell-based phenotypic screens of natural product libraries can be extremely fruitful when the hit compounds target druggable molecules. Eisai.lnc. isolated a natural product pladienolide B in 2004 and later employed photoaffinity/biotin (PB)-labelled "chemical probes" to identify its target as a 140-kDa protein within the SF3b splicing factor complex[292]. E7107[292,293], the first clinical-stage SF3B1 inhibitor, was designed for treating locally advanced or metastatic solid tumors. Cryo-electron

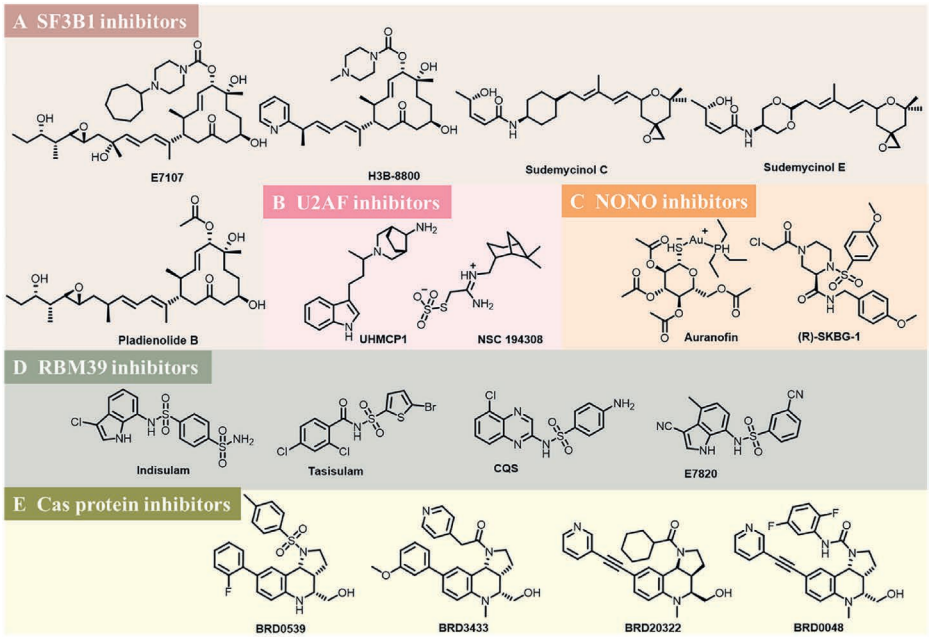

Figure 9 Small-molecule inhibitors of splicing regulators.

microscopic structural studies showed that E7107 binds in the BPA pocket and forms tight contacts with residues 15−17 of the HEAT repeat sequence, interacting particularly with known drug-resistant mutation sites such as SF3B1R1074H-type and PHF5AY36C-type[290]. Unfortunately, the trial was halted due to toxic bilateral optic neuritis. Through medicinal chemistry optimization, H3B-8800[294] was developed as an orally available drug that selectively kills spliceosome-mutant cancer cells by targeting dysfunctional RNA splicing machinery. Mutations of either SF3B1, SRSF2, or U2AF1 confer on cancer cells a dependency on the remaining WT spliceosome[295]. Mechanistic studies reveal that H3B-8800 induces GC-rich intron retention in mRNAs encoding splicing regulators thereby disrupting spliceosomal integrity and preferentially eliminating mutant cells[6]. Currently Phase I clinical trials of H3B-8800 have been conducted in patients with myelodysplastic syndromes (MDS), CMML or AML[296]. Small molecules are shown in Fig. 9A.

Notably, other well-known drugs have recently demonstrated inhibitory effects on RNA splicing. Shi et al.[297] used a cell-based tri-exon skipping luciferase reporter (TESLR) system to screen FDA-approved drugs, identifying three clinical anti-tumor candidates (milciclib, PF-3758309, and PF-562271). These compounds function as splicing modulators by inhibiting distinct splicing factor kinases rather than through direct target binding. Concurrently, sudemycinol C and sudemycinol E[297] have emerged as novel SF3B1 antagonists that target the sudemycin-binding site of SF3B1[298]. Structural representations of relevant small molecules are provided in Fig. 9A.

5.1.2.2. U2AF. While SF3b plays a crucial role in stabilizing U2 snRNP at the branch point[299], the U2AF complex is equally essential for the accurate recognition of the 3′ss, ensuring the precision of spliceosome assembly[300]. Functioning as a cofactor essential for U2 snRNP binding to pre-mRNA branch sites, the U2AF heterodimer comprises two subunits, where the large subunit U2AF65 binds the polypyrimidine tract, and its 35-kDa subunit (U2AF35) contacts the 3′ss. U2AF homology motifs (UHMs) and U2AF ligand motifs (ULMs) interactions play a crucial role in early spliceosome assembly in eukaryotic gene regulation, which mediates heterodimerization of the constitutive splicing factors U2AF65 and U2AF35 and between other splicing factors that regulate spliceosome assembly at the 3′ss[301]. Dysregulation of U2AF function has been linked to several human diseases, particularly hematologic malignancies. Mutations in U2AF1, such as the common S34F and Q157P variants, are frequently observed in MDS and AML[302]. These mutations alter the splicing of key genes involved in cell cycle regulation and apoptosis, promoting oncogenesis. UHMCP1[127] and NSC194308[303] are small-molecule inhibitors of the U2AF splicing factors U2AF65 and U2AF35, respectively. UHMCP1 disrupts U2AF65-polypyrimidine-tract binding, impairing 3′ss recognition, inducing aberrant splicing and, in preclinical models, suppressing tumor growth[127] (Fig. 9). NSC194308 likewise abolishes U2AF35 3′ss association, triggers mis-splicing and exhibits anticancer efficacy *in vitro* and *in vivo*[303] (Fig. 9B). Additionally, recent efforts have focused on developing compounds that disrupt U2AF−RNA interactions, offering a novel strategy for correcting splicing defects in cancer[304,305].

5.1.2.3. NONO. Non-POU domain-containing octamer-binding protein (NONO), a member of *Drosophila* behavior/human splicing (DBHS) family, predominantly functions as a nuclear protein containing two RRM and is a component of subnuclear body-paraspeckles. The paraspeckle complex was known to regulate DNA repair and RNA metabolism, including splicing, stabilization and export[306]. In glioblastoma multiforme (GBM), Wang et al.[126] found that NONO binds to another DBHS protein family member, PSPC1[307], at a consensus motif within the GPX1 pre-mRNA intron. Downregulation of NONO through aberrant splicing of GPX1 impairs tumor growth, invasion and redox homeostasis[126]. Auanofin (Fig. 9C), an FDA-approved anti-inflammatory agent for rheumatoid arthritis, was shown to be a useful

drug for the treatment of TNBC, due to its ability to inhibit NONO, STAT3 mRNA and protein expression levels in MDA-MB-231 cells[308].

Androgen receptor (AR) splice variants drive prostate cancer therapy resistance[309]. After screening approximately 500 electrophilic compounds containing cysteine-directed reactive moieties, Cravatt's team[310] identified piperazine chloroacetamide B21 and its structural analogue (*R*)-SKBG-1 (Fig. 9C), which were able to covalently modify C145 of NONO, inhibit transcription and protein expression of full-length AR-FL and splice variant AR-V7 in 22Rv1 cells, and ultimately reduce the number of ARs. Furthermore, there is evidence that ligand-induced recruitment of NONO to nuclear foci promotes its accumulation at the 5′ end of immature transcripts while preventing compensatory action of the paralog proteins PSPC1 and SFPQ, which in turn reshape the transcriptome and proteome of cancer cells[310].

5.1.2.4. RBM39. RBM39 is a nuclear protein, functioning as dual-functional regulator mediating pre-mRNA splicing and transcriptional co-activation. RBM39 is indirectly involved in tumor growth and progression by regulating transcription, protein translation and selective splicing of many tumor-related genes. RBM39 is characterized by upregulated expression in many cancers, but its molecular mechanisms in specific cancers remain incompletely characterized. It could colocalize with splicing factors SRSF2, SC35, and m3G at the nuclear spot, which was rich in pre-mRNA splicing proteins. RBM39 could interact with key components of the spliceosome, including U2AF65, SF3b155, and RSRC1 through its UHM domain[123]. These UHM/ULM-mediated interactions facilitate the recruitment of U2 snRNP and promote the assembly and the coordination of splicing factors, resulting in the formation of active spliceosomes and accurate processing of pre-mRNA substrates. Thus, RBM39 may interact with splicing factors associated with the early recognition of the 3′ss, thereby affecting the progression of the splicing response.

Studies have shown that RBM39 is identified as a target of sulfonamides, including E7820, indisulam, tasisulam, and CQS-collectively termed SPLAMs (splicing inhibitor sulfonamides)-provide a strategy to target RBM39-dependent pre-mRNA splicing in cancer[311] (Fig. 9D). DCAF15 is the main target of ubiquitination by SPLAMs. Therefore, SPLAMs recruit the splicing factor RBM39 to the E3 ligase receptor DCAF15, promoting RBM39 degradation *via* CRL4−DCAF15-mediated ubiquitination. This disrupts normal pre-mRNA splicing, leading to aberrant patterns marked by intron retention and exon skipping. The mechanism involves SPLAMs binding simultaneously to DCAF15 and RBM39, forming a stable three-dimensional complex. Within this assembly, sulfonamides engage the central helix of RBM39, while the adapter protein DDA1 stabilizes the CRL4−DCAF15 ubiquitin ligase complex, thereby promoting efficient recruitment and ubiquitination of RBM39[123]. E7820 and indisulam (E7070)[312] (Fig. 9D) are an antitumor agent discovered by phenotypic screening that acts as a molecular glue by recruiting CUL4−DCAF15 ubiquitin ligase, leading to polyubiquitination and proteasomal degradation of RBM39[311]. Although it had cell growth inhibitory activity in both haematopoietic and non-haematopoietic cells, it showed limited clinical efficacy in several trials and was ultimately discontinued. CQS and tasisulam[313] (Fig. 9D), are acyl-sulfonamide small molecules identified through a phenotypic drug screen of over 14,000 compounds that use a similar mechanism to target RBM39, with IC_{50} values of 7.1 and 6.5 μmol/L, respectively, but their efficacy remains to be determined[314]. Last year SEED successfully discovered the targeting of RBM39 degradation agent ST-00937 for tumors using proximity assays, which is currently in the investigational phase[315], which demonstrates total tumor regression in a model of Ewing sarcoma[316]. However, novel genetic dependencies in AML presents promising opportunities for clinical intervention. The newest molecular glue targeting RBM39, REC1245, has received FDA approval for Phase I/II clinical trials in lymphoma and solid tumors enriched for DCAF15 (NCT06678659)[317].

5.1.2.5. Cas proteins. Cas proteins are functional effectors of the CRISPR-Cas system, an RNA-mediated adaptive immune mechanism that has evolved in bacteria and archaea to defend against viral and plasmid invasion. These defenses rely on small RNAs for sequence-specific detection and silencing of foreign nucleic acids. As the hallmark protein of Type II systems, Cas9 requires a base-paired structure formed between the activating trac-rRNA and the targeting crRNA to cleave target dsDNA[318]. Studies show that although Cas9-mediated genome editing is highly specific, elevated Cas9 activity can cause off-target effects, chromosomal translocations, and genotoxicity[319]. This risk necessitates precise control over the dosage and timing of both wild-type and engineered SpCas9, creating a demand for inhibitory anti-CRISPR molecules. Choudhary's team[320] developed high-throughput primary and secondary assays for SpCas9−DNA binding and SpCas9 DNA cleavage activity, respectively. For the primary assay, they used a biochemical technique called fluorescence polarization to monitor the interaction between SpCas9 and fluorophore-labelled DNA fragments containing PAM sequences. In the secondary assay, they used an automated microscope to measure the fluorescence changes produced in cells after SpCas9-mediated DNA cleavage of a reporter gene. In a cell-based enhanced green fluorescent protein disruption assay, they identified two compounds BRD0539 and BRD3433 (EC_{50} values of 11.5 and 9.3 μmol/L, respectively)[321] (Fig. 9E). The binding of fluorescein isothiocyanate (FITC)-labelled crRNA−tracrRNA to SpCas9 was evaluated using a fluorescence polarization assay. The results show that BRD0539 did not interfere with the SpCas9−gRNA interaction, whereas a cellular thermal shift assay indicated that BRD0539 specifically disrupted the interaction between SpCas9−gRNA and DNA[321]. In dCas9-based transcriptional activation inhibition assays, BRD20322 and BRD0048 (Fig. 9E) were the most potent inhibitors, showing dose-dependent inhibition with EC_{50} values of 12.2 and 9 μmol/L, respectively. Such inhibitors not only provide new regulatory tools for gene editing technology but also offer the possibility of developing safer and more precise CRISPR therapies.

