

# Multifaceted functions of Y-box binding protein 1 in RNA methylated modifications (Review)

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**Abstract.** Y-box binding protein 1 (YBX1/YB-1) is a DNA/RNA-binding protein, which plays a crucial role in promoting tumor progression and resistance to anti-cancer drugs. YBX1 is widely involved in a range of biological processes such as DNA repair, mRNA transcription, pre-mRNA splicing, mRNA stability regulation, translation and exosome sorting. In addition to these canonical DNA/RNA-binding protein functions, YBX1 can also have a regulatory role in N6-methyladenine (m<sup>6</sup>A) and 5-methylcytosine (m<sup>5</sup>C) RNA modification. Moreover, YBX1 functions as an m<sup>5</sup>C reader to regulate mRNA stability, thus modulating gene expression and affecting disease development. Furthermore, SU056, an inhibitor of YBX1, has been shown to reverse drug resistance and prevent tumor development. In the present review, the structure of YBX1 and its functions in RNA methylation modifications are summarized, and its effects on

m<sup>5</sup>C and m<sup>6</sup>A RNA modifications in cancer progression and drug resistance are emphasized.

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## 1. Introduction

Recent research has indicated that Y-box binding protein 1 (YBX1/YB-1) has multifaceted functions in regulating drug resistance, PANoptosis, stress response, ferroptosis and cell proliferation (1-5). YBX1 is identified as an oncogene which is overexpressed and positively associated with poor outcomes and survival in numerous cancers including liver, endometrial, non-small-cell lung cancer (NSCLC), ovarian, breast, gastric cancer, kidney renal papillary and clear cell renal cell carcinoma (4-11). YBX1 performs the roles through the regulation of nucleotide metabolism, pre-mRNA splicing, DNA repair, stress granule formation, transcription and translation, and sorting of microRNAs (miRNAs) into exosomes (12-14). Previous studies have shown that YBX1 also plays a crucial role in regulating RNA methylation modification which affects mRNA stability and translation, including N6-methyladenine (m<sup>6</sup>A) and 5-methylcytosine (m<sup>5</sup>C) RNA modifications (5,15). The performance of these functions depends on the structure and location of YBX1. The structural features of YBX1 are crucial for its diverse functions, mediating interactions with DNA, RNA and protein molecules (3,16).

SU056 has been demonstrated to specifically target and inhibit the YBX1 protein, rendering it a valuable tool for investigating YBX1 inhibition (17-20). Multiple studies have demonstrated that SU056 effectively hinders tumor

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**Abbreviations:** Y-box binding protein 1; m<sup>5</sup>C, 5-methylcytosine; m<sup>6</sup>A, N6-methyladenine; CDS, cold shock domain; SKIL, SKI like proto-oncogene; NSCLC, non-small cell lung cancer; NRF2, nuclear factor erythroid 2-related factor 2; SLC7A11, solute carrier family 7 member 11; TSPAN13, tetraspanin 13; CRC, colorectal cancer; LUSC, lung squamous cell carcinoma; QSOX1, quiescin sulfhydryl oxidase 1; EMCN, endomucin; BMP4, bone morphogenetic protein 4; ULK1, Unc-51 like autophagy activating kinase 1; GPR30, G protein-coupled receptor 30; YWHAZ, tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta; BCL2, BCL2 apoptosis regulator

**Key words:** Y-box binding protein 1, m<sup>5</sup>C modification, m<sup>6</sup>A modification, drug resistance, SU056

progression in diverse types of cancer including pancreatic cancer (18), triple-negative breast cancer (17) and ovarian cancer (19,20).

In the present review, the focus is mainly on the function of YBX1 in RNA modification. The mechanisms by which YBX1 is involved in RNA modification, including m<sup>5</sup>C, m<sup>6</sup>A and RNA editing are clarified, and YBX1 is proposed as a potential therapeutic target. Furthermore, the roles of YBX1 in regulating anticancer drug resistance through RNA modification are discussed, and its functions on tumor progression are encompassed. This provides a research foundation for the development of anticancer drugs targeting YBX1.

## 2. Structure of YBX1

YBX1 was initially isolated using double-stranded oligonucleotides in a phage  $\lambda$ gt11 library screening as the interacting molecule of the MHC class II gene Y-box element (21). In 1992, the murine (m) CCAAT-binding protein was identified and termed mYB-1 (22). The amino acid sequence of mYB-1 has a 95% homology with human YB-1 (22). In addition, YBX1 cDNA was isolated by screening the binding site through the enhancer oligonucleotide of type 18 human papillomavirus in an expression library of HeLa (23). Researchers found that YBX1 is a nuclear protein with a molecular weight of 42 kDa (23). YBX1 is expressed in most tissues, including the liver, spleen, lung and heart (23). Shortly thereafter, it was shown that YBX1 acted as a binding protein of human multidrug resistance 1 (MDR1) gene and regulated MDR1 gene expression in response to adverse environments (24). In humans, YBX1 genes are located on chromosome 1p34 as identified by *in situ* fluorescence hybridization (25).

YBX1 belongs to the superfamily of the cold shock proteins and is considered to be evolutionarily conserved (26). The structure of YBX1 consists of three distinct domains, the alanine/proline-rich domain (A/P site) in the N-terminal, the cold shock domain (CSD) in the central region and the C-terminal domain (CTD; Fig. 1). The A/P site domain is involved in protein-protein interactions and mediates the assembly of ribonucleoprotein complexes. Additionally, the A/P site domain functions as a regulatory element, modulating the stabilization of RNA-binding proteins (27). The highly conserved CSD facilitates both DNA and RNA binding, plays a crucial role in mRNA translation, and regulates the adaptation of bacteria to low temperatures (28). In previous studies, CSD was identified to contribute to the identification of m<sup>5</sup>C modification, enhancing mRNA stability and promoting translation (29,30). The CTD contains two important domains that mediate the localization of YBX1, the cytoplasmic retention site (CRS) and the nuclear localization signals (NLS), regulating the location of YBX1 between the cell nucleus and cytoplasm in response to cellular stimuli. Furthermore, CTD has been shown to mediate interactions with diverse protein partners and DNA/RNA-binding proteins (27,28). YBX1 is usually localized in the cell cytoplasm due to the stronger influence of CRS compared with that of NLS. The various functions of YBX1 stem from its diverse domains, making it a key DNA/RNA-binding protein.

## 3. Role of YBX1-mediated m<sup>5</sup>C modification

*Mechanism of m<sup>5</sup>C modification.* Research has revealed that the cytidine residues at position five of RNA could be methylated by m<sup>5</sup>C methyltransferases, such as the NOP2/Sun RNA methyltransferase (NSUN) protein family (31). During the m<sup>5</sup>C modification, numerous methyltransferases and proteins are involved in this process, including m<sup>5</sup>C writers, m<sup>5</sup>C erasers and m<sup>5</sup>C readers (31,32). In humans, m<sup>5</sup>C writers consist of the NSUN protein family 1-6 and DNA methyltransferase 2, which catalyze cytosine-5 methylation (32). Among them, NSUN2 is considered the most prominent m<sup>5</sup>C methyltransferase (32). The m<sup>5</sup>C erasers contain the ten-eleven translocation (TET) protein family and AlkB homolog 1, histone H2A dioxygenase (32,33). However, the functions of the m<sup>5</sup>C eraser and those of additional eraser proteins require further investigation (33). The m<sup>5</sup>C readers include YBX1, YTH N6-methyladenosine RNA binding protein F2 (YTHDF2) and Aly/Ref export factor (ALYREF), and assume the recognition of the m<sup>5</sup>C modification (34,35). In addition, ALYREF is required for the nuclear export of m<sup>5</sup>C-modified mRNA (34). Furthermore, YBX1 can identify m<sup>5</sup>C-modified mRNA in the cytoplasm and maintain mRNA stability (36,37). YTHDF2 can regulate the maturation of m<sup>5</sup>C-modified ribosomal RNA (rRNA) (35).

