ACCSCIENCE PUBLISHING

Tumor Discovery

REVIEW ARTICLE

Targeting the interplay between biomolecular condensates and regulatory RNAs in cancer

Palmiro Poltronieri[1]* and Sudipta Joardar[2]

[1]National Research Council of Italy, Department of Agrofood, Institute of Sciences of Food Productions, CNR-ISPA, Lecce, Apulia, Italy

[2]Autonomous University of Barcelona, Center for Research in Agricultural Genomics, Cerdanyola Del Valles, Barcelona, Spain

Abstract

Biomolecular condensates (BCs), RNA–protein complexes, have emerged as potential therapeutic targets for various cellular pathologies, including cancer. The mechanisms underlying liquid–liquid phase separation rely on the properties of proteins with intrinsically disordered regions and prion-like domains, which drive phase separation in conjunction with their RNA partners. These ribonucleoprotein complexes are distinct in their localization, compartmentalization, epigenetic regulation, and dynamics. BCs are categorized as either nuclear—such as promyelocytic leukemia nuclear bodies, speckles, paraspeckles, and Cajal bodies—or cytosolic, including stress granules (SGs), P bodies, and U bodies. Regulatory RNAs, assembled with protein partners through phase separation, exhibit oncogenic properties and perform key biological functions, including gene transcription, euchromatin/heterochromatin formation, mRNA splicing, mRNA translation, protein compartmentalization, and degradation. Epitranscriptome-modifying enzymes regulate the stability and oncogenic potential of noncoding RNAs (ncRNAs). These RNAs, along with their associated epitranscriptomic and protein modifications, play critical roles in the functioning and dissolution of condensates. Recent advancements in cancer therapy have focused on developing drugs targeting the epitranscriptomic machinery, including the writers, readers, and erasers of RNA modifications. Therapeutic strategies aim to target oncogenic RNAs, tumor-promoting proteins, and RNA–protein interaction domains. Several cancer therapeutic compounds have been developed using the PROTAC and RIBOTAC approaches. Moreover, small molecules targeting protein–RNA interactions and antisense oligonucleotides have been developed. Promising avenues in cancer therapeutics involve the inhibition of ncRNAs and their associated protein complexes, modulation of BCs, regulation of SGs and paraspeckles, and development of small molecule compounds with potential applications across various cancer types.

Keywords: Biomolecular condensates; Noncoding RNAs; RNA–protein interactions; Therapeutic targets; Cancer; Epitranscriptomics; Epigenetics

***Corresponding author:**
Palmiro Poltronieri
(palmiro.poltronieri@ispa.cnr.it)

Citation: Poltronieri P, Joardar S. Targeting the interplay between biomolecular condensates and regulatory RNAs in cancer. *Tumor Discov.* 2024;3(4):4657. doi: 10.36922/td.4657

Received: August 26, 2024

Accepted: October 25, 2024

Published Online: December 6, 2024

Copyright: © 2024 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Biomolecular condensates (BCs) are membraneless organelles (MLOs) that are crucial for intricate cellular biochemical reactions. Condensates within the nucleus include the

nucleolus and various ribonucleoprotein (RNP) granules, such as promyelocytic leukemia (PML) nuclear bodies, speckles, paraspeckles, Cajal bodies, DNA damage foci, and processing (P) bodies. In contrast, U bodies, stress granules (SGs), signalosomes, and the pyrenoid are found outside the nucleus. A single protein capable of simultaneously interacting with multiple copies of itself drives homotypic phase separation, whereas interaction with multiple other biomolecules leads to heterotypic phase separation, as observed in RNA–protein complexes.[1,2] Figure 1 illustrates a schematic of various MLOs and their cellular localization. In heterotypic phase separation, a molecule interacts with various biomolecules to aggregate and undergo liquid–liquid phase separation (LLPS). The structure of RNA and similar polymers, such as poly-ADP ribose (PAR), plays a pivotal role in determining the dense-phase identity within condensates.[3,4] RNA involvement in condensate formation near enhancers or promoters suggests regulatory roles of noncoding RNAs (ncRNAs). BCs are various, and this review discusses Bcs formed by ncRNAS and proteins.[3,5]

The role of RNA in condensates holds therapeutic potential, enabling innovative applications such as active ribozymes. The role of altered phase separation, oncogenic RNAs, and BC-forming proteins in cancer is well established.[6-13] Targeting condensates in cancer therapy aims to address condensatopathies, impair aberrant formation, inhibit target functions, and deliver drugs. This review focuses on the significance of BC formation, oncogenic RNAs, and RNAs, modified epigenetically or epigenetically and epitranscriptome regulation relevant to the field of cancer cell biology.

2. BC localization and compartmentalization

There are five mechanisms of messenger RNA (mRNA) localization: (1) diffusion and local entrapment, (2) stabilization and controlled degradation, (3) active transport by molecular motors, (4) vesicular trafficking through endosomes, and (5) integration into BCs.[13-17] A RNP particle undergoes various transitions throughout its lifetime; it leaves transcription sites, reaches nuclear speckles for splicing, moves into the cytoplasm through the nuclear pore, and appears in the cytoplasmic granules of specific cells. These granules include transport granules, P bodies for degradation, and SGs under stress conditions.[3,11] Collectively, these miniature LLPS structures are referred to as BCs.[12-14] Localized condensates consist of components that anchor the structure to specific functional cellular locations. For instance, in nuclei, proteins may bind to specific DNA or RNA sequences to form BCs, whereas in the cytoplasm, BCs are often located near the membrane.[15,16]

Compartmentalization is a critical determinant in achieving high local concentrations of biomolecules and their substrates while excluding functionally irrelevant molecules.[17-19] Another contributing factor is transcriptional bursting, during which a BC located in the promoter region of a gene can recruit RNA polymerase molecules.[20,21] Over short time frames, condensates can rapidly form

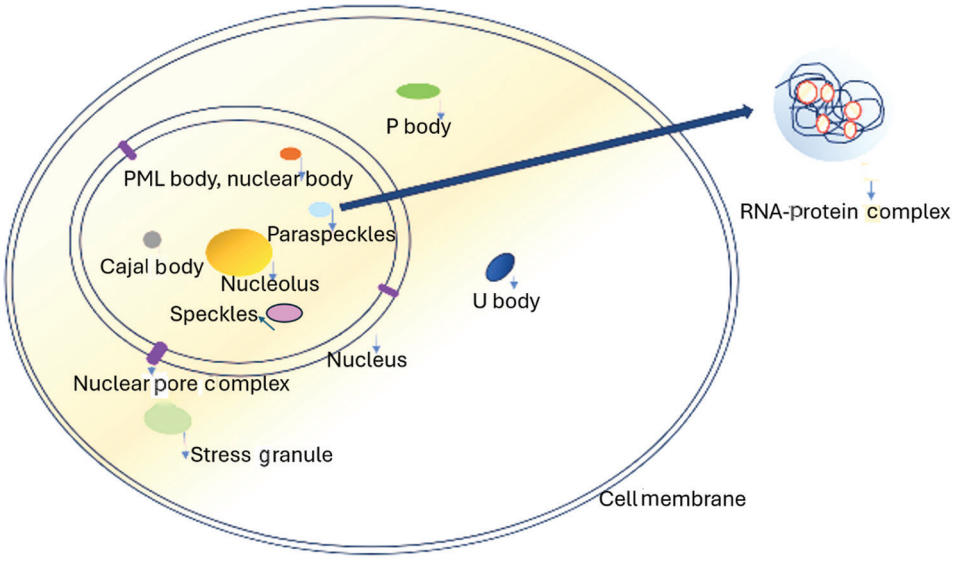


Figure 1. Occurrence of different biomolecular condensates inside the nucleus (promyelocytic leukemia nuclear bodies, paraspeckles, and Cajal bodies) and outside the nucleus (stress granules, P bodies, and U bodies). As an example, an RNA–protein complex representing a paraspeckle is marked outside the cell. Image created by the authors

and dissolve, providing cells with a mechanism to create temporary compartments. This allows biomolecules to be released and relocated when no longer needed at a specific site.[15] Furthermore, compartmentalization within condensates helps stabilize protein concentrations in cells, acting as a buffer against the inherent stochasticity of gene expression.[16-18]

2.1. Interactions between amino acids of protein partners and the role of post-translational modification (PTM)

In the nucleus, chromatin subdomains can undergo liquid–liquid phase separation driven by the IDRs of histone tails, leading to the formation of dense and dynamic droplets. Various proteins contribute to the aberrant formation of protein aggregates. These proteins often contain prion-like domains (PrLDs) enriched in uncharged polar amino acids, such as asparagine, glutamine, tyrosine, and glycine, which are essential for phase separation. One such protein is fused in sarcoma (FUS), which can self-assemble in paraspeckles. FUS, similar to TAR DNA-binding protein 43 (TDP-43), contains IDRs and PrLDs that drive protein aggregation within SGs, as observed in neurodegenerative diseases.[12,14,16] The tumor suppressor p53 protein is prone to amyloid-like aggregation, especially in its mutated forms, and the p53-MDM2 interaction is influenced by the presence of IDRs. Tau protein, which localizes in SGs and is relevant to Alzheimer's disease development, can also undergo LLPS.

Oppositely charged species regulate condensate formation based on RNA levels: low RNA levels promote formation, while excessive RNA levels trigger dissolution. Transcription and condensates create a feedback loop where short-lived RNA enhances condensate formation, and high RNA levels induce dissolution.[17,19] The phase separation of RNA-binding proteins depends on RNA length.[20] RNA structure determines dense-phase identity within BCs. For instance, Whi3, an ER-associated protein with a C-terminal RNA recognition motif (RRM), forms distinct RNA granules based on RNA structural differences, demonstrating RNA specificity.[21]

Lysines play a significant role in the condensation of BCs. This was studied in Alzheimer's-associated Tau protein, which exhibits a distinct phase separation mechanism compared with Tau/RNA coacervation.[22] Ukmar-Godec *et al.*[23] explored the role of lysine in disordered protein regions within P bodies, highlighting its ability to drive phase separation and form lysine/RNA coacervates. Glycine enhances fluidity, whereas glutamine and serine promote hardening. Amino acids such as arginine exhibit distinct properties in protein condensates, such as cation–π interactions between tyrosine and arginine as well as Coulomb interactions with the phosphate groups of nucleic acids. PTMs, including tyrosine and serine phosphorylation and arginine methylation, regulate LLPS. Arginine methyltransferases methylate the charged guanidine group of arginine, altering or inhibiting the electrostatic interactions required for phase separation. PTMs often accelerate LLPS by facilitating biorecognition, conformational changes, electrostatic interactions, and local accumulation of negative charges. Lysine ubiquitination increases Tau's propensity to form BCs but weakens Tau/RNA interactions. Conversely, lysine acetylation reverses LLPS, reducing Tau's localization in SGs. Tau acetylation blocks phase transition by neutralizing lysine-positive charges, thereby interrupting the electrostatic interactions between Tau residues and microtubules. Heterogeneous ubiquitination stabilizes droplets against dissolution.[24-26] Tau undergoes LLPS with DNA, mononucleosomes, and nucleosome arrays under low-salt conditions and localizes within droplets formed by nucleosomes and phosphorylated HP1α. Aberrant Tau hyperphosphorylation disrupts chromatin interactions and LLPS formation.[26] PTMs and RNA and protein modifications can influence condensate behavior.[24-26]

2.2. ncRNAs and small RNAs

Cellular RNA transcripts include mRNAs, rRNAs, tRNAs, and ncRNAs. Small RNAs include microRNAs (miRNAs), which are 22 nucleotides in length and play roles in the post-transcriptional control of target mRNAs, small interfering RNAs (SiRNAs), trans-acting small interfering RNAs (tasi-RNAs), and small nucleolar RNAs (sno-RNAs). Non-small RNAs include circular RNAs, noncapped RNAs (nap-RNAs), which are involved in gene expression regulation, and ncRNAs exceeding 500 nucleotides in length.

The majority of transcribed RNAs are functional.[27,28] Studies on RNA have employed siRNA libraries for high-throughput silencing of many ncRNAs as well as chromatin immunoprecipitation and RNA immunoprecipitation (RNA-IP) methods combined with next-generation sequencing to explore RNA functionality.[28] RNA modifications, such as 5′-end capping and polyadenylation (polyA tails), are essential for RNA localization and function. In addition, RNAs undergo epigenetic modifications, including those mediated by adenine deaminase and nucleotide-methylating enzymes.[27,29] These RNA modifications are transient and include methylation of adenine (m6A, m1A), cytosine (m6C), and guanine (m7G) as well as acetylation of adenine (ac4A).[27,30-32] These modifications can alter base pairing, reduce the affinity for complementary sequences, or mask target sites on proteins or mRNAs.

2.3. ncRNAs are required for LLPS, BC formation, and BC activity

ncRNAs, polyadenylated or nonpolyadenylated, perform diverse genome-regulatory functions, including encoding of micropeptides and miRNAs as well as acting as decoys for DNA–protein interactions. For example, p21-associated RNA DNA damage-activated (PANDA) acts as a decoy for nuclear transcription factor Y subunit-α (NF-YA), sequestering NF-YA from target gene promoters. ncRNAs can also function as miRNA sponges, sequestering miRNAs away from their mRNA targets. Both linear ncRNAs and circular RNAs (circRNAs) function as RNA sponges and compete endogenous RNAs (ceRNAs). CircRNAs are deregulated in various cancers (https://ngdc.cncb.ac.cn/circatlas/disease.php) and primarily function as RNA sponges, influencing target miRNAs based on cell type and miRNA expression profiles. The mechanism involves the interaction of three partners: circRNA/miRNA/protein target. miRNAs downregulate mRNA and target protein levels, whereas circRNAs block miRNAs through complementarity. Increased levels of miRNAs reduce target protein levels by blocking or degrading target mRNAs. Similar to ncRNAs, circRNAs may act as decoys, protecting amino acids in interacting partners from modifications or degradation or sequestering partners to prevent interactions with other proteins. These interactions are stoichiometric for ceRNAs and super-stoichiometric for RNA sponges. RNA sponges and RNA decoys are not discussed further here. CircRNAs, devoid of a 5′-cap structure and a 3′ poly(A) tail, are generated through a back-splicing process and can be translated through 5′ cap-independent internal translation initiation. In some cases, circRNAs are produced from protein-coding genes, such as circBRD7, derived from the bromodomain protein BRD7. Adenine methylation (m6A) modifications occur in ncRNAs, circRNAs, and protein-coding mRNAs. However, circRNA m6A methylation is more variable and occurs randomly, whereas ncRNA m6A methylation is more stable and tumor-type specific. Specific cases of circRNA functioning in the epigenetic regulation of transcription and its relationship with m6A modifications in cancer will be discussed in the following sections. RNAs have been found to act as oncogenes, contributing to cell proliferation and activation of oncogenic signals through overexpression or increased stability. Conversely, RNAs can function as tumor suppressors, blocking oncogenic signaling depending on the cellular context and specific functions (e.g., sponging oncogenic miRNAs, silencing promoters of genes involved in cell cycle regulation, proliferation, or antiapoptotic function). These tumor-suppressive RNAs are often downregulated in tumors.

In the formation of local condensates, ncRNAs can assemble proteins into chromatin-regulating complexes[33,34] and DNA damage repair complexes.[35]

In the following paragraphs, the roles of ncRNAs in cancer development will be described from the perspective of potential therapeutic approaches. RNA–protein complexes determine local LLPS and regulate cellular physiology and pathology. Local compartmentalization within BC loci is a critical determinant that facilitates the high local concentration of biomolecules and their substrates while excluding functionally irrelevant molecules.

Specific pathways and cellular responses that determine LLPS formation and function include mRNA transcription, mRNA splicing in speckles and paraspeckles, orchestration of chromatin domains, the DNA damage response in the nucleus, and stress responses through the formation of SGs in the cytoplasm. Unique ncRNAs are essential for the formation of certain BCs. For instance, NEAT1_2 is crucial for paraspeckle formation, whereas MALAT1 is recruited to speckles through interactions with multiple splicing-associated proteins, although it is not essential for speckle formation. These BCs, including speckles and paraspeckles, play vital roles in transcription and splicing. Specific pathways and cellular responses, such as the formation of euchromatin and heterochromatin and the activation or silencing of genes, rely on LLPS. These events occur through riboprotein complexes involved in assembling histone locus bodies and other BCs associated with chromatin regulation. In the nucleus, chromatin subdomains can undergo liquid–liquid phase separation driven by the IDRs of histone tails. This process results in the formation of dense, dynamic droplets, including histone locus bodies.

A significant number of ncRNAs function in concert with protein complexes to guide chromatin-modifying complexes to genomic sites. Polycomb (PcG) repressive complexes (PRC1 and PRC2) are involved in gene silencing, while mixed-lineage leukemia 1 (MLL) complexes promote gene activation. PRC2 represses genes by depositing repressive histone marks, such as H3K27me3 and H3K9me3, which lead to the formation of heterochromatin. Conversely, activating complexes deposit marks like H3K4me3 and H3K36me3, facilitating euchromatin formation. NcRNAs that serve as scaffolds for chromatin-modifying complexes guide these complexes to target genomic loci. In other cases, ncRNAs prevent chromatin-modifying complexes from recognizing specific gene promoters.

Histone marks are recognized by enzyme readers, including chromodomain, Tudor domain, PWWP domain, and PHD domain-containing enzymes. Bromodomain-containing protein 4 (BRD4) is an acetylated histone reader

at actively transcribed genes. It induces phase separation, leading to droplets with distinct physical properties. Acetylation of chromatin promotes a unique phase-separated state, with droplets that exhibit specific physical characteristics.[27] Acetylated chromatin is immiscible with heterochromatin containing non-acetylated chromatin. This property reflects the segregation of chromatin into subdomains within the cell. Chromatin forms phase-separated condensates, grouping regions with modified and unmodified chromatin states.

Repressed genes are located in heterochromatin regions marked by H3K27 methylation and non-acetylated nucleosomes, whereas active genes are associated with acetylated nucleosomes in euchromatin. Euchromatin and heterochromatin regions remain dynamically accessible to regulation by chromatin-modifying enzymes and protein readers of modified nucleosomes.[36,37]

Chrom-Seq methods utilize biotinylation tags combined with peptides that localize to specific chromatin regions and histone marks. One example is the mouse CBX7 peptide (containing a chromodomain between amino acids 2 and 76), and another is the Drosophila polycomb (dPC) protein. Fan *et al.*[38] used the Chrom-Seq method to identify RNAs proximal to H3K27me3 marks and validated their findings using RNA-IP quantitative PCR (RIP-qPCR). They identified 542 H3K27me3-associated ncRNAs. These histone marks define transcribed loci on euchromatin. Other ncRNAs that associate with H3K9me3 marks indicate repressed genes on heterochromatin. In some cases, ncRNAs are associated with both active and repressive PTMs; such ncRNAs are known as bivalent chromatin-associated RNAs. Double-site–interacting RNAs, which localize to both H4K20me3 and H3K4me3 marks, play roles in chromatin organization and RNA processing. H4K20me3-interacting RNAs are linked to cell differentiation, whereas H3K4me3-interacting RNAs are associated with metabolism and RNA processing.[36] H4K20me3 has been recognized as a key epigenetic regulator of chromatin structure and disease.[37]

A schematic summary of the various roles of ncRNAs in BC functioning is presented in a series of tables. Several of these ncRNAs have been the subject of cancer-related studies.[39] Tables 1-3 describe ncRNAs that act alongside protein complexes, guiding them to the target gene sites. Table 1 outlines ncRNAs involved in chromatin regulation, which guide Polycomb (PcG) repressive complexes (PRC) in PcG bodies to specific gene promoters for silencing. Table 2 describes ncRNAs that guide DNMT1 for CpG methylation at specific promoters. Table 3 details ncRNAs that guide chromatin-activating complexes and histone modification enzymes for gene activation.

3. NEAT1 and paraspeckles

Speckles and parapeckles regulate protein complexes competing with oncogene signaling. For instance, the interaction between sirtuin1 (SIRT1) and deleted in breast cancer 1 (DBC1), which then releases SIRT1 and enhances its deacetylation activity on p53. Consequently, the deacetylation of p53 reduces the transcription of its downstream target genes and promotes cell proliferation.[102] Paraspeckles are nuclear BCs that appear as chains of spheroids.[103-107] They involve over 60 proteins[106] and one RNA, namely, nuclear paraspeckle assembly transcript 1 (NEAT1). There are two variants of NEAT1: NEAT1_1, which is 3.7 kb in length, and NEAT1_2, which is 23 kb in length. Nascent 2,300-nucleotide–long NEAT1_2 transcripts recruit nuclear RNA-binding proteins to construct paraspeckles. NEAT1_2 is regulated by p53 and is a direct target of p53.[108] It is induced by stress related to DNA damage and replication stress.[109] NEAT1_1 is associated with cancer metabolism, enhanced glycolysis, and the Warburg effect.[110] NEAT1_2, which is essential for paraspeckle formation, recruits and retains proteins required for their assembly and is particularly noteworthy due to its presence in different variants.[105] NEAT1_2 is expressed in up to 50 copies per paraspeckle. The number of paraspeckles in a cell varies by cell type, with HeLa cells containing 13 – 17 foci/nucleus and NIH3T3 mouse fibroblasts containing 5 – 10 foci/nucleus.[106] Eight proteins are critical for paraspeckle nucleation: non-POU domain-containing octamer binding (NONO); splicing factor rich in proline and glutamine (SFPQ); paraspeckle protein component 1 (PSPC1); heterogeneous nuclear RNPs HNRNPA1, HNRNPA2, HNRNPK, and HNRNPH3; fused in sarcoma (FUS); DAZAP1; Brahma homolog component of SWI/SNF (BRG1); and the RNA-binding protein RBM14 (Figure 2). Notably, knockdown of these critical proteins leads to paraspeckle disintegration.[106]

In a search for paraspeckle modulators, An *et al.* identified several dual PI3K/mTOR inhibitors—Torin 1, PP242, LY3023414 (samotolisib), and INK128-as potent negative modulators of paraspeckles.[96] Rapamycin kinase T (ORK) inhibitors were also shown to inhibit PI3K. Additional dual PI3K/mTOR inhibitors, such as GSK1059615 and CAY10626, as well as the PI3K/mTOR/DNA-PK inhibitor PI-103, which has been used in clinical trials for chronic lymphocytic leukemia (CLL), similarly reduced either the NEAT1_2 area or the number of paraspeckles.

NEAT1_2-dependent clusters influence the interaction of proteins like FUS, which aggregate around RNA, with the RNA-binding protein RBP14 and paraspeckle proteins PSPC1, NONO, and SFPQ. During tumor progression, NEAT1_2, along with NONO, RBM14, and PSPC1, is

Table 1. RNAs that inhibit gene expression through PRC2 binding and deposition of H3K27me marks

Gene	Partner	Target	Modification	Tumor	References
LINC01133	EZH2, LSD1	KLF2, p21, E-cadherin	H3K27me	NSCLC	40
ANRIL-CDKN2B-AS1	PRC1–CBX7, PRC1	P14arf, p16ink4	H3K27me	-	41
LL22NC03-N64E9.1	PRC2	KLF2	H3K27me	CRC	42
HOTTIP	CTCF, DNMT1	MTUS1	-	NSCLC	43
ARHGAP27P1	PRC2	CDKIs p15, p16	H3K27me	-	44
SNHG7	PRC2	CDKIs	H3K27me	ovary	45
TUG1	PRC2	KLF2	H3K27me	HCC	46
SNHG6	PRC2	P21, KLF2	H3K27me	Osteosarcoma	47
DUXAP8	EZH2, LSD1	CDK1A, KLF2	H3K27me	Pancreas	48
SNHG20	PRC2	CDKis	H3K27me	NSCLC	49
PVT1	EZH2	miR-200b	H3K27me	Cervical cancer	50,51
UCA1	PRC2	P27	H3K27me	Breast cancer	52
MYLK-AS1	PRC2	LATS2	H3K27me	Gastric	53
HOXA-AS2	EZH2, LSD1	P21, KLF2	H3K27me	Colorectal	54
SNHG17	PRC2	CDKIs	H3K27me	Gastric	55
CHASERR, HASTER	unknown	Transcription factors CHD2 chromatin remodeler	-	Various	56
GIHCG	EZH2, DNMT1	miR-200b/a/429	H3K27me CpGme	Hepatocell HCC renal cell cancer	57
PVT1	PRC2	Apoptotic genes	H3K27me	MM	58
NEAT1	BRG1, SWI/SNF	GADD45A	Silencing	GC	59
LINC00675	LSD1	SPRY4	H3K4me2 demethylated	GC	57
HOXA11-AS	EZH2, LSD1, DNMT1	KLF2, PRSS8	H3K27 me3, H3K4 me demethylation	-	57
BST2/BISPR	-	Tetherin	Positive regulator of BST2/tetherin	Antiviral	57
SNHG12	HDAC9	miR-320a downregulated	Resistance to doxorubicin carboplatin sunitinib and temozolomide	OC, Osteosarcoma	60,61
SNHG13/DANCR	KAT6A (H3K23ac), EZH2	CDK inhibitors	-	CRC, endocrine cancers	62
SNHG14, SNHG15	EZH2, PRC2	-	-	Endocrine cancers	63
lincRNA-CMPK2, NRAV/NRIR	-	Block IFN response, downregulate IRENA	Stop protumor inflammatory cytokines	Macrophage antitumor response	64
FEZF2-AS1	LSD1	p21	H3K4me2	Gastric cancer	65
*LINC*0144660	LSD1	RASD1	Suppression by demethylating H3K4	Gastric cancer	66
SNHG22	EZH2	-	-	.	67
ATRX	EZH2	Xist targets	H3K27me	Chromatid silencing	68
XIST	PRC2, SMRT TRIM28, SHARP, HDAC3	RNA Pol II exclusion	Histone deacetylation	X chromosome silencing	69

(Cont'd...)