5.1.2.6. PTBP1. PTBP1 is ubiquitously expressed and binds to multiple downstream transcripts. It thereby regulates diverse processes, including tumor growth, body metabolism, cardiovascular homeostasis, and central nervous system function, highlighting its potential as a multifaceted regulatory factor. The most well-characterized function of PTBP1 is as a splicing factor that regulates alternative splicing of mRNAs. In addition, PTBP1 regulates RNA stability through nucleoplasmic shuttling and influences polyadenylation, translation, and cytoplasmic localization of target transcripts. These functions are inextricably linked to the phenotypic regulation of many cell types[322]. Recent studies indicate that PTBP1 promotes or inhibits exon splicing by binding to

the CU repeats in pre-mRNAs *via* its four RRM domains[323]. Despite its clear therapeutic potential, clinical efforts to target PTBP1 are still in their infancy. Clinical evidence from clinical trials is insufficient to advance PTBP1 inhibitors into clinical practice. For instance, while oligonucleotide-based therapy holds promise, safety profiles currently relegate them to adjuvant roles. Consequently, the translation of PTBP1-targeting strategies necessitates further foundational and clinical research.

5.1.3. Small molecules targeting RNA stability and degradation factors

RNA stability and degradation constitute pivotal determinants of gene expression. Recent research has increasingly focused on developing small molecules that target factors involved in these processes. These small molecules can interfere with the interaction of RBP with RNA or directly affect the activity of RNA degradation complexes, such as RISC, and in this way, they can precisely regulate gene expression, thus providing new drug targets for the treatment of diseases related to RNA regulation. The roles of these small molecules in the regulation of RNA stability and degradation are described in detail below.

5.1.3.1. HnRNP

5.1.3.1.1. HnRNP A2/B1. The m^6A binding protein hnRNPA2/B1, a member of the hnRNP protein family, has been extensively investigated for its frequent dysregulation and pivotal role in diverse tumor types. It mediates alternative splicing, maintains RNA stability, and regulates translation and transport through recognition of m^6A-modified sites, thereby contributing critically to tumor development, metabolism, and regulation of the immune microenvironment.

In glioma cells, β-synephrine inhibited hnRNPA2/B1, leading to increased expression of MMP-9 and p-STAT3 and inducing a malignant phenotype[324]. Studies have shown that treatment with extracts from the South African plant *Cotyledon orbiculata* induced alternative splicing of hnRNPA2/B1 to the hnRNPA2 isoform, accompanied by an elevated Bcl-xS/Bcl-xL ratio, caspase-3 activation, and apoptosis[325]. Epirubicin treatment induces secretion of exosomes carrying anti-tumor miR-503 by blocking the interaction of hnRNPA2/B1 with miR-503/ANXA2 in endothelial cells[326]. The natural product MO-460 binds to the glycine-rich structural domain of hnRNPA2/B1 and inhibits its binding to the 3′ UTR of HIF-1[327]. Additionally, the aptamer C6−8 targets ROS 17/2.8 in rat osteosarcoma cells and exerts antiproliferative effects by specifically binding to hnRNPA2/B1 after coupling with fluorescent carbon nanodots (CDots)[328]. L-Norleucine interacts with the RRM1 and RRM2 structural domains of hnRNPA2/B1, inhibits Twist1 and Snail and increases E-Calcineurin, thereby impeding EMT and tumor metastasis[329]. Dietary flavonoids, such as apigenin, have also been suggested as potential chemosensitizers. Apigenin sensitizes TNBC spheroids to Adriamycin through interaction with hnRNPA2/B1 and promotes apoptosis induced by ABCC4 and ABCG2 transporter proteins[330].

5.1.3.1.2. HnRNP D(AUF1). AU-rich elements (AREs) located in mRNA 3′ UTR can be recognized and bound by the ARE binding protein (AU-rich Element factor (AUF1)) to recruit RNase for degradation. This process plays a key role in cellular stress response, inflammatory reactions, and tumorigenesis. Li et al.[331] screened a CDK inhibitor JNJ-7706621 (IC_{50} of 0.11−0.51 μmol/L) (Fig. 10A) from 1890 approved drugs or peptidomimetics commercially available library by SPR, which interferes with AUF1−RNA complex formation. This disruption impairs mRNA degradation homeostasis and inhibits the expression of the target gene IL8.

5.1.3.1.3. HnRNP K. Another extensively studied member of the hnRNP family is hnRNP K, a multifunctional protein involved in various nuclear processes, including chromatin remodeling, transcription, splicing, translation, and mRNA stability. HnRNP K is distinguished from other hnRNPs by its

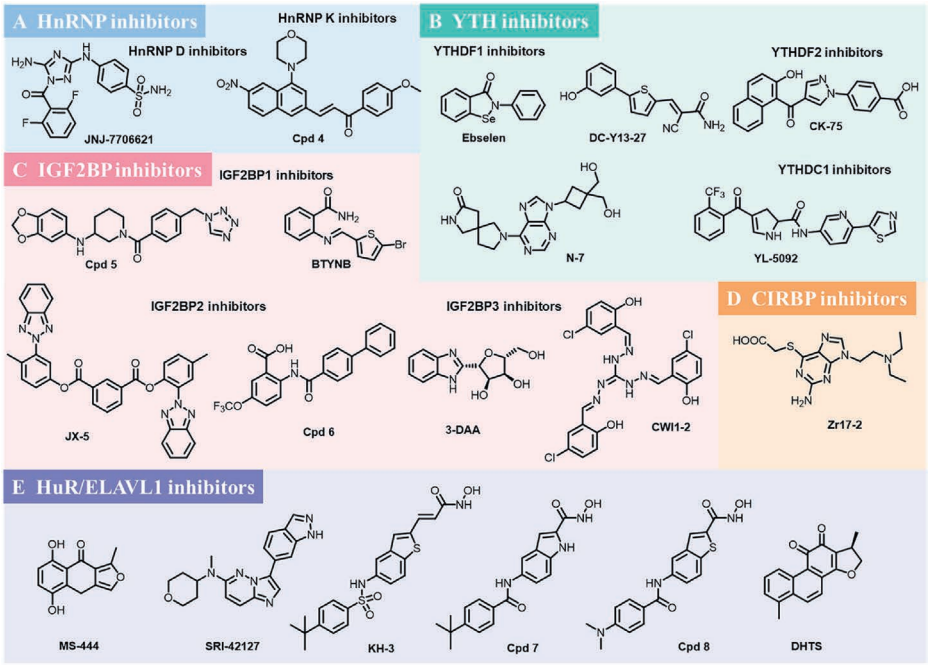

Figure 10 Small-molecule inhibitors of RNA stability and degradation factors.

functional versatility, which stems from its ability to interact with multiple proteins through its KH domains[332]. Several studies have demonstrated that hnRNP K could upregulate c-Myc gene transcription through binding to C-rich sequence[333] or i-motif in its promoter, functioning as a transcriptional activator. Consequently, Shu et al.[334] synthesized a series of quinoline derivatives and identified **Cpd 4** as a tight-binding ligand of hnRNP K, with K_D values of 4.6 μmol/L (SPR) and 2.6 μmol/L (MST), which was determined to be the first-reported hnRNP K targeting molecule. It showed good tumor growth inhibition in the HeLa xenograft tumor mode (Fig. 10A).

5.1.3.2. YTH. The YTH (YT521-B homology) domain was identified by sequence comparison and was found in 174 different proteins expressed in eukaryotes[335]. Mammalian systems contain five YTH domain-containing proteins, classified into three YTHDF and two YTHDC subtypes, which exhibit divergent YTH domain sequence homology and distinct biological functions. Among these, YTHDC1 localizes to the nucleus and regulates gene expression by mediating exon selection during pre-mRNA splicing. In contrast, YTHDF1 resides predominantly in the cytoplasm, while YTHDF2 migrates to mitotic chromatin in human induced pluripotent stem cells (hiPSCs)[336]. Recent structural characterizations have revealed a hydrophobic pocket in these proteins to preferentially bind the methyl group of m^6A[45]. Critically, the pocket-forming residues exhibit cross-species conservation (yeast to human), indicating that the function of selective m^6A binding is evolutionarily preserved. A high-throughput screen leveraging intrinsic tryptophan fluorescence in the YTHDF m^6A-binding pocket identified ebselen, an organoselenium compound, as the first inhibitor of this domain. Ebselen (Fig. 10B) forms a covalent Se−S bond with YTHDF at C412, adjacent to the m^6A-binding pocket of YTHDF1. This modification prevents the conformational rearrangement of the $\beta4-\beta5$ loop into a configuration competent for m^6A recognition, thereby inhibiting the binding of m^6A-modified RNA[337]. Wang et al.[338] discovered that YTHDF2 depletion in myeloid cells enhances ionizing radiation (IR)-induced antitumor immunity. Mechanistically, the IR−YTHDF2−NF-κB axis controls myeloid-derived suppressor cell (MDSC) migration and immunosuppressive activity, thereby modulating tumor response to radiotherapy. DC-Y13-27 (Fig. 10C), a derivative of DC-Y13 identified by small-molecule screening, enhanced the antitumor effects of radiotherapy and radio-immunotherapy combinations, comparable to the deletion of YTHDF2, and it exhibits a preference for inhibiting YTHDF2 binding to m^6A-modified RNA, of which IC_{50} was determined to be 21.8 μmol/L. Through an FP-based screening campaign, Qiu et al.[339] identified a novel series of phenylpyrazole derivatives, represented by the potent compound CK-75, as YTHDF2 inhibitors that potentially bind to a small hydrophobic pocket on YTH domain of the protein. Cellular studies demonstrated that these inhibitors induce cell cycle arrest and apoptosis, significantly suppressing the viability of cancer cells. Yang et al. reported a highly potent and selective YTHDC1 inhibitor YL-5092[340] (IC_{50} = 7.4 nmol/L, K_D = 29.6 nmol/L) (Fig. 10B), which plays essential roles in the pathological process of AML. Interestingly, Wang et al.[341] discovered N-7, an adenosine-mimetic inhibitor that exhibits unique, competitive pan-inhibitory activity against five YTH domains. Notably, YTHDF2 is also significantly implicated in neurodegenerative pathology[168] and has additionally been shown to shape the transcriptional landscape in AD patients' brain[169]. Mechanistically, it impacts cognitive function by degrading specific mRNAs, including SEMA4B, thereby reducing the level of a protein that suppresses synaptic protein synthesis and restricts memory capacity. Consequently, inhibiting YTHDF2 enhances synaptic plasticity and memory, a finding that provides direct evidence for the functional role of the m^6A-dependent RNA epigenetic regulation in neural function[170].

5.1.3.3. IGF2BP. As previously established, YTHDF proteins, defined by their YTH domains, are established m^6A readers that orchestrate mRNA processing through modulation of splicing, translation, or decay pathways. In contrast, researchers have identified a new family of m^6A readers, the IGF2BPs/IMPs, which regulate a spectrum of processes in RNA lifecycle. IGF2BPs comprises three subtypes, the structures of which are notably similar in order and spacing of domains including two N-terminal RRMs and four C-terminal KH domains arranged as a tandem repeat[342].

Initially, IGF2BP1 was characterized as a protein that stabilized c-Myc mRNA *in vitro* through binding to the coding region stability determinant (CRD). Subsequently, IGF2BP1 was also found to control ACTB mRNA localization through binding to a "zipcode" element in its 3′ UTR. This interaction ensures the localized translation of β-actin at the cell periphery and facilitates neuronal outgrowth in an IGF2BP1 phosphorylation-dependent manner[343]. BTYNB[344] and **Cpd 5** (Fig. 10C) are two small-molecule inhibitors developed against IGF2BP1. BTYNB, identified through FA screening, reduces c-Myc mRNA stability and exhibits broad antitumor activity in solid tumor cell lines (IC_{50} of 2.3−4.5 μmol/L). In parallel, **Cpd 5**, discovered *via* FP-based high throughput screening, directly binds to IGF2BP1 and inhibits its interaction with KRAS RNA, thereby suppressing oncogenic activity of IGF2BP1[345]. To develop a more selective, potent, and safer IGF2BP1 inhibitor, Amandeep et al.[346] performed SAR studies and luciferase-based cell division assays. They identified AVJ16 as the most potent and specific IGF2BP1 inhibitor, effectively suppressing cell migration and showing a 12-fold binding efficiency improvement over **Cpd 5**. IGF2BP2 was originally shown to bind to the 5′ UTR of *IGF2* mRNA to facilitate IGF2 translation *via* internal ribosome entry. Weng et al.[347] reported that IGF2BP2 is highly expressed in leukemia stem cells (LSCs) and promotes AML development/maintenance by regulating glutamine metabolism as an m^6A reader. Silencing IGF2BP2 or deleting METTL3/14 significantly reprograms cellular metabolism, especially glutamine and glutamate pathways, thereby impairing mitochondrial function and reducing ATP production in AML cells. Three compounds have been reported to be active against IGF2BP2 to date: the small-molecule inhibitor JX-5 (IC_{50}: undisclosed)[348], **Cpd 6** (IC_{50}: 18 μmol/L)[349] and CWI1-2[347] (IC_{50}: 0.20−0.78 μmol/L) (Fig. 10C). Another study found that IGF2BP2 expression increases in heart muscle cells under cardiac stresses and remodeling conditions but normalizes during cardiac recovery[350]. Its overexpression in the heart leads to downregulation of sarcomeric and mitochondrial proteins, mitochondrial fragmentation, and elongation with thinning of sarcomeres. These results suggest that IGF2BP2 may be an attractive target for therapeutic intervention in cardiomyopathies[350]. The human IGF2BP3 was initially identified on a screen for overexpressed genes in pancreatic cancer. Studies have shown that IGF2BP3 is upregulated in various cancers, including colorectal

and NSCLC, and promotes tumor cell growth and drug resistance by stabilizing and facilitating translation of specific mRNAs. Although no small-molecule inhibitors directly targeting IGF2BP3 have been reported, the inhibitor 3-DAA[351] (Fig. 10C) shows greater efficacy in colorectal cancer cells with high IGF2BP3 expression than in those with low expression[352]. In malignant glioma studies[353], the BET inhibitor JQ1 significantly inhibited IGF2BP3-induced neutrophil inflammatory death (NETosis) and enhanced viral replication by recruiting the CDK9/RPB-1 complex to the HSV gene promoters. These findings provide novel insights for IGF2BP3-targeted cancer therapy.