The m<sup>5</sup>C modification of RNA can affect its stability, which is important for translation (31). It is a common and conserved phenomenon in various RNAs, including non-coding RNAs (ncRNAs) and mRNAs (38). Over the past years, the RNA m<sup>5</sup>C modification has been demonstrated to be linked to diverse diseases, including cancers (32), viral infections (39) and autoimmune diseases (40). For instance, m<sup>5</sup>C-modified SKI like proto-oncogene (SKIL) may facilitate the progression of colorectal cancer (CRC) (41). Liu *et al* (7) revealed that the m<sup>5</sup>C modification could enhance the expression of E2F transcription factor 1, thus accelerating ovarian cancer development. These findings indicate that the RNA m<sup>5</sup>C modification plays a vital role in disease progression.

*m<sup>5</sup>C-mediated YBX1 functions in oncogenesis.* In 2019, Chen *et al* (29) first characterized YBX1 as an m<sup>5</sup>C reader protein on the distribution of m<sup>5</sup>C modifications in human cancer. They identified the amino acid residue W65 as a key component involved in recognizing the m<sup>5</sup>C modification. YBX1 was previously identified as a DNA/RNA-binding protein that performs a proto-oncogene role in cancers. As an m<sup>5</sup>C reader protein, YBX1 plays significant roles, making it a potential therapeutic target in cancer treatment (5,19,29,42-45). For instance, Chen *et al* (46) identified an NSUN2/YBX1/nuclear factor erythroid 2-related factor 2 (NRF2) axis that promotes resistance to ferroptosis in NSCLC cells. Mechanistically, NSUN2 was demonstrated to enhance NRF2 expression by adding m<sup>5</sup>C modifications to the mRNA in the 5' untranslated region (UTR). YBX1 was shown to bind to the m<sup>5</sup>C-modified mRNA, which increased the stability of NRF2 mRNA without affecting the translation process (46). This suggests that YBX1 contributes to resistance through m<sup>5</sup>C modification of RNA rather than by influencing MDR1 expression. Similarly, YBX1 can also regulate the stability of solute carrier family 7 member 11

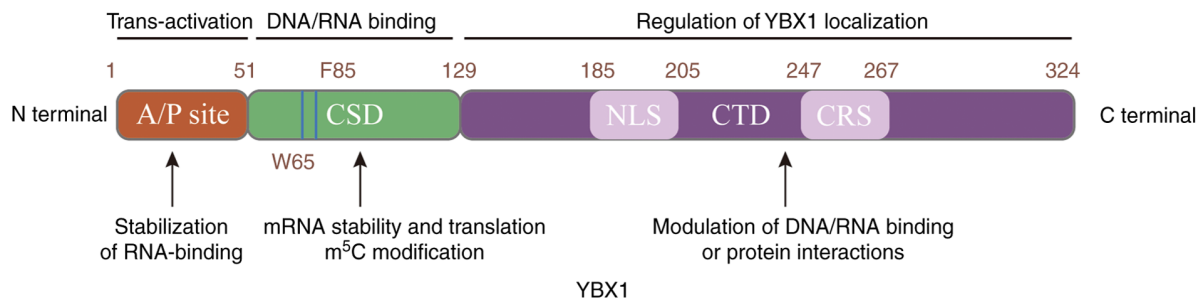


Figure 1. Schematic of YBX1 structure. The main domains of the YBX1 protein contain the A/P site, the CSD, and the CTD. The CTD is composed of the CRS and the NLS. The W65 amino acid is necessary for the recognition of m<sup>5</sup>C RNA modification. The F85 amino acid is important for mRNA stability. YBX1, Y-box binding protein 1; A/P, alanine/proline rich domain; CSD, cold shock domain; CTD, C-terminal domain; CRS, cytoplasmic retention site; NLS, nuclear localization signals; m<sup>5</sup>C, 5-methylcytosine.

(SLC7A11) mRNA, impacting ferroptosis resistance via m<sup>5</sup>C modification in endometrial cancer (4). YBX1 was shown to bind to m<sup>5</sup>C-modified SLC7A11 mRNA, enhancing its stability and developing ferroptosis resistance (4). The inhibition of YBX1 through ubiquitination was demonstrated to decrease the expression of m<sup>5</sup>C-modified mRNAs, which in turn increased the sensitivity of epithelial ovarian cancer cells to cisplatin (47). Additionally, in EGFR-mutant NSCLC cells, the YBX1/quiescin sulphydryl oxidase 1 (QSOX1) axis was responsible for mediating resistance to gefitinib. YBX1 was found to be upregulated in cells resistant to gefitinib (5). Furthermore, YBX1 recognized the m<sup>5</sup>C modification in the coding sequence of QSOX1 mRNA, which led to an increase in QSOX1 translation and a corresponding decrease in gefitinib sensitivity in NSCLC cells (5). This indicates that the YBX1-mediated m<sup>5</sup>C modification may contribute to the drug resistance observed in cancer cells, providing novel insights into potential strategies for overcoming this resistance.

YBX1 can not only impact drug resistance through m<sup>5</sup>C modification, but also promote tumor development. In lung squamous cell carcinoma (LUSC), YBX1 recognized the m<sup>5</sup>C modification in the 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 4 mRNA 3'UTR region, leading to strengthened stability, thereby promoting LUSC progression (48). In CRC, YBX1 stabilized SKIL mRNA by m<sup>5</sup>C modification and increased SKIL expression. SKIL then facilitated the activation of transcriptional coactivator with PDZ-binding motif, thus accelerating tumor progression (41). Furthermore, YBX1 was shown to be increased in immune cells of tumor-bearing mice, elucidating the reason for m<sup>5</sup>C upregulation in CRC blood immune cells (49). This perspective suggests that YBX1 is not only involved in the m<sup>5</sup>C modification of tumor cells, but also influences the m<sup>5</sup>C modification of immune cells. Moreover, m<sup>5</sup>C-mediated RNA modification has also been shown to promote tumor metastasis. Tetraspanin 13 (TSPAN13) promoted acute myeloid leukemia stem cell migration/homing through the C-X-C motif chemokine (CXC) R4/CXCL12 pathway. In TET-mutant cells, YBX1 stabilized TSPAN13 mRNA via the m<sup>5</sup>C modification, thus enhancing migration/homing and cell self-renewal (43). Liu *et al* (50) also found that m<sup>5</sup>C-modified Orai calcium release-activated calcium modulator 2 promoted gastric cancer metastasis in a YBX1-dependent manner. In addition, YBX1 could stabilize leucine-rich repeat-containing 8 VRAC subunit A mRNA in

an m<sup>5</sup>C-dependent manner to inhibit cervical cancer apoptosis (51).

*m<sup>5</sup>C-mediated YBX1 functions in other diseases.* Although YBX1 is mainly studied in cancers, it has also been demonstrated to regulate bone formation and metabolic diseases through m<sup>5</sup>C modification (52,53). Li *et al* (52) demonstrated that elevated YBX1 could facilitate osteogenesis and reduce bone loss. YBX1 deletion could repress the morphology of CD31-high, endomucin-high (CD31<sup>high</sup>EMCN<sup>high</sup>) endothelial cells, leading to decreased bone mass in an m<sup>5</sup>C-dependent manner. YBX1 could modulate the stability of EMCN, CD31 and bone morphogenetic protein 4 (BMP4), and influence the release of BMP4, thereby controlling bone formation (52). Furthermore, YBX1 could promote adipogenesis and autophagy in an m<sup>5</sup>C-dependent manner, thus leading to obesity (45). In a previous study it was found that YBX1 directly recognized m<sup>5</sup>C-modified Unc-51 like autophagy activating kinase 1 (ULK1) mRNA and improved its stability. In addition, YBX1 enhanced ULK1-mediated autophagy and increased obesity formation (53). These findings indicate that YBX1-mediated m<sup>5</sup>C modification assumes a crucial function in various diseases.