Table 1. ***(Continued)***

Gene	Partner	Target	Modification	Tumor	References
FIRRE	HnRNP U	X chromosome	H3K27me	Set up of specific chromosomal domains	70
CASC11	EZH2	PTEN	H3K27me	CRC, HCC	71
LNMAT1	EZH2	CADM	H3K27me	Melanoma	72,73
ZFAT-AS1	PRC2	CDX2	H3K27me	Glioma	74
LINC01271 (*MaTAR25*)	PUB	Tensin 1 promoter	Upregulates tensin 1 in focal adhesions, affecting migration	CRC, BC	64,75

Abbreviations: ANRIL: Antisense noncoding RNA in the INK4 locus; ARHGAP27: Rho GTPase activating protein 27, antisense. CASC11: Cancer susceptibility 11; CHASERR: CHD2 Adjacent suppressive regulatory RNA; FIRRE: Functional intergenic repeating RNA element; GIHCG: Gradually increased during hepatocarcinogenesis; IRENA: IFN-responsive nuclear factor-κB activator; LINC01271: Mammary tumor associated RNA 25 (MaTAR25) homolog; LNMAT1: Long noncoding RNA lymph node metastasis-associated transcript 1; NRAV/NRIR: Negative regulator of antiviral response; NRIR: PVT1: Plasmacytoma variant translocation 1; HOXA-AS: Homeobox gene A, antisense; HOTTIP: HOXA transcript at the distal tip; Xist: X-inactive specific transcript; ZFAT-AS1: Zinc finger and AT hook domain (ZFAT) antisense 1. Proteins. CADM: Cell adhesion molecule 1; CBX7: Chromobox protein homolog 7; CDKi: Cyclin-dependent kinase inhibitor; CDX2: Caudal-related homeobox transcription factor 2; CHD2: Chromodomain helicase DNA-binding protein 2; CTCF: CCCTC-binding factor; GADD45A: Growth arrest and DNA damage-inducible alpha; PTEN: Phosphatase and tensin homolog. Cancers. AML: Acute myeloid leukemia; BC: Breast cancer; CRC: Colorectal cancer; GC: Gastric cancer; HCC: Hepatocellular cancer; LC: Lung cancer; MM: Multiple myeloma; NSCLC: Non-small cell lung cancer; OC: Ovarian cancer.

Table 2. LncRNAs associated with DNMTs, silencing genes through CpG methylation

ncRNA	Recruitment	Target	Mechanism	References
DACOR	DNMT1	Fos, Jun, DNMT1	CpG methylation, Decoy	76
LINC0051	EZH2	PTEN	CpG methylation	77
HOTAIR	DNMT1	PTEN	CpG methylation	78
SAMD12-AS1	DNMT1	P53	CpG	79
KIF9-AS1	DNMT1	RAI2	CpG	80
ANRIL	Steric hindrance, block of Pol II binding	IGF2R	CpG methylated	81
HITT	EZH2, PRC2	Hif-1α	Triplex formation	82
CDKN2B-AS1/ANRIL	PRC2	CDKN2B	Triplex formation	83

Notes: A link to ncRNA databases can be found at https://lncipedia.org/db and http://www.noncode.org/; for RNAs related to biomolecular condensates, a link can be found at https://rps.renlab.org/#/Browse
Abbreviations: ANRIL: Antisense noncoding RNA in the INK4 locus; CDKN2B: Cyclin-dependent kinase inhibitor 2B; CpG: Cytosine-phosphate-guanine; DACOR: DNMT1-associated colon cancer repressed LncRNA; HIF-1α: Hypoxia inducible factor 1α; HITT: HIF-1α inhibitor at the translation level; HOTAIR: HOX transcript antisense RNA; IGF2R: Insulin growth factor 2 receptor; KIF9-AS: Kinesin family member 9-antisense; LINC0051: Long intergenic non-protein coding RNA 51; PTEN: Phosphatase and TENsin homolog deleted on chromosome 10; RAI2: Retinoic acid induced 2; SAMD12-AS: Sterile alpha motif domain-containing 12-Antisense.

upregulated in hepatocellular carcinoma (HCC) and is associated with poor survival outcomes.[111-117] NEAT1_2 is also overexpressed and dysregulated in multiple cancers, including breast, ovarian, prostate, and lung cancers, as well as multiple myeloma. Furthermore, elevated NEAT1 levels are linked to chemotherapy resistance and are associated with cancer stemness.[117] NEAT1 promotes resistance to cisplatin and taxol,[118] while downregulation or silencing of NEAT1 sensitizes tumors to these chemotherapeutic agents. NEAT1_2 also facilitates cancer progression and metastasis, particularly in thyroid cancer.[119,120] It has been suggested that NEAT1_2 could serve as a therapeutic target in HCC and papillary thyroid cancer using small molecule inhibitors.[121]

Paraspeckle components have been implicated in cancer development through expression analyses, knockout cell studies, and RNA silencing approaches. Proteins such as NONO, SFPQ, and PSPC1 have been extensively studied.[122-129] NONO, a core paraspeckle component, is involved in RNA- and DNA-tethered condensates and undergoes phase separation *in vitro*, which is sustained by nucleic acid binding. NONO plays a role in the transcription of super-enhancer-regulated genes, such as *HAND2* and *GATA2*. Inhibition of the RNA-binding ability

Table 3. Gene activation by lncRNAs through euchromatin regulation and histone marks

Gene	Interaction	Target	Histone mark	References
GClnc1	WDR5, KAT2A	SOD2 promoter	H3K4me3, H3K9ac	84
GCAWKR	WDR5, KAT2A	PTP4A1	H3K4me3, H3K9ac	85
LincRNA-P21	hnRNP K	P21	H3K4me3, H3K9ac	86
TM4SF19-AS1	WDR5	TM4SF19	H3K4me3	87
TARID	GADD45A	TCF21	CpG demethylation	88
CCAT1-L	CTCF, hnRNP K	MYC	Chromatin loop, NUP153 binding to cohesin	89
HOTTIP	WDR5, MLL/SET1	HOXA	H3K4me3	90
PVT1	CTCF, hnRNP K	MYC	Chromatin loop, NUP153 binding to cohesin	91
NRIP enhancer	Cohesin	ER-dependent genes	Chromatin loop nuclear receptor-interacting protein	92
HASTER	-	HNF1A	Promoter–enhancer interaction	93,94
lncPRESS1	SIRT6 deacetylase	Embryonic state	Preserves H3K56ac and H3K9ac	95
NEAT1_2	RBP14	Euchromatin binding	Paraspeckle condensates	96
THRIL	hnRNPs	TNF-α	Promoter/enhancer activation	97
HOTAIR	LSD1, HBXIP	MYC target genes	Lysine demethylation	98
NeST	WDR5	IFN-gamma	H3K4me	99
CircRNA0000285	Unknown	FUS involved in back-splicing to form circRNAs	Cervical cancer, proliferation, metastasis	100
circRap1b	KAT2A, KAT7	The HOXA5 gene H3K9ac mark, Fam3a antiapoptotic	Prevents stroke	101

Abbreviations: CCAT1-L: Colon cancer-associated transcript 1-long; circRap1b: Circular RNA from Ras-related protein 1b mRNA; CHD2: Chromodomain helicase DNA-binding protein 2; CpG: Cytosine-phosphate-guanine; Fam3A: Family with sequence similarity 3A, a cytokine-like protein; FUS: Fused-in sarcoma; HOXA5: Homeobox gene A5; IFN-gamma: Interferon-gamma; MYC: Viral myelocytomatosis homolog; NEAT1: Nuclear enriched abundant transcript 1; THRIL: TNFα and hnRNPL related immunoregulatory LincRNA; TARID: Tcf21 antisense RNA inducing demethylation; TNF-α: Tumor necrosis factor-α.

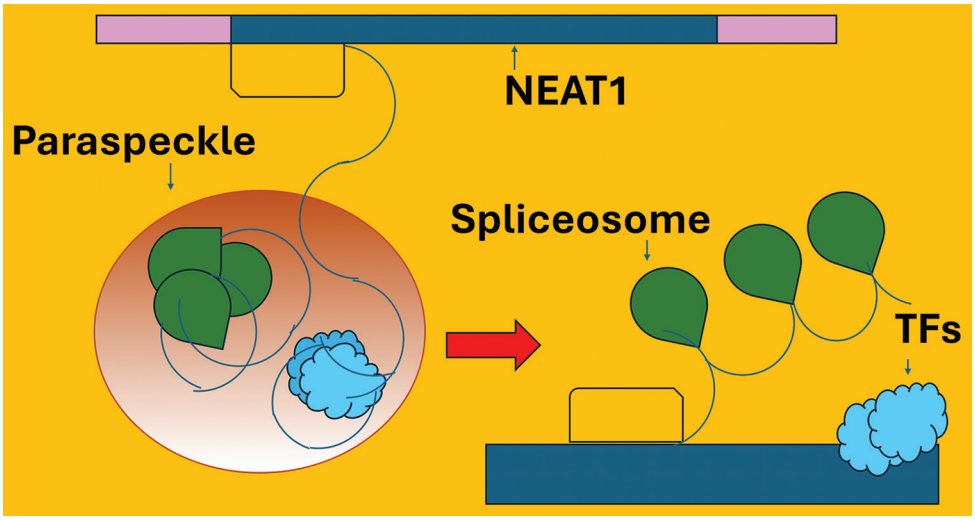


Figure 2. Function of paraspeckles in the transcription and splicing of mRNAs. The splicing factors NONO and SFPQ assemble with NEAT1_2 and then associate with PSPC1, HNRNPK, HNRNPA1, FUS, and RBM14, forming the NEAT1_2 ribonucleoprotein (RNP) complex. Image created by the authors

of NONO or its phase separation activity leads to decreased expression of *HAND2* and *GATA2*. This highlights the potential therapeutic application of compounds targeting the RNA-binding activity of NONO, particularly in neuroblastoma.[123]

The Drosophila behavior human splicing complex, comprising PSPC1, SFPQ, and NONO, plays a critical role in genome stability and gene regulation at both transcriptional and post-transcriptional levels. These functions depend on the heterodimerization of the proteins

and their subcellular compartmentalization, particularly within paraspeckles.[125]

PSPC1 potentiates IGF1R expression, enhancing cell adhesion and motility. It has been demonstrated that every component of paraspeckles is involved in this process. Knockdown experiments of PSPC1-interacting paraspeckle components, including NONO, FUS, and NEAT1, have shown that these are essential for PSPC1-regulated IGF1R expression.[126] Focal adhesion kinase and sarcoma kinase (Src) signaling pathways cooperate to increase cell adhesion and motility in HCC. Insulin-like growth factor 1 receptor (IGF1R), a membrane tyrosine kinase receptor, is a targetable molecule overexpressed in tumor metastasis, drug resistance, and poor prognosis across various cancers. In colorectal cancer (CRC), MALAT1 binds to SFPQ, releasing the oncogene PTBP2 from the SFPQ/PTBP2 complex.[130] In the same cancers, SFPQ depletion has been shown to be synthetically lethal in the presence of BRAF V600E mutations.[131] In addition, SFPQ promotes lung cancer malignancy[131] and contributes to the proliferation, migration, and invasion of HCC.[128] SFPQ condensates also sequester SMAD4, thereby preventing tumor-suppressive signaling through the TGF-β pathway.[129] PSPC1 interacts with lysine demethylase KDM5C, and both proteins are recognized as oncogenic factors in prostate cancer (PCa). Inhibition of KDM5C and PSPC1 using specific compounds shows potential as a therapeutic strategy for PCa.[132,133] In sporadic amyotrophic lateral sclerosis (ALS), NONO and PSPC1 remain localized within the nuclei of motor neurons,[134] whereas SFPQ and FUS exhibit nuclear loss, and TDP-43 displays cytoplasmic localization.[135]

RNA-binding proteins (RBPs) are critical components of BCs. Many RBPs colocalize with RNA polymerase II (Pol II) at promoter and enhancer loci. The paraspeckle protein PSPC1 utilizes RNAs as multivalent molecules to form transcription condensates, which are followed by the phosphorylation and release of Pol II.[136]

The PSPC1 protein contains a PrLD enriched in uncharged polar amino acids, such as asparagine, glutamine, and tyrosine. Glycine is also abundant and contributes to the liquid–gel phase separation properties of PSPC1. The PrLD domain contributes to the phase separation ability of PSPC1. Immunofluorescence assays have detected PSPC1 in mouse oocytes at the germinal vesicle (GV) stage. PSPC1 knockdown resulted in the blocking of oocyte maturation *in vitro*. Checkpoint kinase 1 (CHK1) is vital during the GV stage of mouse oocytes. PSPC1 interacts with the serine/threonine protein phosphatase PPP5C, which regulates CHK1 phosphorylation.[138]

PSPC1 also functions as an activator of transcription factors involved in epithelial-to-mesenchymal transition (EMT) and stemness. It sustains Myc activation and promotes tumor growth in breast and prostate cancer. PSPC1 enhances the secretion of transforming growth factor-β1 (TGF-β1) through interactions with phosphorylated nuclear Smad2/3. PSPC1 promotes a TGF-β1 prometastatic switch by altering the binding preference of Smad2/3 from tumor suppressor genes to prometastatic genes.[137,138]

In CRC, LOC105369504 expression is downregulated, leading to the inhibition of proliferation, invasion, migration, and EMT. LOC105369504 binds to PSPC1, regulating PSPC1 stability through the ubiquitin-proteasome pathway.[139]

The pro-oncogenic activities of PSPC1 are closely linked to those of the orphan nuclear receptor 4A1 (NR4A1, Nur77). NR4A1 knockdown decreases PSPC1 expression in various cell lines. Bisindole-derived NR4A1 antagonists (CDIMs) also induce PSPC1 downregulation in breast cancer.[140] Following NR4A1 silencing, genes associated with cancer stemness and EMT are also downregulated.

NEAT1_2-dependent clusters influence how proteins such as FUS, which aggregate around RNA, interact with the RNA-binding protein RBP14 and paraspeckle proteins PSPC1, NONO, and SFPQ. Activation of the mechanistic target of rapamycin (mTOR) reduces NEAT1_2 transcription, diminishes paraspeckles, and releases NONO, SFPQ, and RBP14, which are essential for RNA splicing.[141] Table 4 provides a detailed overview of ncRNAs necessary for the formation of different BC types.

3.1. Speckles and MALAT1

The ncRNA MALAT1 is a key RNA constituent of nuclear speckles and is overexpressed in cervical, colorectal, lung, breast, liver, and bladder tumors.[142] Elevated *MALAT1* expression is associated with poor prognosis and metastasis formation in lung cancer and other tumors.[143,144] Cells with aberrant *MALAT1* expression exhibit various dysregulated functions, with mechanisms of action often inconsistent and sometimes conflicting. It is plausible that the deregulation of oncogenic RNAs affects condensate function. MALAT1 is recruited to speckles through direct interactions with multiple splicing-associated proteins; however, it is not strictly required for speckle formation.[143] MALAT1, also known as *NEAT2*, is an ~8 kb highly abundant ncRNA conserved across vertebrates and considered an oncogene. Using capture hybridization analysis of RNA targets, researchers demonstrated MALAT1 binding to active genes, suggesting that both NEAT1 and MALAT1 contribute structurally to the organization of nuclear bodies at heavily transcribed sites.[144] Engreitz *et al.*[124] employed RNA–RNA interaction assays (RAP-RNA) and showed that MALAT1 localizes to actively transcribed

Table 4. ncRNAs required for the formation of biomolecular condensates (BCs) or interaction with protein components

Type	ncRNA	Interactome	Deregulated in cancer
Speckle	MALAT1	DBC1, PRPF6, SRSF, hnRNPs, ELAVL1/HuR	Breast cancer, CRC[102]
Paraspeckle	NEAT1_2	NONO, SFPQ, and PSPC1	Triple-negative BC, HCC[103]
PML body	DUXAP8	PTEN	Prostate, ovary, bladder, breast, pancreas, RCC, GC[48]
Stress granules (SGs)	RP11-435F13.2	ELAVL1 (HuR)	Pancreatic and esophageal cancer[57]
SG	NORAD	ALKBH5, AGO, DDX6	Various cancers[57]

Abbreviations: AGO: Argonaute; ALKBH5: ALKB homolog 5, erasing m6A; BC: Breast cancer; CRC: Colorectal cancer; DBC1: Depleted in breast cancer; DDX6: Death box family RNA-dependent helicase ATPase 6; DUXAP8: Double homeobox A pseudogene 8; GC: Gastric cancer; HuR: Human R antigen; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; NEAT1: Nuclear enhanced paraspeckle assembling transcript 1; NORAD: Noncoding RNA activated by DNA damage; PML: Promyelocytic leukemia; PRPF6: Pre-mRNA-processing factor; RCC: Renal cell carcinoma; SRSF: Serine/arginine-rich splicing factors.

genes through interactions with proteins that guide this RNA to nascent pre-mRNAs. MALAT1 functions as a scaffold for speckle proteins, facilitating the positioning of nuclear speckles at active gene loci.

3.2. PML bodies, p53 guardian of the genome, and cancer

PML bodies are dynamic nuclear MLO compartments[145] that compartmentalize diverse proteins, such as p53 and DNA repair protein complexes. PML bodies regulate various cellular processes, including apoptotic pathways and genome stability. Failures in DNA damage repair (DDR) result in chromosomal instability, a hallmark of cancer. Various ncRNAs contribute to DNA stability and repair, which are essential processes in cancer development.

PML bodies participate in activities such as transcription regulation, cell cycle control, antiviral defense, and apoptosis promotion. These functions are mediated by PTMs, such as phosphorylation by protein kinase 2 (PK2) and deubiquitination by USP7/HAUSP, which regulate protein ubiquitination for proteasomal degradation. PML bodies are also targeted by various oncolytic viruses.[146] The Momordica anti-HIV protein MAP30 has been shown to decrease HBV replication by inhibiting EBNA1, which directs PML proteins to degradation and promotes PML loss.[147]

Among the tripartite motif (TRIM) proteins, which include a series of RING-type E3 ligases, the TRIM 19 protein is encoded by *PML*. The N-terminal RBCC (RING, B-Box 1/2, coiled-coil) domain facilitates PML protein scaffold self-oligomerization. The C-terminus contains small ubiquitin-like modifier (SUMO) sites and a SUMO-interacting motif (SIM), which enhance granule assembly through SUMO and SIM arrays, promoting liquid-like condensate formation. In cancer, PML bodies exhibit diverse roles. In acute promyelocytic leukemia (APL), chromosomal translocation results in the fusion protein PML-RARα, which lacks C-terminal SIM and SUMOylation sites. This alteration impairs PML phase separation, causing dispersed microspeckles and concentrating transcriptional machinery at oncogenes, potentially impacting RNA splicing and contributing to oncogenesis. Novel therapeutic approaches targeting PML in cancer have been recently reviewed.[148]

Condensates are regulated at multiple levels, with alterations in their properties influencing their formation, viscoelasticity, dissolution, and other physicochemical aspects, ultimately modifying their functions. Several factors are critical for the regulation of BCs. Dysregulation in the concentration of components, chemical modifications, involvement of ncRNAs, and selective partitioning are observed in cancer cells. Among these, the concentration of biomolecules is a pivotal parameter in condensate dynamics. Condensation occurs when a critical threshold concentration is reached, which can be achieved through protein accumulation, inhibition of degradation, confinement within a membrane-bound compartment, or sequestration by binding to a substrate with multiple binding sites. Notably, the dissolution of condensates occurs during mitosis when the loss of the nuclear membrane reduces the concentration of nuclear components. Condensates reform in the nucleus once the nuclear envelope is re-established, facilitated by an increase in component concentrations through protein transport into the nucleus. Alterations in BCs are pervasive in cancer and are driven by diverse stresses within the tumor microenvironment. The phase separation of cancer-associated proteins influences numerous cellular processes, contributing to cancer development.

One notable role of ncRNAs interacting with condensates involves the activation of the tumor suppressor protein p53 and its downstream signaling pathways.[149] The p53 protein is prone to amyloid-like aggregation, particularly in its mutated forms. Interactions between p53 and MDM2, an E3 ubiquitin ligase that degrades p53, are influenced by IDRs. MDM2 inhibits p53 by inducing

its degradation and blocking its transcriptional activity, whereas p53 induces MDM2 expression, forming a regulatory feedback loop.[150] In the DNA repair pathway, phase-separated DNA repair foci containing the DNA damage-response factor p53-binding protein 1 (53BP1) also concentrate p53 protein.[151] Disruptions in these phase-separated foci impair the 53BP1-dependent induction of p53, reducing the expression of p53 target genes. Among the transcripts activated by p53,[152-154] several ncRNAs, such as LINC1, Guardin, and NEAT1_2, play significant roles, in addition to 53BP1.[155-157]

Since p53 acts as a tumor suppressor, its altered activity due to mutations, reduced concentration, or impaired signaling at DNA repair foci can promote cancer progression. In response to DNA damage, different repair mechanisms are activated depending on the type of damage. Double-strand breaks are repaired by mechanisms such as homologous recombination (HR), classical non-homologous end-joining (NHEJ), alternative end-joining, and single-strand annealing. Larger nucleotide adducts are repaired through nucleotide excision repair, whereas smaller base lesions are repaired through base excision repair. LINP1 ncRNA assembles proteins such as RPA, Ku70, Ku80, and ISWI, bringing in proximity breast cancer type 1 susceptibility protein (BRCA1), PAR polymerase 1 (PARP1), cadherin 4 (CDH4), and 53BP1.[158] NIHCOLE RNA acts as a scaffold for proteins, interacting with multiple Ku80 units and promoting phase separation, facilitating the formation of multimeric NHEJ complexes to optimize ligation efficiency.[159] It supports repair complexes like the XRCC4-DNA Ligase IV ligation complex. Another ncRNA, LRIK, binds to Ku70 – Ku80 heterodimers.