5.1.3.4. HuR/ELAVL1. The Hu/ELAV family of mammalian RBP, originally described in *Drosophila* as ELAV (Embryonic Lethal Abnormal Vision), consists mainly of the neuron-specific HuB, HuC and HuD, along with the ubiquitously expressed HuR proteins[354]. HuR contains three highly conserved RBDs, RRM1, RRM2 and RRM3. Specifically, the N-terminal RRM1 and RRM2 domains bind to AREs whereas the C-terminal RRM3 domain is involved in poly(A) tail interaction and the multimerization of HuR on mRNA target[355]. HuR preferentially binds to U-rich sequences[356] located approximately 17−20 nucleotides within the 3′ UTR of its target mRNA and typically displaces mRNA destabilizing factors from AREs to enhance transcript stability and translational efficiency[357]. The non-conserved hinge region between RRM2 and RRM3 contains the HuR nucleocytoplasmic shuttle (HNS) sequence, which is primarily responsible for HuR translocation[358]. Although HuR predominantly resides in the nucleus, it has been shown to bind mRNAs within the nucleus and facilitate their translocation to the cytoplasm, where it protects them from degradation. By binding AU-rich elements in the 3′ UTR, HuR post-transcriptionally regulates genes involved in cancer-related processes such as proliferation, angiogenesis, and metastasis[354].

The small-molecule inhibitors of HuR that have been studied and developed so far are divided into two main classes based on their mechanism of action: inhibition of HuR translocation from the nucleus to the cytoplasm and inhibition of HuR-target RNA interaction. The first class of inhibitors includes MS-44 (Fig. 10D), which was identified through HTS and confocal fluctuation spectroscopy to inhibit HuR−ARE interaction. Subsequent investigations demonstrated that MS-44, along with dehydromuctactin and okicenone, disrupts HuR dimerization, a crucial step for its subcellular trafficking[359]. MS-44 has demonstrated efficacy in inhibiting HuR cytoplasmic translocation and suppressing tumor growth in CRC, PDAC and glioma models. Furthermore, it was shown to attenuate ectopic HuR expression, accelerate Renca xenograft tumor progression, and improve survival in syngeneic mice[355,359]. Additionally, MS-44 prevents the nucleoplasmic translocation of *Agbl2* mRNA by inhibiting HuR dimerization, resulting in developmental arrest at the 2-cell stage in mouse embryos[360]. Recently, a new class of HuR dimerization inhibitors, SRI-42127 (Fig. 10D), was discovered after multiple rounds of optimization of hit compound A-92. Hit compound A-92 is a generally controlled non-depressor-2 kinase inhibitor with the potential to increase the inhibition of HuR dimeriation and reduce kinase inhibition. It facilitates CNS penetration and inhibits tumor growth in a primary patient-derived glioblastoma xenograft model. This investigation represents the first documented evidence of HuR inhibitor efficacy against intracranial neoplasms[361].

The second category is equivalent to target binding inhibitors. Since the discovery of CMLD-2, a variety of compounds inhibiting HuR mRNA target binding have emerged, such as, AZA-9, Quercetin, b-40, KH-3 (Fig. 10D), DHTS (Fig. 10D), ZM-32. From a FP screen of ∼2000 compounds, Xu et al.[233] identified the KH-3, a benzothiophene hydroxamate, as a potent inhibitor of HuR-RNA interaction. It inhibits breast cancer cell invasion *in vitro*, delays lung colony formation, and improves survival in mice. Mechanistically, KH-3 interferes with HuR-FOXQ1 mRNA interaction in breast cancer cells and HuR-Snail mRNA interaction in pancreatic cancer cells. Wu et al.[362] identified two small-molecule inhibitors of HuR, **Cpd 7** (IC_{50} = 4.7 μmol/L) and **Cpd 8** (IC_{50} = 1.31 μmol/L) (Fig. 10D), by combining a screening method with fragment analysis and inspired by the structure of KH-3, which directly binds to the RNA-binding pocket to block HuR function, inhibit the dependence of cancer cells on HuR growth, and suppress cancer cell invasion. In a breast cancer xenograft model, intraperitoneally administered inhibitor **Cpd 7** inhibited tumor growth as a single agent and showed synergistic effects in combination with chemotherapy docetaxel. Provenzani's team[363] screened the natural product DHTS from a panel of anti-inflammatory agents using AlphaScreen technology[362]. DHTS acts as a competitive inhibitor by binding to the RNA-binding pocket of HuR, thereby stabilizing it in a locked conformation and preventing subsequent RNA binding[364]. Treatment of HCT116 xenografts with 10 mg/kg DHTS resulted in an approximately 4-fold reduction in tumor size. HeLa cells treated with DHTS yielded the opposite results to those expected, with a paradoxical increase in the levels of some target transcripts[365]. They suggest that DHTS may prevent HuR binding to low AU-rich density mRNA but enriches it for high AU-rich density species.

5.1.3.5. CIRBP. Cold-inducible RNA-binding protein (CIRBP), a stress protein and the first cold-inducible protein found in mammals, exhibits ubiquitous expression across various tissues and organs. Under normal physiological conditions, CIRBP is mainly a nuclear protein, but the protein can be translocated to the cytoplasm and even released into the extracellular space upon specific stimulations, such as mild hypothermia, inflammation or exposure to ultraviolet (UV) light. They preferentially bind to the 3′ UTR of their target mRNA and regulate the selection, stability and translation of their polyadenylation sites, thereby affecting key cellular pathways[366]. For instance, CIRBP can bind to specific mRNAs involved in the cell survival and anti-apoptotic cascade response, such as MAPK/ERK1/2 cascade pathway, NF-κB, Akt and ERK pathway, and serves as an important mediator of therapeutic hypothermia. This protective response inhibits Bax/Bad-mediated, caspase-9-dependent apoptosis. Hypothermia has demonstrated therapeutic benefits in the management of various conditions, including stroke, coronary bypass surgery, neurodegenerative disorders, neonatal asphyxia, trauma, and obesity. Building upon these findings, Coderch et al.[367] identified a small molecule Zr-17-2, mimicking therapeutic hypothermia (positive modulation) (Fig. 10E) as determined by high-throughput virtual screening (HTVS) and protein imprinting of given cells. The binding modes of Zr-17-2 could account for the possible modulation of CIRBP activity through the stabilization of the terminal ends as described for RNA bound structures[368]. In hypothermic conditions, Zr-17-2 treatment elevated CIRBP protein expression levels in both R28 cells and Male Sprague−Dawley *albino* rats,

without showing any apparent toxicity relative to normothermic conditions. In addition, CIRBP, as a translational regulator in cancer cells, recognizes the 3′ UTR of transcripts associated with tumor progression (such as Trx VEGF and RPA) as well as the immune checkpoint CTLA-4. Carrier's team[369] developed four probes that specifically disrupt CIRBP−RNA interactions, downregulate Trx and CTLA-4 protein levels and inhibit proliferation in RKO, D54, MiaPaCa and HMEC cell lines without affecting the viability of normal epithelial cells. Among the four compounds, Chembridge 7646184 and Chembridge 6823240 are the most effective. It should be noted that CIRBP plays a dual role in both protecting against and exacerbating injury. While moderate stress response shields the organism from harm, excessive stress is irreversible and can trigger inflammatory diseases, potentially promoting tumorigenesis[366].

5.1.3.6. ZFP36/TTP. The Zinc finger protein 36 (ZFP36) family comprises RBPs that regulate mRNA metabolism. This family includes ZFP36 (tristetraprolin/TTP), ZFP36L1, ZFP36L2, and rodent-specific ZFP36L3. Through their CCCH ZnF domains, these proteins directly bind AREs in the 3′ UTR of target mRNAs, triggering mRNA decay. ZFP36 (the most extensively characterized among ZFP36 family members) plays a critical role in modulating immune responses and suppressing inflammatory diseases. It inhibits the production of key inflammatory cytokines, such as TNF-α, IL-6 and IL-10 in macrophages[370]. Consistent with this function, ZFP36-deficient mice develop a severe inflammatory syndrome characterized by arthritis, dermatitis, cachexia, autoimmunity, and myeloid hyperplasia—phenotypes mirroring excessive TNF-α production, as observed in TNF-transgenic models.

Furthermore, ZFP36 recruits the translation repressor complex eIF4E2−GIGYF2 to inhibit mRNA translation. Its C-terminal motif directly binds CNOT1—the core scaffold of the CCR4-NOT deadenylase complex—enabling ZFP36-mediated mRNA deadenylation. Notably, ZFP36 targets the glycolytic enzyme ENO2, inducing deadenylation-dependent decay of its transcript that depletes ENO2 protein and suppresses glycolysis. This metabolic perturbation is particularly pronounced in retinal neural cells, where ENO2 is predominantly expressed[199].

ZFP36 is phosphorylated by multiple kinases (*e.g.*, ERK, p38 MAPK, JNK, AKT). Specifically, p38 MAPK inactivates ZFP36 through serine phosphorylation in humans and mice, while PP2A-mediated dephosphorylation reactivates it[371]. Functionally, ZFP36 binds the BARX1 mRNA 3′ UTR to mediate its destabilization. Consequently, loss of ZFP36 upregulates BARX1 expression, thereby enhancing the proliferation, migration, and invasion of NSCLC cells[372]. Within the immune system, ZFP36 family members redundantly enforce T cell quiescence at homeostasis[373]. Crucially, ZFP36L1 and ZFP36L2 specifically regulate antigen-specific T cell clonal expansion and stabilize Treg function by modulating CTLA-4 recycling, IL-2/IL-7 receptor expression, and IFN-γ sensitivity—thereby suppressing autoimmunity[374].

5.1.4. Small molecules influencing the dynamic regulation of the RNA

The dynamic regulation of RNA involves two mechanisms: chemical modification and sequence editing. Chemical modifications are coordinated by three functional enzyme categories, writer (such as methyltransferase METTL3), reader (such as YTHDF protein), and eraser (such as demethylases FTO/ALKBH5), which are responsible for the addition, recognition, and removal of modifications, respectively. Sequence editing is carried out by enzymes such as ADARs through the direct alteration of RNA nucleotides. Recent advancements in elucidating RNA modification mechanisms have propelled pharmacological targeting of these enzymatic regulators to the forefront of biomedical research. In this section, we focus on discussing specific inhibitors of these three RBPs: METTL3, FTO/ALKBH5 and ADARs.

5.1.4.1. METTLs. The successful cloning of METTL3 in 1997, an enzyme that catalyzes almost all m^6A methylation in mRNA transcriptome, marked a significant milestone. Subsequent seminal studies in the 2000s demonstrated that deleting its homologues in yeast and *Arabidopsis* led to specific developmental arrests during spore formation and seed development, respectively[375]. These studies suggest that m^6A is a regulated modification essential for specific developmental processes[376]. Typically, METTL3 forms a heterodimer with METTL14, and the m^6A writing complex is joined by WTAP, which does not have methyltransferase activity, and WTAP localizes the complex to specific nuclear regions, as well as RNA substrates to the complex[377]. While the METTL3/14 complex is established as the primary m^6A writer, its depletion reduces m^6A levels by only $\sim$60% in certain cells, underscoring remaining gaps in our understanding of the m^6A methylation system. Moreover, METTL16—an emerging m^6A methyltransferase—exhibits restrictive substrate specificity, methylating merely four validated targets (U6 snRNA, MALAT1, XIST, MAT2A)[378].

STM2457[379] (Fig. 11A), the first small-molecule inhibitor targeting the METTL3 enzyme, was developed by the British pharmaceutical company STORM THERAPEUTICS. Initially, the Kouzarides's team[379] carried out a high throughput screening of 250,000 compounds and led to the identification of the initial hit STM1760 possessing an IC_{50} value against METTL3 of 51.7 μmol/L. Through systematic pharmacodynamic optimization and extensive *in vitro* ADME and *in vivo* pharmacokinetic profiling, STM2457 demonstrated high target specificity (IC_{50} = 16.9 nmol/L), with SPR confirming its high-affinity binding (K_D = 1.4 nmol/L) to the METTL3/METTL14 heterodimer. STM2457 did not inhibit other RNA methyltransferases, which induced apoptosis in AML patients and mouse AML models but not in normal non-leukaemic haematopoietic cells. Excitingly, a Phase 2 clinical study is currently evaluating the safety, tolerability, and antitumor activity of STC-15[380] (Fig. 11A), a latest-generation METTL3 inhibitor, in combination with toripalimab in selected advanced cancers (NCT06975293)[381].