The dysregulation of YBX1-mediated RNA m<sup>5</sup>C modification represents a potential target for therapeutic strategy in human diseases. Regulating the relationship between YBX1 and m<sup>5</sup>C-modified transcripts holds promise for developing novel therapeutic strategies aimed at restoring normal RNA metabolism and cellular homeostasis. Furthermore, elucidating the mechanisms underlying YBX1-mediated m<sup>5</sup>C modification will advance our understanding of RNA biology and disease pathogenesis. Future investigations should concentrate on unraveling the spatiotemporal dynamics of YBX1-m<sup>5</sup>C co-actions and their function in different cellular microenvironments.

In conclusion, YBX1 plays a crucial role in modulating the RNA m<sup>5</sup>C modification, which is vital for controlling gene expression essential for cellular function and adaptation, especially in cancers and drug resistance (Fig. 2). Through its interactions with m<sup>5</sup>C methyltransferases, readers and RNA molecules, YBX1 influences various aspects of RNA metabolism and cellular physiology. Dysregulation of the YBX1-mediated m<sup>5</sup>C modification has implications for human health and disease, emphasizing its potential as a therapeutic

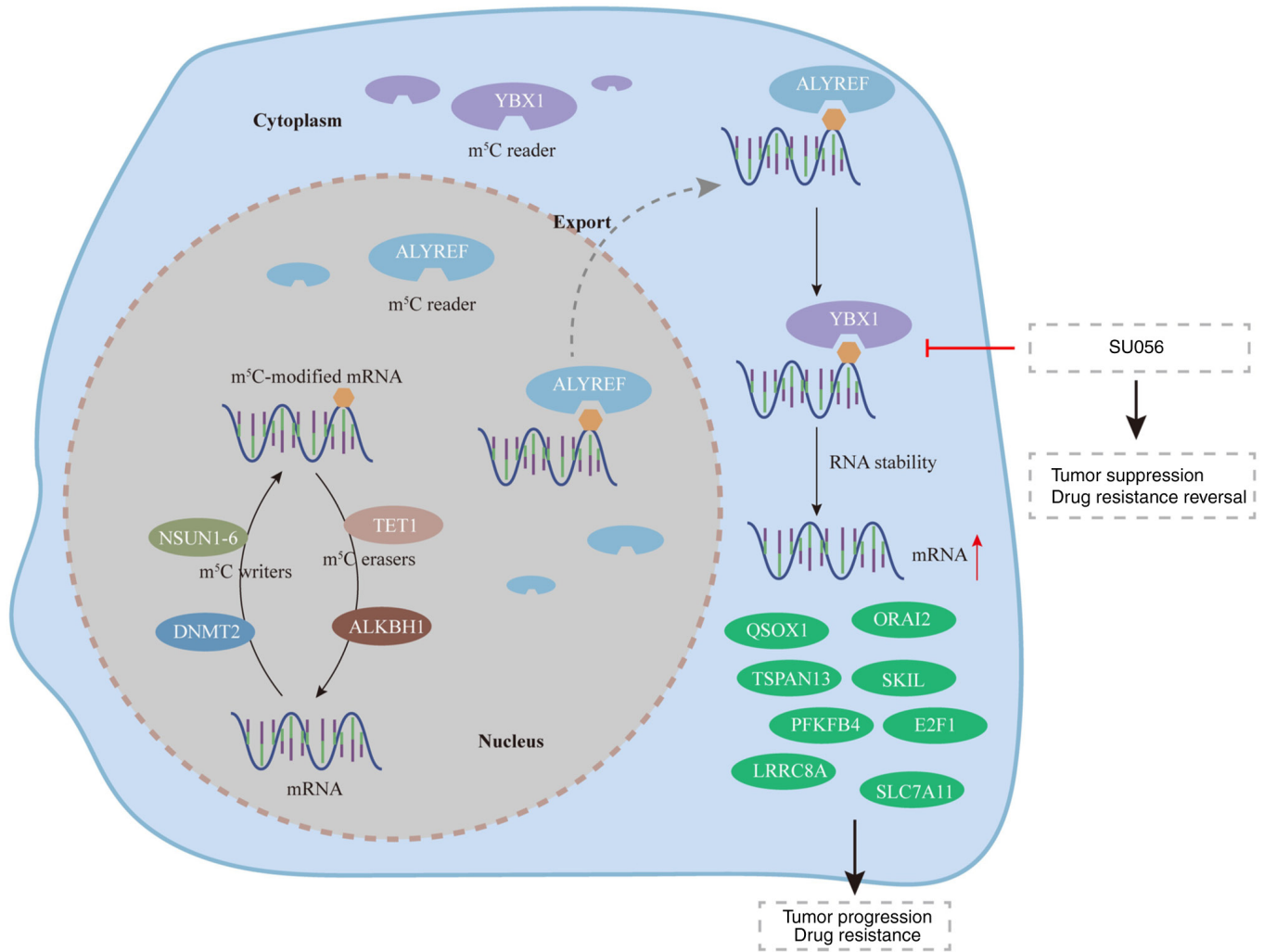


Figure 2. Functions of YBX1 in m<sup>5</sup>C RNA modification. m<sup>5</sup>C writers and erasers dynamically modulate m<sup>5</sup>C modification, catalyze and remove methylation, and ALYREF facilitates the export of m<sup>5</sup>C-tagged mRNA. YBX1 recognizes the m<sup>5</sup>C-modified mRNA in the cytoplasm, thus enhancing mRNA stability, thereby promoting tumor progression and resistance. YBX1, Y-box binding protein 1; m<sup>5</sup>C, 5-methylcytosine; ALYREF, Aly/Ref export factor; NSUN, NOP2/Sun RNA methyltransferase; TET1, ten-eleven translocation 1; DNMT2, DNA methyltransferase 2; ALKBH1, AlkB homolog 1.

target. Current research focuses on understanding the connection between YBX1 and the m<sup>5</sup>C modification, which will enhance our knowledge of RNA regulation and offer novel strategies for disease therapy.

#### 4. YBX1 is a regulatory protein of RNA m<sup>6</sup>A modification

**Mechanism of m<sup>6</sup>A modification.** To date, the most extensively studied RNA modification is m<sup>6</sup>A. This modification involves the methylation of adenosine residues at position six of RNA by m<sup>6</sup>A methyltransferases (31). The m<sup>6</sup>A modification regulates various molecular events, including RNA stability, RNA transport, the splicing of pre-mRNA, transcription, post-transcription and translation (54-56). The m<sup>6</sup>A methylation is the most abundant modification of RNA, found in long ncRNA (57-62), circular RNAs (63,64), miRNAs (65,66), mRNA (58,67), and rRNA and mtRNA (68), modulating the fates of RNA and affecting a variety of biological processes including spermatogenesis (69), pluripotency of embryonic stem cells (70), cell differentiation (71), proliferation (72), tumor metastasis (73), drug resistance of cancer (74) and the metabolism of tumor cells (75).

During the m<sup>6</sup>A modification processes, a variety of enzymes and proteins are involved, including m<sup>6</sup>A methyltransferases (commonly referred to as 'writers'), m<sup>6</sup>A demethylases (known as 'erasers') and m<sup>6</sup>A-recognized factors (called 'readers'). The writers contain methyltransferase-like (METTL3, METTL14, WT1 associated protein, METTL16 and RNA binding motif protein 15, which assume the catalysis of m<sup>6</sup>A in RNA (76-79). Notably, two proteins, AlkB homolog 5, RNA demethylase and FTO  $\alpha$ -ketoglutarate-dependent dioxygenase, have been demonstrated to be capable of removing the m<sup>6</sup>A modification from RNA (80-83). Furthermore, YTHDF1-3, YTHDC1-2, heterogenous nuclear ribonucleoprotein A2/B1, heterogenous nuclear ribonucleoprotein A/C and insulin-like growth factor 2 mRNA binding protein (IGF2BP)1-3 have been identified as factors that recognize and bind to m<sup>6</sup>A-modified RNA (80,84-91). Normally, methyltransferases and demethylases dynamically cooperate to regulate gene expression and determine the fate of molecules and cells (56). However, aberrant hypermethylation of m<sup>6</sup>A can lead to the development of multiple diseases, including cancers (92), intestinal inflammation (58) and liver disease (93).