SNHG12 RNA stabilizes the interaction between DNA-PK and Ku70/Ku80, promoting NHEJ-based DNA repair. HITT RNA binds to ataxia-telangiectasia mutated (ATM) and prevents the formation of the MRE11-RAD50-NBS1 (MRN) complex, playing a role in both HR and NHEJ.[160]

Protein–protein interactions are crucial for assembling DNA repair complexes. BRCA1, through its leucine-zipper domain, interacts with PARP1, which performs poly-ADP-ribosylation, creating PAR chains that recruit PAR-binding proteins. MALAT1 forms a complex with PARP1 and ligase 3 (LIG3), facilitating HR. Inhibiting this complex has shown therapeutic benefits in prostate cancer and multiple myeloma.[161,162] H19, an ncRNA silenced in clonal sheep reproduction, increases BRCA1 stability by interfering with BRCA1 degradation mediated by ubiquitin ligases HUWE1 and UBE2T. Silencing H19 disrupts the DNA repair process and enhances sensitivity to PARP inhibitors (PARPi), offering potential therapeutic advantages.[163]

3.3. Microspeckles and superenhancers

Recent research has revealed that gain-of-function mutations in the miR-1400 seed sequence, caused by chondrocyte-activated superenhancers, lead to skeletal dysplasia, emphasizing the role of superenhancers in disease mechanisms. While the correlation between superenhancers and ncRNAs in controlling cell identity remains underexplored, it is proposed that super-enhancer-driven ncRNAs (SE-ncRNAs) are associated with tumor development and pathogenesis. RNA molecules facilitate condensate formation, initiate transcription, and contribute to the fusion or pairing of enhancer condensates with promoter sites, leading to transcriptional bursts. RNA-mediated feedback may terminate these transcriptional bursts, highlighting the roles of ncRNAs near enhancers or promoters.[91,93,94] Interactions between such RNAs and enhancers could regulate the rate and magnitude of transcriptional bursts. The accumulation of ncRNA near genes may influence condensate size or dissolution through feedback mechanisms. Furthermore, ncRNAs can modulate transcription by interacting with CTCF (CCCTC-binding factor), stabilizing genomic boundaries, and limiting the territory over which an enhancer or super-enhancer operates.[164,165] Functional crosstalk between superenhancers and ncRNAs—spanning gene regulation in cis and trans and the regulation of superenhancers by ncRNAs—has also been proposed. Noncoding mutations play a significant role in the dysregulation of superenhancers in cancer. For example, in approximately 5% of T-cell acute lymphoblastic leukemias (T-ALL), small insertions near the TAL1 gene induce ectopic super-enhancer creation. This presents a working hypothesis for studying how noncoding mutations trigger ectopic super-enhancer establishment.[165] Drugs targeting BCs, such as cyclopamine (a steroidal alkaloid[166]) and nucleolin,[167] could enable the pharmacological modulation of oncolytic virus replication and control transcription factors at cancer-driving superenhancers.

3.4. SGs

Key components of SGs include the Ras-GTPase-activating protein (GAP) SH3 domain-binding proteins G3BP1 and G3BP2, which are pivotal in cell behavior and cancer.[13,168,169] DDX3, a DEAD-box RNA helicase and RNA-binding protein,[170] localizes with DDX6 to SGs alongside Gle1A,[171] a DDX regulator, and CAPRIN1. DDX3 is essential for SG assembly, which occurs through nucleation mediated by the RNA decay factor G3BP1. G3BP1 prevents ribosome and initiation factor localization in silenced SG foci, assisted by other SG-associated proteins, such as DDX3, DDX6 (Rck/p54), Y-box-binding protein (YBX1/YB-1), translational suppressors TIA1 and TIAR, CAPRIN1,

USP10, poly-A-binding protein, and Lsm1. YB-1, with its low-complexity sequence domains, activates G3BP1 translation, thereby promoting SG assembly. Acetylation of YB-1, induced by entinostat, suppresses G3BP1 translation and SG formation. YB-1 interaction with G3BP1 also promotes metastasis in RCC by upregulating secreted phosphoprotein 1 (SPP1).

SGs play a critical role in enhancing tumor growth, invasiveness, migration, apoptosis inhibition, immune evasion, and metabolic reprogramming. SGs also contribute to the development of resistance against chemotherapy, immunotherapy, and radiotherapy across various cancer types.

A small molecule, C108, inhibits G3BP2, delays stress response, suppresses cancer cell metastasis, and promotes CD8 T-cell proliferation and infiltration, improving survival in animal models with breast tumor xenografts. LINC01554 protects G3BP2 against degradation through ubiquitination. RNA-seq analysis has revealed that hepatoma-derived growth factor (HDGF) is regulated by G3BP2. G3BP2 binds to HDGF mRNA, stabilizing its expression, while C108 inhibits G3BP2 function.[169]

Cancer cells exploit SGs as condensates to sequester drugs, protecting cellular components during stress. G3BP1, a key nucleation protein in SGs, is highly expressed in various cancers and promotes proliferation, migration, and invasion.[3] Although the mechanism underlying the upregulation of SG formation is not fully understood, G3BP1 expression is regulated by Y-box binding protein 1 (YB1), a nucleocytoplasmic shuttle protein. YB1 binds to the 5′ UTR of G3BP1 mRNA, promoting its translation. Notably, YB1 is highly expressed in sarcomas and nasopharyngeal cancers.[172] SG formation also favors cancer cells by inhibiting apoptosis.[173] Drug-based inhibition of SG components, such as DDX3, has been shown to reduce SG formation.[174] SG formation can also be triggered by lipid signaling molecules.[175] Independent of SG formation, G3BP1 contributes to cancer progression by participating in growth-related signaling pathways and promoting EMT in tumors.[176]

G3BPs (G3BP1 and G3BP2) regulate mRNA expression outside of SGs through interactions with RNA. They are implicated in cancer progression, invasion, metastasis, and viral infections by regulating SG dynamics, RNA stability, and tumorigenesis.[177] Consequently, compounds that target G3BPs, block SG formation, or promote SG dissolution hold potential as therapeutic agents. G3BPs may serve as therapeutic targets for both antiviral and anticancer strategies.[177-179]

G3BP1 is a central player in SG dynamics, with its RNA-binding ability essential for SG formation. The RNA-binding function of G3BP1 is impaired by acetylation at lysine 376 (K376) in its RRM domain.[178] A mutation mimicking this acetylation, K376Q, disrupts G3BP1 interaction with poly(A)-binding protein 1 (PABP1) but does not affect interactions with Caprin-1 or USP10. Substituting G3BP1 with its K376Q mutant or an RNA-binding-deficient mutant (F380L/F382L) blocks SG formation. During SG resolution, K376-acetylated G3BP1 is observed outside SGs.[178] MAGE-B2 (melanoma-associated antigen B2) suppresses SG initiation by reducing G3BP levels below the concentration critical for phase separation.[179] G3BP2 also induces changes in condensate and mRNA expression under endoplasmic reticulum (ER) stress.[168] Residues critical for G3BP condensation, such as V11, is essential for forming the G3BP-Caprin-1 complex and assembling SGs.[169]

During arsenite administration, oxidative stress or elongation factor eIF2 phosphorylation causes cell to enter a translation arrest phase. In this phase, RNAs are stalled within a ternary complex comprising eukaryotic initiation factor 2 (eIF2)/GTP/Met-tRNA. SGs play a critical role during this phase by sequestering mRNAs and inhibiting their translation until the stress subsides. Depending on the severity and type of stress, SGs may also lead to the processing or degradation of mRNAs. SGs contain enzymes of the RNA silencing pathway, including Argonaute2, trans-acting factors, Hsp90 complexes, and RBPs, which participate in the small RNA-mediated repression of RNA targets. Interestingly, viruses exploit SG formation to their advantage, either by facilitating the translation of their own RNAs or by binding to SG protein scaffolds to inhibit SG formation.[14,15]

SGs have been implicated in cancer development and neurodegenerative diseases. In human HCC tissues, four genes—*KPNA2*, *MEX3A*, *WDR62*, and *SFN*—are highly expressed. Knocking down any of these genes reduces HCC cell proliferation by disrupting SG formation.[180] A small molecule, C108, binds to G3BP2, decreasing PD-L1 mRNA and protein levels, increasing CD8 T-cell proliferation and infiltration, and improving survival and long-term cures in breast tumor-bearing mice.

Raloxifene, an estrogen receptor modulator, prevents SG dissolution in glioblastoma cells, induces protein synthesis failure, and promotes cell death during hypoxia. Thus, SG modulation can be a promising strategy to target the hypoxic niche of GBM tumors.

Knockdown of *G3bp1* and *G3bp2* prevents SG formation in response to eIF2α phosphorylation or eIF4A inhibition, although cells remain SG-competent under heat or osmotic stress. CAPRIN1 binding to G3BP promotes SG formation, whereas USP10 binding inhibits

it. G3BP, through its RGG motif, interacts with 40S ribosomal subunits, and this motif is essential for G3BP-mediated SG assembly. G3BP facilitates SG condensation through S149 phosphorylation and its interactions with CAPRIN1 or USP10.[169] CAPRIN1 is a phase-separating protein with significant roles in dendritic spines and SG formation, often in association with ncRNAs.[181] SG-associated CAPRIN1 is involved in the progression of nasopharyngeal carcinoma.[182] In ovarian cancer, the upregulation of SNHG8 RNA enhances its binding with CAPRIN1, positively regulating its expression and promoting the stability of catenin beta 1 (CTNNB1) and Axin.[183] These interactions activate Wnt/β-catenin signaling, thereby facilitating cell migration and EMT and maintaining the stemness of ovarian cancer cells. Given their pivotal role in cellular stress responses, SGs are promising therapeutic targets for cancer treatment.[184] For example, small peptides derived from the G3BP1 sequence have shown encouraging results in cancer therapy.[185]

CAPRIN1 is an RNA-binding protein that confers specificity to enzymes depositing the (m6A) mark on RNAs, particularly near stop codons. An *et al.* demonstrated that TRA2A and CAPRIN1 promote the methylation of m6A sites colocalized with their RNA-binding targets. CAPRIN1 interacts with METTL3 and METTL14, forming the m6A methyltransferase METTL3/METTL14 complex, which associates with Wilms' tumor 1-associated protein (WTAP).[186]

3.5. P bodies

P bodies are dynamic structures similar to SGs and are organized during stress-induced translational arrest. They serve as sites for mRNA silencing and decay. Specific RBPs are essential for P body formation, including DEAD-box RNA helicase 6 (DDX6), LSM14A, and eukaryotic translation initiation factor 4E transporter (EiF4E), which participate in the nucleation process. Other P body-associated proteins include SAMD4A, AJUBA, YB-1, and Wilms' tumor-1 interacting protein (WTIP). Enzymes such as DCP1A and DCP2 and enhancers of mRNA decapping proteins (EDC3 and EDC4) reinforce the protein interaction network and are required for stress-induced P body formation.

P bodies are closely linked to tumor progression. In CRC, DCP1A is highly expressed, and this upregulation correlates with advanced tumor-node-metastasis stage, worse prognosis, increased lymph node metastasis, tumor invasiveness, and lower survival rates. In mammary epithelial cells, treatment with TGF-β promotes P body formation and EMT. Activation of autophagy can clear P bodies, thereby blocking EMT.

P bodies are enriched in mRNAs with m6A modifications, attracting the m6A reader YTHDF2, which colocalizes with P body markers DCP1A, DDX6, and EDC4. DCP1A is post-translationally modified through ubiquitination by the E3 ubiquitin ligase TRAF6 and phosphorylation. These PTMs favor interactions with P body factors such as DCP2, EDC4, and XRN1, enhancing P body formation. Notably, phosphorylation promotes mRNA storage, whereas ubiquitination drives mRNA decay.

Knockdown of DDX6 in a mouse model of late-stage BC prevents P body formation, inhibits EMT, and reduces metastatic nodule size and number. Snail zinc finger transcription factors, which are key regulators of EMT, are recruited to P bodies by the RNA-binding protein muscleblind-like 1 (MBNL1), suppressing metastasis formation.

Y-box binding protein 1 (YB-1) activates SNAIL transcription, promoting EMT and cell invasiveness in BC. This mechanism is also significant in pancreatic cancer and in resistance to gemcitabine. YB-1 additionally protects against oxidative stress by regulating NRF2, a transcription factor with antioxidant functions. Several inhibitors of YB-1 have been identified, including PI3K/mTOR inhibitors, which suppress YB-1 activity.[184]

3.6. Regulation of ncRNAs at the epitranscriptome level

RNA modifications, particularly m6A and m5C, are critical regulators of RNA structure, stability, and function.[27] The deposition of m6A induces structural changes in ncRNAs, altering ncRNA-protein interactions, regulating transcription, influencing subcellular localization, and stabilizing ncRNAs. Other RNA modifications include m7G and acetylation marks, such as m1A in MALAT1 and Ac4C on cytosine.[27,187,188] NAT10 is the enzyme responsible for the deposition of N4-acetylcytidine (Ac4C), a modification implicated in cancer.[189] NAT10 serves as a metastasis suppressor in CRC, acetylating RNA CTC-490G23.2, which binds to polypyrimidine tract-binding protein 1 (PTBP1) and increases alternative splicing of CD44 in esophageal squamous cell carcinoma. However, NAT10 may also act as a metastasis promoter and EMT inducer by stabilizing COL5A1 mRNA through direct binding.[190]

The N6-adenosine–methyltransferase complex catalytic subunit (METTL3) is an S-adenosylmethionine (SAM)-dependent enzyme. The methyltransferase complex, formed by METTL3 and METTL14 and associated with WTAP, methylates adenines, producing m6A-modified RNAs. Interestingly, METTL14 acts as a chromatin

regulator independent of its RNA m6A methyltransferase activity,[191,192] as it colocalizes with repressive H3K27me3 marks on chromatin. METTL14 binds to H3K27me3 and KDM6Brecruits facilitating H3K27me3 demethylation, a process essential for the transition from embryonic stem cells to differentiated cells.[193] Another methyltransferase complex (MTC) is formed by the association of RNA-binding motif protein 15 (RBM15), vir-like m6A methyltransferase-associated protein (VIRMA), zinc finger CCHC-type containing 4 (ZCCHC4), and zinc finger CCCH-type containing 13 (ZC3H13).[27]

Regarding internal m7G (N7-methylguanosine) writers, METTL1 forms a protein complex with WD repeat domain 4 (WDR4). This complex is active on tRNAs, rRNAs, mRNAs (enhancing mRNA translation), and miRNAs. The insulin-like growth factor 2 mRNA-binding protein (IGF2BP) family serves as readers of m6A modifications, regulating the stability of m6A-modified mRNAs. m6A influences RNA-driven phase separation by altering RNA–RNA and RNA–protein interactions. For example, the loading of m6A readers facilitates phase separation.[194] Notably, IGFBP2/3 act as m6A readers, binding ncRNAs and promoting the stability of m6A-modified mRNAs.[27] Other m6A readers include eukaryotic initiation factor (eIF3), proteins of the heterogeneous nuclear RNP (HNRNP) family, and YTHDF1 and YTHDF2, which contain the YT521-B homologous (YTH) domain.

The cytoplasmic protein YTHDF2 binds to m6A marks, either leading to degradation of m6A-modified RNAs by erasers or facilitating the localization and translation of bound mRNAs through interactions with translation initiation factors. In the nucleus, YTHDC1 regulates pre-mRNA splicing by recruiting splicing factors.

Demethylases such as fat mass- and obesity-associated protein (FTO) and alkylation repair AlkB homolog protein 5 (ALKBH5) remove m6A modifications. PSPC1, a regulatory subunit of ALKBH5, binds to K235-acetylated ALKBH5, enhancing its recognition of m6A-modified RNAs and promoting its erasing activity. Elevated K235 acetylation of ALKBH5 is observed in cancers and is linked to tumorigenesis.[132] Table 5 highlights the ncRNAs and circRNAs regulated by m6A-associated enzymes.

An internal N7-methylguanosine (m7G) modification in ncRNAs has been identified as a significant factor in resistant acute myeloid leukemia (AML).[188] However, limited information exists on m7G readers and erasers.

Each ncRNA possesses unique properties, with m6A modifications sometimes enhancing stability through interactions with m6A readers, while in other cases, they make ncRNAs susceptible to degradation through recognition by m6A erasers. This variability, coupled with cell type-specific interactions with m6A writers, readers, and erasers, contributes to differences in cancer susceptibility and progression. Different cancers exhibit distinct expression levels of m6A-modifying enzymes, further influencing cancer development and therapeutic outcomes.

Similar to ncRNAs, there is a dynamic crosstalk between circRNAs and m6A modifications. CircRNAs impact cancer response to chemotherapeutics through mechanisms such as modulating drug transport, DNA repair, apoptosis, the TME, autophagy, EMT, cancer stem cells, and glycolysis.[209]

4. Epitranscriptome regulation of ncRNAs and cancer therapeutics

Recent databases have compiled information on ncRNAs involved in epigenetic regulation.[207,208] A significant resource, curated by Yulia Medvedeva's laboratory at the Institute of Bioengineering, Russian Academy of Science, lists over 4,100 such ncRNAs and is accessible at https://github.com/lab-medvedeva/himorna-frontend. Similar to how amino acid charges and PTMs[209] confer new properties, epitranscriptomic modifications in ncRNAs influence interaction strength, base pairing, and RNA stability.

The METTL3 inhibitor STM2457 entered phase I clinical trials in 2022, demonstrating inhibition of proliferation in AML.[211] S-adenosylmethionine (SAM), an essential cofactor, is required for both DNMT1 (a DNA methylating enzyme) and METTL3.[212,213] METTL3A, a component of the m6A writer complex, is a key target in cancers with elevated m6A levels. METTL3 inhibitors, including STC-15, have been tested in clinical trials.[214]

Various epitranscriptomic modifications of ncRNAs affect RNA stability and function in cancer. Researchers have developed drugs targeting the writers, readers, and erasers of m6A modifications.[211-214,216] Promising anticancer effects have been reported for inhibitors targeting the METTL3–METTL14 methylation complex. These inhibitors exhibit diverse chemical structures, such as adenine derivatives, sinefungin, UZH derivatives, CDIBA derivatives, STM2457, and eltrombopag.[217] In addition, compounds such as mitoxantrone, suramin, KH3, and eltrombopag inhibit the RNA-binding domain of ELAVL/HuR, demonstrating antiangiogenic properties.[217] Notably, various METTL3 inhibitors entered phase 1 clinical trials for AML in 2022.[211,214,217] Researchers have explored two main approaches: developing m6A writer inhibitors[217] and allosterically activating m6A writing complexes. Drug compounds targeting METTL14, a transcriptional

Table 5. m6A modification: Role of ncRNA interactions with m6A writers, readers, and erasers

lncRNA	Interaction	Modified	Effect	References
FEZF1-AS1	IGF2BP1 sequestration	m6A	Apoptosis	195
DARS1-AS1	METTL3-METTL14	m6A	Proliferation	196
THOR	Readers YTHDF1 and YTHDF2	m6A	Oncogenesis	197
LNCAROD	METTL3-METTL14	m6A	Prevents YBX1 degradation	198
GAS5	Reader YTHDF3	m6A	GAS5 degradation	199
LINC021	IGF2BP2	m6A	MSX1 stability	200
LINC0047	METTL3	m6A	PTEN-m6A degradation	125
CASC11	ALKBH5	m6A	Decrease in m6A UBE2T	200
NEAT1_2	ALKBH5, YTHDF2	m6A	Destabilize mRNA	201,202
PVT1	Silencing ALKBH5	m6A	Decrease levels	58
LEAWBIH	YTHDC1	m6A	Recruits H3K9me2 demethylase KDM3B	203
MALAT1	The serine/arginine-rich splicing factor TRA2A forms a complex with writers METTL14, RBMX, KIAA1429	m6A	lncRNA m6A methylation	204
LINC00022	FTO	m6A	Block degradation by YTHDF2	205
DANCR	IGF2BP2	m6A	Stabilized DANCR	206
circARHGAP35/ circDLC1	METTL3, HNRNPL	m6A	Promotes its translation, producing an oncogenic protein	102
circDDIT4	METTL3-WTAP	m6A	Suppresses anoctamin (ANO7) binding to ELAVL1/HuR, reduces PC progression	189
circRBM33	METTL3/YTHDC1	m6A	RNA stability, abdominal aortic aneurysm	207
circ0049271	WTAP	m6A	IGF2BP3 binding, regulation of the TGF-b/ SMAD signal, and promotion of EMT in gastric cancer	208
circPTPRA, circNSUN, circ1662, circMEG3	WTAP writer complex, IGF2BP1 binding, recruitment of YTHDF3 and YTHDC1	m6A	Cytoplasmic export and formation of protein ternary complexes	209
circMARK2	METTL3	m6A	Cytoplasmic export, Lin28B stabilization, Wilms tumor progression	210

Note: An extensive database (http://www.xjtlu.edu.cn/biologicalsciences/m7ghub) is available as a tool to check RNA modifications.
Abbreviations: FTO: Fat mass and obesity; ALHB1: AlkB homolog protein 5; IGF2BP1: Insulin-like growth factor mRNA-binding protein 1; METTL3: Methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit; CircARHGAP35/CircDLC1: Rho GTPase activating protein 35 circular RNA; CircDDIT4: Damage inducible transcript 4 circular RNA; CircPPTRA; Protein tyrosine phosphatase receptor type A circular RNA; DARS1-AS1: Aspartyl-tRNA synthetase, antisense; FEZF1-AS: FEZ family zinc finger1, antisense; GAS5: Growth arrest specific 5; LNCAROD: LncRNA activating regulator of DKK1; DANCR: Differentiation antagonizing non-protein coding RNA; LEAWBIH: Long noncoding RNA epigenetically activating Wnt/β-catenin signaling in HCC.

activator, have also been identified.[191,215] New studies are investigating the role of m7G modification in cancer through METTL1 activity, with efficient inhibitors undergoing testing.[218]

Studies have also focused on inhibitors and activators of m6A readers. IGF2BP1 and IGF2BP2 inhibitors have shown antiproliferative effects.[219-222] For instance, SU056, an azopodophyllotoxin-derived small molecule, effectively inhibits IGF2BP2, promoting apoptosis and RNA degradation while reducing splicing pathways, with inhibitory effects in ovarian, lung, and breast cancers and AML.[219] Silencing the YTHDF1 m6A reader using vesicle-like nanoparticles encapsulating YTHDF1-siRNA enhanced immune responses and improved anti-PD-1 therapy outcomes *in vivo*.[223]

ONC213 suppressed mitochondrial respiration, elevated α-ketoglutarate by inhibiting α-ketoglutarate dehydrogenase (αKGDH), and exhibited potent antileukemia activity with minimal toxicity. ALK-04 is a selective ALKBH5 inhibitor.[220]

Several classes of FTO inhibitors have been developed to target m6A erasers,[224] including metal-chelating inhibitors, substrate-competitive inhibitors, and various

structural scaffolds.[225,226] Blocking FTO activity with inhibitors such as FB23 and FB23-2, developed by Huang *et al.*,[225] increased m6A levels and inhibited AML cell growth. These inhibitors, which bind to FTO and block its demethylase activity, hold promise as therapeutic agents for AML.

Inhibitors of the RNA-binding protein IGF2BP have shown significant potential as anticancer agents.[225] Recent advancements in small molecules targeting m6A regulators were reviewed by Feng *et al.* in 2024.[226] Novel compounds with high binding specificity and selectivity for m6A readers, including YTHFD1-YTHFD3 and YTHFC2, have been proposed for therapeutic applications in AML, owing to their antiproliferative effects.[227]

In tumors with low m6A levels, such as certain breast cancers, m6A erasers exhibit increased activity. In these cases, small molecule activators of m6A writers, such as METTL3, may be effective. Depending on the tumor type and ncRNAs involved, m6A writers may require either inhibition or activation using suitable drugs.

4.1. Epigenetic modifications, cancer, and clinical therapeutics

Phase separation properties in cellular processes depend on amino acids favoring this transition, with charges and influencing their behavior.[209] Lysine and arginine residues, found in both histones and other associated proteins, are primary targets of epigenetic modifications.

Several inhibitors targeting histone mark writers, readers, and erasers have been identified and tested in clinics trials. SET domain proteins, including lysine-specific demethylase 1 (LSD1) and the histone-lysine N-methyltransferase 2 family (MLL1-4SETD1A, SETD1B), are prominent targets.

Lysine methyltransferase (KMT) enzymes, such as EZH1 and EZH2, are integral to the PRC complex, relying on the catalytic SET domain. KMT activity, including that of NSD1, depends on S-adenosylmethionine (SAM) availability, which inversely correlates with nicotinamide-N-methyltransferase (NNMT) activity. NNMT produces 1-methyl nicotinamide, a methyl sink for SAM-derived methyl groups. FIDAS-5, a methionine-adenosyltransferase (MAT2A) inhibitor, has been shown to reduce tumor size in 5TGM1 murine cells. MAT2A inhibition by FIDAS-5 enhances the effects of bortezomib, a proteasome inhibitor, in MM.