Similar to STM2457, which targets the SAM adenosine binding pocket, Caflisch's team[382] identified another METTL3 inhibitor, UZH1a, developed through structure-based drug design and validated using an HTRF-based enzymatic inhibition assay. Subsequently, they optimized the compounds in the METTL3 hit through a protein crystallography-based medicinal chemistry optimization, where the fluorine atom exerted some potency, with TR-FRET analysis showing a 1400-fold increase in potency. This optimization yielded the production of the first single digit nanomolar METTL3 inhibitor, UZH2 (IC_{50} = 5 nmol/L) (Fig. 11A), with a high degree of cellular permeability. UZH2 shows target engagement in cells and can reduce the m^6A/A level of polyadenylated RNA in MOLM-13 and PC-3 cell lines[383]. Furthermore, another possible way to reduce METTL3 enzyme activity involves the use of allosteric inhibitors characterized by reversible and non-competitive interactions in conjunction with the METTL3/METTL14 complex. CDIBA, the first reported

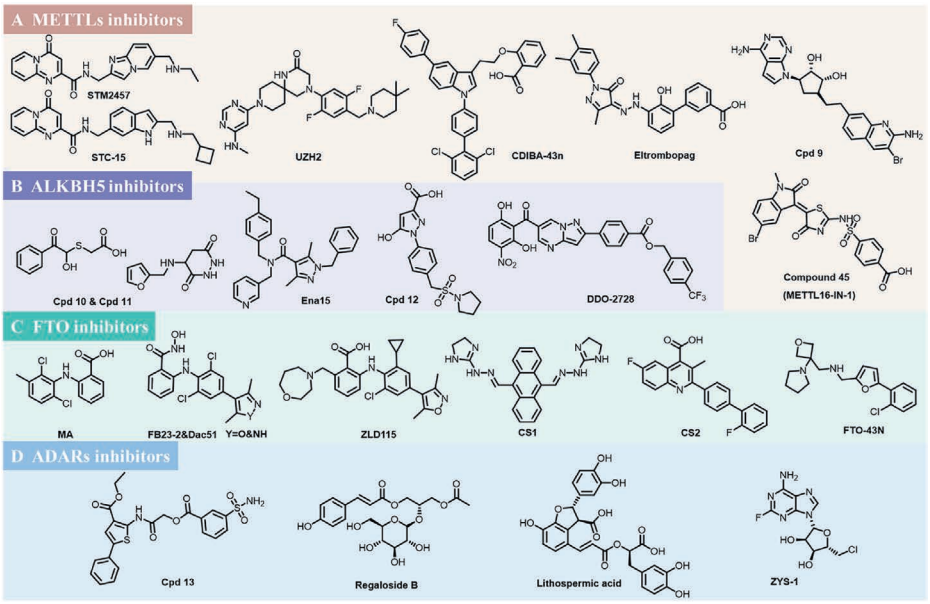

Figure 11 Small-molecule inhibitors of dynamic RNA modification.

allosteric inhibitor of METTL3[384] (Fig. 11A), was identified from a screen of a Korea Chemical Bank compound library and exhibited an IC_{50} of 17.3 μmol/L against the METTL3/14 complex. Notably, CDIBA was previously reported as a cytoplasmic phospholipase A2 (cPLA2) inhibitor. Kim's team[385] attempted to optimize the structure of the three side chains of its core backbone indole ring based on conformational relationships, and the optimized METTL3/14 inhibitor CDIBA-43n (Fig. 11A) exhibited not only inhibitory potency of the METTL3/14 complex (IC_{50} = 2.81 μmol/L), but also antiproliferative activity in the various AML cell lines by suppressing the m^6A level of mRNA. Eltrombopag (Fig. 11A), a non-SAM-competitive METTL3 variant inhibitor similar to the previously identified CDIBA-4, selectively inhibits the METTL3/14 complex with an IC_{50} of 3.65 μmol/L[386]. EPICS Therapeutics has developed EP102[387], a METTL3 inhibitor, that exhibits robust single-agent efficacy *in vivo* and acts synergistically with venetoclax for the treatment of AML.

In addition, Wang et al.[388] identified **Cpd 9** (Fig. 11A) through hybrid virtual screening of a 500,000-compound library. **Cpd 9** effectively alleviated renal dysfunction and mitigated tissue injury and inflammation. Structural modeling revealed that its core scaffold overlaps with the purine ring of sinefungin within the METTL3 binding site. Distinct from sinefungin, **Cpd 9** forms unique hydrogen bonds with Asp395 through its quinoline nitrogen and a substituted amine group, underscoring its potential as a novel METTL3 inhibitor. Significantly, Liu et al.[389] reported the discovery and validation of first-in-class aminothiazolone inhibitors METTL16-IN-1 (commercial code from MedChemExpress) targeting the METTL16-MAT2A-hp1 mRNA interaction, exhibiting potent single-digit micromolar inhibitory activity (IC_{50} = 1.7 μmol/L). These inhibitors provide foundational chemical probes to elucidate METTL16 biology and enable therapeutic development.

5.1.4.2. FTO/ALKBH5. Both FTO and ALKBH5 belong to the AlkB family of iron (II) and 2-oxoglutarate (2-OG)-dependent oxygenases, one important class of nucleic acid demethylase, which also consist of *Escherichia coli* AlkB, and human homologues ALKBH1-4,6-8. By removing the m^6A tag, these two enzymes altered the epitranscriptome and the stability of some key mRNA molecules (*e.g.*, TACC3, ASB2 and RARA)[390]. Accumulating evidence demonstrates their dysregulated expression plays a pivotal role in the pathogenesis of certain leukemia subtypes and solid tumors, underscoring their potential as targets for cancer treatment[391].

Crystal structure of the FTO protein in 2010 provided critical insights into its substrate specificity[392]. Subsequently, rhein, a natural anthraquinone, was identified through structure-guided *in silico* screening and biochemical assays as a potent FTO inhibitor (IC_{50} = 2.2 μmol/L), and was the first reported competitive inhibitor of FTO[393]. Due to the poor selectivity of rhein, including inhibition of the DNA repair function of ALKBH2 and ALKBH3, it leads to an accumulation of DNA damage and makes cells susceptible to methylated DNA damage[394]. Yang's team[395] identified meclofenamic acid (MA) (Fig. 11C), a nonsteroidal anti-inflammatory drug of the anthranilic acid class, as a selective FTO inhibitor *via* a high-throughput fluorescence polarization screening. MA achieves selective inhibition of FTO (IC_{50} = 8 μmol/L) by interacting with two β-sheet motifs within the nucleotide recognition lid (NRL), particularly involving the first loop, a structural feature absent in ALKBH5. The unique binding mode of MA enabled the rational design of highly potent and selective FTO inhibitors, culminating in FB23-2 and Dac51 (Fig. 11C). Among them, FB23-2[41] mimics FTO depletion, which promotes differentiation/apoptosis of human AML cells and inhibits progression of progenitor cells from xenografted mice. Similarly, Dac51[396] can block FTO-mediated immune escape and impair glycolytic activity of tumor cells. This effect restores $CD8^+$ T cells function, ultimately inhibiting the growth of solid tumors *in vivo*. In light of the aforementioned studies, the team developed several substrate-competitive FTO inhibitors from MA using a structure-based rational design, and subsequent studies showed that there may be metabolic instability and poor durability, and thus ZLD115[397] (Fig. 11C) was born, which is designed

to introduce flexible alkaline side chains at solvent-accessibility surface by using SAR analysis and lipophilic efficiency (LipE)-guided optimization, resulting in more balanced physicochemical properties and retained or enhanced anti-leukaemic activity. ZLD115 treatment markedly enhanced m^6A modification on RNA in AML cells, upregulated RARA and suppressed Myc expression in MOLM13 cells, mirroring the effects of FTO gene knockdown. *In vivo*, ZLD115 suppressed leukemia progression in xenografted mice without evident toxicity.

Meanwhile, Chen's Lab[398] conducted a structure-based virtual screening of 260,000 compounds from NCI DTP library, and identified two compounds (CS1, CS2) (Fig. 11C) that showed consistent and potent effects in inhibiting AML cell viability and FTO demethylase activity. Docking modelling indicated that both CS1 and CS2 bind tightly to FTO proteins and block their catalytic orifices. Indeed, CLIP-qPCR data confirmed that CS1 and CS2 block the binding of FTO with its known target mRNAs, such as Myc, CEBPA and RARA. CS1 and CS2 potently suppressed the growth of human AML cells at low nanomolar concentrations, exhibiting IC_{50} values at least 10-fold lower than those of previous FTO inhibitors. The novel oxetanyl FTO inhibitor, FTO-43[399] (Fig. 11C), was recently reported to impair growth in multiple gastric cancer cell lines with potency comparable to 5-fluorouracil (a clinical chemotherapeutic agent) without significant toxicity to healthy colon cells.

ALKBH5 is mainly localized in nuclear speckles, indicating its role in m^6A demethylation of nascent or pre-mRNAs. Unlike FTO, it lacks catalytic activity toward *N*-6,2-*O*-dimethyladenosine. ALKBH5 demethylates m^6A-modified ssRNA and ssDNA, with its activity slightly inhibited by citrate. Structural insights into ALKBH5 provide a basis for the rational design of selective inhibitors or activators, which would serve as valuable tools to elucidate the physiological and pathological roles of ALKBH5-mediated m^6A demethylation. Combining a computer-aided approach with an m6A antibody-based enzymatic assay, Karelson et al.[400] identified two low-micromolar ALKBH5 inhibitors, **Cpd 10** (IC_{50} = 0.84 μmol/L) and **Cpd 11** (IC_{50} = 1.8 μmol/L), which represent distinct chemical scaffolds (Fig. 11B). Moreover, Kazutake et al.[401] used a high-throughput screening to discover two selective small-molecule inhibitors, Ena15 (Fig. 11B) and Ena21 from a chemically diverse library. Notably, Ena15, a serendipitously identified compound, acts as an uncompetitive inhibitor of 2-OG, a previously unreported mechanism. Both Ena15 and Ena21 inhibited proliferation across four glioblastoma (GBM)-derived cell lines.

Despite the recent progress in the development of ALKBH5 inhibitors, highly potent and selective candidates remain limited. Almost concurrently, Xiang et al.[402] identified **Cpd 12** through FP screening, which was subsequently optimized to achieve an IC_{50} of 0.021 μmol/L. **Cpd 12** (Fig. 11B) demonstrated high selectivity for ALKBH5 over FTO and other AlkB family members. You's team[403] discovered DDO-2728 (Fig. 11B), a novel pyrazolopyrimidine-based inhibitor. Its lead compound was identified from a library of 180,000 compounds by structure-based virtual screening and FP analysis. Subsequent structural optimization yielded DDO-2728, which demonstrated a 6-fold potency in inhibiting ALKBH5 (IC_{50} = 2.97 μmol/L) compared to the initial lead compound. Furthermore, DDO-2728 showed excellent selectivity for ALKBH5 over FTO (IC_{50} > 200 μmol/L). Binding experiments of the mutant proteins suggested that DDO-2728 binds to ALKBH5 by occupying the binding pocket of m^6A instead of the 2-OG. In addition, DDO-2728 exhibited significant *in vivo* activity in the MV4-11 xenograft model. Li et al.[404] demonstrated that ALKBH5 deletion enhances response to immunotherapy in melanoma. Consistent with this, the ALKBH5 inhibitor ALK-04 significantly reduced tumor growth, supporting its therapeutic potential for combination treatment. Recently, HOIST Co., Ltd., initiated the investigation of an ALKBH5-targeting small molecule for glioblastoma treatment, aiming to explore its potential therapeutic value in preclinical models.

5.1.4.3. ADARs. ADARs are members of the RNA editing enzyme family, and ADARs modify dsRNA by catalyzing the post-transcriptional deamination of A-to-I, leading to changes in its sequence, coding potential and secondary structure. Evolutionary analysis reveals dynamic duplication and loss events within the ADAR gene family. Mammalian systems possess three ADARs, ADAR1 and ADAR2, both of which form stable homodimeric complexes that are required for enzyme activity, whereas ADAR3 remains in a monomeric, enzymatically inactive form[405]. ADAR1 and ADAR2 are derived from gene duplication events, whereas ADAR3 is produced by further duplication of ADAR2[406]. Among them, ADAR1 is the most widely studied RNA editing enzyme, with two isoforms, an interferon-induced cytoplasmic p150 and a constitutive nuclear p110, synthesized *via* translation initiation at an alternative methionine codon with two isoforms[407]. Elevated ADAR1 expression and activity are closely linked to the progression of various cancers and viral infections. Its depletion not only suppresses tumor cell proliferation and induces apoptosis but also restores sensitivity to immune checkpoint blockade. Two adenosine analogues, 8-azaadenosine[408,409] and 8-chloroadenosine, were previously reported to exert anticancer effects by improving A-to-I editing of ADAR and decreasing ADAR expression, respectively, which was at least what was believed by studies at the time. However, this view has since been refuted, and both have unavoidable toxicity and are not selective inhibitors of ADAR, rendering them unsuitable for further preclinical studies[410]. Avammune Therapeutics has developed an ADAR1 inhibitor, **Cpd 13** (Fig. 11D), which induces in a concentration-dependent manner in p110-knockout A549 cancer cells IFN-β and other interferon-stimulated gene expression and showed antitumor activity in a xenograft tumor model of mice bearing B16-F10 cancers and showed stronger effects when co-administered with an anti-PD-1 antibody[411]. ADAR1 also directly regulates microRNAs; for example, A-to-I editing alters the dsRNA structure of pri-miR-142, impeding Drosha-mediated processing and thereby reducing mature miR-142-5p and miR-142-3p levels[407].