*m<sup>6</sup>A-regulated YBX1 functions.* YBX1 can serve as a transcription factor or DNA-binding protein that regulates the expression of multiple genes (75). Accumulating evidence has revealed that YBX1 is a regulatory protein involved in the m<sup>6</sup>A modification. In 2021, Feng *et al* (15) demonstrated the significance of YBX1 in myeloid leukemia cell survival via m<sup>6</sup>A modification of BCL2 apoptosis regulator (BCL2). It was found that YBX1 was notably upregulated, promoting proliferation in myeloid leukemia cells. Mechanistically, YBX1 stabilized m<sup>6</sup>A-modified BCL2 and MYC proto-oncogene, BHLH transcription factor by cooperating with IGF2BP1 and IGF2BP3. Furthermore, the loss of YBX1 led to an accelerated decay of m<sup>6</sup>A-tagged BCL2 mRNA, suggesting that YBX1 can regulate BCL2 expression in an m<sup>6</sup>A-dependent manner, thus playing a critical role in the survival of myeloid leukemia cells (15). Similarly, YBX1 is required for the survival of leukemia stem cells (94). YBX1 was revealed to interact with the IGF2BP protein to enhance the stability of m<sup>6</sup>A-tagged tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta (YWHAZ) mRNA. YBX1 deficiency downregulated the expression of YWHAZ by promoting YWHAZ mRNA degradation in an m<sup>6</sup>A-dependent manner, thereby maintaining leukemia cell survival (94). Additionally, YBX1 has been shown to affect embryonic development (95,96) and ischemic stroke (97) in an m<sup>6</sup>A-dependent manner. YBX1 was found to influence the gene expression of zygotic genome activation by m<sup>6</sup>A-modified RNA, thereby regulating early embryonic development. YBX1 fine-tuned polycomb repressive complex 2 activity to regulate embryonic neural development (95) Peng *et al* (97) also observed that NSC-derived exosomes loaded with YBX1 inhibited neuronal pyroptosis, thereby mitigating the development of ischemic stroke. YBX1 interacted with IGF2BP1 to heighten the stability of m<sup>6</sup>A-tagged G protein-coupled receptor 30 (GPR30) mRNA, which increased the expression of GPR30. GPR30 then facilitated the degradation of NLRP3 by ubiquitination, alleviating the progression of ischemic stroke. The inhibition of IGF2BP1 decreased YBX1 binding to GPR30, which contributed to the progression of ischemic stroke (97). YBX1 is a regulatory protein involved in the m<sup>6</sup>A modification of RNA. It stabilizes the mRNA of target genes, thereby enhancing their expression. Unlike the YBX1 regulation model in the m<sup>5</sup>C modification, the IGF2BP protein is required for YBX1 to maintain mRNA stability in the m<sup>6</sup>A modification. Furthermore, YBX1 can function as an m<sup>6</sup>A reader, dependent on the IGF2BP protein (98-100). The functions of YBX1 in N1methyladenosine (m<sup>1</sup>A) and 7methylguanosine (m<sup>7</sup>G) remain unknown. Therefore, further investigation is needed to explore the contributions and potential mechanisms of YBX1 in RNA methylation modifications.

The dysregulation of YBX1-mediated RNA m<sup>6</sup>A modification has emerged as a hallmark of numerous diseases, making it a potential target for therapeutic interventions (15,101-105). Targeting the interaction between YBX1 and m<sup>6</sup>A-modified transcripts holds promise for developing novel therapeutic approaches aimed at restoring normal RNA modification in diseased states. Furthermore, elucidating the mechanisms of the YBX1-mediated m<sup>6</sup>A modification will provide novel insights into the complex dynamics of RNA regulation. In addition, it is essential to uncover the roles of YBX1 in m<sup>6</sup>A

modification and its effects on cellular processes and the development of diseases.

## 5. YBX1 inhibitor SU056 could reverse drug resistance

Research has shown that YBX1 upregulation could promote tumor development by regulating m<sup>5</sup>C and m<sup>6</sup>A modifications. SU056 is a small molecule of azopodophyllotoxin that inhibits YBX1, and helps reverse drug resistance and inhibit tumor development (17-20). YBX1 knockdown was shown to reduce gemcitabine resistance, and SU056 in combination with gemcitabine overcame gemcitabine resistance in pancreatic cancer (18). Additionally, SU056 was demonstrated to inhibit triple-negative breast cancer growth in preclinical models by targeting YB-1 to disrupt protein translation mechanisms (17). SU056 also reduced the progression of ovarian cancer while sensitizing to paclitaxel-mediated cytotoxicity (20). Furthermore, platinum-induced cell stress enhanced YBX1, which was expressed at high levels in platinum-resistant ovarian cancer. YBX1 recognized and stabilized CHD3 mRNA through m<sup>5</sup>C modification. By targeting YBX1, SU056 reversed platinum resistance and enhanced tumor cell killing (19). In addition, another YBX1 inhibitor, 2,4-dihydroxy-5-pyrimidinyl imidothiocarbamate, also exerted similar antitumor effects, although its mechanism of action remains unexplored (106). The activities and efficacy profiles of other YBX1 inhibitors also remain incompletely characterized.

Collectively, SU056 has been demonstrated to exert anti-tumor effects and reverse drug resistance by targeting YBX1, with its effectiveness dependent on the cellular expression of YBX1 (20). Additionally, YBX1 has been shown to facilitate tumor progression and confer drug resistance through its regulation of RNA m<sup>5</sup>C and m<sup>6</sup>A modifications (5,107-109). Therefore, it is hypothesized that the antitumor effect and reversal of drug resistance exerted by SU056 may be attributed to its inhibition of RNA m<sup>5</sup>A and m<sup>6</sup>A methylation.

## 6. Perspectives and conclusions

YBX1, a DNA/RNA-binding protein, is implicated in DNA repair, mRNA transcription, pre-mRNA splicing, mRNA stability regulation, translation and exosome sorting (28,110), influencing the development of multiple diseases. Notably, extensive evidence has shown that YBX1 plays multifunctional roles in cancer progression and drug resistance (111,112). Furthermore, RNA methylation modifications are dysregulated in cancers and serve as potential targets of tumor therapy (31). Although YBX1 is implicated in various cancer hallmarks, its underlying mechanisms, particularly those related to RNA methylation modifications during cancer development such as m<sup>1</sup>A, m<sup>5</sup>C, m<sup>6</sup>A and m<sup>7</sup>G require further investigation. Understanding the functional role of YBX1 in RNA modifications could provide novel insights into the regulation of gene expression, cellular homeostasis and molecular pathogenesis. This knowledge may also lead to promising therapeutic strategies that target RNA modifications for cancer treatment.

Given its critical roles in cancer pathogenesis and treatment resistance, YBX1 has emerged as an attractive therapeutic target for anticancer therapy. Several approaches have been explored to modulate YBX1 activity, including

Table I. Main roles of YBX1 in disease through RNA-methylated modification.