EZH2 overexpression has been observed in lymphoma and other cancers. Tazemetostat, an EZH2 inhibitor, has been approved for treating epithelioid sarcoma.[227] Novel inhibitors have been designed to block EZH2 and histone-modifying enzymes.[229] Targeting EZH2 activity prevents histone methylation at chromatin sites, enhancing heterochromatin accessibility through inhibition of H3K27 methylation. Small sequences such as AC1NOD4Q and AC1Q3QWB have been developed to block EZH2's interaction with ncRNAs.[229] These peptides prevent the PRC2 complex from engaging ncRNAs and exerting histone methylation. Administration of AC1Q3QWB increases the antitumor activity of 3-deazaneplanocin (DZNep), an S-adenosyl homocysteine hydrolase inhibitor targeting histone methyltransferases (HMTs), including EZH2.[230] CC-90011, a reversible LSD1 inhibitor, has entered phase I human trials.[227] This dual approach targets histone methylation by inhibiting either histone methyltransferases like EZH2 in cases of hypomethylation or histone demethylases like LSD1 in cases of hypodemethylation. In addition, the interaction between lncRNAs and EZH2 has been identified as a promising therapeutic target in cutaneous melanoma.[73] METEOR-1, a phase I study of GSK3326595 (EPZ015938), a first-in-class protein arginine methyltransferase 5 (PRMT5) inhibitor, is underway in advanced solid tumors.[228]

Epigenetic and epitranscriptomic mechanisms significantly influence the levels of ncRNAs and circRNAs, which play critical roles in cancer progression. Consequently, these enzymes must be targeted using specific drugs.[231]

Numerous companies are actively developing novel small molecules targeting epigenetic enzymes. Well-known examples include HDAC inhibitors such as heliostat,[232] vorinostat,[233] amidepsine,[234] and panobinostat, which is approved for T-cell lymphoma treatment, as well as thioamide,[235] approved for treating leukemia and multiple myeloma.[236]

In blood malignancies such as AML,[237] effective treatments have been achieved using 5-azacitidine,[238] decitabine,[239] and guadecitabine, which target DNMTs. Similarly, inhibitors of m5C methylase, such as azacitidine, decitabine, and cytidine analogs, are approved therapies for blood tumors.

A recent study on long noncoding RNAs (lncRNAs) has provided insight into their roles in therapeutic resistance.[29] For example, APAF1-binding lncRNA (ABL) promotes proliferation and drug resistance in gastric cancer by inhibiting apoptosis and caspase activation. It achieves this by binding to APAF1 and preventing its interaction with cytochrome c. Encapsulated liposomal siRNAs targeting ABL have been shown to restore chemotherapy sensitivity. Another example is ARHGAP5-AS1, which facilitates m6A modification of ARHGAP5 mRNA, stabilizing it by recruiting the m6A writer METTL3 in the cytoplasm, thereby inducing chemoresistance in gastric cancer.

Drugs that inhibit enzymes involved in PTMs can disrupt condensate behavior and influence epitranscriptome modifications of RNA. These modifications include m6A, m6Am (dimethyladenosine), m1A, m5C, m7G, and ac4C, which are regulated by PTMs. The dependencies of transcriptomic modifications on PTM regulation are illustrated in Figure 3.[241] PTMs such as phosphorylation (targeted by kinase inhibitors), acetylation (targeted by HAT and HDAC inhibitors), ADP-ribosylation (targeted by PARP inhibitors), methylation (targeted by histone methyltransferase inhibitors), lactation, acylation (targeted by sirtuin inhibitors), 2-hydroxyisobutyrylation, citrullination, and ubiquitination can be targeted by drugs already approved for human therapeutics. The significance of these PTMs, particularly epitranslational modifications, has been comprehensively reviewed along with an updated list of inhibitors targeting m6A writers, readers, and erasers.[241] Understanding the mechanisms underlying drug resistance provides critical insights into optimizing drug efficacy in clinical settings.

4.2. Targeting ncRNAs to overcome resistance against drug inhibitors

The first phase of research focused on understanding the cooperative mechanisms between ncRNAs and antiapoptotic factors in tumor cells. In the laboratory, significant progress has been made through the application of oligonucleotide libraries, RNA silencing, antisense oligonucleotides (ASOs), short hairpin RNAs (shRNAs), and single guide RNAs (sgRNAs) for CRISPR/Cas technology.[242-245] CRISPR/Cas9-based gene editing has been particularly effective, enabling high-throughput

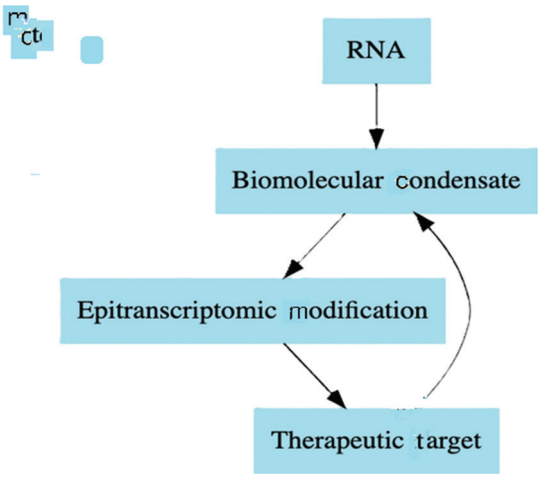


Figure 3. A schematic illustrating the involvement of PTM regulation of proteins and intrinsically disordered domain-containing proteins in the formation of LLPS, with a role for epitranscriptome modifications of RNAs in their stability and recognition by RNA-binding proteins. Image created by the authors

delivery of synthetic sgRNAs in conjunction with the Cas9 nuclease to target RNAs. Liu *et al.* compared chemical inhibitors of methylation enzymes with CRISPRoff/on methylation editing systems.[244] CRISPRoff is a relatively recent gene editing technology based on ZNF10 KRAB, Dnmt3A, and Dnmt3L domains, combined with catalytically inactive Cas9 (dCas9). This method allows researchers to manipulate the methylation landscape and alter gene expression without modifying the genome sequence. CRISPRon, on the other hand, facilitates the reversal of epigenetic changes induced by CRISPRoff by employing sgRNA-dCas9 complexes fused with DNA demethylases. Research using CRISPR technology, such as UCA1 knockout, has shown efficacy when combined with apoptosis regulation.[245]

Defective or dysregulated proteins can also be targeted using proteolysis targeting chimeras (PROTACs).[245-247] PROTACs enable protein knockdown with high efficiency at nanomolar concentrations. A few ncRNAs have been identified that contribute to chemoresistance and unresponsiveness to kinase inhibitors. For instance, some ncRNAs promote the oncogenicity of BRAF mutations and confer resistance to BRAF inhibitors (BRAFi) in melanoma cells. These ncRNAs, overexpressed in BRAFi-resistant cell lines, induce gain-of-function phenotypes.[248] Remarkably, BRAF-resistant cell lines respond well to PROTAC-based BRAF inhibition, offering advantages over conventional inhibitors.[249] In addition, small molecules have been identified that efficiently bind RNAs,[206] enabling the targeting of epigenetic alterations.

Several therapeutic approaches have been developed to inhibit ncRNAs in BCs. These include novel ribonuclease-targeting chimeras (RIBOTAC)[249,250] RNA therapeutics[251,252] that selectively regulate RNA-modifying enzymes, and targeting major SG proteins.

4.3. Targeting the mechanisms of therapy resistance by ncRNA knockdown

Gene silencing and knockdown methods are commonly used to inhibit ncRNAs. Antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) suppress the expression of target genes in a sequence-specific manner. Catalytic nucleic acids, such as ribozymes, also suppress transcripts by cleaving mRNAs and template RNAs.[251]

Oncogenic RNAs can be targeted through RNA silencing with ASOs as well as small molecules that interact with RNA-binding protein domains.[252-255]

Cancers are frequently associated with chromosomal instability (CIN). Various approaches are being employed to restore sensitivity to radiotherapy and chemotherapy by targeting the CIN pathway. One strategy is to accelerate CIN

pathways, generating less-fit karyotypes. In gastrointestinal cancers, the ncRNA colon cancer-associated transcript 2 (CCAT2) plays a role in an RNA–protein complex formed by WD40-containing protein block-of-proliferation 1 (BOP1) and aurora kinase B (AURKB). This complex disrupts chromosome segregation, causing chaotic cell division. The CCAT2–BOP1–AURKB network is linked to 5-fluorouracil and oxaliplatin resistance.[256] The presence of active AURK, functional BOP1, and highly expressed CCAT2 RNA is crucial for driving chaotic cell division in this context.

Targeting ncRNAs often aims to overcome chemotherapy resistance. Researchers have tested nanoparticle-mediated RNA interference to knock down ncRNAs using delivery systems such as nanoparticles, liposomes, and PEG-conjugated particles. In triple-negative breast cancer (TNBC), the role of DANCR ncRNA has been identified. Silencing DANCR with siRNA technology resulted in decreased proliferation and blocked tumor growth. Following DANCR downregulation, EZH2 activity was restored, silencing the promoters of CD44 and ABCG2.[257] Another strategy is to inhibit CIN and therapeutically address genetically frozen cancer cell populations. To provide oncologists with safe and cost-effective medications, establishing production lines capable of synthesizing large quantities of modified oligonucleotides is crucial.

The European Medicines Agency has issued guidelines on RNA-based medicines,[258] highlighting advances in chemical modifications of ASOs, sequence engineering, and tumor-specific delivery methods.[259] In 2022, Benhamou designed an oncogenic noncoding RNA inhibitor by selecting optimal sequences from an RNA library and comparing them with a DNA library.[259] This pioneering work has laid the groundwork for developing efficient ncRNA-targeting drugs.

Patents have already been filed for targeting miR-22 in cancer and metabolism. ASO-based drugs are being developed for therapeutic applications. Examples include oligonucleotides antisense to protein-coding genes (e.g., BCL-2, VEGF, AP1) and antagomiRs targeting small RNAs, such as anti-miR-155 for cutaneous T-cell lymphomas and anti-miR-122. Miravirsen has demonstrated efficacy in primates for liver diseases, and other oligonucleotides function as miRNA mimics.

Efforts to standardize RNA-based therapeutics and address technical challenges have been optimized to preserve bioactivity from production to delivery. Nucleic acid-based drugs and delivery systems are now mature enough for industrial production, ensuring safe and efficient delivery to patients.

4.4. Targeting the interaction between BC components and the role of PTM

This section highlights how mutations in cancer gene fusions affect phase separation properties, potentially driving cancer initiation and progression. Insights into this mechanism can inform therapy design for cancers associated with aberrant phase separation. A central player in this process is the speckle-type POZ (Poxvirus and Zinc finger) protein (SPOP), which serves as a substrate adaptor for cullin 3 RING E3 ubiquitin ligase. SPOP facilitates the ubiquitination and proteasomal degradation of oncogenic proteins, exerting anti-proliferative effects. Localized in nuclear speckles, SPOP oligomerization and substrate interaction induce the formation of nuclear phase-separated droplets, known as SPOP droplets. These droplets facilitate the ubiquitination of substrates like DAXX (death domain-associated protein), marking them for proteasomal turnover. Studies have shown that the co-expression of DAXX with SPOP forms condensates enriched in SPOP/DAXX, facilitating DAXX ubiquitination and subsequent degradation.[260] Cancer-associated SPOP mutations disrupt the recruitment of DAXX and prevent the nucleation of SPOP/DAXX condensates, stabilizing DAXX instead. DAXX, in turn, promotes tumor development by repressing p53 activity. Its cytoplasmic and nuclear accumulation contributes to malignancy.[260]

Genetic systems can be leveraged to deliver proteins capable of dissolving p53 aggregates, potentially through mechanisms involving DAXX degradation, or to develop crosslinked mimic condensates for selective drug delivery. Synthetic peptides and nucleic acid-based oligonucleotides (e.g., RNA mimics, RNA sponges, siRNAs, and ASOs) hold promise for targeting mutant phenotypes. Investigating the dynamics of mutant p53 can enhance our understanding of protein misfolding and aggregation mechanisms. Novel drugs targeting abnormal phase transitions and p53 aggregation may have significant potential for clinical oncology applications.[11] Inhibition of mutant p53 aggregation by small molecules could effectively block tumor proliferation and migration.

Certain chemotherapeutics preferentially accumulate in specific BCs due to interactions linked to the drug's affinity for its target. For instance, cisplatin tends to accumulate in transcriptional condensates, whereas tamoxifen localizes in ER-alpha condensates. Estrogen-induced mediator (MED) activity dilutes transcriptional condensates, along with tamoxifen concentrations in these BCs. Interestingly, some therapeutics selectively interfere with condensates, presenting opportunities to regulate compartments critical for disease development.

Emerging evidence highlights the interplay between ncRNAs and epigenetic enzymes, particularly through

established and validated epigenetic drugs. Concurrently, small molecules targeting RNAs and their interacting partners are being explored for applications in RNA therapeutics.

Drugs that inhibit enzymes involved in PTMs can influence condensate behavior and modify oncogenic activities localized in these condensates. Alterations in the charges of residues within protein–protein interaction domains can impact proteins with IDR or prion-like domains ability to form BCs and undergo LLPS.

While chemotherapies aim to induce cancer cell death, certain drugs (e.g., bortezomib, sorafenib, 5-fluorouracil (5-FU), lapatinib, morusin, 5-azacytidine, 6-thioguanine, cisplatin, oxaliplatin, doxorubicin, and sodium selenite) paradoxically enhance cancer cell survival by promoting SG formation. For instance, K-RAS-dependent tumors upregulate SG formation.[261] Targeting or reducing SGs and their functions may yield therapeutic benefits. A notable PTM affecting condensate formation is myristoylation. In lung cancer cells, EZH2 myristoylation induces phase-separated liquid droplets containing EZH2, leading to compartmentalization, activation of STAT3, and enhanced cell proliferation.[262,263] Inhibiting myristoylation may potentially suppress cell growth. The subsequent section will discuss approaches for SG inhibition and specific cases of oncogenic protein chimeras impacting BCs in cancer.

4.5. Targeting the interaction between intrinsically disordered proteins and their partners

Proteins essential for BC formation, such as G3BP1, which assembles SGs, are promising targets for interfering with stress responses in cancer.[168,176] Key residues like V11 in G3BP are necessary for the formation of the G3BP–Caprin-1 complex; mutations at these sites block SG assembly. This opens the possibility for small compounds targeting protein interactions and specific G3BP domains to disrupt SG and BC formation or stability.[176,264] Small molecule interactors of SG proteins have shown potential in addressing cancer resistance to environmental stresses.[264,265]

SG inhibitory peptides (SIPs), derived from Caprin1 and USP10, have been fused with cell-penetrating peptides to create cancer inhibitors such as TAT-SIP-C1/2 and SIP-U1-Antp. These SIPs disrupt SGs[265] and enhance the sensitivity of cancer cells to sorafenib.

Inhibitors based on small compounds targeting the disordered regions of proteins have shown promise, with some progressing to clinical trials or therapeutic approval. For example, AC1Q3QWB selectively disrupts HOTAIR-mediated PRC2 recruitment, preventing silencing of gene promoters.[206]

In pancreatic cancer, the inhibitor ZW-115 targets the stress-inducible nuclear protein 1 (NUPR1), an intrinsically disordered protein, triggering apoptosis in PDAC cells that depend on K-RAS expression.[259,260]

The androgen receptor (AR), involved in nuclear condensates, has transiently stable secondary structures that are targeted by small molecules. Antiandrogens and abiraterone used in androgen-deprivation therapy induce the expression of constitutively active AR splice variants (AR-Vs), which promote resistance to radiotherapy by aiding DDR. Small molecules such as EPI-001 (ralaniten) selectively bind to the transactivation domain of AR, forming a binding pocket that blocks AR-DNA interaction. Other molecules like ETI-516 and EPI-7170 (a derivative of EPI-001) also block AR transcriptional activity and condensate formation in prostate cancer. EPI-7170 is currently in clinical trials (NCT04421222).[266] The ReACp53 peptide (patent WO2014182961A1) inhibits p53 amyloid-like aggregation, effectively targeting high-grade serous ovarian carcinomas (HGSOC).[267] BAY 249716 stabilizes both wild-type p53 and its mutants (R175H and Y220C),[11,268] while ADH-6 rescues mutant p53 activity. The aminothiazole compound BAY 1892005 covalently binds to mutant p53 variants (e.g., R175H, R282W, and Y220C) and dissolves nuclear condensates. In addition, PRIMA-1 reactivates mutated p53, inducing apoptosis under normoxic and hypoxic conditions, whereas nutlin-3 inhibits the MDM2-p53 interaction, increasing p53 stability and longevity.

Small molecule ligands have been screened from libraries of backbone-modified compounds for their RNA-binding capabilities. For example, diphenylfuran (DPF) compounds targeting MALAT1 bind to its triple helix, inducing RNA degradation.[269]

Small molecules targeting RNAs are under development with promising therapeutic applications. In alignment with the experimental work by Kovachka,[253] Meyer *et al.*[270] described receptor tyrosine kinase inhibitors (RTKis). RTKis can serve as RNA binders and can be reprogrammed and repurposed, given that they are FDA-approved drugs. For instance, the RTKi dovitinib inhibited the biogenesis of oncogenic miR-21 through direct interaction,[270] paving the way for designing small molecule RNA inhibitors to minimize off-target effects. Recently, the FDA approved a small molecule capable of interacting with the U1 snRNP complex of the splicing machinery. Risdiplam, tested in clinical trials for both infantile and later-onset spinal muscular atrophy (SMA), is now an orally administered drug for SMA treatment.[271] Furthermore, small molecules targeting RNA G-quadruplexes have been explored for the downregulation of K-RAS and N-RAS mRNAs and

are under development for addressing the GGGGCC repeat expansion in C9orf72, a mutation linked to ALS and frontotemporal dementia. For instance, DB1273 promotes G-quadruplex formation, reducing RNA foci and dipeptide translation in a Drosophila model of the neurological disease derived from all three independent C9orf72 repeat expansion iPSC lines and Drosophila with adult-onset ubiquitous expression of 36 G4C2 repeats which causes neurodegeneration due to arginine-rich proteins.[271] Recent work by Xiao *et al.* reviewed machine learning approaches for studying small molecules targeting RNAs and provided a list of FDA-approved drugs based on oligonucleotide technology. Their work highlighted the potential of machine learning in identifying RNA structures and prospective structural targets for small molecules.[272] Moreover, Kim and Kim reviewed the current understanding of RNAs, including circRNAs, and the therapeutic frontiers in targeting regulatory RNAs.[273]

In cell-specific pathways and responses, such as chromatin foci formation, transcription activation, and DNA damage response, BC formation is essential and depends on liquid–gel phase separation. These MLOs can be targeted by small molecules that block protein domains. One such BC target is the nuclear speckle, demonstrated by the use of diphenylfuran to target MALAT1.

Regarding the relationship between BCs and cancer, notable work has been conducted on the splicing factor ZMAT2. This protein contains two disordered regions critical for the formation of spliceosome complex condensates and regulates the expression of the tripartite motif protein 28 (TRIM28),[274,275] also known as Krüppel-Associated Box (KRAB)-Associated Protein 1 (KAP1). TRIM28 is a SUMOylation and RING-type ubiquitin-E3 ligase involved in the degradation of programmed cell death ligand 1 (PD-L1), thereby modulating immunosuppression in cancers. Targeting immune checkpoints has become a focus in cancer therapy. Verteporfin, for example, inhibits PD-L1 expression through Golgi-related autophagy mechanisms, interfering with the interaction of TRIM28 with interferon regulatory factor 1 and blocking PD-L1 induction. ZMAT2 also has RNA-binding activity and promotes phase transition, playing a role in the maturation of TRIM28 mRNA during the formation of protein-nucleic acid condensates. By upregulating TRIM28, this process reduces ROS accumulation in HCC and supports cell proliferation. Finally, SGs, as previously discussed, contribute to cancer cells' resistance to chemotherapy.

Pharmacological inhibition of DDX3 has been shown to attenuate SG assembly.[173] Consequently, small compounds targeting protein interactions and specific G3BP domains could be used in combination with novel drugs and small molecule interactors of SG proteins[264,265] to modulate SG stability.[176,265] This strategy could help overcome cancer resistance to environmental stress and chemotherapy. The eIF2α phosphorylation-induced SG assembly occurs during chemotherapy and involves various serine/threonine protein kinases, including GCN2, HRI, PKR, and PERK. Natural compounds such as psammaplysin F[276] reduce phosphorylated eIF2α levels, while cannabidiol attenuates the formation of SGs and BCs in glioblastoma. Similarly, medium-chain fatty acids, such as lauric acid, lipoic acid, and their amides,[277] show inhibitory effects. Notably, lipoamide has been demonstrated to inhibit SGs.[277]

Lipoamide reduces the formation of cytoplasmic FUS-linked SGs induced by arsenate and mitigates SG formation triggered by mitochondrial electron transport chain inhibition and hyperosmotic stress. However, it does not affect SGs formed in response to heat shock or glycolysis inhibition. This suggests that lipoamide functions as either an antioxidant or an inhibitor of specific BC forms. Importantly, lipoamide selectively inhibits SGs without affecting other BCs, such as Cajal bodies, nucleoli, and DNA damage foci.[277]

BCs can be targeted through three primary mechanisms. The first involves targeting the driver components, i.e., proteins and nucleic acids, to downregulate or inactivate them. The second focuses on disrupting physicochemical interactions essential for BC formation involving proteins and nucleic acids. The third strategy involves stabilizing or destabilizing condensates using drugs that partition into a BC, thereby modulating its activity.[13] Table 6 provides a summary of the inhibitors discussed in this section (Table 6).

Arsenic compounds, such as sodium arsenite, play a role in oxidative stress-induced SG formation, in which DDX3 acetylation is involved.[278] Arsenic trioxide (ATO), a highly toxic compound, has been used to induce PML-RARα degradation and inhibit PML nuclear bodies, particularly in PML-RARα translocation. Arsenite and ATO exhibit a dual role in paraspeckle formation, depending on the dose and duration of application. ATO promotes the formation of speckles and processing bodies by inducing spliceosome activity, induces SGs, and inhibits PML bodies by degrading PML-RARα. Trisenox was approved in 2002 as a drug for the treatment of multiple myeloma (MM). In 2004, the FDA approved its use for hepatocellular carcinoma therapy, and in 2018, the combination of Trisenox/Tretinoin was also approved. In addition, a phase II clinical trial in patients with refractory peripheral T-cell lymphoma (rPTCL) demonstrated the antitumor activity of darinaparsin, an organic arsenical compound comprising dimethylated arsenic conjugated to glutathione.[278]

Table 6. Molecules acting on intrinsically disordered proteins and biomolecular condensates (BCs)

Compound	Target	Application	References
AC1Q3QWB	HOTAIR-EZH2 binding	Various cancers, BC favors euchromatin	206
RK33 inhibits ATPase 16D inhibits helicase	DDX3, resulting in the block of SGs assembly	CRC, head/neck cancer, PC, brain cancer, drug resistance	173
G3BP inhibitor G3Ia nSP3 peptide	Block the interaction of G3BP with caprin 1 and USP10 and dissolves the preformed SG	VCP multisystem proteinopathy	168,176
ZW-115	Stress-inducible NUPR1	Induces apoptosis, K-RAS tumors, PDAC	259,260
TAT-SIP-C1/2, TAT-SIP-U1-Antp	Inhibitory peptides (SIPs) derived from Caprin 1 and USP10	Induce sensitivity to sorafenib	265
Ralaniten, EPI-7170	Blocks AR binding to DNA	Prostate cancer, androgen resistant	266
ReACp53 peptides	Bind p53 intrinsically disordered region	High-grade serous ovarian carcinoma	267
Aminothiazole BAY 249716, BAY 1892005	Stabilize p53 variants R175H, R282W and Y220C	Dissolution of the nuclear condensates	11,268
PRIMA-1, ADH-6	Reactivates mutated p53	Induce apoptosis in normoxia and hypoxia	268
Nutlin-3 p	Prevents the MDM2-p53 interaction	Increases the p53 shelf-life	268
Dyphenylfurans (DPF)	Triple helix containing MALAT1	Degradation of MALAT1 in overexpressing cancers	269
Dovitinib	Multiple RTK inhibitors	Blocks miR-21 biogenesis	270
Small molecule DB1273	RNA G-quadruplexes targets	K-RAS and N-RAS-bearing cancer	271
Verteporfin	Blocks TRIM28 interaction with IRF1	Inhibits IRF-induced PD-L1 expression and Golgi-related autophagy mechanisms	274,275
Psammaplysin F	Decreases the levels of phosphorylated eIF2α, inhibits SG formation after eIF2 phosphorylation	Improves chemotherapy, increases the efficacy of bortezomib sorafenib	276
Cannabidiol, lipoamide	Attenuates the formation of SGs and BCs	GBM; reduce FUS-linked stress granules induced by arsenate	277,278
Trisenox/Tretinoin	Inhibit PML bodies	Induce PML-RARa degradation HCC, MM	278,281
VTP50469	Disrupts the interactions between the NUP98 fusion proteins and chromatin	Therapy for NUP98-rearranged leukemia	282
Emodin, MLN4924, and TSA	Increase the levels of PML protein	Restore PML body activity	282
MLN4924	NEDDylation inhibitor	Suppresses APL	282
SU056, fisetin, CX-5461	Y-box-binding protein 1 (YB1)	CRC, melanoma, block invasiveness in BC	184
PI3K/mTOR dual inhibitors: GSK1059615, CAY10626, samotolisib, 4Torin 1, PP242, PI-103, LY3023414, INK128	Inhibit NEAT1_2 and paraspeckle	CLL therapy	96
Dual PI3K/TOR inhibitor BEZ235	Inhibit YB-1 expression	Favors radiotherapy cytotoxicity in CRC, blocks EMT, and invasiveness in melanoma	184
YK-4-279	Targets the IDR of EWS-FLI1	Ewing sarcoma tumors	280,281
SHP2 inhibitors AB-3068, TNO155, RMC-4630, and RLY-1971	Therapy of SHP2 mutations inducing BC formation and promoting MAPK signaling, leading to ERK1/2 activation	Trials in solid cancers	282
Elvitegravir	Disrupts SRC-1 condensates, P bodies, YAP/TEAD/SRC-1 BCs	Suppresses the growth of YAP-dependent tumors, favors anti-PD-1 immunotherapy	282

(Cont'd...)