Furthermore, accumulating evidence demonstrates that ADAR1 can form complexes with Dicer through direct PPIs[412], and miRNAs produced by Dicer/ADAR1 complexes are functional in that they are loaded onto Ago2/RISC and are able to silence target RNAs. In contrast, ADAR1 homodimers, subjected to the A-to-I RNA editing mechanism, inhibits miRNA processing; therefore, the ratio of ADAR1 homodimers to Dicer/ADAR1 heterodimers may determine the effect of ADAR1 on mature miRNA processing[413]. A recent report[414] summarizes potential inhibitors of ADARs, such as regaloside B[410], lithospermic acid[415], AVA-ADR-001[416] and ZYS-1[417] (Fig. 11D).

5.1.5. Small molecules targeting protein translation

The efficiency and accuracy of mRNA translation affect the level of protein expression. Targeting this process not only solves the

problem that traditional drugs are difficult to directly target certain proteins, but also indirectly regulates the expression of proteins by targeting RNA-binding proteins, thus providing a novel avenue to treat diseases. In this section, we will focus on the mechanism and therapeutic potential of small molecules that target key regulators of protein translation, including but not limited to eIF4, CPEB1, MSI, CRSF, etc.

5.1.5.1. eIF4A. eIF4A is a highly conserved DEAD-box RNA deconjugating enzyme in eukaryotes with ATPase and RNA deconjugating enzyme activities[418]. eIF4A exists in two conformations: a free form (eIF4Af) and a complexed form (eIF4Ac) as part of the eIF4F heterotrimer[419]. In the eIF4F complex, its helicase activity is enhanced by approximately 20-fold, facilitating unwinding of the 5′ UTR secondary structure in coordination with eIF4E and eIF4G to promote ribosome binding and start codon scanning. In addition, several macromolecules have been characterized as inhibitors of eIF4A activity. For instance, the tumor suppressor PDCD4 inhibits translation by binding to eIF4A and competing with eIF4G for binding[420]. Additionally, PDCD4 is involved in translational regulation by binding to other translational regulators such as p97 and PABP-interacting proteins (PAIPs). eIF4A1 expression correlates with malignancy and poor prognosis in breast cancer. Recent studies have shown that inhibition of eIF4A1 specifically downregulates the translation of oncogenes and epigenetic regulators, including NOTCH1, Myc, MYB, ETS1, EZH2, and MDM2. These genes are particularly vulnerable to suppression of eIF4A1 helicase activity, because it disrupts the translation of mRNAs with complex structures in their 5′ UTRs[421].

In 2004, Pelletier's group[422] employed a bicistronic mRNA reporter to screen for eukaryotic protein translation inhibitors, identifying three natural products, hippuristanol (Fig. 12A), pateamine A (Pat A) and silvestrol (Fig. 12A), all of which specifically target eIF4A[419]. Subsequent studies identified hippuristanol[423] as a selective inhibitor of eIF4A, specifically targeting eIF4A1 and eIF4A2 while sparing other eIF4A-associated enzymatic activities. It binds to the C-terminal domain (CTD) of eIF4A, impeding both eIF4Af and eIF4Ac forms from interacting with RNA, thereby reducing RNA-binding affinity and effectively blocking translation initiation[424]. Pateamine A has been reported to irreversibly bind eIF4A, facilitating stabilization of an RNA/eIF4A complex discordant with translation[425]. Silvestrol binds to eIF4Af and increases its affinity for specific RNA sequences, thereby stabilizing a ternary complex and blocking the unwinding of RNA secondary structures. This effect is particularly pronounced in mRNAs containing G-quadruplexes or polypurine-rich sequences within the 5′ UTR, resulting in translational repression of these transcripts[426,427]. Furthermore, subsequent studies revealed that silvestrol exhibits broad-spectrum antiviral activity, including against SARS-CoV-2 and hepatitis E virus (HEV).

Recent studies have revealed that eIF4A extends beyond its canonical role in translation initiation, potentially exerting regulatory effects during translation elongation. For example, the study of rocaglamide A (RocA), an eIF4A inhibitor, revealed that eIF4A may have a bimodal, selective translational repressor function that affects the dynamics of translational elongation[428]. Building on this, Ernst et al.[429] developed eFT226 (zotarifen) (Fig. 12A) by optimizing RocA through a ligand-based approach, further supported by small molecule crystal structure analysis. eFT226 inhibits eIF4A1 by reversibly and sequence-selectively enhancing the binding of eIF4A1 to mRNAs with specific polypurine motifs within the 5′ UTR. Formation of the stable ternary complex-eIF4A1/eFT226/mRNA with specific sequence recognition motifs impedes ribosomal scanning of the selected mRNAs[430]. eFT226 shows good cross-species IV PK and exhibits potent antitumor efficacy with good tolerability in an *in situ* TNBC xenograft model. Based on its therapeutic potential, eFT226 received Fast Track Designation from the FDA for use in combination therapies for metastatic breast cancer (NCT04092673)[431].

5.1.5.2. eIF4E. Eukaryotic translation initiation factor 4E (eIF4E) is a key regulator of mRNA translation, primarily responsible for recognizing and binding to the 5′ end cap structure (7-methylguanylate cap) of mRNAs to facilitate translation initiation. eIF4E is essential for cell growth, proliferation, and differentiation, and its overexpression is closely associated with tumorigenesis, metastasis, and therapeutic resistance. Furthermore, oncogenic mRNAs characterized by long 5′ UTRs and GC-rich content—often referred to as "weak mRNAs"—exhibit enhanced translation under high eIF4E activity, thereby contributing to tumorigenesis[432]. As one of the least abundant

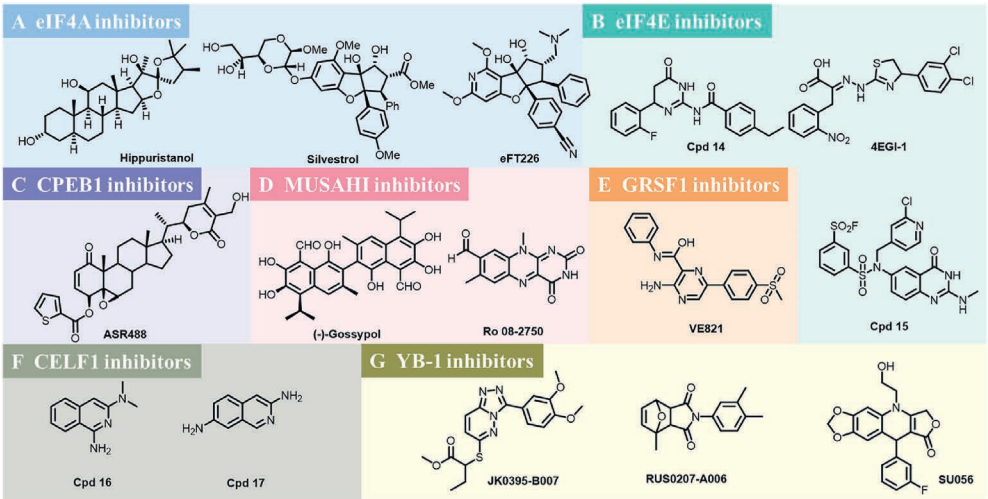

Figure 12 Small-molecule inhibitors targeting protein translation.

translational factors, eIF4E is stringently regulated at multiple levels, including transcription, post-transcription, and post-translation, and through the suppression of PPIs[433].

The p53 transcription factor is involved in many aspects of tumor suppression as a key tumor suppressor and a major regulator of many signaling pathways. Previous studies have shown that RBM38 interacts with eIF4E on p53 mRNA, preventing its binding to the m^7G cap and thereby repressing p53 translation[434]. Accordingly, **Cpd 14** was identified *via in silico* virtual screening to disrupt this interaction. Photoaffinity labeling (PAL) demonstrated that **Cpd 14** directly targets a previously uncharacterized C-terminal pocket of eIF4E, displacing RBM38 and enhancing p53 translation[435]. In contrast, 4E-BPs are a class of inhibitory proteins that isolate eIF4E by interacting with the same binding site recognized by eIF4G, thereby preventing the assembly of the eIF4F complex. To mimic the function of 4E-BPs, Moerke et al.[236] identified the potent compound 4EGI-1 by HTS FP-binding assay, which specifically disrupts eIF4E/eIF4G binding and inhibits cap-dependent translation, without affecting initiation factor non-dependent translation. Beyond the aforementioned PPI-based strategies, Taunton's team[436] developed a covalent inhibition approach targeting the m^7GTP-binding pocket of eIF4E. They identified **Cpd 15** (Fig. 12B), which forms a covalent bond between its sulfonyl group and K162 of eIF4E.

In addition, the activity of eIF4E is controlled by its own phosphorylation. Phosphorylated eIF4E is widely recognized to selectively enhance the translation of oncogenic mRNAs. The RAS/MAPK pathway phosphorylates Ser209 of eIF4E *via* MNK1/2, making it more readily available for binding to the 5′-cap structure. The MNK1/2−eIF4E signaling axis has been implicated as a critical driver in various malignancies, including glioblastoma multiforme, breast and prostate cancers, as well as hematologic cancers such as CML and AML. Recently, NSP-1047 (structural details pending), a novel polycyclic compound, was identified as a potent inhibitor of MNK1 and MNK2, demonstrating sub-nanomolar cellular potency in inhibiting eIF4E phosphorylation[437]. It exhibited favorable ADME and pharmacokinetic profiles, along with significant *in vivo* antitumor activity, including tumor regression in an AML animal model.

5.1.5.3. CPEB1. CPEB proteins are sequence-specific RBPs that regulate poly(A) tail elongation and translation by controlling cytoplasmic polyadenylation *via* binding to CPE motifs (UUUUUUAU) in mRNA 3′ UTRs[438]. While vertebrates typically express four isoforms (CPEB1-4), invertebrates such as *Drosophila* possess only two homologs (Orb and Orb2). Nevertheless, all CPEB proteins share a conserved structure, featuring C-terminal region consisting of two RRMs, two zinc-finger motifs and a regulatory N-terminal domain[439]. SELEX (Systematic Evolution of Ligands by Exponential Enrichment) data indicates that CPEB1 binds CPE sequences with high affinity, unlike other CPEB isoforms. CPEBs regulate mRNA translation in mother cells, control meiotic cell cycle progression, and stage-regulate polyadenylation and translational activation in various somatic cells. Dysfunction of different CPEBs leads to pathophysiological phenotypes resembling specific human diseases[438], suggesting that CPEBs are not functionally redundant. Studies have demonstrated that CPEB1 binds to and downregulates the expression of Twist1 mRNA, indicating that loss of CPEB1 results in increased Twist1 translation and promotes EMT-associated metastasis[440]. DAMODARAN's team[441] screened the small-molecule inhibitor ASR488 (Fig. 12C) to activate the mRNA to bind protein CPEB1, which has significant growth inhibitory and apoptosis-inducing effects on MIBC cells. Other studies have shown that in CPEB knockout cells, skin and lung cells are able to circumvent the M1 crisis phase of senescence through telomere erosion and that reintroduction of CPEB restores the affinity senescence-like phenotype[147]. CPEB plays a central role in synaptic plasticity, learning and memory. CPEB knockout mice have defects in synaptic plasticity and hippocampal-dependent learning[438].

5.1.5.4. MUSAHI. Musashi (MSI) is an evolutionarily conserved family of RNA-binding proteins, consisting of the two closely related members MUSASHI-1 (MSI1) and MUSASHI-2(MSI2). They both contain two highly conserved RRMs located at the N-terminus. RRM1 is a determinant of RNA binding specificity, whereas RRM2 mainly increases affinity[442]. MSI1 was first identified in *Drosophila*, where it established different levels of Notch signaling in the daughter cells of sensory organ progenitor (SOP) cells. Subsequent studies revealed that it is strongly expressed in foetal and adult neural stem cells (NSCs)[443], where it regulates the switch between symmetric and asymmetric cell division by modulating Notch signal[148]. Some studies have shown that MSI inhibits the overexpression of NUMB, APC and P21. This inhibition increases Notch and Wnt signaling, which play an important role in colon cancer, thereby enabling MSI to act as a cancer maintenance factor. (−)-Gossypol[443] (Fig. 12D), a natural product, was found to bind to RRM1 of MSI1, leading to down-regulation of Notch and Wnt signaling, thereby inhibiting colon cancer cell proliferation and inducing apoptosis and autophagy. However, it is a pan-active compound that lacks selective specificity against the expression of a wide range of genes. MSI2, initially identified as a translocation partner of HOXA9 in CML-BC[444], is overexpressed in aggressive tumors like gliomas, pancreatic cancer, and neurinotubular tumors etc. It also plays a crucial role in haematopoietic malignancies, including CML-BC, AML, and B-cell acute lymphoblastic leukaemia, serving as a negative prognostic marker. Using FP screening, Kharas's team[442] identified Ro 08-2750 (K_D = 12.3 μmol/L) (Fig. 12D) as a selective MSI inhibitor that disrupts RNA binding by engaging three critical amino acid residues, thereby inhibiting MSI-mediated regulation of the oncogene c-Myc. It demonstrates efficacy in inhibiting the development of myeloid leukaemia in both *in vitro* and *in vivo* models. Notably, Ro 08-2750 inhibits MSI1 and MSI2, potentially blocking residual MSI1 activity despite MSI1 being expressed at low levels in myeloid leukaemia[442].