Gene symbol	Type of enzyme	Disease type	Role	Main target	Modification	Expression	(Refs.)
YBX1	m <sup>5</sup> C reader	Colorectal cancer	Oncogene	SKIL	N/A	No change	(41)
		Ovarian cancer	Oncogene	E2F1	3'-UTR	Upregulated	(7)
		NSCLC	Oncogene	NRF2	5'UTR	Upregulated	(46)
		Endometrial cancer	Oncogene	SLC7A11	N/A	No change	(4)
		AML	Oncogene	TSPAN13	N/A	No change	(49)
		KIRP and CRC	Oncogene	N/A	N/A	Upregulated	(10,52)
		LUSC	Oncogene	PFKFB4	3'UTR	No change	(48)
		Pancreatic cancer	Oncogene	TIAM2	N/A	No change	(36)
		EGFR-mut NSCLC	Oncogene	QSOX1	CDS	Upregulated	(5)
		Gastric cancer	Oncogene	ORAI2	N/A	No change	(50)
		Cervical cancer	Oncogene	LRRC8A	N/A	No change	(51)
		ccRCC	Oncogene	PEBP1	3'UTR	No change	(11)
		Pancreatic cancer	Oncogene	Androgen receptor	5' end	Upregulated	(37)
		Cervical cancer	Oncogene	KRT13	3'-UTR	No change	(45)
		Cholangiocarcinoma	Oncogene	lncRNA NKILA	N/A	No change	(61)
		Epithelial ovarian cancer	Oncogene	E2F5, YY1 and RCC2	N/A	No change	(47)
		Gastric cancer	Oncogene	FOXC2	N/A	No change	(62)
		UCB	Oncogene	HDGF	3'-UTR	Upregulated	(29)
		Osteoporosis	N/A	CD31, EMCN and BMP4	3'-UTR	Downregulated	(52)
			Obesity	N/A	ULK1	5'UTR	Upregulated
	MZT	NA	CAP1, TEX2 and TPP2	CDS	No change	(30)	
YBX1	m <sup>6</sup> A	Ischemic stroke	N/A	GPR30	N/A	No change	(97)
		Embryo development	N/A	PRC2	N/A	No change	(96)
		CML	Oncogene	YWHAZ	N/A	Upregulated	(94)
		AML	Oncogene	MYC and BCL2	3' UTR	Upregulated	(15)

YBX1, Y-box binding protein 1; m<sup>5</sup>C, 5-methylcytosine; SKIL, SKI like proto-oncogene; E2F1, E2F transcription factor 1; UTR, untranslated region; N/A, information not available; NSCLC, non-small cell lung cancer; NRF2, nuclear factor erythroid 2-related factor 2; SLC7A11, solute carrier family 7 member 11; AML, acute myeloid leukemia; TSPAN13, tetraspanin 13; KIRP, kidney renal papillary cell carcinoma; CRC, colorectal cancer; LUSC, lung squamous cell carcinoma; PFKFB4, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4; TIAM2, TIAM Rac1 associated GEF 2; QSOX1, quiescin sulfhydryl oxidase 1; ORAI2, calcium release-activated calcium modulator 2; LRRC8A, leucine-rich repeat-containing 8 VRAC subunit A; ccRCC, clear cell renal cell carcinoma; PEBP1, phosphatidylethanolamine binding protein 1; NKILA, NF- $\kappa$ B-interacting lncRNA; FOXC2, forkhead box C2; HDGF, heparin-binding growth factor; EMCN, endomucin; BMP4, bone morphogenetic protein 4; ULK1, Unc-51 like autophagy activating kinase 1; MZT, maternal-to-zygotic transition; m<sup>6</sup>A, N6-methyladenine; GPR30, G protein-coupled receptor 30; CML, chronic myeloid leukemia; YWHAZ, tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta; BCL2, BCL2 apoptosis regulator; EGFR, epidermal growth factor receptor; KRT13, keratin 13; E2F5, E2F transcription factor 5; YY1, Yin Yang 1; RCC2, regulator of chromosome condensation 2; UCB, urothelial carcinoma of the bladder; CAP1, cyclase-associated protein 1; TEX2, testis expressed 2; TPP2, tripeptidyl peptidase 2; CDS, cold shock domain; PRC2, polycomb repressive complex 2; NA, not available.

the use of small molecule inhibitors. The YBX1 inhibitor SU056 has shown promising efficacy in inhibiting tumor growth, promoting cell apoptosis and sensitizing cancer cells to chemotherapy. Despite the significance of YBX1 in cancer, the clinical application of YBX1 inhibitors remains limited. Further investigations should focus on the regulatory networks between YBX1 and RNA modifications, which will broaden the understanding of the role of YBX1 in cellular activity and tumorigenesis.

In summary, YBX1 plays a pivotal role in regulating RNA modifications specifically m<sup>6</sup>A and m<sup>5</sup>C RNA modifications influencing a variety of cellular processes and diseases (Table I). Understanding the underlying mechanisms of YBX1 in RNA modification is crucial for developing effective strategies to treat cancers. Targeting YBX1 and RNA modifications may help overcome the challenges of drug resistance in the clinic, and the YBX1 inhibitor SU056 exhibits great potential as an antitumor agent.

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## Authors' contributions

XX conceived and designed the review, as well as drafted and provided overall supervision of the manuscript. GX performed and contributed to specific sections of the review and participated in manuscript revision. YX was involved in revising the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

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## Competing interests

The authors declare that they have no competing interests.