Table 6. ***(Continued)***

Compound	Target	Application	References
Reserpine	Induce cell death through BAX and MST-1 upregulation and downregulation of Bcl2, LATS-1, and YAP	Antiproliferative effects on MDA-MB-231	283
pH-responsive hexapeptide (VEALYL)	Swelling of lysosomes	Chemotherapy of MDR-overexpressing tumors	284
Actinomycin D (ActD), etoposide, flavopiridol	Inhibit paraspeckles	Reduction in size	285
AKT inhibitor TAS0612, everolimus	Inhibits YB-1 phosphorylation	Reverse resistance to tamoxifen in BC	287
2,4-dihydroxy-5-pyrimidinyl imidothiocarbomate, 6-O-angeloylplenolin sesquiterpene lactone	Block YB-1 translocation to the nuclei	YB-1 cannot induce target genes, blocking BC growth	287
MG132 proteasome inhibitor	Activates GCN2 for the hyperphosphorylation of eIF2-alpha	Cells defective in UPR, B-cell lymphoma, leukemias; hyper phosphorylated eIF2a increases bortezomib anticancer activity through eradication of quiescent cancer cells	288
ISRIB peptide		Pulmonary veno-occlusive disease, Fragile X syndrome, neurodegenerative diseases, diseases involving SG formation	289,290
FYVE finger-containing phosphoinositide kinase) modulator plus an integrated stress response antagonist	Induce a MiT/TFE transcription factor promoting lysosomal gene translation	Improve glucocerebrosidase function in Gaucher patient-derived fibroblasts	291

Abbreviations: CLL: Chronic lymphocytic leukemia; PDAC: Pancreatic ductal adenocarcinoma; PML: Promyelocytic leukemia protein; GBM: Glioblastoma multiforme.

Pancreatic cancer cells have been shown to be sensitive to 1,6-hexanediol, an LLPS inhibitor that also modulates kinase and phosphatase activities. Experimentally applied to cell cultures, 1,6-hexanediol reduced pancreatic cancer growth in an orthotopic BxPC-3 xenograft model using the BXPC-3 human pancreatic adenocarcinoma cell line. This compound inhibits the stability of SGs and disrupts weak intermolecular hydrophobic interactions, likely through alterations in hydrogen bonding. Transcriptional studies revealed that 1,6-hexanediol downregulates *myc* expression as well as other genes involved in key signaling pathways, including cytokine-cytokine receptor interactions, Wnt signaling pathway, extracellular matrix-integrin/cadherin receptor interactions, mitogen-activated protein kinase (MAPK) signaling, and focal adhesion pathways.[277]

Therapeutic approaches aimed at modifying cancer phenotypes (proliferation, invasiveness, and chemotherapy unresponsiveness) are collectively referred to as condensate-modifying therapeutics (c-mods). The targets of c-mods include the regulation of physical properties, macromolecular networks, composition, dynamics, and functions of specific BCs.[280]

Several oncogenes are influenced by ncRNA regulation, making these ncRNAs potential targets for small molecules that inhibit their activity. For instance, the ncRNA MTAR1 recruits IGF2BPs into condensates, promoting their interaction with PABP1 and enhancing the stability and translation of *myc* Mrna.[241] Similarly, MNX1-AS1, which is upregulated in NSCLC, facilitates MYC-mediated transcriptional activation. MNX1-AS1 induces IGF2BP1 phase separation, thereby increasing its interaction with the mRNAs *E2F1* and *myc*, both of which encode oncogenic transcription factors and promote NSCLC cell proliferation.[241] Since the MYC signaling pathway is oncogenic, it can serve as a key target for therapeutic strategies.

The PML nuclear body, a BC formed through LLPS, is relevant in leukemias where mutations in *PML* render patients resistant to arsenic-targeted therapy.[281]

The induction of LLPS by NUP98 fusion oncoproteins (FOs) is implicated in leukemia. Nearly 30 NUP98-FOs have been identified, associated with 5% of pediatric acute myeloid leukemia (pAML) cases and 50% of chemotherapy-resistant pAML cases.[281] Strategies to counteract the oncogenic activity of NUP98-FOs depend on the specific fusion protein involved. These strategies may include targeting transcriptional and epigenetic machinery (e.g., HDAC inhibitors), addressing alterations in cooperating partners, or disrupting signaling and cell cycle pathways. For instance, VTP50469 disrupts interactions between NUP98 fusion proteins and chromatin in

NUP98-rearranged leukemia models.[282] To restore PML body activity, molecules such as emodin, MLN4924, and TSA increase PML protein levels. MLN4924, an inhibitor of neddylation, has been shown to suppress APL development. Synthetic protein disaggregates, such as modified Hsp104 variants, can disaggregate condensates formed by the EWS-FLI and FUS-CHOP fusion proteins.[282]

YB-1 represents another promising therapeutic target, as it is involved in both P bodies and SGs. Various approaches have demonstrated positive impacts on YB-1 inhibition. TOR kinase inhibitors, such as rapamycin, also inhibit PI3K: PI3K/TOR inhibitors and suppress NEAT1_2 and paraspeckles. The dual PI3K/TOR inhibitor BEZ235 reduces YB-1 expression, inhibits cancer growth, and enhances the cytotoxicity of radiotherapy in CRC.[184] In addition, the AKT inhibitor TAS0612, which acts on p70S6K and p90RSK, inhibits YB-1 phosphorylation and reverses antiestrogen resistance in BC. SU056 (azopodophyllotoxin) directly binds to YB-1. Fisetin, a small molecule, inhibits the AKT–YB-1 interaction, thereby preventing cancer migration in prostate tumors. It also reduces melanoma tumor growth *in vivo* through a dual mechanism: inhibition of RSK kinase activity and reduction of YB-1 protein levels. Fisetin forms a complex with RSK2, which then binds to YB-1. Furthermore, CX-5461 inhibits RNA polymerase I and blocks YB-1 activity. The compound 2,4-dihydroxy-5-pyrimidinyl imidothiocarbomate (DPI) prevents YB-1 nuclear translocation, downregulates target gene expression, and inhibits BC growth. Similarly, the sesquiterpene lactone 6-O-angeloylplenolin blocks YB-1 nuclear translocation and downregulates the expression of the multidrug efflux pump MDR1 in colon cancer.

LLPS plays a crucial role in the transcriptional programs regulated by Yes-associated protein (YAP) and the transcriptional coactivator with PDZ-binding motif (TAZ), both key components and regulators of Hippo signaling. The complex formed by YAP/TAZ promotes P body formation in various cancer cell lines. P bodies act as downstream effectors of YAP/TAZ. The interaction between YAP/TEAD and steroid receptor coactivator 1 (SRC-1) is critical for the formation of SRC-1/YAP/TEAD condensates, which promote YAP transcription. Interestingly, the anti-HIV drug elvitegravir disrupts SRC-1 condensates and suppresses the growth of YAP-dependent tumors.[282]

YAP condensates are associated with resistance to anti-PD-1 immunotherapy. These BCs concentrate epigenetic enzymes such as histone acetylase, making drugs targeting these enzymes potentially beneficial when combined with existing therapies.

The methanolic extract (RTE) from *Rauvolfia tetraphylla* and its isolated compound, reserpine, exhibit antiproliferative effects on the TNBC cell line MDA-MB-231. Reserpine-treated cells cease proliferation and undergo apoptosis through the upregulation of BAX and MST-1 and the downregulation of Bcl2, LATS-1, and YAP. Consequently, YAP levels decline, the TEAD-YAP complex fails to form, and cell growth is inhibited.[283]

The transcriptional coactivators YAP and TAZ, which interact with PDZ-binding domains, serve as downstream effectors of the Hippo kinase cascade. YAP/TAZ plays significant roles in cell growth, differentiation, tissue development, and carcinogenesis. Recent studies reveal that in addition to the Hippo kinase cascade, several non-Hippo kinases regulate YAP/TAZ signaling, influencing tumorigenesis and progression. YAP/TAZ oncogenes also promote P body formation across various cancer cell lines. Mechanistically, this involves the transcriptional activation of P body-related genes (e.g., SAMD4A, AJUBA, and WTIP) and the suppression of the tumor suppressor gene PNRC1. Re-expression of PNRC1 or knockdown of P body core genes (e.g., DDX6, DCP1A, and LSM14A) demonstrates that P bodies attenuate cell proliferation, migration, and tumor growth induced by YAP overexpression in CRC. Since P bodies act as downstream effectors of YAP/TAZ, re-expressing PNRC1 or disrupting P bodies may serve as potential therapeutic strategies for YAP-driven tumors.

An additional treatment avenue involves targeting cancers with deregulated phase transitions caused by IDRs. For example, YK-4-279 targets the IDR of phase-separating EWS-FLI1 and blocks its interaction with RNA helicase A in Ewing sarcoma tumors.[280-282] Wild-type SHP2 (protein tyrosine phosphatase non-receptor type 11) forms BCs in response to factors such as EGF and FGF. Mutations in SHP2 that promote BC formation drive MAPK signaling, leading to ERK1/2 activation. Several SHP2 allosteric inhibitors, including AB-3068, TNO155, RMC-4630, and RLY-1971, are under clinical evaluation for solid cancers.[282]

Advancements in permeable peptide and material design have also shown promise in LLPS regulation.[284] An aromatic motif-based pH-responsive hexapeptide (VEALYL), referred to as the lysosome-targeting peptide, was derived from the insulin sequence. Cancer cells internalize this peptide through endocytosis, triggering proton-induced phase separation within lysosomes, transitioning from solution to hydrogel. This hydrogelation increases lysosomal volume and permeability, causing lysosomal rupture and subsequent cancer cell death. Lysosomal assemblies have been shown to enhance the efficacy of chemotherapy against multidrug-resistant cells in xenografted tumors.[284]

Paraspeckle disintegration has been achieved using DNA intercalators. Actinomycin D (ActD) binds to the DNA minor groove, promoting paraspeckle disassembly and resulting in smaller condensates. While ActD administration reduces the size of NEAT1_2 speckles, it does not alter their number. Meanwhile, core paraspeckle proteins SFPQ and NONO remain localized to the perinucleolar caps.

Because DNA-binding molecules can induce double-strand breaks, it has been demonstrated that paraspeckle disintegration is not linked to DNA damage or RNA polymerase inhibition. An increase in smaller NEAT1_2 paraspeckles was observed following treatment with etoposide, a topoisomerase II inhibitor, and flavopiridol, an inhibitor of cyclin-dependent kinases. In contrast, the microtubule inhibitor vincristine had no effect, as it does not bind to dsDNA.[285]

The structural basis of double-stranded DNA helix binding underpins the assembly and maintenance of paraspeckles, speckles, and other nuclear ncRNA-based condensates. This insight opens new avenues for studying the mechanisms of drugs such as etoposide, actinomycin D, and mithramycin A, which are widely used in osteosarcoma treatment. Targeting P bodies also holds potential for cancer therapy. A recent review discussed the therapeutic implications of modulating P body formation.[184,286,287]

Hyperphosphorylation of eIF2a enhances the anticancer activity of bortezomib by eradicating quiescent cancer cells and inhibiting their survival. Under ER stress, the transmembrane protein kinase/endoribonuclease inositol-requiring enzyme 1 (IRE1) is activated, clustering into ER membrane-bound condensates associated with SGs. IRE1α clusters tether SGs to the ER in response to various stressors. This clustering facilitates the splicing of XBP1 mRNA to produce the XBP1 isoform 2, which is involved in the unfolded protein response.[288] Diseases linked to XBP1 dysfunction include bipolar disorders, B-cell lymphomas, and leukemias. XBP1 is frequently overexpressed in BCs and metastatic malignancies. MG132, a proteasome inhibitor, has been shown to activate GCN2.

The integrated stress response (ISR) inhibitor, ISRIB (M7425, AbMole, Huston, USA), is a selective small molecule inhibitor of eukaryotic translation initiation factor 2-alpha kinase 3, also known as protein kinase R (PKR)-like ER kinase (PERK) signaling. ISRIB effectively reverses eIF2α phosphorylation and disassembles SGs. When administered to be stressed cells with preformed SGs, ISRIB induces their rapid disassembly, releasing mRNAs into the RNA pool for active translation. ISRIB reverses the translational inhibition caused by stress and eIF2α phosphorylation. ISRIB prevents SG formation induced by eIF2α phosphorylation, ER stress from unfolded protein retention, thapsigargin, and arsenite (an SG inducer).

Notably, P bodies remain functional and unaffected by ISRIB treatment or stressors. ISRIB increases the activity of eIF2B, eIF5, and other initiation factors by directly or indirectly reversing the effects of phosphorylated eIF2α. It acts as a molecular glue, linking eIF2B tetramers to decameric active enzymes.

A hollow nanoparticle-based delivery system was developed for ISRIB. PEGylated copper sulfide nanoparticles (HCuS NPs) encapsulating ISRIB, combined with phase-change material lauric acid (LA), were used in photothermal therapy (PTT). This light-controlled ISRIB release inhibited SG formation during PTT, enhancing the antitumor effect and inducing immunogenic cell death (ICD).[289] In addition, a pH-driven and NIR photo-responsive smart drug delivery system (IL@H-PP) promoted the production of ROS by tumor-associated macrophages (TAMs). TAMs were repolarized toward an M1 phenotype, remodeling the tumor microenvironment from immunosuppressive to immunity-competent. ISRIB has demonstrated therapeutic potential beyond cancer treatment. It has shown promise in addressing pulmonary veno-occlusive disease, Fragile X syndrome, neurodegenerative disorders associated with SG formation, eIF2α phosphorylation, and cognitive impairment.[289,290]

Inhibition of the ISR has also been explored for the treatment of diseases beyond cancer. In lysosomal storage disorders, two compounds (patent U.S. Ser. No. 63/675,391) have been found to enhance glucocerebrosidase function in Gaucher patient-derived fibroblasts through an MiT/TFE transcription factor that promotes lysosomal gene translation. An ISR antagonist was combined with a PIKfyve (FYVE finger-containing phosphoinositide kinase) modulator to improve cellular glucocerebrosidase activity. This combination likely succeeded because ISR signaling appears to be slightly activated by treatment with either of these small molecules individually.[291]

5. Application of emerging technologies in BC studies

The potential of RNA to adopt diverse structures within or outside condensates can be utilized for innovative therapeutic purposes. This includes enzymatic RNA molecules, known as ribozymes, exhibiting activity exclusively within condensates. These structures influence RNA–RNA interactions, affecting the material properties of RNA-seeded condensates and impacting RNA sorting during the development of phase-separated assemblies. Analyzing RNA structures in dense phases and the supramolecular formations within them poses significant

challenges, resulting in limited data on RNA structure within BCs. A key obstacle is isolating this specific RNA quantitatively. A recently reported needle-shearing method has proven effective for RNA extraction in this context. RNA structural biology is crucial for advancing knowledge, with cryo-EM SPA revealing protein-free RNA structures. RNA structure determination using cryo-EM methods provides useful information, including resolving maps of RNA-based systems. These data can offer subnanometer resolution and coordinate estimation, especially when combined with multidimensional chemical mapping and computational modeling, such as with Rosetta DRRAFTER. The "Ribosolve" pipeline aids in validating macromolecular complexes.[292] Applying this workflow to ncRNA modules may uncover new structural elements.

Super-resolution microscopy, based on various techniques, produces images with a resolution surpassing the diffraction limit, achieving the 30-nm range. A series of fluorophores, acting in complementary absorbance zones and emitting light at separate times and wavelengths, enables resolving images over time. Among these methods are super-resolution optical fluctuation imaging and single-molecule localization methods (SMLM). Examples of applications include imaging cell nuclei and mitotic stages. Stimulated emission depletion microscopy (STED), a frontline method in recent years, uses two laser pulses: an excitation pulse to excite fluorophores and a STED pulse for de-excitation through stimulated emission. Spectral precision distance microscopy resolves multiple light sources by isolating a few at a time. Cryogenic optical localization in 3D (COLD) localizes fluorescent sites within small- to medium-sized biomolecules at near-Angstrom resolution. Binding-activated localization microscopy is a potential approach for SMLM. Stochastic optical reconstruction microscopy, another frontline method, is similar to photo-activated localization microscopy (PALM) and fluorescence photo-activation localization microscopy, which exploit sequential activation and time-resolved localization of photoswitchable fluorophores to produce high-resolution images. PALM of mEos3.2 fluorescent protein tags combined with DNA-PAINT revealed BC organization and patterns in a cell cycle–dependent manner. Spectrally resolved SMLM (SR-SMLM) combined with an environment-sensitive dye for displacement/diffusivity mapping (SMdM) analyzed distinct hydrophobic nanodomains at the condensate surface.[293-296] Xia, Doudna, and colleagues[290] developed single-molecule live-cell fluorescence *in situ* hybridization (smLiveFISH), employing a programmable RNA-guided CRISPR–Csm complex with catalytically inactivated Csm for specific and durable RNA binding.[297] Using smLiveFISH, they visualized single NOTCH2 and MAP1B mRNA transcripts in living cells, identifying mechanisms such as cotranslational translocation of NOTCH2 mRNA at the ER and MAP1B mRNA transfer to the cell periphery. These technologies provide insights into mRNA mislocalization and BC dysregulation in diseases and cancer.[15] New frontiers on treatment of cancers by targeting RNA modifications and BC dysregulation with new drugs are surging interest and could be applied in a clinical setting.[298]

6. Conclusion

In conclusion, this review highlights the frontier of condensate- and oncogenic RNA-targeted drug discovery, pointing to potential breakthroughs in therapeutic interventions. The role of BCs, including SGs, cancer-associated proteins, and tumor suppressors and repressors, in cancer cell biology and their dysregulation within the cancer milieu has gained attention. Several avenues exist for developing cancer therapeutics. The first involves targeting oncogenic ncRNAs, potentially delivering drugs to specific cell types to prevent their role in forming phase-separated condensates with oncogenic potential. This can be achieved through RNA silencing through shRNA or ASO or by targeting triple helix structures. The second approach focuses on targeting domains responsible for RNA–protein interactions. A third strategy is the use of drugs aimed at epigenetic enzymes. The final approach involves validating compounds that chemically disrupt BC formation or target the protein organizers of BCs. Future research directions in BCs hold significant promise, offering not only a deeper understanding of degenerative diseases and cancer but also paving the way for advancements in clinical applications.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Palmiro Poltronieri
Visualization: Sudipta Joardar
Writing – original draft: Sudipta Joardar
Writing – review & editing: Palmiro Poltronieri

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

Further disclosure

Part of the work has been presented in the virtual conference "International Forum on Traditional and Alternative Medicine" on November 16, 2023.

References

1. Boeynaems S, Alberti S, Fawzi NL, *et al.* Protein phase separation: A new phase in cell biology. *Trends Cell Biol*. 2018;28(6) 420-435.

   doi: 10.1016/j.tcb.2018.02.004

2. Banani SF, Lee HO, Hyman AA, Rosen MK. Biomolecular condensates: Organizers of cellular biochemistry. *Nat Rev Mol Cell Biol*. 2017;18(5):285-298.

   doi: 10.1038/nrm.2017.7

3. Guillén-Boixet J, Kopach A, Holehouse AS, *et al.* RNA-induced conformational switching and clustering of G3BP drive stress granule assembly by condensation. *Cell*. 2020;181:346-361.e17.

   doi: 10.1016/j.cell.2020.03.049

4. Rhine K, Odeh HM, Shorter J, Myong S. Regulation of biomolecular condensates by Poly(ADP-ribose). *Chem Rev*. 2023;123(14):9065-9093.

   doi: 10.1021/acs.chemrev.2c00851

5. Fay MM, Anderson PJ. The role of RNA in biological phase separations. *J Mol Biol*. 2018;430(23):4685-4701.

   doi: 10.1016/j.jmb.2018.05.003

6. Lavalée M, Curdy N, Laurent C, Fournié JJ, Franchini DM. Cancer cell adaptability: Turning ribonucleoprotein granules into targets. *Trends Cancer*. 2021;7(10):902-915.

   doi: 10.1016/j.trecan.2021.05.006

7. Taniue K, Akimitsu N. Aberrant phase separation and cancer. *FEBS J*. 2022;289(1):17-39.

   doi: 10.1111/febs.15765

8. Mullard A. Biomolecular condensates pique drug discovery curiosity. *Nat Rev Drug Discov*. 2019;18:324-326.

   doi: 10.1038/d41573-019-00069-w

9. Conti BA, Oppikofer M. Biomolecular condensates: New opportunities for drug discovery and RNA therapeutics. *Trends Pharmacol Sci*. 2022;43(10):820-837.

   doi: 10.1016/j.tips.2022.07.001

10. Chakravarty AK, Mcgrail DJ, Lozanoski TM, *et al.* Biomolecular condensation: A new phase in cancer research. *Cancer Discov*. 2022;12:2031-2043.

    doi: 10.1158/2159-8290.CD-21-1605

11. Silva JL, Foguel D, Ferreira VF, *et al.* Targeting biomolecular condensation and protein aggregation against cancer. *Chem Rev*. 2023;123(14):9094-9138.

    doi: 10.1021/acs.chemrev.3c00131

12. Kilgore HR, Young RA. Learning the chemical grammar of biomolecular condensates. *Nat Chem Biol*. 2022;18(12):1298-1306.

    doi: 10.1038/s41589-022-01046-y

13. Maqsood Q, Sumrin A, Saleem MZ, *et al.* An insight into cancer from biomolecular condensates. *Cancer Screen Prevent*. 2023;2(3):177-190.

    doi: 10.14218/CSP.2023.00018

14. Ginell GM, Holehouse AS. An introduction to the stickers-and-spacers framework applied to biomolecular condensates. *Methods Mol Biol*. 2023;2563:95-116.

    doi: 10.1007/978-1-0716-2663-4_4

15. Otis JP, Mowry KL. Hitting the mark: Localization of mRNA and biomolecular condensates in health and disease. *Wiley Interdiscipl Rev RNA*. 2023;14(6):e1807.

    doi: 10.1002/wrna.1807

16. Villegas JA, Heidenreich M, Levy ED. Molecular and environmental determinants of biomolecular condensate formation. *Nat Chem Biol*. 2022;18(12):1319-1329.

    doi: 10.1038/s41589-022-01175-4

17. Schmidt HB, Görlich D. Transport selectivity of the nuclear pores, phase separation, and membraneless organelles. *Trends Biochem Sci*. 2016;41(1):46-61.

    doi: 10.1016/j.tibs.2015.11.001

18. Forman-Kay JD, Ditlev JA, Nosella ML, Lee HO. What are the distinguishing features and size requirements of biomolecular condensates and their implications for RNA-containing condensates? *RNA*. 2022;28:36-47.

    doi: 10.1261/rna.079026.121

19. Kwon I, Kato M, Xiang S, *et al.* Phosphorylation-regulated binding of RNA polymerase II to fibrous polymers of low-complexity domains. *Cell*. 2013;155(5):1049.

    doi: 10.1016/j.cell.2013.10.033

20. Peran I, Mittag T. Molecular structure of the biomolecular condensates. *Curr Opin Struct Biol*. 2020;60:17-26.

    doi: 10.1016/j.sbi.2019.09.007

21. Holmes KJ, Klass DM, Guiney EL, Cyert MS. Whi3, an S. cerevisiae RNA-binding protein, is a component of stress granules that regulates levels of its target mRNAs. *PLoS One*.