5.1.5.5. GRSF1. G-rich sequence binding factor 1 (GRSF1), a member of the F/H family of hnRNPs, recognizes target mRNA through its three RRM domains. It plays a critical role in post-transcriptional regulation and participates in processes, such as embryonic development, stem cell differentiation, cell cycle control, and apoptosis. Yin-Yang 1 (YY1) functions as a dual-functional transcriptional regulator capable of activating or repressing oncogenes and has been identified as a key promoter of hepatocarcinogenesis. GRSF1 specifically binds to the GUUUU sequence in the 3′ UTR of YY1 to enhance the stability of YY1 and form a feedback pathway to promote hepatocellular carcinoma. VE821 (Fig. 12E) reduces the stability of YY1 mRNA by destabilizing the GRSF1 protein. It appears to block HCC

progression by inhibiting the GRSF1/YY1 pathway and relieving miR-30e-5p-mediated repression[150].

5.1.5.6. CELF1. CELF1 and CELF2 proteins are ubiquitously expressed and play essential roles in embryogenesis, whereas CELF proteins 3−6 are restricted to adult tissues primarily within the nervous system. CELF1 contains three highly conserved RRMs, with the two N-terminal RRMs and the C-terminal RRM separated by a highly flexible linker domain. RRM confers RNA-binding activity, enabling CELF1 to bind specifically to GU-rich elements in mRNA and regulate mRNA translation, splicing and decay. Transcript deadenylation is often the first step in the mRNA degradation process, and CELF1 has been shown to promote transcript deadenylation in diverse species[445]. Using the binding of a single guanine to CELF1 as a virtual screening center strategy, Xu's team[151] identified and validated a lead compound **Cpd 16** (Fig. 12F) as a competitive inhibitor of CELF1−RNA binding using FP assays. **Cpd 16** modulates the degradation of anti-fibrotic *IFN-γ* mRNA and inhibits hepatic stellate cell activation, thereby ameliorating hepatic fibrosis in mice. Further structural optimization of the **Cpd 16** led to the development of **Cpd 17** (Fig. 12F)[151], a more specific CELF1 inhibitor, which achieves its improved specificity by forming an additional interaction with residue Ile115. It is expected to be a candidate compound for new drug development.

5.1.5.7. YB-1. YB-1 was first identified in the 1970s during analysis of cytoplasmic mRNPs in eukaryotic cells as a p50, and was later formally characterized as Y-box binding protein 1 (YB-1/YBX1). YB-1 coordinates transcription and translation and is involved in the splicing, packaging, and stabilization of mRNAs, as well as in the replication and repair of DNA. YB-1 promotes mRNA stability and sustains gene expression by blocking 5′ end-mediated mRNA decay. Clinical evidence implicates YB-1 as an oncogenic driver across diverse malignancies, including tumors of the breast, ovary, bowel, lung, liver, prostate, skin and blood. YB-1 RNA levels serve as a prognostic indicator in breast cancer, with elevated YB-1 promoting paclitaxel resistance in rapidly proliferating cell lines by downregulating the levels of EGR1, a downstream target of YB-1. YB-1 has been shown to preferentially transactivate genes encoding proteins associated with cell proliferation, including cyclins, E2F transcription factor 1 (E2F1) targets and E2F family members, and is highly expressed in tumors with high mitotic index or chemoresistance[446]. Wang et al.[446] developed a complementary functional assay, that is using two different luminescent signal (AlphaScreen and luciferase reporter gene assays) outputs to detect the binding of YB-1 to two discrete nucleic acid sequences and ultimately identified three YB-1 inhibitors. Two of these, JK0395-B007 (Fig. 12G) and RUS0207-A006 (Fig. 12G), bind to the CSD of YB-1, suppress its activity, upregulate EGR1, and inhibit the proliferation of A375, HCT116 and MDA-MB-231 cells *in vivo*. SU056 (Fig. 12G), an azopodophyllotoxin small molecule, effectively inhibited YB-1, suppressing proliferation and apoptotic resistance of ovarian cancer cells and thereby reduced disease progression[152].

5.2. Targeted RBPs indirectly

While only ∼1.5% of the human genome encodes proteins—an even smaller portion is druggable, nearly 75% is transcribed to produce RNA, offering a far broader landscape for therapeutic targeting. As our understanding of targetable RNA structures and RNA-binding chemotypes deepens, advances in RNA structural modeling further illuminate the functional relevance of these structures, opening new avenues for RNA-targeted drug discovery[230]. Therefore, we summarized three major modes of RNA-targeting small molecules, ranging from simple binding to RNA secondary structure and functional sites to targeted RNA degradation. Representative small molecules are compiled in Table 2[447-469].

5.2.1. Targeted RNA secondary structure

RNAs can exhibit discrete secondary and tertiary structures[470] that provide binding sites for small molecules. Abnormal expansions of trinucleotide repeats in RNA are implicated in several neurological disorders, including spinocerebellar ataxia type 31 (SCA31), Fragile X-associated Tremor-Ataxia Syndrome (FXTAS), dystrophic muscular dystrophy type 1 (DM1) and c9ALS/FTD. All RNA trinucleotide repeats fold into a hairpin with periodically repeating 1 × 1 nucleotide internal loops in the stem[451]. Small molecules such as NCD[450], **Cpd 18**[451], CB096 and CB253[449] selectively bind these internal loop motifs, disrupting pathological RNA−protein interactions and abnormal translation events (Fig. 13A−C). Especially Cugamycin, conjugated with bleomycin A5, selectively cleaves r(CUG) repeat expansions to alleviate DM1 phenotypes *in vivo* (Fig. 13D)[453].

5.2.2. Targeted RNA functional sites

Risdiplam and branaplam (Fig. 14), are small molecules that target an RNA−protein manifold to direct alternative pre-mRNA splicing. Risdiplam was approved in 2020 as the first RNA-targeting small molecule drug for SMA[457]. Risdiplam promotes exon 7 inclusion in SMN2 pre-mRNA[471], increasing functional SMN protein levels and improving spinal muscular atrophy (SMA). Sivasankaran et al.[458] demonstrated that branaplm acted by enhancing the binding of U1 snRNP to SMN2 exon 7 5′ss. The development of risdiplam and branaplam exemplify phenotypic drug discovery driven by desired biological effects rather than target-based strategies[230]. Certain RNA functional motifs, such as the kink-turn (K-turn) structure in the U4 small nuclear RNA 5′sl[459], recruit essential proteins during splicing.

Small-molecule inhibitors are systematically compiled in Table 2.

5.2.3. Novel targeted degradation strategies

Emerging degradation technologies harness RNA motifs to selectively degrade pathogenic RNAs or RNA-binding proteins. Approaches include RNA-PROTACs, RIBOTAC and TF-PROTACs.

RNA-PROTACs exploit the sequence-specific binding affinity of RNA to recruit RBPs for targeted degradation. Hall's team[464] uses a short oligonucleotide binding selectively to Lin28A and mediates its degradation in an ubiquitin-dependent manner. Similarly, the latest study developed novel rG4-PROTACs that potently degrade DHX36 with high specificity in mammalian cells[465]. Related research demonstrates selective degradation of RNA through the design of small molecules that bind RNA to RNA-degrading enzymes such as RNase L. For example, Disney's team[466] has previously designed a small molecule, Targapremir-210 (TGP-210), that selectively targets pre-miR-210 without binding to DNA (Fig. 15A and B). Engineering TGP-210-RL by appending an RNase L module enables the precise recruitment of RNase L to pre-miR-210, triggering its degradation. Transcription

Table 2 Representative small-molecule inhibitors that targeted RBPs indirectly.

Classification	Small molecules/AOS	Targets	Diseases	Mechanism	Detection method	Ref.
Targeted RNA secondary structure	BIXO1294 CP-31398	CGG and/or GGGGCC repeat RNAs	FXTAS, FTD, ALS	Inhibits the RAN translation of the extended CGG repeats associated with FXTAS	HTS, reporter assay based on a nanoluciferase reporter	447
	CB096, CB253	r (G4C2)8	c9ALS/FTD	Selectively inhibits RAN translation and stress granule formation, and rescues the nuclear transport defect in the c9ALS/FTD cell model	TO-PRO-1, MST	448,449
	NCD	r(UGGAA)9	SCA31	Inhibits the nuclear stressor nSB-mediated splicing event by interfering with RNA−protein interactions	SPR	450
	Cpd 18	r(CGG) exp	FXTAS	Specifically replaces the DGCR8δ protein around r(CGG) exp and corrects the pre-mRNA splicing defect	Chemical similarity searches	451
	Cpd 19	r(G4C2) exp	c9ALS/FTD	Inhibits c9ALS/FTD−RAN translation and formation of r(G4C2) exp-protein complexes		452
	Cugamycin	r(CUG) exp	DM1	Recognizes and cleaves the structure of r(CUG) exp	CRISPR	453
Targeted RNA functional sites	DMA-155	5′ UTR of SARS-CoV-2	Viral infection	Interferes with viral RNA−host protein interactions by binding a conserved internal stem-loop sequence of the SARS-Cov-2 RNA, thereby inhibiting translation	Fragment-based screen	454
	Synucleozid	Iron-responsive element in α-synuclein mRNA	PD	Selectively targets the IRE site in the 5′ UTR of α-synuclein mRNA, resulting in inhibition of α-synuclein translation	Infona, ASO-Bind-Map	455
	Cpd 20	A hairpin at the exon 10 −intron 10 junction (Tau pre-mRNA)	Neurodegenerative disorders	Directly targets tau pre-mRNA and rescues disease-relevant splicing of tau pre-mRNA	A cell-based luciferase reporter assay	456
	Risdiplam (Approved in 2020)	Exon 7−intron junction (SMN2 pre-mRNA)	SMA	Binds directly to the *SMN2* mRNA-spliceosome complex to promote exon 7 inclusion and increase SMN protein expression	Traditional medicinal lead optimization	457
	Branaplam phase II(NCT05111249)			Enhances the binding affinity of U1 snRNP to the 5′ss	Phenotypic screening	458
	Topotecan	U4 5′sl	Cancer	Disrupts the interaction between NHP2L1 and U4 5′sl by binding to U4 and inhibits RNA splicing.	TR-FRET	459
	Pyridostatin	rG4	Cancer, cellular senescence	Disrupts the G3BP1−rG4 interaction, thus eliminating the	SAR, TRIBE-ID	460

(*continued on next page*)

Table 2 (*continued*)

Classification		Small molecules/AOS	Targets	Diseases	Mechanism	Detection method	Ref.
					regulation of mRNA stability and translation efficiency by G3BP1		
		Targaprimir-515	Pre-miR-515	Breast cancer	Dimeric compound that targets Drosha processing site and adjacent site for enhanced selectivity	Sequence-based lead optimization, Infona	461
		Nusinersen (AOS) (Approved in 2016)	Exon 7 of SMN2	SMA	Promotes SMN2 exon 7 inclusion and restores splicing	PMO transformASO-tiling	462
		Eteplirsen (AOS) (Approved in 2016)	Exon 51 of the DMD gene	DMD	Induces exon 51 skipping and increases dystrophin expression	PMO transform	463
Targeted RNA degradation	RNA-PROTACs	Chimeric oligonucleotide	LIN28A/VHL	Cancer	Selectively binds to Lin28 and inhibits the levels of Lin28A in both cancer cell lines in a ubiquitin-dependent manner	Rational design	464
		rG4-PROTACs	rG4/DHX36	Cancer	Degrades DHX36, inhibits rG4-mediated APP protein expression, and impacts the proliferative capacity of skeletal muscle SCs by negatively regulating Gnai2 protein expression		465
	RIBOTAC	TGP-210-RL	Pre-miR-210	TNBC, Alport syndrome	Selectively binds to pre-miR-210 and recruits RNase L to induce its degradation	Informa	466
		Dovitinib-RIBOTAC			Exhibits a 2500-fold increase in selectivity for pre-miR-210	Informa	467
		Cpd 21	r(G4C2) exp	c9ALS/FTD	Degrades r(G4C2) exp by targeting c9ALS/FTD pathology model	Rational design, BLI, Chem-CLIP	468
	TF-PROTACs	alncRNAs-PROTAC	TF	Cancer	Targets oncogenic transcription factors and tumor-related proteins, such as c-Myc, NF-κB, ETS-1, KRAS and EGFR and facilitates the ubiquitination and degradation	SELEX, RIP-seq	469