## References

- Lin C, Lin P, Yao H, Liu S, Lin X, He R, Teng Z, Zuo X, Li Y, Ye J and Zhu G: Modulation of YBX1-mediated PANoptosis inhibition by PPM1B and USP10 confers chemoresistance to oxaliplatin in gastric cancer. *Cancer Lett* 587: 216712, 2024.
- Mao S, Xie C, Liu Y, Zhao Y, Li M, Gao H, Xiao Y, Zou Y, Zheng Z, Gao Y, *et al*: Apurinic/aprimidinic endodeoxyribonuclease 1 (APE1) promotes stress granule formation via YBX1 phosphorylation in ovarian cancer. *Cell Mol Life Sci* 81: 113, 2024.
- Zhang J, Fan JS, Li S, Yang Y, Sun P, Zhu Q, Wang J, Jiang B, Yang D and Liu M: Structural basis of DNA binding to human YB-1 cold shock domain regulated by phosphorylation. *Nucleic Acids Res* 48: 9361-9371, 2020.
- Chen SJ, Zhang J, Zhou T, Rao SS, Li Q, Xiao LY, Wei ST and Zhang HF: Epigenetically upregulated NSUN2 confers ferroptosis resistance in endometrial cancer via m(5)C modification of SLC7A11 mRNA. *Redox Biol* 69: 102975, 2024.
- Wang Y, Wei J, Feng L, Li O, Huang L, Zhou S, Xu Y, An K, Zhang Y, Chen R, *et al*: Aberrant m5C hypermethylation mediates intrinsic resistance to gefitinib through NSUN2/YBX1/QSOX1 axis in EGFR-mutant non-small-cell lung cancer. *Mol Cancer* 22: 81, 2023.
- Xu J, Ji L, Liang Y, Zheng W, Song X, Gorshkov K, Sun Q, Lin H, Zheng X, Chen J, *et al*: CircRNA-SORE mediates sorafenib resistance in hepatocellular carcinoma by stabilizing YBX1. *Signal Transduct Target Ther* 5: 298, 2020.
- Liu X, Wei Q, Yang C, Zhao H, Xu J, Mobet Y, Luo Q, Yang D, Zuo X, Chen N, *et al*: RNA m(5)C modification upregulates E2F1 expression in a manner dependent on YBX1 phase separation and promotes tumor progression in ovarian cancer. *Exp Mol Med* 56: 600-615, 2024.
- Song S, He X, Wang J, Song H, Wang Y, Liu Y, Zhou Z, Yu Z, Miao D and Xue Y: A novel long noncoding RNA, TMEM92-AS1, promotes gastric cancer progression by binding to YBX1 to mediate CCL5. *Mol Oncol* 15: 1256-1273, 2021.
- Xu T, Xiong M, Hong Q, Pan B, Xu M, Wang Y, Sun Y, Sun H, Pan Y, Wang S and He B: Hsa\_circ\_0007990 promotes breast cancer growth via inhibiting YBX1 protein degradation to activate E2F1 transcription. *Cell Death Dis* 15: 153, 2024.
- Zhang Z, Cao C, Zhou CL, Li X, Miao C, Shen L, Singla RK and Lu X: Identification of a novel 5-methylcytosine-related signature for prognostic prediction of kidney renal papillary cell carcinoma and a Putative target for drug repurposing. *Transl Oncol* 36: 101741, 2023.
- Yang L, Yin H, Chen Y, Pan C, Hang H, Lu Y, Ma W, Li X, Gan W, Guo H and Li D: Low expression of PEBP1P2 promotes metastasis of clear cell renal cell carcinoma by post-transcriptional regulation of PEBP1 and KLF13 mRNA. *Exp Hematol Oncol* 11: 87, 2022.
- Gandhi M, Groß M, Holler JM, Coggins SA, Patil N, Leupold JH, Munschauer M, Schenone M, Hartigan CR, Allgayer H, *et al*: The lncRNA lincNMR regulates nucleotide metabolism via a YBX1-RRM2 axis in cancer. *Nat Commun* 11: 3214, 2020.
- Lyabin DN, Eliseeva IA and Ovchinnikov LP: YB-1 protein: Functions and regulation. *Wiley Interdiscip Rev RNA* 5: 95-110, 2014.
- Liu XM, Ma L and Schekman R: Selective sorting of microRNAs into exosomes by phase-separated YBX1 condensates. *Elife* 10: e71982, 2021.
- Feng M, Xie X, Han G, Zhang T, Li Y, Li Y, Yin R, Wang Q, Zhang T, Wang P, *et al*: YBX1 is required for maintaining myeloid leukemia cell survival by regulating BCL2 stability in an m6A-dependent manner. *Blood* 138: 71-85, 2021.
- Budkina K, El Hage K, Clément MJ, Desforges B, Bouhss A, Joshi V, Maucuer A, Hamon L, Ovchinnikov LP, Lyabin DN and Pastré D: YB-1 unwinds mRNA secondary structures in vitro and negatively regulates stress granule assembly in HeLa cells. *Nucleic Acids Res* 49: 10061-10081, 2021.
- Dheeraj A, Garcia Marques FJ, Tailor D, Bermudez A, Resendez A, Pandrala M, Grau B, Kumar P, Haley CB, Honkala A, *et al*: Inhibition of protein translational machinery in triple-negative breast cancer as a promising therapeutic strategy. *Cell Rep Med* 5: 101552, 2024.
- Li B, Xing F, Wang J, Wang X, Zhou C, Fan G, Zhuo Q, Ji S, Yu X, Xu X, *et al*: YBX1 as a therapeutic target to suppress the LRP1- $\beta$ -catenin-RRM1 axis and overcome gemcitabine resistance in pancreatic cancer. *Cancer Lett* 602: 217197, 2024.
- Meng H, Miao H, Zhang Y, Chen T, Yuan L, Wan Y, Jiang Y, Zhang L and Cheng W: YBX1 promotes homologous recombination and resistance to platinum-induced stress in ovarian cancer by recognizing m5C modification. *Cancer Lett* 597: 217064, 2024.
- Tailor D, Resendez A, Garcia-Marques FJ, Pandrala M, Going CC, Bermudez A, Kumar V, Rafat M, Nambiar DK, Honkala A, *et al*: Y box binding protein 1 inhibition as a targeted therapy for ovarian cancer. *Cell Chem Biol* 28: 1206-1220.e6, 2021.
- Didier DK, Schiffenbauer J, Woulfe SL, Zacheis M and Schwartz BD: Characterization of the cDNA encoding a protein binding to the major histocompatibility complex class II Y box. *Proc Natl Acad Sci USA* 85: 7322-7326, 1988.
- Gai XX, Lipson KE and Prystowsky MB: Unusual DNA binding characteristics of an in vitro translation product of the CCAAT binding protein mYB-1. *Nucleic Acids Res* 20: 601-606, 1992.
- Spitkovsky DD, Royer-Pokora B, Delius H, Kisseljev F, Jenkins NA, Gilbert DJ, Copeland NG and Royer HD: Tissue restricted expression and chromosomal localization of the YB-1 gene encoding a 42 kD nuclear CCAAT binding protein. *Nucleic Acids Res* 20: 797-803, 1992.
- Asakuno K, Kohno K, Uchiumi T, Kubo T, Sato S, Isono M and Kuwano M: Involvement of a DNA binding protein, MDR-NF1/YB-1, in human MDR1 gene expression by actinomycin D. *Biochem Biophys Res Commun* 199: 1428-1435, 1994.
- Makino Y, Ohga T, Toh S, Koike K, Okumura K, Wada M, Kuwano M and Kohno K: Structural and functional analysis of the human Y-box binding protein (YB-1) gene promoter. *Nucleic Acids Res* 24: 1873-1878, 1996.
- Kuwano M, Shibata T, Watari K and Ono M: Oncogenic Y-box binding protein-1 as an effective therapeutic target in drug-resistant cancer. *Cancer Sci* 110: 1536-1543, 2019.
- Sun X, Gao C, Xu X, Li M, Zhao X, Wang Y, Wang Y, Zhang S, Yan Z, Liu X and Wu C: FBL promotes cancer cell resistance to DNA damage and BRCA1 transcription via YBX1. *EMBO Rep* 24: e56230, 2023.