2013;8(12):e84060.

doi: 10.1371/journal.pone.0084060

22. Ukmar-Godec T, Wegmann S, Zweckstetter M. Biomolecular condensation of the microtubule-associated protein tau. *Semin Cell Dev Biol*. 2020;99:202-214.

doi: 10.1016/j.semcdb.2019.06.007

23. Ukmar-Godec T, Hutten S, Grieshop MP, *et al.* Lysine/RNA-interactions drive and regulate biomolecular condensation. *Nat Commun*. 2019;10(1):2909.

doi: 10.1038/s41467-019-10792-y

24. Boyko S, Surewicz WK. Tau liquid-liquid phase separation in neurodegenerative diseases. *Trends Cell Biol*. 2022;32(7):611-623.

doi: 10.1016/j.tcb.2022.01.011

25. Abasi LS, Elathram N, Movva M, Deep A, Corbett KD, Debelouchina GT. Phosphorylation regulates tau's phase separation behavior and interactions with chromatin. *Commun Biol*. 2024;7(1):251.

doi: 10.1038/s42003-024-05920-4

26. Parolini F, Tira R, Barracchia CG, *et al.* Ubiquitination of Alzheimer's-related tau protein affects the liquid-liquid phase separation in a site- and cofactor-dependent manner. *Int J Biol Macromol*. 2022;201:173-181.

doi: 10.1016/j.ijbiomac.2021.12.191

27. Farooqi AA, Fayyaz S, Poltronieri P, Calin G, Mallardo M. Epigenetic deregulation in cancer: Enzyme players and noncoding RNAs. *Semin Cancer Biol*. 2022;83:197-207.

doi: 10.1016/j.semcancer.2020.07.013

28. Mattick JS, Amaral PP, Carninci P, *et al.* Long noncoding RNAs: Definitions, functions, challenges and recommendations. *Nat Rev Mol Cell Biol*. 2023;24:430-447.

doi: 10.1038/s41580-022-00566-8

29. Poltronieri P. Regulatory RNAs: Role as scaffolds assembling protein complexes and their epigenetic deregulation. *Explor Target Antitumor Ther*. 2024;5(4):841-876.

doi: 10.37349/etat.2024.00252

30. Cusenza VY, Tameni A, Neri A, Frazzi R. lncRNA epigenetics: The significance of m6A and m5C lncRNA modifications in cancer. *Front Oncol*. 2023;13:1063636.

doi: 10.3389/fonc.2023.1063636

31. Bure IV, Nemtsova MV, Kuznetsova EB. Histone modifications and non-coding RNAs: Mutual epigenetic regulation and role in pathogenesis. *Int J Mol Sci*. 2022;23:5801.

doi: 10.3390/ijms23105801

32. Yang X, Liu M, Li M, *et al.* Epigenetic modulations of noncoding RNA: A novel dimension of Cancer biology. *Mol Cancer*. 2020;19:64.

doi: 10.1186/s12943-020-01159-9

33. Gibson BA, Doolittle LK, Schneider WG, Gerlich DW, Redding S, Rosen MK. Organization of chromatin by intrinsic and regulated phase separation. *Cell*. 2019;179:470-484.

doi: 10.1016/j.cell.2019.08.037

34. Nylund P, Garrido-Zabala B, Kalushkova A, Wiklund HJ. The complex nature of lncRNA-mediated chromatin dynamics in multiple myeloma. *Front Oncol*. 2023;13:1303677.

doi: 10.3389/fonc.2023.1303677

35. Hu WL, Jin L, Xu A, *et al.* GUARDIN is a p53-responsive long noncoding RNA that is essential for genomic stability. *Nat Cell Biol*. 2018;20:492-502.

doi: 10.1038/s41556-018-0066-7

36. Kurup JT, Kidder BL. Identification of H4K20 me3-and H3K4 me3-associated RNAs using CARIP-Seq expands the transcriptional and epigenetic networks of embryonic stem cells. *J Biol Chem*. 2018;293(39):15120-15135.

doi: 10.1074/jbc.RA118.004974

37. Agredo A, Kasinski AL. Histone 4 lysine 20 tri-methylation: A key epigenetic regulator of chromatin structure and disease. *Front Genet*. 2023;14:1243395.

doi: 10.3389/fgene.2023.1243395

38. Fan L, Sun W, Lyu Y, *et al.* Chrom-seq identifies RNAs at chromatin marks. *Sci Adv*. 2024;10(31):eadn1397.

doi: 10.1126/sciadv.adn1397

39. Ahmad A, Poltronieri P, Uddin S. Editorial: LncRNAs in cancer metastasis and therapy resistance. *Front Oncol*. 2021;11:813274.

doi: 10.3389/fonc.2021.813274

40. Zang C, Nie FQ, Wang Q, *et al.* Long noncoding RNA LINC01133 represses KLF2, P21 and E-cadherin transcription through binding with EZH2 and LSD1 in non-small cell lung cancer. *Oncotarget*. 2016;7:11696-11707.

doi: 10.18632/oncotarget.7077

41. Kong Y, Hsieh CH, Alonso LC. ANRIL: A lncRNA at the CDKN2A/B locus with roles in cancer and metabolic disease. *Front Endocrinol* (*Lausanne*). 2018;9:405.

doi: 10.3389/fendo.2018.00405

42. Lian Y, Yan C, Ding J, *et al.* A novel lncRNA, LL22NC03-N64E9.1, represses KLF2 transcription by binding with EZH2 in colorectal cancer. *Oncotarget*. 2017;8:59435-59445.

doi: 10.18632/oncotarget.19738

43. Quagliata L, Matter MS, Piscuoglio S, *et al.* Long noncoding RNA HOTTIP/HOXA13 expression is associated with disease progression and predicts the outcome in hepatocellular carcinoma patients. *Hepatology.*

2014;59:911-923.

doi: 10.1002/hep.26740

44. Zhang G, Xu Y, Zou C, *et al.* The long noncoding RNA ARHGAP27P1 inhibits gastric cancer cell proliferation and cell cycle progression by epigenetically regulating p15 and p16. *Aging* (*Albany NY*). 2019;11:9090-9110.

doi: 10.18632/aging.102377

45. Bai Z, Wu Y, Bai S, *et al.* Long noncoding RNA SNHG7 Is activated by SP1 and exerts oncogenic properties by interacting with EZH2 in ovarian cancer. *J Cell Mol Med*. 2020;24:7479-7489.

doi: 10.1111/jcmm.15373

46. Huang MD, Chen WM, Qi FZ, *et al.* Long noncoding RNA TUG1 is upregulated in hepatocellular carcinoma and promotes cell growth and apoptosis by epigenetically silencing KLF2. *Mol Cancer*. 2015;14:165.

doi: 10.1186/s12943-015-0431-0

47. Ruan J, Zheng L, Hu N, *et al.* Long noncoding RNA SNHG6 promotes osteosarcoma cell proliferation by regulating p21 and KLF2. *Arch Biochem Biophys*. 2018;646:128-136.

doi: 10.1016/j.abb.2018.03.036

48. Lian Y, Yang J, Lian Y, Xiao C, Hu X, Xu H. DUXAP8, a pseudogene-derived lncRNA, promotes the growth of pancreatic carcinoma cells by epigenetically silencing CDKN1A and KLF2. *Cancer Commun* (*Lond*). 2018;38:64.

doi: 10.1186/s40880-018-0333-9

49. Chen Z, Chen X, Chen P, *et al.* Long noncoding RNA SNHG20 promotes non-small cell lung cancer cell proliferation and migration by epigenetically silencing of P21 expression. *Cell Death Dis*. 2017;8:e3092.

doi: 10.1038/cddis.2017.484

50. Statello L, Guo CJ, Chen LL, Huarte M. Gene regulation by long noncoding RNAs and its biological functions. *Nat Rev Mol Cell Biol*. 2021;22:96-118.

doi: 10.1038/s41580-020-00315-9

51. Cai Z, Cao C, Ji L, *et al.* RIC-seq for global in situ profiling of RNA-RNA spatial interactions. *Nature*. 2020;582(7812):432-437.

doi: 10.1038/s41586-020-2249-1

52. Huang J, Zhou N, Watabe K, *et al.* Long noncoding RNA UCA1 promotes breast tumor growth by suppressing p27 (Kip1). *Cell Death Dis*. 2014;5:e1008.

doi: 10.1038/cddis.2013.541

53. Luo J, Xiang H. LncRNA MYLK-AS1 acts as an oncogene by epigenetically silencing large tumor suppressor 2 (LATS2) in gastric cancer. *Bioengineered*. 2021;12:3101-3112.

doi: 10.1080/21655979.2021.1944019

54. Ding J, Xie M, Lian Y, *et al.* Long noncoding RNA HOXA-AS2 represses P21 and KLF2 expression transcription by binding with EZH2 and LSD1 in colorectal cancer. *Oncogenesis*. 2017;6:e288.

doi: 10.1038/oncsis.2016.84

55. Zhang G, Xu Y, Wang S, *et al.* LncRNA SNHG17 promotes gastric cancer progression by epigenetically silencing of p15 and p57. *J Cell Physiol*. 2019;234(4):5163-5174.

doi: 10.1002/jcp.27320

56. Rom A, Melamed L, Gil N, *et al.* Regulation of CHD2 expression by the Chaserr long noncoding RNA gene is essential for cell viability. *Nat Commun*. 2019;10:5092.

doi: 10.1038/s41467-019-13075-8

57. Jiang X, Li Q, Zhang S, Song C, Zheng P. Long noncoding RNA GIHCG induces cancer progression and chemoresistance and indicates poor prognosis in colorectal cancer. *Onco Targets Ther*. 2019;12:1059-1070.

doi: 10.2147/OTT.S192290

58. Li L, Chen J, Wang A, Yi K. ALKBH5 regulates ovarian cancer growth via demethylating long noncoding RNA PVT1 in ovarian cancer. *J Cell Mol Med*. 2023;28(2):e18066.

doi: 10.1111/jcmm.18066

59. Ma P, Pan Y, Yang F, *et al.* KLF5-Modulated lncRNA NEAT1 contributes to tumorigenesis by acting as a scaffold for BRG1 to silence GADD45A in gastric cancer. *Mol Ther Nucleic Acids*. 2020;22:382-395.

doi: 10.1016/j.omtn.2020.09.003

60. Abildgaard C, do Canto LM, Rainho CA, *et al.* The long non-coding RNA SNHG12 as a mediator of carboplatin resistance in ovarian cancer via epigenetic mechanisms. *Cancers* (*Basel*). 2022;14(7):1664.

doi: 10.3390/cancers14071664

61. Huang X, Chen J, Li H, *et al.* LncRNA SNHG12 suppresses adipocyte inflammation and insulin resistance by regulating the HDAC9/Nrf2 axis. *FASEB J*. 2024;38(13):e23794.

doi: 10.1096/fj.202400236RR

62. Zhang KJ, Tan XL, Guo L. The long noncoding RNA DANCR regulates the inflammatory phenotype of breast cancer cells and promotes breast cancer progression via the EZH2-dependent suppression of SOCS3 transcription. *Mol Oncol*. 2020;14(2):309-328.

doi: 10.1002/1878-0261.12622

63. Xie F, Huang Q, Wang C, *et al.* Downregulation of the long noncoding RNA SNHG14 suppresses cell proliferation and invasion by regulating EZH2 in pancreatic ductal adenocarcinoma (PDAC). *Cancer Biomark*. 2020;27(3):357-364.

doi: 10.3233/CBM-190908

64. Cable J, Heard E, Hirose T, *et al.* Noncoding RNAs: Biology and applications: A Keystone symposia report. *Ann N Y Acad Sci*. 2021;1506:118-141.

doi: 10.1111/nyas.14713

65. Liu YW, Xia R, Lu K, *et al.* LincRNA FEZF1-AS1 represses p21 expression to promote gastric cancer proliferation through LSD1-Mediated H3K4me2 demethylation. *Mol Cancer*. 2017;16(1):39.

doi: 10.1186/s12943-017-0588-9

66. Lian Y, Yan C, Lian Y, *et al.* Long intergenic non-protein-coding RNA 01446 facilitates the proliferation and metastasis of gastric cancer cells by interacting with the histone lysine-specific demethylase LSD1. *Cell Death Dis*. 2020;11(7):522.

doi: 10.1038/s41419-020-2729-0

67. Mao X, Ji T, Liu A, Weng Y. ELK4-mediated lncRNA SNHG22 promotes gastric cancer progression through interacting with EZH2 and regulating miR-200c-3p/Notch1 axis. *Cell Death Dis*. 2021;12(11):957.

doi: 10.1038/s41419-021-04228-z

68. Sarma K, Cifuentes-Rojas C, Ergun A, *et al.* ATRX directs binding of PRC2 to Xist RNA and polycomb targets. *Cell*. 2014;159:869-883. Erratum in *Cell*. 2014;159:1228. Erratum in Cell. 2015;160:568-569.

doi: 10.1016/j.cell.2014.10.019

69. McHugh CA, Chen CK, Chow A, *et al.* The Xist lncRNA interacts directly with SHARP to silence transcription through HDAC3. *Nature*. 2015;521:232-236.

doi: 10.1038/nature14443

70. Lu Y, Liu X, Xie M, *et al.* The NF-κB-responsive long noncoding RNA FIRRE regulates the posttranscriptional regulation of inflammatory gene expression by interacting with hnRNPU. *J Immunol*. 2017;199(10):3571-3582.

doi: 10.4049/jimmunol.1700091

71. Wang B, Xu W, Hu C, *et al.* Critical roles of the lncRNA CASC11 in tumor progression and cancer metastasis: The biomarker and therapeutic target potential. *Genes Dis*. 2020;9(2):325-333.

doi: 10.1016/j.gendis.2020.11.016

72. Mou K, Zhang X, Mu X, *et al.* LNMAT1 promotes invasion-metastasis cascade in malignant melanoma by epigenetically suppressing CADM1 expression. *Front Oncol*. 2019;9:569.

doi: 10.3389/fonc.2019.00569

73. Wozniak M, Czyz M. lncRNAs-EZH2 interaction as promising therapeutic target in cutaneous melanoma. *Front Mol Biosci*. 2023;10:1170026.

doi: 10.3389/fmolb.2023.1170026

74. Zhang F, Ruan X, Ma J, *et al.* DGCR8/ZFAT-AS1 promotes CDX2 transcription in a PRC2 complex-dependent manner to facilitate the malignant biological behavior of glioma cells. *Mol Ther*. 2020;28(2):613-630.

doi: 10.1016/j.ymthe.2019.11.015

75. Chang KC, Diermeier SD, Yu AT, *et al.* MaTAR25 lncRNA regulates the Tensin1 gene to impact breast cancer progression. *Nat Commun*. 2020;11(1):6438.

doi: 10.1038/s41467-020-20207-y

76. Somasundaram S, Forrest ME, Moinova H, *et al.* DNMT1-associated lincRNA DACOR1 reprograms genome-wide DNA methylation in colon cancer. *Clin Epigenet*. 2018;10:127.

doi: 10.1186/s13148-018-0555-3

77. Wang Q, Mao X, Luo F, Wang J. LINC00511 promotes gastric cancer progression by regulating SOX4 and epigenetically repressing PTEN to activate PI3K/AKT pathway. *J Cell Mol Med*. 2021;25:9112-9127.

doi: 10.1111/jcmm.16656

78. Dai Z, Liu X, Zeng H, Chen Y. Long noncoding RNA HOTAIR facilitates pulmonary vascular endothelial cell apoptosis via DNMT1-mediated hypermethylation of the Bcl-2 promoter in COPD. *Respir Res*. 2022;23(1):356.

doi: 10.1186/s12931-022-02234-z

79. Lu GH, Zhao HM, Liu ZY, Cao Q, Shao RD, Sun G. LncRNA SAMD12-AS1 promotes the progression of gastric cancer via DNMT1/p53 axis. *Arch Med Res*. 2021;52(7):683-691.

doi: 10.1016/j.arcmed.2021.04.004

80. Yu Y, Lu X, Yan Y, *et al.* lncRNA KIF9-AS1 accelerates hepatocellular carcinoma growth by recruiting DNMT1 to promote RAI2 DNA methylation. *J Oncol*. 2022;2022:3888798.

doi: 10.1155/2022/3888798

81. Hao A, Wang Y, Stovall DB, Wang Y, Sui G. Emerging roles of LncRNAs in the EZH2-regulated oncogenic network. *Int J Biol Sci*. 2021;17(13):3268-3280.

doi: 10.7150/ijbs.63488

82. Wang X, Wang Y, Li L, *et al.* lncRNA coordinates with Ezh2 to inhibit HIF-1α transcription and suppress cancer cell adaptation to hypoxia. *Oncogene*. 2020;39(9):1860-1874.

doi: 10.1038/s41388-019-1123-9

83. Aguilo F, Di Cecilia S, Walsh MJ. Long non-coding RNA ANRIL and polycomb in human cancers and cardiovascular disease. *Curr Top Microbiol Immunol*. 2016;394:29-39.

doi: 10.1007/82_2015_455

84. Sun TT, He J, Liang Q, *et al.* LncRNA GClnc1 promotes gastric carcinoma and may act as a modular scaffold of WDR5 and KAT2A complexes to specify the histone modification pattern. *Cancer Discov*. 2016;6(7):784-801.

doi: 10.1158/2159-8290.CD-15-0921

85. Ma M, Zhang Y, Weng M, *et al.* lncRNA GCAWKR promotes gastric cancer development by scaffolding the chromatin modification factors WDR5 and KAT2A. *Mol Ther*. 2018;26(11):2658-2668.

doi: 10.1016/j.ymthe.2018.09.002

86. Dimitrova N, Zamudio JR, Jong RM, *et al.* LincRNA-p21 activates p21 in cis to promote Polycomb target gene expression and to enforce the G1/S checkpoint. *Mol Cell*. 2014;54(5):777-790.

doi: 10.1016/j.molcel.2014.04.025

87. Luo M, Xie L, Su Y, *et al.* TM4SF19-AS1 facilitates the proliferation of lung squamous cell carcinoma by recruiting WDR5 to mediate TM4SF19. *Mol Cell Probes*. 2022;65:101849.

doi: 10.1016/j.mcp.2022.101849

88. Arab K, Park YJ, Lindroth AM, *et al.* Long noncoding RNA TARID directs the demethylation and activation of the tumor suppressor TCF21 via GADD45A. *Mol Cell*. 2014;55:604-614.

doi: 10.1016/j.molcel.2014.06.031

89. Ghafouri-Fard S, Dashti S, Taheri M. The HOTTIP (HOXA transcript at the distal tip) lncRNA: Review of oncogenic roles in humans. *Biomed Pharmacother*. 2020;127:110158.

doi: 10.1016/j.biopha.2020.110158

90. Xiang JF, Yin QF, Chen T, *et al.* Human CRC-specific CCAT1-L lncRNA regulates long-range chromatin interactions at the MYC locus. *Cell Res*. 2014;24(5):513-531.

doi: 10.1038/cr.2014.35

91. Hakami MA, Hazazi A, Khan FR, *et al.* PVT1 lncRNA in lung cancer: A key player in tumorigenesis and therapeutic opportunities. *Pathol Res Pract*. 2024;253:155019.

doi: 10.1016/j.prp.2023.155019

92. Li W, Notani D, Ma Q, *et al.* Functional roles of enhancer RNAs for estrogen-dependent transcriptional activation. *Nature*. 2013;498(7455):516-520.

doi: 10.3390/ijms21103711

93. Ferrer J, Dimitrova N. Transcription regulation by long noncoding RNAs: Mechanisms and disease relevance. *Nat Rev Mol Cell Biol*. 2024;25(5):396-415.

doi: 10.1038/s41580-023-00694-9

94. Beucher A, Miguel-Escalada I, Balboa D, *et al.* The HASTER lncRNA promoter is a cis-acting transcriptional stabilizer of HNF1A. *Nat Cell Biol*. 2022;24(10):1528-1540.

doi: 10.1038/s41556-022-00996-8

95. Jain AK, Xi Y, McCarthy R, *et al.* LncPRESS1 is a p53-regulated LncRNA that safeguards pluripotency by disrupting SIRT6-mediated de-acetylation of histone H3K56. *Mol Cell*. 2016; 64:967-981.

doi: 10.1016/j.molcel.2016.10.039

96. An H, Elvers KT, Gillespie JA, *et al.* A toolkit for the identification of the NEAT1_2/paraspeckle modulators. *Nucleic Acids Res*. 2022;50(20):e119.

doi: 10.1093/nar/gkac771

97. Li Z, Chao TC, Chang KY, *et al.* The long noncoding RNA THRIL regulates TNFα expression through its interaction with hnRNPL. *Proc Natl Acad Sci U S A*. 2014;111(3):1002-1007.

doi: 10.1073/pnas.1313768111

98. Li Y, Wang Z, Shi H, *et al.* HBXIP and LSD1 Scaffolded by lncRNA hotair mediate transcriptional activation by c-Myc. *Cancer Res*. 2016;7:293-304.

doi: 10.1158/0008-5472.CAN-14-3607

99. Gomez JA, Wapinski OL, Yang YW, *et al.* The NeST long ncRNA controls microbial susceptibility and epigenetic activation of the interferon-γ locus. *Cell*. 2013;152(4):743-754.

doi: 10.1016/j.cell.2013.01.015

100. Swaminathan G, Rogel-Ayala DG, Armich A, Barreto G. Implications in cancer of nuclear micro RNAs, long non-coding RNAs, and circular RNAs bound by PRC2 and FUS. *Cancers* (*Basel*). 2024;16(5):868.

doi: 10.3390/cancers16050868

101. Lei P, Guo Q, Hao J, *et al.* Exploring the evolving roles and clinical significance of circRNAs in head and neck squamous cell carcinomas. *J Cancer*. 2024;15:3984-3994.

doi: 10.7150/jca.96614

102. Chen R, Liu Y, Zhuang H, *et al.* Quantitative proteomics revealed that the long noncoding RNA MALAT1 interacts with DBC1 to regulate p53 acetylation. *Nucleic Acids Res*. 2017;45(17):9947-9959.

doi: 10.1093/nar/gkx600

103. Yamazaki T, Souquere S, Chujo T, *et al.* Functional domains of NEAT1 architectural lncRNA induce paraspeckle assembly through phase separation. *Mol Cell*. 2018;70(6):1038-1053.e7.

doi: 10.1016/j.molcel.2018.05.019

104. Nakagawa S, Yamazaki T, Hirose T. Molecular dissection of nuclear paraspeckles: Toward understanding the emerging world of the RNP milieu. *Open Biol*. 2018;8:180150.

doi: 10.1098/rsob.180150

105. Hirose T, Yamazaki T, Nakagawa S. Molecular anatomy of the architectural NEAT1 noncoding RNA: The domains, interactors, and biogenesis pathway required to build phase-separated nuclear paraspeckles. *Wiley Interdiscipl Rev RNA*. 2019;10(6):e1545.

doi: 10.1002/wrna.1545

106. Fox AH, Nakagawa S, Hirose T, Bond CS. Paraspeckles: Where long noncoding RNA meets phase separation. *Trends Biochem Sci*. 2018;43(2):124-135.

doi: 10.1016/j.tibs.2017.12.001

107. Todorovski V, McCluggage F, Li Y, *et al.* Confined environments induce polarized paraspeckle condensates. *Commun Biol*. 2023;6(1):145.

doi: 10.1038/s42003-023-04528-4

108. Mello SS, Sinow C, Raj N, *et al.* Neat1 is a p53-inducible lincRNA essential for transformation suppression. *Genes Dev*. 2017;31(11):1095-1108.

doi: 10.1101/gad.284661.116

109. Taiana E, Favasuli V, Ronchetti D, *et al.* Long noncoding RNA NEAT1 targeting impairs the DNA repair machinery and triggers antitumor activity in multiple myeloma. *Leukemia*. 2020;34:234-244.

doi: 10.1038/s41375-019-0542-5

110. Smith NE, Spencer-Merris P, Fox AH, Petersen J, Michael MZ. The long and the short of it: NEAT1 and cancer cell metabolism. *Cancers* (*Basel*). 2022;14(18):4388.

doi: 10.3390/cancers14184388

111. Kessler SM, Hosseini K, Hussein UK, *et al.* Hepatocellular carcinoma and nuclear paraspeckles: Induction of chemoresistance and prediction for poor survival. *Cell Physiol Biochem*. 2019;52(4):787-801.