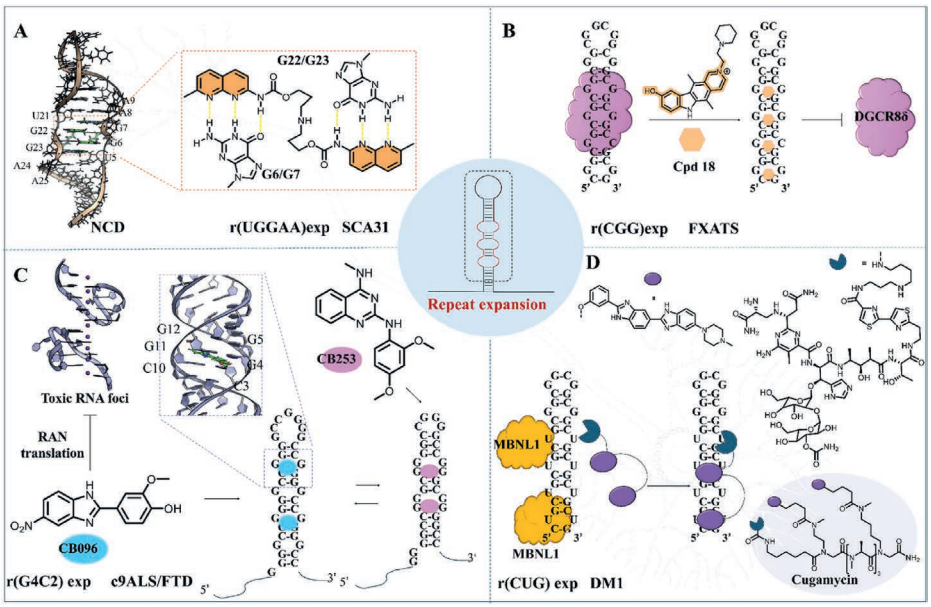

Figure 13 Some examples that targeted RNA secondary structure. (A) The four naphthyridine moieties of two NCD molecules form hydrogen bonds with the four guanines in the UGGAA/UGGAA quintet of SCA31 RNA, disrupting RNA-protein interactions and thereby inhibiting nSB-mediated splicing (PDB ID:6IZP). (B) Cpd 18 selectively displaces the DGCR8δ protein from the r(CGG)exp region in FXTAS, thereby restoring the normal pre-mRNA splicing. (C) CB096 and CB253 specifically bind to the r(G4C2) exp hairpin associated with C9ALS/FTD, selectively inhibiting RAN translation and stress granule formation, and rescue of the c9ALS/FTD by direct targeting nuclear translocation defects in a cellular model (PDB ID:5EW7, 8 $\times$ 0S). The r(G4C2) exp hairpin interconverts between 1 $\times$ 1 and 2 $\times$ 2 internal loops through the process of strand slippage, while CB253 binds and stabilizes these 2 $\times$ 2 GG internal loops. (D) Cugamycin binds r(CUG) repeat expansions displacing MBNL1 and been conjugated to bleomycin A5 to cleave the RNA target selectively in myotubes derived from patients with DM1 and in a mouse model.

factors (TFs), such as c-Myc and NF-κB, are considered undruggable due to their lack of active or allosteric sites, making them inaccessible to traditional small-molecule inhibitors[469]. Cao et al.[472] designed an artificial lncRNA (alncRNA), combining a protein-targeting RNA aptamer with HOTAIR-derived sequences. RNA aptamer selectively binds to TF, whereas alncRNA specifically recruits RBP E3 ligase[473] (Fig. 15C). Table 2 summarizes comprehensive information on RNA-binding small molecules and their mechanisms.

5.3. *Targeted upstream of RBPs*

Targeting upstream regulators of RBPs is another important indirect strategy. The activity of many RBPs is regulated by post-translational modifications such as phosphorylation, methylation and ubiquitination. Therefore, enzymes or other regulatory proteins that target these modification processes can indirectly affect RBP activity.

5.3.1. *FMRP*

FMRP is a widely expressed RNA-binding protein whose deficiency leads to the neurodevelopmental disorder FXS[176]. Due to the inability to directly target FMRP, most therapeutic interventions focus on upstream targets of translational control. The absence of FMRP unleashes a cascade of hyper-translation, largely mediated through the overactivation of the mTORC1 signaling axis[474]. Ribosomal S6 kinase 1 (S6K1), as a key effector of mTORC1[475], sits at a critical nexus, directly phosphorylating substrates that drive ribosomal biogenesis and cap-dependent translation initiation. Consequently, inhibiting S6K1 represents a potent strategy to indirectly restore translational homeostasis that is lost due to FMRP deficiency[476]. Preclinical studies demonstrate that genetic or pharmacological inhibition of S6K1 (*e.g.*, with compounds like PF-4708671) can correct aberrant protein synthesis, dendritic spine morphology, and behavioral deficits in Fmr1 KO mice[477]. Another prime example is the targeting of metabotropic glutamate receptor 5 (mGluR5). Many neurological and behavioral deficits stem from exaggerated signaling through mGluR5, which in a healthy state is normally restrained by FMRP's translation-repressing function[478]. The application of mGluR5 negative allosteric modulators (NAMs) aims to dampen hyperactive upstream signaling, thereby indirectly restoring FMRP-dependent translational homeostasis[474,479].

5.3.2. *PRMT5*

AG-270 is an inhibitor of MAT2A, a key enzyme that catalyzes the synthesis of *S*-adenosylmethionine (SAM). SAM is the methyl donor for all protein methyltransferases, including PRMT5. PRMT5 is a protein arginine methyltransferase that catalyzes the symmetric dimethylation of arginine residues on multiple intra-nuclear and cytoplasmic protein, thereby modulating critical cellular processes including gene expression, ribosome biosynthesis, mRNA splicing, protein translation, DNA damage response, and immune function. By inhibiting MAT2A, AG-270 reduces intracellular SAM levels and indirectly suppresses PRMT5 activity, which is dependent on SAM for its methyltransferase function[480]. This effect is particularly potent in MTAP-deficient cancers, where accumulated methylthioadenosine (MTA), the substrate of MTAP, acts as an endogenous PRMT5 inhibitor[481]. AG-270 synergizes with MTA by lowering SAM,

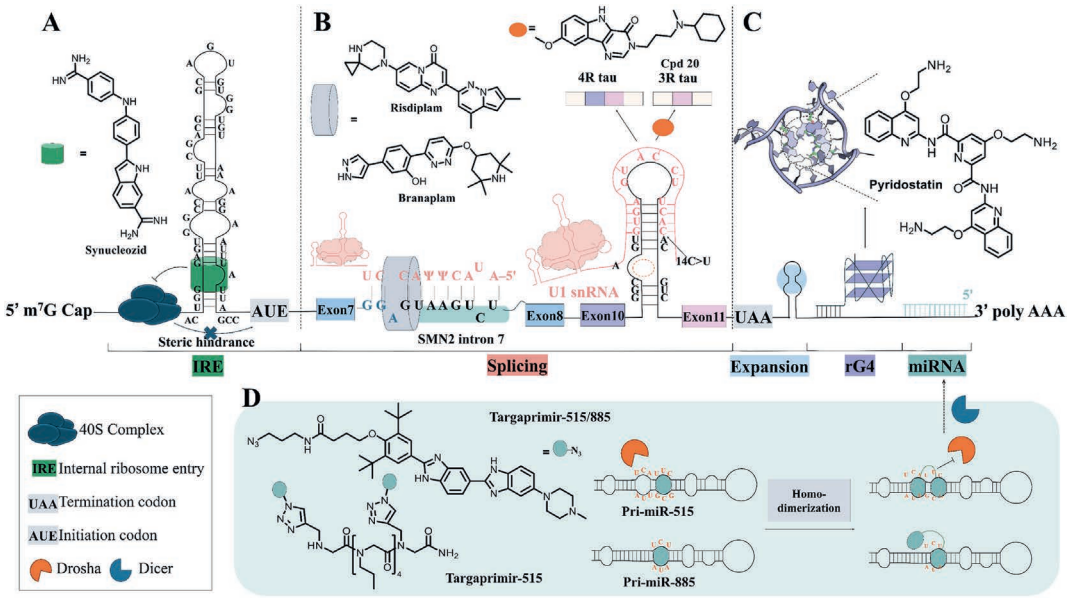

Figure 14 Some examples that targeted RNA functional sites. Structured RNA regions with critical biological functions include the IRE, splicing sites, RNA repeat expansions, RNA G-quadruplex (rG4) sites, and miRNA processing sites. (A) Synucleozid selectively targets IRE within the 5′ UTR of α-synuclein (SNCA) mRNA, interfering with its loading into polysomes and/or the assembly of functional ribosomes, thereby inhibiting α-synuclein translation. (B) Risdiplam and branaplam bind the SMN2 pre-mRNA exon 7-intron 7 junction, enhancing U1 snRNP recruitment to exon 7 and thereby elevating SMN2 protein levels; similarly, a 14 C to U mutation at the exon 10-intron 10 junction destabilizes the local hairpin, promoting U1 snRNP binding, exon 10 inclusion, and 4R tau production. In contrast, Cpd 20 binds the adenine-containing bulge (A-bulge) within this hairpin, stabilizing its structure, driving exon 10 skipping, and favoring 3R tau synthesis. (C) Resolution of rG4 structures in the 5′ UTR of mRNAs serves as a regulatory mechanism for translation, whereas rG4 processing in the 3′ UTR is associated with stress responses and transcript stability. Pyridostatin interferes with RBP-rG4 interactions, thereby disrupting RBP-mediated control of mRNA stability and translational efficiency. (D) Targaprimir-515/885 equally inhibits the biogenesis of pri-miR-885 and pri-miR-515 by binding their Drosha processing internal loops-5′ UCU/3′ AUA (miR-885) and 5′ UUC/3′ GCG (miR-515). Uniquely, pri-miR-515 also contains a secondary targaprimir-515/885 binding site adjacent to the Drosha cleavage site, which is absent in pri-miR-885. A homodimeric version, targaprimir-515, engages both the primary and adjacent sites, conferring enhanced selectivity for pri-miR-515 processing.

leading to significant suppression of cancer cell growth. This strategy indirectly affects the function of RBP by modulating its upstream metabolic pathway, offering high selectivity and a potential therapeutic window. PRMT5 inhibitors working with MTA are expected to more effectively exploit this synthetic lethality. However, since SAM serves as a key methyl donor in cells, decreasing its levels could disrupt multiple methylation processes regulated by methyltransferases, raising safety considerations. Ongoing clinical trials (NCT03435250) assess both effectiveness and potential risks of AG-270[480].

Additionally, the function of PRMT5 depends on its interactions with substrate adapter proteins (SAPs) (*e.g.*, pICln and RIOK1), which bind to PRMT5 through the PRMT5-binding motif (PBM) to regulate their substrate methylation. For instance, pICln directs PRMT5 to spliceosomal subunits (*e.g.*, SmB/B′, SmD1/D2)[482] and ribosomal proteins (*e.g.*, LSM4, LSM10/11), thereby modulating spliceosome function and processing body formation[483]. BRD0639 is a small-molecule inhibitor that disrupts PRMT5−SAP interactions by covalently binding to the PBM site on PRMT5[484]. This competitive binding inhibits the PRMT5−RIOK1 complex and suppresses methylation of downstream targets, thereby impairing the growth of MTAP-deficient cancer cells. Preclinical studies show that MAT2A inhibitors enhance tumor-fighting effects when combined with chemotherapy drugs like paclitaxel or gemcitabine[480].

In addition to AG-270 and BRD0639, strategies targeting upstream of RBP have been used in other studies. Notably, mTOR signaling pathway inhibitors exert indirect control over RBP functionality through dual mechanisms: (1) Modulating translation initiation factors to alter protein synthesis dynamics; (2) phosphorylation-dependent regulation of RBP activity. mTOR inhibitors, such as rapamycin, and its derivatives (*e.g.*, Everolimus) have shown promising results in a variety of cancer treatments[485]. Hsp90 inhibitors such as 17-AAG indirectly affect the function of RNA-binding proteins by regulating the folding and stability of a variety of client proteins[486].