28. Bates M, Boland A, McDermott N and Marignol L: YB-1: The key to personalised prostate cancer management? *Cancer Lett* 490: 66-75, 2020.
29. Chen X, Li A, Sun BF, Yang Y, Han YN, Yuan X, Chen RX, Wei WS, Liu Y, Gao CC, *et al*: 5-methylcytosine promotes pathogenesis of bladder cancer through stabilizing mRNAs. *Nat Cell Biol* 21: 978-990, 2019.
30. Yang Y, Wang L, Han X, Yang WL, Zhang M, Ma HL, Sun BF, Li A, Xia J, Chen J, *et al*: RNA 5-methylcytosine facilitates the maternal-to-Zygotic transition by preventing maternal mRNA Decay *Mol Cell* 75: 1188-1202.e11, 2019.
31. Barbieri I and Kouzarides T: Role of RNA modifications in cancer. *Nat Rev Cancer* 20: 303-322, 2020.
32. Nombela P, Miguel-López B and Blanco S: The role of m(6)A, m(5)C and Ψ RNA modifications in cancer: Novel therapeutic opportunities. *Mol Cancer* 20: 18, 2021.
33. Guo G, Pan K, Fang S, Ye L, Tong X, Wang Z, Xue X and Zhang H: Advances in mRNA 5-methylcytosine modifications: Detection, effectors, biological functions, and clinical relevance. *Mol Ther Nucleic Acids* 26: 575-593, 2021.
34. Wang C, Hou X, Guan Q, Zhou H, Zhou L, Liu L, Liu J, Li F, Li W and Liu H: RNA modification in cardiovascular disease: Implications for therapeutic interventions. *Signal Transduct Target Ther* 8: 412, 2023.
35. Dai X, Gonzalez G, Li L, Li J, You C, Miao W, Hu J, Fu L, Zhao Y, Li R, *et al*: YTHDF2 Binds to 5-Methylcytosine in RNA and modulates the maturation of ribosomal RNA. *Anal Chem* 92: 1346-1354, 2020.
36. Zhang G, Liu L, Li J, Chen Y, Wang Y, Zhang Y, Dong Z, Xue W, Sun R and Cui G: NSUN2 stimulates tumor progression via enhancing TIAM2 mRNA stability in pancreatic cancer. *Cell Death Discov* 9: 219, 2023.
37. Zhu W, Wan F, Xu W, Liu Z, Wang J, Zhang H, Huang S and Ye D: Positive epigenetic regulation loop between AR and NSUN2 promotes prostate cancer progression. *Clin Transl Med* 12: e1028, 2022.
38. Han X, Wang M, Zhao YL, Yang Y and Yang YG: RNA methylations in human cancers. *Semin Cancer Biol* 75: 97-115, 2021.
39. Cui L, Ma R, Cai J, Guo C, Chen Z, Yao L, Wang Y, Fan R, Wang X and Shi Y: RNA modifications: Importance in immune cell biology and related diseases. *Signal Transduct Target Ther* 7: 334, 2022.
40. Wang N, Tang H, Wang X, Wang W and Feng J: Homocysteine upregulates interleukin-17A expression via NSun2-mediated RNA methylation in T lymphocytes. *Biochem Biophys Res Commun* 493: 94-99, 2017.
41. Zou S, Huang Y, Yang Z, Zhang J, Meng M, Zhang Y, Feng J, Sun R, Li W, Wang W, *et al*: NSUN2 promotes colorectal cancer progression by enhancing SKIL mRNA stabilization. *Clin Transl Med* 14: e1621, 2024.
42. Chen B, Deng Y, Hong Y, Fan L, Zhai X, Hu H, Yin S, Chen Q, Xie X, Ren X, *et al*: Metabolic recoding of NSUN2-Mediated m(5)C modification promotes the progression of colorectal cancer via the NSUN2/YBX1/m(5)C-ENO1 positive feedback loop. *Adv Sci (Weinh)* 11: e2309840, 2024.
43. Li Y, Xue M, Deng X, Nguyen LXT, Ren L, Han L, Li C, Xue J, Zhao Z, Li W, *et al*: TET2-mediated mRNA demethylation regulates leukemia stem cell homing and self-renewal. *Cell Stem Cell* 30: 1072-1090.e10, 2023.
44. Zheng S, Hu C, Lin Q, Li T, Li G, Tian Q, Zhang X, Huang T, Ye Y, He R, *et al*: Extracellular vesicle-packaged PIAT from cancer-associated fibroblasts drives neural remodeling by mediating m5C modification in pancreatic cancer mouse models. *Sci Transl Med* 16: eadi0178, 2024.
45. Wang L, Zhang J, Su Y, Maimaitiyiming Y, Yang S, Shen Z, Lin S, Shen S, Zhan G, Wang F, *et al*: Distinct roles of m(5)C RNA methyltransferase NSUN2 in major gynecologic cancers. *Front. Oncol* 12: 786266, 2022.
46. Chen Y, Jiang Z, Zhang C, Zhang L, Chen H, Xiao N, Bai L, Liu H and Wan J: 5-Methylcytosine transferase NSUN2 drives NRF2-mediated ferroptosis resistance in non-small cell lung cancer. *J Biol Chem* 300: 106793, 2024.
47. Gao W, Chen L, Lin L, Yang M, Li T, Wei H, Sha C, Xing J, Zhang M, Zhao S, *et al*: SIAH1 reverses chemoresistance in epithelial ovarian cancer via ubiquitination of YBX-1. *Oncogenesis* 11: 13, 2022.
48. Yu T, Zhang Q, Yu SK, Nie FQ, Zhang ML, Wang Q and Lu KH: THOC3 interacts with YBX1 to promote lung squamous cell carcinoma progression through PFKFB4 mRNA modification. *Cell Death Dis* 14: 475, 2023.
49. Yin H, Huang Z, Niu S, Ming L, Jiang H, Gu L, Huang W, Xie J, He Y and Zhang C: 5-Methylcytosine (m(5)C) modification in peripheral blood immune cells is a novel non-invasive biomarker for colorectal cancer diagnosis. *Front Immunol* 13: 967921, 2022.
50. Liu K, Xu P, Lv J, Ge H, Yan Z, Huang S, Li B, Xu H, Yang L, Xu Z and Zhang D: Peritoneal high-fat environment promotes peritoneal metastasis of gastric cancer cells through activation of NSUN2-mediated ORAI2 m5C modification. *Oncogene* 42: 1980-1993, 2023.
51. Chen Y, Zuo X, Wei Q, Xu J, Liu X, Liu S, Wang H, Luo Q, Wang Y, Yang Y, *et al*: Upregulation of LRRC8A by m(5)C modification-mediated mRNA stability suppresses apoptosis and facilitates tumorigenesis in cervical cancer. *Int J Biol Sci* 19: 691-704, 2023.
52. Li YJ, Guo Q, Ye MS, Cai G, Xiao WF, Deng S and Xiao Y: YBX1 promotes type H vessel-dependent bone formation in an m5C-dependent manner. *JCI Insight* 9: e172345, 2024.
53. Wu R, Feng S, Li F, Shu G, Wang L, Gao P, Zhu X, Zhu C, Wang S and Jiang Q: Transcriptional and post-transcriptional control of autophagy and adipogenesis by YBX1. *Cell Death Dis* 14: 29, 2023.
54. Boo SH and Kim YK: The emerging role of RNA modifications in the regulation of mRNA stability. *Exp Mol Med* 52: 400-408, 2020.
55. Delaunay S and Frye M: RNA modifications regulating cell fate in cancer. *Nat Cell Biol* 21: 552-559, 2019.
56. Liu Y, Yang D, Liu T, Chen J, Yu J and Yi P: N6-methyladenosine-mediated gene regulation and therapeutic implications. *Trends Mol Med* 29: 454-467, 2023.
57. Fazi F and Fatica A: Interplay between N (6)-Methyladenosine (m(6)A) and non-coding RNAs in cell development and cancer. *Front Cell Dev Biol* 7: 116, 2019.
58. Olazagoitia-Garmendia A, Rojas-Márquez H, Sebastian-delaCruz M, Agirre-Lizaso A, Ochoa A, Mendoza-Gomez LM, Perugorria MJ, Bujanda L, Madrigal AH, Santin I and Castellanos-Rubio A: m(6)A methylated long noncoding RNA LOC339803 regulates intestinal inflammatory response. *Adv Sci (Weinh)* 11: e2307928, 2024.
59. Wang R, Xu X, Yang J, Chen W, Zhao J, Wang M, Zhang Y, Yang Y, Huang W and Zhang H: BPDE exposure promotes trophoblast cell pyroptosis and induces miscarriage by up-regulating lnc-HZ14/ZBP1/NLRP3 axis. *J Hazard Mater* 455: 131543, 2023.
60. Zhang Q, Wei T, Yan L, Zhu S, Jin W, Bai Y, Zeng Y, Zhang X, Yin Z, Yang J, *et al*: Hypoxia-Responsive lncRNA AC115619 encodes a micropeptide that suppresses m6A modifications and hepatocellular carcinoma progression. *Cancer Res* 83: 2496-2512, 2023.
61. Zheng H, Zhu M, Li W, Zhou Z and Wan X: m(5) C and m(6) A modification of long noncoding NKILA accelerates cholangiocarcinoma progression via the miR-582-3p-YAP1 axis. *Liver Int* 42: 1144-1157, 2022.
62. Yan J, Liu J, Huang Z, Huang W and Lv J: FOXC2-AS1 stabilizes FOXC2 mRNA via association with NSUN2 in gastric cancer cells. *Hum. Cell* 34: 1755-1764, 2021.
63. Li H, Lin R, Zhang Y, Zhu Y, Huang S, Lan J, Lu N, Xie C, He S and Zhang W: N6-methyladenosine-modified circPLPP4 sustains cisplatin resistance in ovarian cancer cells via PIK3R1 upregulation. *Mol Cancer* 23: 5, 2024.
64. Zeng K, Peng J, Xing Y, Zhang L, Zeng P, Li W, Zhang W, Pan Z, Zhou C and Lin J: A positive feedback circuit driven by m(6)A-modified circular RNA facilitates colorectal cancer liver metastasis. *Mol Cancer* 22: 202, 2023.
65. Wu S, Tang W, Liu L, Wei K, Tang Y, Ma J, Li H and Ao Y: Obesity-induced downregulation of miR-192 exacerbates lipopolysaccharide-induced acute lung injury by promoting macrophage activation. *Cell Mol Biol Lett* 29: 36, 2024.
66. van den Homberg DAL, van der Kwast R, Quax PHA and Nossent AY: N-6-Methyladenosine in Vasoactive microRNAs during Hypoxia; A novel role for METTL4. *Int J Mol Sci* 23: 1057, 2022.
67. Zhou L, Jiang J, Huang Z, Jin P, Peng L, Luo M, Zhang Z, Chen Y, Xie N, Gao W, *et al*: Hypoxia-induced lncRNA STEAP3-AS1 activates Wnt/β-catenin signaling to promote colorectal cancer progression by preventing m(6)A-mediated degradation of STEAP3 mRNA. *Mol Cancer* 21: 168, 2022.
68. Qi YN, Liu Z, Hong LL, Li P and Ling ZQ: Methyltransferase-like proteins in cancer biology and potential therapeutic targeting. *J Hematol Oncol* 16: 89, 2023.