doi: 10.33594/000000055

112. Takakuwa H, Yamazaki T, Souquere S, *et al.* The shell protein composition specified by the lncRNA NEAT1 domains dictates the formation of paraspeckles as distinct membraneless organelles. *Nat Cell Biol*. 2023;25(11):1664-1675.

doi: 10.1038/s41556-023-01254-1

113. Long F, Li X, Pan J, *et al.* The role of lncRNA NEAT1 in human cancer chemoresistance. *Cancer Cell Int*. 2024;24(1):236.

doi: 10.1186/s12935-024-03426-x

114. Jia X, Wei L, Zhang Z. NEAT1 overexpression indicates a poor prognosis and induces chemotherapy resistance via the miR-491-5p/SOX3 signaling pathway in ovarian cancer. *Front Genet*. 2021;12:616220.

doi: 10.3389/fgene.2021.616220

115. Ma F, Lei YY, Ding MG, Luo LH, Xie YC, Liu XL. LncRNA NEAT1 interacted with DNMT1 to regulate malignant phenotype of cancer cell and cytotoxic T cell infiltration via epigenetic inhibition of p53, cGAS, and STING in lung cancer. *Front Genet*. 2020;11:250.

doi: 10.3389/fgene.2020.00250

116. Mamontova V, Trifault B, Gribling-Burrer AS, *et al.* NEAT1 promotes genome stability via m^6A methylation-dependent regulation of CHD4. *Genes Dev.* 2024; 38(17-20):915-930.

doi: 10.1101/gad.351913.124

117. Shin VY, Chen J, Cheuk IWY, *et al.* Long noncoding RNA NEAT1 confers an oncogenic role in triple-negative breast cancer by modulating chemoresistance and cancer stemness. *Cell Death Dis*. 2019;10(4):270.

doi: 10.1038/s41419-019-1513-5

118. Dong P, Xiong Y, Yue J, *et al.* Long non-coding RNA NEAT1: A novel target for diagnosis and therapy in human tumors. *Front Genet*. 2018;9:471.

doi: 10.3389/fgene.2018.00471

119. Peng X, Zhang K, Ma L, Xu J, Chang W. The role of long non-coding RNAs in thyroid cancer. *Front Oncol*. 2020;10:941.

doi: 10.3389/fonc.2020.00941

120. Sun W, Qin Y, Wang Z, *et al.* The NEAT1_2/miR-491 axis modulates papillary thyroid cancer invasion and metastasis through TGM2/NFκb/FN1 signaling. *Front Oncol*. 2021;11:610547.

doi: 10.3389/fonc.2021.610547

121. Sun W, Lan X, Zhang H, *et al.* NEAT1_2 functions as a competing endogenous RNA to regulate ATAD2 expression by sponging microRNA-106b-5p in papillary thyroid cancer. *Cell Death Dis*. 2018;9(3):1-15.

doi: 10.1038/s41419-018-0418-z

122. Schell B, Legrand P, Fribourg S. Crystal structure of SFPQ-NONO heterodimer. *Biochimie*. 2022;198:1-7.

doi: 10.1016/j.biochi.2022.02.011

123. Zhang S, Cooper JA, Chong YS, *et al.* NONO enhances mRNA processing of super-enhancer-associated GATA2 and HAND2 genes in neuroblastoma. *EMBO Rep.* 2023;24(2):e54977.

doi: 10.15252/embr.202254977

124. Engreitz JM, Sirokman K, McDonel P, *et al.* RNA-RNA interactions enable specific targeting of noncoding RNAs to nascent Pre-mRNAs and chromatin sites. *Cell*. 2014;159(1):188-199.

doi: 10.1016/j.cell.2014.08.018

125. Lee PW, Marshall AC, Knott GJ, *et al.* Paraspeckle subnuclear bodies depend on the dynamic heterodimerisation of DBHS RNA-binding proteins via their structured domains. *J Biol Chem*. 2022;298(11):102563.

doi: 10.1016/j.jbc.2022.102563

126. Jen HW, Gu DL, Lang YD, Jou YS. PSPC1 potentiates IGF1R expression to augment cell adhesion and motility. *Cells*. 2020;9(6):1490.

doi: 10.3390/cells9061490

127. Yang L, Yang J, Jacobson B, *et al.* SFPQ promotes lung cancer

malignancy *via* regulation of CD44 v6 expression. *Front Oncol*. 2022;12:862250.

doi: 10.3389/fonc.2022.862250

128. Lin Y, Zhong W, Lin Q, *et al.* SFPQ promotes the proliferation, migration and invasion of hepatocellular carcinoma cells and is associated with poor prognosis. *Am J Cancer Res*. 2023;13(6):2269-2284.

129. Xiao M, Wang F, Chen N, *et al.* Smad4 sequestered in SFPQ condensates prevents TGF-β tumor-suppressive signaling. *Dev Cell*. 2024;59(1):48-63.e8.

doi: 10.1016/j.devcel.2023.11.020

130. Ji Q, Zhang L, Liu X, *et al.* Long noncoding RNA MALAT1 promotes tumor growth and metastasis in colorectal cancer by binding to SFPQ and releasing the oncogene PTBP2 from the SFPQ/PTBP2 complex. *Br J Cancer*. 2014;111:736-748.

doi: 10.1038/bjc.2014.383

131. Klotz-Noack K, Klinger B, Rivera M, *et al.* SFPQ depletion is synthetically lethal with BRAFV600E in colorectal cancer cells. *Cell Rep.* 2020;32(12):108184.

doi: 10.1016/j.celrep.2020.108184

132. Zhang XL, Chen XH, Xu B, *et al.* K235 acetylation couples with PSPC1 to regulate the m6A demethylation activity of ALKBH5 and tumorigenesis. *Nat Commun*. 2023;14(1):3815.

doi: 10.1038/s41467-023-39414-4

133. Lemster AL, Weingart A, Bottner J, *et al.* Elevated PSPC1 and KDM5C expression indicates poor prognosis in prostate cancer. *Hum Pathol*. 2023;138:1-11.

doi: 10.1016/j.humpath.2023.05.007

134. Tyzack GE, Manferrari G, Newcombe J, Luscombe NM, Luisier R, Patani R. Paraspeckle components NONO and PSPC1 are not mislocalized from motor neuron nuclei in sporadic ALS. *Brain*. 2020;143(8):e66.

doi: 10.1093/brain/awaa205

135. Harley J, Hagemann C, ASerio A, Patani R. TDP-43 and FUS mislocalization in VCP mutant motor neurons is reversed by pharmacological inhibition of the VCP D2 ATPase domain. *Brain Commun*. 2021;3:fcab166.

doi: 10.1093/braincomms/fcab166

136. Shao W, Bi X, Pan Y, *et al.* Phase separation of RNA-binding protein promotes polymerase binding and transcription. *Nat Chem Biol*. 2022;18(1):70-80.

doi: 10.1038/s41589-021-00904-5

137. Yeh HW, Hsu EC, Lee SS, *et al.* PSPC1 mediates TGF-β1 autocrine signaling and Smad2/3 target switching to promote EMT, stemness and metastasis. *Nat Cell Biol*. 2018;20(4):479-491.

doi: 10.1038/s41556-018-0062-y.

138. Li J, Cui P, Sun Q, *et al.* PSPC1 regulates CHK1 phosphorylation through phase separation and participates in mouse oocyte maturation. *Acta Biochim Biophys Sin* (*Shanghai*). 2021;53(11):1527-1537.

doi: 10.1093/abbs/gmab123

139. Zhan T, Cheng X, Zhu Q, *et al.* LncRNA LOC105369504 inhibits tumor proliferation and metastasis in colorectal cancer by regulating PSPC1. *Cell Death Discov*. 2023;9(1):89.

doi: 10.1038/s41420-023-01384-3

140. Mohankumar K, Shrestha R, Safe S. Nuclear receptor 4A1 (NR4A1) antagonists target paraspeckle component 1 (PSPC1) in cancer cells. *Mol Carcinog*. 2022;61(1):73-84.

doi: 10.1002/mc.23362

141. Zhang H, Su X, Burley SK, Zheng XFS. mTOR regulates aerobic glycolysis through NEAT1 and nuclear paraspeckle-mediated mechanisms in hepatocellular carcinoma. *Theranostics*. 2022;12:3518-3533.

doi: 10.7150/thno.72581

142. Hussein MA, Valinezhad K, Adel E, Munirathinam G. MALAT-1 is a key regulator of epithelial-mesenchymal transition in cancer: A potential therapeutic target for metastasis. *Cancers* (*Basel*). 2024;16(1):234.

doi: 10.3390/cancers16010234

143. Nakagawa S, Ip JY, Shioi G, *et al.* Malat1 is not an essential component of nuclear speckles in mice. *RNA*. 2012;18:1487-1499.

doi: 10.1261/rna.033217.112

144. Arratia F, Fierro C, Blanco A, *et al.* Selective concurrence of the long non-coding RNA MALAT1 and the polycomb repressive complex 2 to the promoter regions of active genes in MCF7 breast cancer cells. *Curr Issues Mol Biol*. 2023;45(6):4735-4748.

doi: 10.3390/cimb45060301

145. Frappier L. Viral disruption of promyelocytic leukemia (PML) nuclear bodies by hijacking host PML regulators. *Virulence*. 2011;2(1):58-62.

doi: 10.4161/viru.2.1.14610

146. Huang WH, Su WM, Wang CW, *et al.* The Momordica anti-HIV protein MAP30 abrogates the Epstein-Barr virus nuclear antigen 1-dependent functions in host cells. *Heliyon*. 2023;9(11):e21486.

doi: 10.1016/j.heliyon.2023.e21486

147. D'Amico F, Mukhopadhyay R, Ovaa H, Mulder MPC. Targeting TRIM proteins: A quest toward drugging an emerging protein class. *Chembiochem*. 2021;22(12):2011-2031.

doi: 10.1002/cbic.202000787

148. Dodel M, Guiducci G, Dermit M, *et al.* TREX reveals proteins that bind to specific RNA regions in living cells. *Nat*

Methods. 2024;21(3):423-434.

doi: 10.1038/s41592-024-02181-1

149. Sullivan KD, Galbraith MD, Andrysik Z, Espinosa JM. Mechanisms of transcriptional regulation by p53. *Cell Death Differ*. 2018;25(1):133-143.

doi: 10.1038/cdd.2017.174

150. Wang S, Zhao Y, Aguilar A, Bernard D, Yang CY. Targeting the MDM2-p53 protein-protein interaction for new cancer therapy: Progress and challenges. *Cold Spring Harb Perspect Med*. 2017;7(5):a026245.

doi: 10.1101/cshperspect.a026245

151. Stubbs FE, Flynn BP, Rivers CA, *et al.* Identification of a novel GR-ARID1a-P53BP1 protein complex involved in DNA damage repair and cell cycle regulation. *Oncogene*. 2022;41(50):5347-5360.

doi: 10.1038/s41388-022-02516-2

152. Kozłowska J, Kolenda T, Poter P, *et al.* Long intergenic non-coding RNAs in HNSCC: From "Junk DNA" to important prognostic factor. *Cancers* (*Basel*). 2021;13(12):2949.

doi: 10.3390/cancers13122949

153. Lin T, Hou PF, Meng S, *et al.* Emerging roles of p53-related lncRNAs in cancer progression: A systematic review. *Int J Biol Sci*. 2019;15(6):1287-1298.

doi: 10.7150/ijbs.33218

154. Adriaens C, Standaert L, Barra J, *et al.* p53 induces formation of NEAT1 lncRNA-containing paraspeckles that modulate replication stress response and chemosensitivity. *Nat Med*. 2016;22(8):861-868.

doi: 10.1038/nm.4135

155. Cheng Y, Huang N, Yin Q, *et al.* LncRNA TP53TG1 plays an anti-oncogenic role in cervical cancer by synthetically regulating transcriptome profile in HeLa cells. *Front Genet*. 2022;13:981030.

doi: 10.3389/fgene.2022.981030

156. Shao M, Ma H, Wan X, Liu Y. Survival analysis for long noncoding RNAs identified TP53TG1 as an antioncogenic target for breast cancer. *J Cell Physiol*. 2020;235:6574-6581.

doi: 10.1002/jcp.29517

157. Liao D, Liu X, Yuan X, *et al.* Long non-coding RNA tumor protein 53 target gene 1 promotes cervical cancer development via regulating microRNA-33a-5p to target forkhead box K2. *Cell Cycle*. 2022;21(6):572-584.

doi: 10.1080/15384101.2022.2026705

158. Zhao K, Wang X, Xue X, Li L, Hu Y. A long noncoding RNA sensitizes genotoxic treatment by attenuating ATM activation and homologous recombination repair in cancers. *PLoS Biol*. 2020;18:e3000666.

doi: 10.1371/journal.pbio.3000666

159. Unfried JP, Marín-Baquero M, Rivera-Calzada Á, *et al.* Long noncoding RNA NIHCOLE promotes the ligation efficiency of DNA double-strand breaks in hepatocellular carcinoma. *Cancer Res*. 2021;81(19):4910-4925.

doi: 10.1158/0008-5472.CAN-21-0463

160. Sharma V, Khurana S, Kubben N, *et al.* A BRCA1-interacting lncRNA regulates homologous recombination. *EMBO Rep*. 2015;16:1520-1534.

doi: 10.15252/embr.201540437

161. Yadav A, Biswas T, Praveen A, *et al.* Targeting MALAT1 augments sensitivity to PARP inhibition by impairing homologous recombination in prostate cancer. *Cancer Res Commun*. 2023;3:2044-2061.

doi: 10.1158/2767-9764.CRC-23-0089

162. Hu Y, Lin J, Fang H, *et al.* Targeting the MALAT1/PARP1/LIG3 complex induces DNA damage and apoptosis in multiple myeloma. *Leukemia*. 2018;32:2250-2262.

doi: 10.1038/s41375-018-0104-2

163. Zhao J, Xu J, Wu M, *et al.* LncRNA H19 regulates breast cancer DNA damage response and sensitivity to PARP inhibitors via binding to ILF2. *Int J Mol Sci*. 2023;24:9157.

doi: 10.3390/ijms24119157

164. Wang Y, Nie H, He X, *et al.* The emerging role of super enhancer--derived noncoding RNAs in human cancer. *Theranostics*. 2020;10(24):11049.

doi: 10.7150/thno.49168

165. Saldaña-Meyer R, Rodriguez-Hernaez J, Escobar T, *et al.* RNA interactions are essential for CTCF-mediated genome organization. *Mol Cell*. 2019;76(3):412-422.e5.

doi: 10.1016/j.molcel.2019.08.015

166. Diot C, Richard CA, Risso-Ballester J, *et al.* Hardening of respiratory syncytial virus inclusion bodies by cyclopamine proceeds through perturbation of the interactions of the M2-1 protein with RNA and the P protein. *Int J Mol Sci*. 2023;24(18):13862.

doi: 10.3390/ijms241813862

167. Etibor TA, Vale-Costa S, Sridharan S, *et al.* Defining basic rules for hardening influenza A virus liquid condensates. *Elife*. 2023;12:e85182.

doi: 10.7554/eLife.85182

168. Liboy-Lugo JM, Espinoza CA, Sheu-Gruttadauria J, *et al.* Protein-protein interactions with G3BPs drive stress granule condensation and gene expression changes under cellular stress. bioRxiv [Preprint]. 2024.

doi: 10.1101/2024.02.06.579149

169. Alam U, Kennedy D. Rasputin a decade on and more promiscuous than ever? A review of G3BPs. *Biochim Biophys Acta Mol Cell Res*. 2019;1866(3):360-370.

doi: 10.1016/j.bbamcr.2018.09.001

170. Shih JW, Wang WT, Tsai TY, Kuo CY, Li HK, Wu Lee YH. Critical roles of the RNA helicase DDX3 and its interactions with eIF4E/PABP1 in stress granule assembly and stress response. *Biochem J*. 2012;441(1):119-129.

doi: 10.1042/BJ20110739

171. Aditi, Folkmann AW, Wente SR. Cytoplasmic hGle1A regulates stress granules by modulation of translation. *Mol Biol Cell*. 2015;26(8):1476-1490.

doi: 10.1091/mbc.E14-11-1523

172. Zhan Y, Chen X, Zheng H, *et al.* YB1 associates with oncogenetic roles and poor prognosis in nasopharyngeal carcinoma. *Sci Rep*. 2022;12(1):3699.

doi: 10.1038/s41598-022-07636-z

173. Cui BC, Sikirzhytski V, Aksenova M, *et al.* Pharmacological inhibition of DEAD-Box RNA Helicase 3 attenuates stress granule assembly. *Biochem Pharmacol*. 2020;182:114280.

doi: 10.1016/j.bcp.2020.114280

174. Kitajima H, Maruyama R, Niinuma T, *et al.* TM4SF1-AS1 inhibits apoptosis by promoting stress granule formation in cancer cells. *Cell Death Dis*. 2023;14(7):424.

doi: 10.1038/s41419-023-05953-3

175. Kang W, Wang Y, Yang W, Zhang J, Zheng H, Li D. Research progress on the structure and function of G3BP. *Front Immunol*. 2021;12:718548.

doi: 10.3389/fimmu.2021.718548

176. Freibaum BD, Messing J, Nakamura H, *et al.* Identification of small molecule inhibitors of G3BP-driven stress granule formation. *J Cell Biol*. 2024;223(3):e202308083.

doi: 10.1083/jcb.202308083

177. Mukhopadhyay C, Zhou P. Role(s) of G3BPs in human pathogenesis. *J Pharmacol Exp Ther*. 2023;387(1):100-110.

doi: 10.1124/jpet.122.001538

178. Gal J, Chen J, Na DY, Tichacek L, Barnett KR, Zhu H. Acetylation of lysine-376 of G3BP1 regulates RNA binding and stress granule dynamics. *Mol Cell Biol*. 2019;39(22):e00052-19.

doi: 10.1128/MCB.00052-19

179. Lee AK, Klein J, Fon Tacer K, *et al.* Translational repression of G3BP in cancer and germ cells suppresses stress granules and enhances stress tolerance. *Mol Cell*. 2020;79(4):645-659.e9.

doi: 10.1016/j.molcel.2020.06.037

180. Li M, Fan X, Zhao J, Wang D. Establishment and validation of a four-stress granule-related gene signature in hepatocellular carcinoma. *J Clin Transl Hepatol*. 2024;12(1):1-14.

doi: 10.14218/JCTH.2023.00019

181. Chen S, Cao X, Zhang J, Wu W, Zhang B, Zhao F. circVAMP3 drives CAPRIN1 phase separation and inhibits hepatocellular carcinoma by suppressing c-Myc translation. *Adv Sci* (*Weinh*). 2022;9:e2103817.

doi: 10.1002/advs.202103817

182. Zhang M, Peng S. The association and clinical relevance of the phase-separating protein CAPRIN1 with noncoding RNA. *Cell Stress Chaperones*. 2023;28(2):125-132.

doi: 10.1007/s12192-023-01320-5

183. Schneider C, Schneider G. Stress granules-membraneless organelles as therapeutic targets in pancreatic cancer. *EMBO Mol Med*. 2024;16(3):429-431.

doi: 10.1038/s44321-024-00040-2

184. Kim A, Shim S, Kim YH, Kim MJ, Park S, Myung JK. Inhibition of Y-Box binding protein 1 suppresses cell growth and motility in colorectal cancer. *Mol Cancer Ther*. 2020;19(2):479-489.

doi: 10.1158/1535-7163.MCT-19-0265

185. Wang F, Li J, Fan S, *et al*. Targeting stress granules: A novel therapeutic strategy for human diseases. *Pharmacol Res*. 2020;161:105143.

doi: 10.1016/j.phrs.2020.105143

186. An S, Huang W, Huang X, *et al.* Integrative network analysis identifies cell-specific trans regulators of m6A. *Nucleic Acids Res*. 2020;48:1715-1729.

doi: 10.1093/nar/gkz1206

187. Zhang Y, Jing Y, Wang Y, *et al.* NAT10 promotes gastric cancer metastasis via N4-acetylated COL5A1. *Signal Transduct Target Ther*. 2021;6:173.

doi: 10.1038/s41392-021-00489-4

188. Han J, Liu Q, Zhou Y, Li D, Wang R. Landscape of internal N7-methylguanosine of long noncoding RNA modifications in resistant acute myeloid leukemia. *BMC Genomics*. 2023;24:425.

doi: 10.1186/s12864-023-09526-8

189. Kong Z, Lu Y, Yang Y, *et al.* m6A-Mediated biogenesis of circDDIT4 inhibits prostate cancer progression by sequestrating ELAVL1/HuR. *Mol Cancer Res*. 2023;21:1342-1355.

doi: 10.1158/1541-7786.MCR-22-0271

190. Yu XM, Li SJ, Yao ZT, *et al.* N4-acetylcytidine modification of lncRNA CTC-490G23.2 promotes cancer metastasis through interacting with PTBP1 to increase CD44 alternative splicing. *Oncogene*. 2023;42:1101-1116.

doi: 10.1038/s41388-023-02628-3

191. Dou X, Huang L, Xiao Y, *et al.* METTL14 is a chromatin regulator independent of its RNA N6-methyladenosine methyltransferase activity. *Protein Cell*. 2023;14(9):683-697.

doi: 10.1093/procel/pwad009

192. Hu J, Lin H, Wang C, Su Q, Cao B. METTL14-mediated RNA methylation in digestive system tumors. *Int J Mol Med*. 2023;52(3):86.

doi: 10.3892/ijmm.2023.5289

193. Wang J, Wang S, Yang H, *et al.* Methyltransferase like-14 suppresses growth and metastasis of non-small-cell lung cancer by decreasing LINC02747. *Cancer Sci*. 2024;115(9):2931-2946.

doi: 10.1111/cas.16254

194. Lee JH, Wang R, Xiong F, *et al.* Enhancer RNA m6A methylation facilitates transcriptional condensate formation and gene activation. *Mol Cell*. 2021;81(16):3368-3385.e9.

doi: 10.1016/j.molcel.2021.07.024

195. Long X, Wen F, Li J, Huang X. LncRNA FEZF1-AS1 accelerates multiple myeloma progression by regulating IGF2BP1/BZW2 signaling. *Hematol Oncol*. 2023;41(4):694-703.

doi: 10.1002/hon.3157

196. Shen W, Zhu M, Wang Q, *et al.* DARS-AS1 recruits METTL3/METTL14 to bind and enhance DARS mRNA m(6)A modification and translation for cytoprotective autophagy in cervical cancer. *RNA Biol*. 2022;19:751-763.

doi: 10.1080/15476286.2022.2079889

197. Liu H, Xu Y, Yao B, Sui T, Lai L, Li Z. A novel N6-methyladenosine (m6A)-dependent fate decision for the lncRNA THOR. *Cell Death Dis*. 2020;11:613.

doi: 10.1038/s41419-020-02833-y

198. Ban Y, Tan P, Cai J, *et al.* LNCAROD is stabilized by m6A methylation and promotes cancer progression via forming a ternary complex with HSPA1A and YBX1 in head and neck squamous cell carcinoma. *Mol Oncol*. 2020;14:1282-1296.

doi: 10.1002/1878-0261.12676

199. Ni W, Yao S, Zhou Y, *et al.* Long noncoding RNA GAS5 inhibits the progression of colorectal cancer by interacting with and triggering YAP phosphorylation and degradation and is negatively regulated by the m6A reader YTHDF3. *Mol Cancer*. 2019;18:143.

doi: 10.1186/s12943-019-1079-y

200. Chen F, Li M, Wang L. LncRNA CASC11 promotes hepatocellular carcinoma progression via upregulation of UBE2T in a m6A-dependent manner. *Front Oncol*. 2021;11:772671.

doi: 10.3389/fonc.2021.772671

201. Zhang J, Guo S, Piao HY, *et al.* ALKBH5 promotes invasion and metastasis of gastric cancer by decreasing methylation of the lncRNA NEAT1. *J Physiol Biochem*. 2019;75:379-389.

doi: 10.1007/s13105-019-00690-8

202. Liu T, Wang H, Fu Z, *et al.* Methyltransferase-like 14 suppresses growth and metastasis of renal cell carcinoma by decreasing long noncoding RNA NEAT1. *Cancer Sci*. 2022;113:446-458.

doi: 10.1111/cas.15212

203. Wei H, Huang L, Lu Q, *et al.* N6-methyladenosine-modified LEAWBIH drives hepatocellular carcinoma progression through epigenetically activating Wnt/β-catenin signaling. *J Hepatocellular Carcinoma*. 2023;10:1991-2007.

doi: 10.2147/JHC.S433070

204. Bei M, Hao S, Lin K, *et al.* Splicing factor TRA2A contributes to esophageal cancer progression via a noncanonical role in lncRNA m6 A methylation. *Cancer Sci*. 2023;114:3216-3229.

doi: 10.1111/cas.15870

205. Su T, Liu J, Zhang N, *et al.* New insights into the interplay between m6A modifications and microRNA or lncRNA in gastrointestinal cancers. *Front Cell Dev Biol*. 2023;11:1157797.

doi: 10.3389/fcell.2023.1157797

206. Hu X, Peng WX, Zhou H, *et al.* IGF2BP2 regulates DANCR by serving as an N6-methyladenosine reader. *Cell Death Differ*. 2020;27(6):1782-1794.

doi: 10.1038/s41418-019-0461-z

207. Xu Y, Weng X, Qiu J, Wang S. Biogenesis of circRBM33 mediated by N6-methyladenosine and its function in abdominal aortic aneurysm. *Epigenetics*. 2024;19(1):2392401.

doi: 10.1080/15592294.2024.2392401

208. Zhang Y, Chen Z, Song J, Qian H, Wang Y, Liang Z. The role of m6A modified circ0049271 induced by MNNG in precancerous lesions of gastric cancer. *Heliyon*. 2024;10(16):e35654.

doi: 10.1016/j.heliyon.2024.e35654

209. Liu F, Gu W, Shao Y. Cross-talk between circRNAs and m6A modifications in solid tumors. *J Transl Med*. 2024;22(1):694.

doi: 10.1186/s12967-024-05500-4

210. Shu G, Zhao Z, Zhao T, *et al.* N6-methyladenosine modification of circMARK2 enhances cytoplasmic export and stabilizes LIN28B, contributing to the progression of Wilms tumor. *J Exp Clin Cancer Res*. 2024;43(1):191.

doi: 10.1186/s13046-024-03113-9

211. Yankova E, Blackaby W, Albertella M, *et al.* Small-molecule inhibition of METTL3 as a strategy against myeloid leukemia. *Nature*. 2021;593:597-601.

doi: 10.1038/s41586-021-03536-w

212. Fiorentino F, Menna M, Rotili D, Valente S, Mai A. METTL3 from target validation to the first small-molecule inhibitors: A medicinal chemistry journey. *J Med Chem*. 2023;66(3):1654-1677.

doi: 10.1021/acs.jmedchem.2c01601

213. Qing Y, Dong L, Gao L, *et al.* R-2-hydroxyglutarate attenuates aerobic glycolysis in leukemia by targeting the FTO/m^{6}A/PFKP/LDHB axis. *Mol Cell*. 2021;81:922-939.e9.

doi: 10.1016/j.molcel.2020.12.026

214. Ofir-Rosenfeld Y, Rausch O, McMahon J, *et al.* STC-15, an oral small molecule inhibitor of the RNA methyltransferase METTL3, inhibits tumor growth through activation of anti-cancer immune responses and synergises with immune checkpoint blockade. *J Immunother Cancer*. 2022;10:A1-A1603.