5.4. *Bifunctional molecules: PROTAC and molecular glue*

Unlike RNA-PROTACs leveraging RNA motifs as recruitment anchors (Section 5.2.3.), the strategies discussed in this section highlight small-molecule warheads with enhanced membrane permeability and tunable selectivity, thus representing a complementary approach for RBP elimination. Erraini's group[487] designed METTL3/14 PROTACs *via* CRBN-directed alkyl linkers with pomalidomide-based E3 ligands. Among 26 analogs, five characterized by a rigid "handle" and a longer linker achieved >50% degradation in AML/PC3 cells. This study adds a valuable contribution that linker length and rigidity critically govern METTL3/14 degradation efficacy. Meanwhile, Du et al.[488]

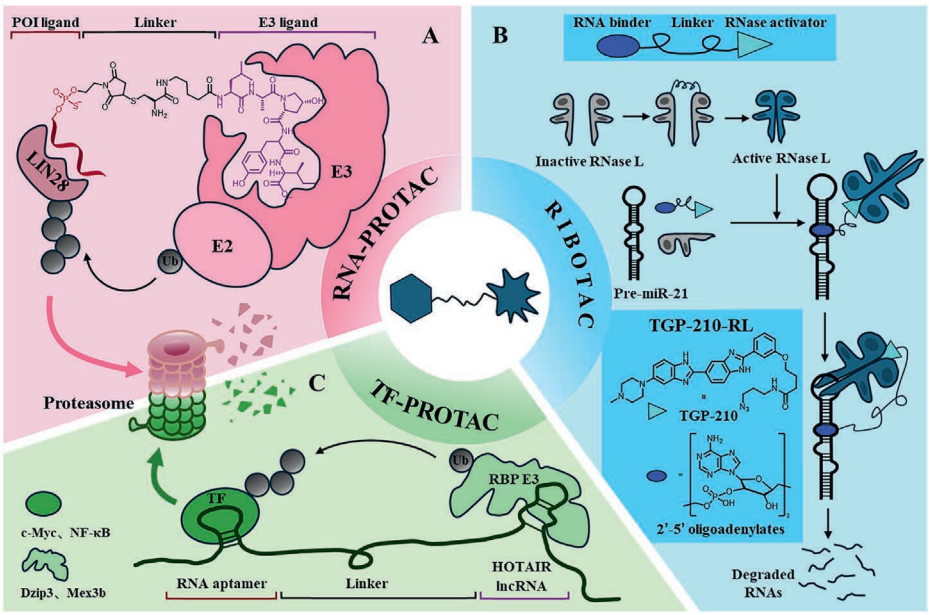

Figure 15 Novel targeted degradation strategies. (A) RNA-PROTAC. An RNA-PROTAC, composed of a 7-nt PS-MOE oligonucleotide analogue, can competitively bind to the ZnF domain of Lin28A with 5′-AGGAGAU-3′-containing microRNAs. The peptide derived from the HIF-1α transcription factor was selected as a ligand for recruiting E3 ligase VHL. (B) RIBOTAC. TGP-210-RL, a compound formed of TGP-210 attached to the RNase L module, can selectively recognize pre-miR-210, triggering its degradation. (C) TF-PROTAC. This alncRNA recruits E3 ligases DAZ interacting zinc finger protein 3 (Dzip3) and mex-3 RNA binding family member B (Mex3b) and enhances Dzip3-mediated ubiquitination and degradation of target proteins.

developed a potent METTL3 degrader WD6305, which comprises UZH2 and a VHL ligand, co-depletes METTL14 and outperforms parent inhibitor UZH2 in suppressing AML proliferation (DC_{50} value against METTL3 of 140 nmol/L, DC_{50} value against METTL14 of 194 nmol/L). Notably, the molecular glue degraders demonstrate exceptional potency, potentially surpassing PROTAC in several aspects. For example, Benhamou's team[489] developed a series of Lin28-degrading PROTACs and molecular glues, with the latter increasing let-7 abundance more significantly than the PROTAC derivative at the same dose. Extending beyond Lin28-targeted degradation, they applied this bifunctional design paradigm to HuR another RBP implicated in breast cancer. Analogous structural optimization yielded MG-HuR2 and PRO-HuR3, which suppressed HuR-associated oncogenic mRNAs and cancer phenotypes while exhibiting nanomolar potency in 2D/3D breast cancer models, with MG-HuR2 demonstrating superior efficacy[490].

6. Clinical translation status and challenges

Despite significant advances in RBP research, drug development remains challenging due to the highly dynamic and often disordered nature of RBP−RNA interactions, which results in an extremely low clinical translation rate. These interfaces typically lack the well-defined hydrophobic pockets that conventional small molecules preferentially bind to. Moreover, functional redundancy among RBPs may activate compensatory mechanisms that limit the efficacy of single-target interventions. For example, the SF3B1 inhibitor E7107 was discontinued due to global spliceosomal inhibition causing optic neuropathy[491], highlighting the narrow therapeutic window between normal and cancerous cells in tolerating splicing perturbation, which complicates selective targeting. Similarly, H3B-8800 showed insufficient efficacy in LMDS, with the low RBC-TI rate (4/43)[492]. This may reflect compensatory pathway activation that reduces dependency on aberrant splicing in malignant cells[493]. Indisulam was evaluated in multiple clinical trials; however, further clinical development was discontinued due to its suboptimal efficacy. Another challenge is the poor translatability of existing screening systems, which fail to adequately simulate the *in vivo* microenvironment. Although (−)-gossypol strongly binds to the newly identified target MSI1 and demonstrates promising *in vitro* activity, it lacks specificity by also interacting with multiple off-targets. Emerging techniques, such as cryo-electron microscopy integrated with deep learning-assisted modeling, offer promising strategies to enhance screening specificity—as exemplified by the discovery of the NONO C145's binding sites, which was identified using this very approach. The HARD-AP method enables the retrieval of RBPs and their tightly bound RNA regulatory complexes and systematically maps RNA-binding sites using machine learning-based modeling[494]. Moreover, drug delivery further complicates clinical translation. Small molecules targeting RNA−protein interactions are often highly hydrophilic and therefore exhibit poor membrane permeability, limiting intracellular uptake. This challenge is especially critical for therapeutics targeting the central nervous system, as the blood-brain barrier—formed by tight junctions among endothelial cells, pericytes, and astrocytes—poses a major obstacle to drug penetration. The eIF4E inhibitor briciclib sodium[495] may have faced discontinuation partly for this reason. Jin et al.[496] developed tHFn(+) nanocarriers that encapsulated siRNA to pass through transferrin protein channels of the BBB. These siRNAs, containing specific RRMs, could offer a novel strategy for selectively targeting RBPs in the brain. Notably,

most foundational studies are conducted in immortalized or cancer cell lines, leaving the physiological roles of many RBPs in normal tissue contexts poorly understood. Critical differences in RBP function between normal and cancerous tissues need to be identified to enhance the accuracy of preclinical prediction, exploiting state-of-the-art experimental systems such as organoids, organ-on-chip or tissue explants[497]. Meanwhile the improved spatial resolution of single-cell multi-omics technology has made it possible to analyze the functional heterogeneity of RBPs in the tissue microenvironment. Significantly, the establishment of an international standard RBP functional annotation database and clinical sample library will accelerate the translation of basic discoveries into clinical applications.

In addition, the real relevance of RBP as a drug target is defined by the specific biological context of the disease, not in isolation. RBM39 serves as a notable example. In previous studies, the clinical development of small molecules targeting RBM39 for solid tumors has been discontinued owing to limited efficacy, which likely occurred owing to the lack of a defined mechanism of action and predictive biomarkers, together with the presence of compensatory mechanisms (*e.g.*, upregulation of paralogs or alternative pathways). However, this does not invalidate RBM39 as a target. Novel genetic dependencies in AML present promising opportunities for clinical intervention[498]. RBM39 inhibition proves critically effective and synergizes with BCL2 inhibitors like venetoclax[499]. The study shows the sensitivity to these agents correlates with DCAF15 expression and gene copy number[311]. Furthermore, REC1245, a novel molecular glue degrader targeting RBM39, has received FDA clearance to proceed to Phase I/II clinical trials for lymphomas and solid tumors with high DCAF15 expression.

Moreover, the intrinsic properties of protein−RNA interactions hinder the development of small-molecule inhibitors. Most inhibitors are designed to function competitively by displacing the bound RNA. However, this strategy is profoundly challenging due to the strong electrostatic attraction between the negatively charged RNA backbone and positively charged domains on the RBPs, as well as the extensive interacting surface[7]. For example, although several compounds with diverse structural scaffolds have been identified for LIN28, they display only weak inhibitory activity in the micromolar range and thus fail to reach therapeutically relevant concentrations. Nevertheless, the emergence of inhibitors such as LN268 and PROTAC degraders is challenging the notion of LIN28 as "undruggable". Similarly, allosteric RBP inhibitors, with their lower risk of off-target effects, will receive growing interest in the coming years.

Furthermore, some RBPs lack the canonical RNA-binding motifs found in most other RBPs. For example, DENR, which exhibits these characteristics, is highly expressed in multiple tumor types and indicates the poor prognosis of patients[500]. DENR binds to the ribosome and counteracts the translational inhibition mediated by upstream open reading frames (uORFs) in JAK2 mRNA, thereby promoting JAK2 protein synthesis[501]. This enhances the JAK2−STAT1 signaling pathway and upregulates PD-L1 expression, ultimately facilitating immune escape. Combining JAK−STAT pathway inhibition with PD-1/PD-L1 immune checkpoint blockade (ICB) has demonstrated superior efficacy over ICB monotherapy[502]. Thus, DENR low patients exhibiting impaired JAK−STAT signaling could be more sensitive to ICB therapy[503]. These findings highlight the potential value of DENR both as a therapeutic target and as a predictive biomarker for immunotherapy.

7. Conclusion and perspective

This review comprehensively analyzes the roles of RBPs in diseases, screening techniques and the current status of development of related small-molecule drugs. RBPs, as the core components of the post-transcriptional regulatory network, play important roles in a wide range of disease pathologies. Existing research results have found that RBPs not only exhibit significant regulatory functions in cancer, neurodegenerative diseases and autoimmune diseases, but also demonstrate substantial potential as therapeutic targets. The integration of advanced high-throughput sequencing technology and computational biology methods has enabled remarkable progress in RBP−RNA interaction mapping, functional resolution and development of targeted intervention strategies, and RBP-related drug development has become a cutting-edge direction in the field of biomedicine.

The intervention of artificial intelligence technologies is transforming the RBP research paradigm. Deep learning models such as HDRNet enable single-nucleotide resolution prediction of RBP binding sites, while transfer learning frameworks facilitate the modeling of dynamic RNA−protein interactions across cell types. Notably, the emergence of recent tools like AlphaFold-RNA has advanced the atomic-level prediction of RBP−RNA 3D structures, providing a robust foundation for structure-based virtual screening. Although still in nascent stages, AI-driven drug design, particularly through generative adversarial networks (GANs), has significantly expanded the accessible chemical space and improved lead compound discovery efficiency.

Expanding the disease landscape of RBP research is a key future direction. Beyond well-studied areas like cancer, neurodegenerative diseases and autoimmune diseases, RBPs also hold therapeutic potential in metabolic, cardiovascular, and rare diseases. For example, LIN28B affects glucose metabolism homeostasis by regulating the translation efficiency of key mRNAs in the insulin signaling pathway, which provides a new target for metabolic disease intervention. At the clinical translation level, modeling the association between the dynamic expression profile of RBP and disease staging will promote the development of individualized treatment strategies. In addition, the development of molecular probes that can monitor RBP activity in real time is expected to enable dynamic assessment of therapeutic response.

The development of bivalent small molecule probes (*e.g.*, PROTAC technology) in chemical biology has introduced innovative strategies for targeting "non-druggable" RBPs. As discussed, the emergence of targeted protein and RNA degradation technologies, such as RNA-PROTACs, RIBOTACs, and TF-PROTACs, has transformed the therapeutic landscape for targeting RBPs. These approaches allow for the permanent degradation of pathogenic RBPs rather than mere transient inhibition, offering sustained therapeutic effects, a reduced resistance risk, and potential applicability to dynamic RBP−RNA interactions. Despite these breakthroughs, several challenges must be addressed to realize the clinical potential of RBP degraders. A critical limitation lies in off-target effects, as RBPs often participate in global RNA metabolism. Techniques like thermal proteome profiling (TPP) and single-cell RNA sequencing (scRNA-seq) are now being employed to map the selectivity landscape of degraders. Additionally, combining degraders with RNA-targeted therapies (*e.g.*, ASOs) or immunomodulators may unlock synergistic effects, particularly in malignancies driven by oncogenic RBPs like Myc. Novel degradation systems (*e.g.*, LYTACs, AUTACs, AUTOTACs) are being actively explored to extend the potential

therapeutic landscape to membrane-associated RBPs and pathogenic aggregates, including those implicated in neurodegenerative diseases, though challenges in delivery and specificity remain. Of note, TF-PROTAC solves historical challenges in targeting transcription factors through small-molecule approaches, however, RNA aptamers are easily degraded by nuclease and need to be chemically modified (*e.g.*, phosphorothioate backbone or 2′-*O*-methylation) to improve stability. Moreover, the aptamer has a large molecular weight and a low *trans*-membrane efficiency and needs to be delivered with the help of lipid nanoparticles or viral vectors. In the coming years, "smart degraders" based on tissue-specific delivery and dynamic modulation are poised to become mainstream, driving curative therapies for neurodegenerative and rare diseases.

In summary, the next decade will likely witness the clinical maturation of RBP-targeted therapies, offering novel strategies for treating some of the most complex and refractory human diseases. Realizing the full potential of the RBP druggable genome will be dependent on deep, interdisciplinary collaboration among chemists, structural biologists, clinical researchers, and computational scientists to bridge the gap from target identification to viable patient therapies.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (82574253), the Natural Science Foundation of Jiangsu Province (BK20231483, China) and the Fundamental Research Funds for the Central Universities (2632025TD01, China).

Author contributions

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Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supporting information

Supporting information to this article can be found online at https://doi.org/10.1016/j.apsb.2025.12.010.

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