215. Guan Q, Lin H, Miao L, *et al.* Functions, mechanisms, and therapeutic implications of METTL14 in human cancer. *J Hematol Oncol*. 2022;15:13.

doi: 10.1186/s13045-022-01231-5

216. Albert L, Xu J, Wan R, Srinivasan V, Dou Y, Vázquez O. Controlled inhibition of methyltransferases using photoswitchable peptidomimetics: Toward an epigenetic regulation of leukemia. *Chem Sci*. 2017;8:4612-4618.

doi: 10.1039/c7sc00137a

217. Lee JH, Choi N, Kim S, Jin MS, Shen H, Kim YC. Eltrombopag as an allosteric inhibitor of the METTL3-14 complex affecting the m6A methylation of RNA in acute myeloid leukemia cells. *Pharmaceuticals* (*Basel*). 2022;15(4):440.

doi: 10.3390/ph15040440

218. Nai F, Flores Espinoza MP, Invernizzi A, *et al.* Small-molecule inhibitors of the m7G-RNA writer METTL1. *ACS Bio Med Chem Au*. 2023;4(2):100-110.

doi: 10.1021/acsbiomedchemau.3c00030

219. Li F, Li W. Readers of RNA modification in cancer and their anticancer inhibitors. *Biomolecules*. 2024;14(7):881.

doi: 10.3390/biom14070881

220. Dahlem C, Abuhaliema A, Kessler SM, *et al.* First small-molecule inhibitors targeting the RNA-binding protein IGF2BP2/IMP2 for cancer therapy. *ACS Chem Biol*. 2022;17(2):361-375.

doi: 10.1021/acschembio.1c00833

221. Wallis N, Oberman F, Shurrush K, *et al.* A small molecule inhibitor of Igf2bp1 represses Kras and a prooncogenic phenotype in cancer cells. *RNA Biol*. 2022;19(1):26-43.

doi: 10.1080/15476286.2021.2010983

222. Feng P, Chen D, Wang X, *et al.* Inhibition of the m6A reader IGF2BP2 as a strategy against T-cell acute lymphoblastic leukemia. *Leukemia*. 2022;36(9):2180-2188.

doi: 10.1038/s41375-022-01651-9

223. Bao Y, Zhai J, Chen H, *et al.* Targeting m6A reader YTHDF1 augments antitumour immunity and boosts anti-PD-1 efficacy in colorectal cancer. *Gut*. 2023;72:1497-1509.

doi: 10.1136/gutjnl-2022-328845

224. Chanda S, Lepikhov K, Dahlem C, *et al.* Gene editing and small molecule inhibitors of the RNA binding protein IGF2BP2/IMP2 show its potential as an anti-cancer drug target. *Front Biosci (Landmark Ed)*. 2024;29(1):41.

doi: 10.31083/j.fbl2901041

225. Huang Y, Su R, Sheng Y, *et al.*, Small-Molecule Targeting of Oncogenic FTO Demethylase in Acute Myeloid Leukemia. *Cancer Cell*. 2019, 35(4):677-691.e10.

doi: 10.1016/j.ccell.2019.03.006

226. Feng G, Wu Y, Hu Y, *et al.* Small molecule inhibitors targeting m6A regulators. *J Hematol Oncol*. 2024;17(1):30.

doi: 10.1186/s13045-024-01546-5

227. Zálešák F, Nai F, Herok M, *et al.* Structure-based design of a potent and selective YTHDC1 ligand. *J Med Chem*. 2023;67:9516-9535.

doi: 10.1021/acs.jmedchem.4c00599

228. Hollebecque A, Salvagni S, Plummer R, *et al.* Clinical activity of CC-90011, an oral, potent, and reversible LSD1 inhibitor, in advanced malignancies. *Cancer* (*Basel*). 2022;128(17):3185-3195.

doi: 10.1002/cncr.34366

229. Sahafnejad Z, Ramazi S, Allahverdi A. An update of epigenetic drugs for the treatment of cancers and brain diseases: A comprehensive review. *Genes* (*Basel*). 2023;14(4):873.

doi: 10.3390/genes14040873

230. Li Y, Ren Y, Wang Y, *et al.* A compound AC1Q3QWB selectively disrupts HOTAIR-mediated recruitment of PRC2 and enhances the cancer therapy of DZNep. *Theranostics*. 2019;9:4608-4623.

doi: 10.7150/thno.35188

231. Yang L, Tang L, Min Q, *et al.* Emerging role of RNA modification and long noncoding RNA interaction in cancer. *Cancer Gene Ther*. 2024;31(6):816-830.

doi: 10.1038/s41417-024-00734-2

232. Poole RM. Belinostat: First global approval. *Drugs*. 2014;74:1543-1554.

doi: 10.1007/s40265-014-0275-8

233. Mann BS, Johnson JR, Cohen MH, Justice R, Pazdur R. FDA approval summary: Vorinostat for treatment of advanced primary cutaneous T-cell lymphoma. *Oncologist*. 2007;12:1247-1252.

doi: 10.1634/theoncologist.12-10-1247

234. VanderMolen KM, McCulloch W, Pearce CJ, Oberlies NH. Romidepsin (Istodax, NSC 630176, FR901228, FK228, depsipeptide): A natural product recently approved for cutaneous T-cell lymphoma. *J Antibiotics* (*Tokyo*). 2011;64:525-531.

doi: 10.1038/ja.2011.35

235. Lu X, Ning Z, Li Z, Cao H, Wang X. Development of chidamide for peripheral T-cell lymphoma, the first orphan drug approved in China. *Intractable Rare Dis Res*. 2016;5:185-191.

doi: 10.5582/irdr.2016.01024

236. Garnock-Jones KP. Panobinostat: First global approval. *Drugs*. 2015;75:695-704. Erratum in *Drugs*. 2015;75:929.

doi: 10.1007/s40265-015-0388-8

237. Ghasemi S. Cancer's epigenetic drugs: Where they are in the cancer medicines? *Pharmacogen J*. 2020;20:367-379.

doi: 10.1038/s41397-019-0138-5

238. Zhou Z, Li HQ, Liu F. DNA methyltransferase inhibitors and their therapeutic potential. *Curr Top Med Chem*. 2018;18:2448-2457.

doi: 10.2174/1568026619666181120150122

239. Kantarjian HM, Roboz GJ, Kropf PL, *et al.* Guadecitabine (SGI-110) in treatment-naive patients with acute myeloid leukemia: Phase 2 results from a multicenter, randomized, phase 1/2 trial. *Lancet Oncol*. 2017;18:1317-1326.

doi: 10.1016/S1470-2045(17)30576-4

240. Poltronieri P, Joardar S. Unravelling the interplay between biomolecular condensates and RNA in cancer and diseases. *J Biol Regul Homeost Agents*, 2024;38(8):5627-5652.

doi: 10.23812/j.biol.regul.homeost.agents.20243808.453

241. Chen XH, Guo KX, Li J, Xu SH, Zhu H, Yan GR. Regulations of m6A and other RNA modifications and their roles in cancer. *Front Med*. 2024;18(4):622-648.

doi: 10.1007/s11684-024-1064-8

242. Gilbert LA, Horlbeck MA, Adamson B, *et al.* Genome-scale CRISPR-mediated control of gene repression and activation. *Cell*. 2014;159:647-661.

doi: 10.1016/j.cell.2014.09.029

243. Shamloo S, Kloetgen A, Petroulia S, *et al.* Integrative CRISPR activation and small molecule inhibitor screening for lncRNA mediating BRAF inhibitor resistance in melanoma. *Biomedicines*. 2023;11:2054.

doi: 10.3390/biomedicines11072054

244. Liu C, Tang H, Hu N, *et al.* Methylomics and cancer: The current state of methylation profiling and marker development for clinical care. *Cancer Cell Int*. 2023;23:242.

doi: 10.1186/s12935-023-03074-7

245. Zhen S, Lu J, Chen W, Zhao L, Li X. Synergistic antitumor effect on bladder cancer by rational combination of programed cell death 1 blockade and CRISPR-Cas9-mediated long non-coding RNA urothelial carcinoma associated 1 knockout. *Hum Gene Ther*. 2018;29:1352-1363.

doi: 10.1089/hum.2018.048

246. Gao J, Hou B, Zhu Q, *et al.* Engineered bioorthogonal POLY-PROTAC nanoparticles for tumor-specific protein degradation and precise cancer therapy. *Nat Commun*. 2022;13(1):4318.

doi: 10.1038/s41467-022-32050-4

247. Wang C, Zhang Y, Chen W, Wu Y, Xing D. New-generation advanced PROTACs as potential therapeutic agents in cancer therapy. *Mol Cancer*. 2024;23(1):110.

doi: 10.1186/s12943-024-02024-9

248. Zhao LP, Rao XN, Zheng RR, *et al.* Carrier-free nano-PROTACs to amplify photodynamic therapy induced DNA damage through BRD4 degradation. *Nano Lett*. 2023;23(13):6193-6201.

doi: 10.1021/acs.nanolett.3c01812

249. Alabi S, Jaime-Figueroa S, Yao Z, *et al.* Mutant-selective degradation by BRAF-targeting PROTACs. *Nat Commun*. 2021;12:920.

doi: 10.1038/s41467-021-21159-7

250. Haj-Yahia S, Nandi A, Benhamou RI. Targeted degradation of structured RNAs via ribonuclease-targeting chimeras (RiboTacs). *Expert Opin Drug Discov*. 2023;18(8):929-942.

doi: 10.1080/17460441.2023.2224960

251. Tong Y, Lee Y, Liu X, *et al.* Programing inactive RNA-binding small molecules into bioactive degraders. *Nature*. 2023;618(7963):169-179.

doi: 10.1038/s41586-023-06091-8

252. Ly HH, Daniel S, Soriano SKV, Kis Z, Blakney AK. Optimization of lipid nanoparticles for saRNA expression and cellular activation using a design-of-experiment approach. *Mol Pharmacol*. 2022;19(6):1892-1905.

doi: 10.1021/acs.molpharmaceut.2c00032

253. Kovachka S, Panosetti M, Grimaldi B, Azoulay S, Di Giorgio A, Duca M. Small-molecule approaches to targeting RNA. *Nat Rev Chem*. 2024;8:120-135.

doi: 10.1038/s41570-023-00569-9

254. Hargrove AE. Small molecule-RNA targeting: Starting with the fundamentals. *Chem Commun* (*Camb*). 2020;56:14744-14756.

doi: 10.1039/d0cc06796b

255. Berdnikova DV. Photoswitches for controllable RNA binding: A future approach in RNA-targeting therapy. *Chem Commun* (*Camb*). 2021;57:10819-10826.

doi: 10.1039/d1cc04241f

256. Chen B, Dragomir MP, Fabris L, *et al.* The long noncoding RNA CCAT2 induces chromosomal instability through BOP1-AURKB signaling. *Gastroenterology*. 2020;159:2146-2162.

doi: 10.1053/j.gastro.2020.08.018

257. Sha S, Yuan D, Liu Y, Han B, Zhong N. Targeting long noncoding RNA DANCR inhibits triple-negative breast cancer progression. *Biol Open*. 2017;6(9):1310-1316.

doi: 10.1242/bio.023135

258. Ehmann F, Kuhn A, Pasmooij AMG, *et al.* Report of the European medicines agency conference on RNA-based medicines. *Nucleic Acid Ther*. 2024;34:4-11.

doi: 10.1089/nat.2023.0021

259. Benhamou RI, Suresh BM, Tong Y, *et al.* DNA-encoded library versus RNA-encoded library selection enables design of an oncogenic noncoding RNA inhibitor. *Proc Natl Acad Sci U S A*. 2022;119:e2114971119.

doi: 10.1073/pnas.2114971119

260. Bouchard JJ, Otero JH, Scott DC, *et al.* Cancer mutations in the tumor suppressor SPOP disrupt the formation of active, phase-separated compartments. *Mol Cell*. 2018;72(1):19-36.e8.

doi: 10.1016/j.molcel.2018.08.027

261. Grabocka E, Bar-Sagi D. Mutant KRAS enhances tumor cell fitness by upregulating stress granules. *Cell*. 2016;167(7):1803-1813.e12.

doi: 10.1016/j.cell.2016.11.035

262. Zhang J, Zeng Y, Xing Y, *et al.* Myristoylation-mediated phase separation of EZH2 compartmentalizes STAT3 to promote lung cancer growth. *Cancer Lett*. 2021;516:84-98.

doi: 10.1016/j.canlet.2021.05.035

263. Xu WX, Qu Q, Zhuang HH, *et al.* The burgeoning significance of liquid-liquid phase separation in the pathogenesis and therapeutics of cancers. *Int J Biol Sci*. 2024;20(5):1652-1668.

doi: 10.7150/ijbs.92988

264. Li J, Zhang Y, Gu J, *et al.* Stress granule core protein-derived peptides inhibit assembly of stress granules and improve sorafenib sensitivity in cancer cells. *Molecules* (*Basel*). 2024;29(9):2134.

doi: 10.3390/molecules29092134

265. Bechara C, Sagan S. Cell-penetrating peptides: 20 years later, where do we stand? *FEBS Lett.* 2013;587:1693-1702.

doi: 10.1016/j.febslet.2013.04.031

266. Chen Y, Lan T. N-terminal domain of androgen receptor is a major therapeutic barrier and potential pharmacological target for treating castration resistant prostate cancer: A comprehensive review. *Front Pharmacol*. 2024;15:1451957.

doi: 10.3389/fphar.2024.1451957

267. Kamagata K, Ariefai M, Takahashi H, *et al.* Rational peptide design for regulating the liquid-liquid phase separation on the basis of the residue-residue contact energy. *Sci Rep.* 2022;12(1):13718.

doi: 10.1038/s41598-022-17829-1

268. Lemos C, Schulze L, Weiske J, *et al.* Identification of small molecules that modulate mutant p53 condensation. *iScience*. 2020;23(9):101517.

doi: 10.1016/j.isci.2020.101517

269. Donlic A, Zafferani M, Padroni G, *et al.* Regulation of the MALAT1 triple helix stability and *in vitro* degradation by diphenylfuran. *Nucleic Acids Res*. 2020;48:7653-7664.

doi: 10.1093/nar/gkaa585

270. Meyer SM, Tanaka T, Taghavi A, Baisden JT, Grefe M, Disney MD. Optimization of a protein-targeted medicine into an RNA-specific small molecule. *ACS Chem Biol*. 2023;18(11):2336-2342.

doi: 10.1021/acschembio.3c00476

271. False JP, Donlic A, Hargrove AE. Targeting RNA with small molecules: From fundamental principles toward the clinic. *Chem Soc Rev*. 2021;50(4):2224-2243.

doi: 10.1039/d0cs01261k

272. Xiao H, Yang X, Zhang Y, Zhang Z, Zhang G, Zhang BT. RNA-targeted small-molecule drug discoveries: a machine-learning perspective. *RNA Biol*. 2023;20(1):384-397.

doi: 10.1080/15476286.2023.2223498

273. Kim T, Kim TK. Regulatory RNA: From molecular insights to therapeutic frontiers. *Exp Mol Med*. 2024;56(6):1233-1234.

doi: 10.1038/s12276-024-01267-2

274. Li K, Wang H, Jiang B, Jin X. TRIM28 in cancer and cancer therapy. *Front Genet*. 2024;15:1431564.

doi: 10.3389/fgene.2024.1431564

275. Zhu Y, Li J, Li S, *et al.* ZMAT2 condensates regulate the alternative splicing of TRIM28 to reduce cellular ROS accumulation, thereby promoting the proliferation of HCC cells. *Cell Commun Signal*. 2024;22(1):407.

doi: 10.1186/s12964-024-01790-9

276. Christen KE, Davis RA, Kennedy D. Psammaplysin F increases the efficacy of bortezomib and sorafenib through the regulation of stress granule formation. *Int J Biochem Cell Biol*. 2019;112:24-38.

doi: 10.1016/j.biocel.2019.04.008

277. Mitrea DM, Mittasch M, Ferreira Gomes B, Klein IA, Murcko MA. Modulation of biomolecular condensates: A novel approach to drug discovery. *Nat Rev Drug Discov*. 2022;21(11):841-862.

doi: 10.1038/s41573-022-00505-4

278. Wheeler RJ, Lee OH, Poser I, *et al. Small Molecules for Modulating Protein Driven Liquid-Liquid Phase Separation in Treating Neurodegenerative Disease*. BioRixv preprint.

doi: 10.1101/721001

279. Qu M, He Q, Bao H, *et al.* The multiple roles of arsenic compounds in phase separation and membraneless organelle formation determine their therapeutic efficacy in tumors. *J Pharm Anal*. 2024;14(8):100957.

doi: 10.1016/j.jpha.2024.02.011

280. Li X, Yu Z. Role of liquid-liquid phase separation in cancer: Mechanisms and therapeutic implications. *Cancer Innov*. 2024;3(5):e144.

doi: 10.1002/cai2.144

281. Zhang W, Li Z, Wang X, Sun T. Phase separation is regulated by posttranslational modifications and participates in the development of human diseases. *Heliyon*. 2024;10(13):e34035.

doi: 10.1016/j.heliyon.2024.e34035

282. Liu Z, Qin Z, Liu Y, *et al.* Liquid-liquid phase separation: roles and implications in future cancer treatment. *Int J Biol Sci*. 2023;19(13):4139-4156.

doi: 10.7150/ijbs.81521

283. Balavaishnavi B, Kamaraj M, Nithya TG, Santhosh P, GokilaLakshmi S, Shaik MR. Regulation of hippo signaling-mediated apoptosis by *Rauvolfia tetraphylla* in triple-negative breast cancer. *Med Oncol*. 2024;41(5):103.

doi: 10.1007/s12032-024-02341-5

284. Wang J, Hu L, Zhang H, Fang Y, Wang T, Wang H. Intracellular condensates of oligopeptides for targeting lysosomes and addressing multiple drug resistance of cancer. *Adv Mater*. 2022;34(1):e2104704.

doi: 10.1002/adma.202104704

285. Grosch M, Ittermann S, Rusha E, *et al.* Nucleus size and DNA accessibility are linked to the regulation of paraspeckle formation in cellular differentiation. *BMC Biol*. 2020;18:42.

doi: 10.1186/s12915-020-00770-y

286. Jia Y, Jia R, Dai Z, *et al.* Stress granules in cancer: Adaptive dynamics and therapeutic implications. *iScience*. 2024;27(8):110359.

doi: 10.1016/j.isci.2024.110359

287. Dinh NTM, Nguyen TM, Park MK, Lee CH. Y-box binding protein 1: Unraveling the multifaceted role in cancer development and therapeutic potential. *Int J Mol Sci*. 2024;25(2):717.

doi: 10.3390/ijms25020717

288. Shen X, Peng X, Guo Y, *et al.* YAP/TAZ enhances P-body formation to promote tumorigenesis. *Elife*. 2024;12:RP88573.

doi: 10.7554/eLife.88573

289. Tong F, Hu H, Xu Y, *et al.* Hollow copper sulfide nanoparticles carrying ISRIB for the sensitized photothermal therapy of breast cancer and brain metastases by inhibiting stress granule formation and reprograming tumor-associated macrophages. *Acta Pharmacol Sin B*. 2023;13:3471-3488.

doi: 10.1016/j.apsb.2022.11.003

290. Zyryanova AF, Kashiwagi K, Rato C, *et al.* ISRIB blunts the integrated stress response by allosterically antagonizing the inhibitory effect of phosphorylated eIF2 on eIF2b. *Mol Cell*. 2021;81:88-103.e6.

doi: 10.1016/j.molcel.2020.10.03

291. Hou WC, Massey LA, Rhoades D, *et al.* A PIKfyve modulator combined with an integrated stress response inhibitor to treat lysosomal storage diseases. *Proc Natl Acad Sci U S A*. 2024;121(34):e2320257121.

doi: 10.1073/pnas.2320257121

292. Cao X, Zhang Y, Ding Y, Wan Y. Identification of RNA structures and their roles in RNA functions. *Nat Rev Mol Cell Biol*. 2024;25(10):784-801.

doi: 10.1038/s41580-024-00748-6

293. He C, Wu CY, Li W, Xu K. Multidimensional super-resolution microscopy unveils nanoscale surface aggregates in the aging of FUS condensates. *J Am Chem Soc*. 2023;145(44):24240-24248.

doi: 10.1021/jacs.3c08674

294. Choi AA, Xu K. Single-molecule diffusivity quantification unveils ubiquitous net charge-driven protein-protein interaction. *J Am Chem Soc*. 2024;146(15):10973-10978.

doi: 10.1021/jacs.4c02475

295. Yao RW, Rosen MK. Advanced surface passivation for high-sensitivity studies of biomolecular condensates. *Proc Natl Acad Sci U S A*. 2024;121(22):e2403013121.

doi: 10.1101/2024.02.12.580000

296. Paul S, Mondal S, Shenogina I, Cui Q. The molecular basis for the increased stability of the FUS-LC fibril at the anionic membrane- and air-water interfaces. *Chem Sci*. 2024;15(34):13788-13799.

doi: 10.1039/d4sc02295e

297. Xia C, Colognori D, Jiang X, Xu K, Doudna JA. Single-molecule live-cell RNA imaging with CRISPR-Csm. bioRxiv [Preprint]. 2024:2024.07.14.603457.

doi: 10.1101/2024.07.14.603457

298. Guan A, Wong JJ. Targeting RNA modifications with pharmacological agents: New frontiers in cancer therapy. *Cancer Med*. 2024;13(7):e6989.