69. Wu Y, Li J, Li C, Lu S, Wei X, Li Y, Xia W, Qian C, Wang Z, Liu M, *et al*: Fat mass and obesity-associated factor (FTO)-mediated N6-methyladenosine regulates spermatogenesis in an age-dependent manner. *J Biol Chem* 299: 104783, 2023.
70. Jin KX, Zuo R, Anastassiadis K, Klungland A, Marr C and Filipczyk A: N6-methyladenosine (m(6)A) depletion regulates pluripotency exit by activating signaling pathways in embryonic stem cells. *Proc Natl Acad Sci USA* 118: e2105192118, 2021.
71. Dou X, Xiao Y, Shen C, Wang K, Wu T, Liu C, Li Y, Yu X, Liu J, Dai Q, *et al*: RBFOX2 recognizes N(6)-methyladenosine to suppress transcription and block myeloid leukaemia differentiation. *Nat Cell Biol* 25: 1359-1368, 2023.
72. Ma L, Zhou X, Yao S, Zhang X, Mao J, Vona B, Fan L, Lou S, Li D, Wang L and Pan Y: METTL3-dependent m(6)A modification of PSEN1 mRNA regulates craniofacial development through the Wnt/ $\beta$ -catenin signaling pathway. *Cell Death Dis* 15: 229, 2024.
73. Li B, Xiong X, Xu J, Peng D, Nie G, Wen N, Wang Y and Lu J: METTL3-mediated m(6)A modification of lncRNA TSPAN12 promotes metastasis of hepatocellular carcinoma through SENP1-dependent deSUMOylation of EIF3I. *Oncogene* 43: 1050-1062, 2024.
74. Ou X, Tan Y, Xie J, Yuan J, Deng X, Shao R, Song C, Cao X, Xie X, He R, *et al*: Methylation of GPRC5A promotes liver metastasis and docetaxel resistance through activating mTOR signaling pathway in triple negative breast cancer. *Drug Resist Updat* 73: 101063, 2024.
75. Jiang T, Qi J, Xue Z, Liu B, Liu J, Hu Q, Li Y, Ren J, Song H, Xu Y, *et al*: The m(6)A modification mediated-lncRNA POU6F2-AS1 reprograms fatty acid metabolism and facilitates the growth of colorectal cancer via upregulation of FASN. *Mol Cancer* 23: 55, 2024.
76. Zhang Y, Geng X, Li Q, Xu J, Tan Y, Xiao M, Song J, Liu F, Fang C and Wang H: m6A modification in RNA: biogenesis, functions and roles in gliomas. *J Exp Clin Cancer Res* 39: 192, 2020.
77. van Tran N, Ernst FGM, Hawley BR, Zorbas C, Ulryck N, Hackert P, Bohnsack KE, Bohnsack MT, Jaffrey SR, Graille M and Lafontaine DLJ: The human 18S rRNA m6A methyltransferase METTL5 is stabilized by TRMT112. *Nucleic Acids Res* 47: 7719-7733, 2019.
78. Zhang L, Li Y, Zhou L, Zhou H, Ye L, Ou T, Hong H, Zheng S, Zhou Z, Wu K, *et al*: The m6A Reader YTHDF2 promotes bladder cancer progression by suppressing RIG-I-Mediated immune response. *Cancer Res* 83: 1834-1850, 2023.
79. Ghazi T, Nagiah S and Chaturgoon AA: Fusaric acid decreases p53 expression by altering promoter methylation and m6A RNA methylation in human hepatocellular carcinoma (HepG2) cells. *Epigenetics* 16: 79-91, 2021.
80. Shulman Z and Stern-Ginossar N: The RNA modification N6-methyladenosine as a novel regulator of the immune system. *Nat Immunol* 21: 501-512, 2020.
81. Cheng W, Li M, Zhang L, Zhou C, Yu S, Peng X, Zhang W and Zhang W: New roles of N6-methyladenosine methylation system regulating the occurrence of non-alcoholic fatty liver disease with N6-methyladenosine-modified MYC. *Front. Pharmacol* 13: 973116, 2022.
82. Jin S, Li M, Chang H, Wang R, Zhang Z, Zhang J, He Y and Ma H: The m6A demethylase ALKBH5 promotes tumor progression by inhibiting RIG-I expression and interferon alpha production through the IKK $\epsilon$ /TBK1/IRF3 pathway in head and neck squamous cell carcinoma. *Mol Cancer* 21: 97, 2022.
83. Ye G, Li J, Yu W, Xie Z, Zheng G, Liu W, Wang S, Cao Q, Lin J, Su Z, *et al*: ALKBH5 facilitates CYP1B1 mRNA degradation via m6A demethylation to alleviate MSC senescence and osteoarthritis progression. *Exp Mol Med* 55: 1743-1756, 2023.
84. Fu Y and Zhuang X: m(6)A-binding YTHDF proteins promote stress granule formation. *Nat Chem Biol* 16: 955-963, 2020.
85. Khan D, Ramachandiran I, Vasu K, China A, Khan K, Cumbo F, Halawani D, Terenzi F, Zin I, Long B, *et al*: Homozygous EPRS1 missense variant causing hypomyelinating leukodystrophy-15 alters variant-distal mRNA m(6)A site accessibility. *Nat Commun* 15: 4284, 2024.
86. Sun R, Tian X, Li Y, Zhao Y, Wang Z, Hu Y, Zhang L, Wang Y, Gao D, Zheng S and Yao J: The m6A reader YTHDF3-mediated PRDX3 translation alleviates liver fibrosis. *Redox Biol* 54: 102378, 2022.
87. Alarcón CR, Goodarzi H, Lee H, Liu X, Tavazoie S and Tavazoie SF: HNRNPA2B1 is a mediator of m(6)A-dependent nuclear RNA processing events. *Cell* 162: 1299-1308, 2015.
88. Jiang L, Lin W, Zhang C, Ash PEA, Verma M, Kwan J, van Vliet E, Yang Z, Cruz AL, Boudeau S, *et al*: Interaction of tau with HNRNPA2B1 and N(6)-methyladenosine RNA mediates the progression of tauopathy. *Mol Cell* 81: 4209-4227.e12, 2021.
89. Wang L, Wen M and Cao X: Nuclear hnRNP2B1 initiates and amplifies the innate immune response to DNA viruses. *Science* 365: eaav0758, 2019.
90. Miller C, Ealy A, Gregory A, Janarthanam C, Albers W, Richardson G, Jin H, Zenitsky G, Anantharam V, Kanthasamy A and Kanthasamy AG: Pathological  $\alpha$ -synuclein dysregulates epitranscriptomic writer METTL3 to drive neuroinflammation in microglia. *Cell Rep* 44: 115618, 2025.
91. Zhang T, Zhang SW, Zhang SY and Ma QQ: m(6)Aexpress-Reader: Prediction of m(6)A regulated expression genes by integrating m(6)A sites and reader binding information in specific-context. *Methods* 203: 167-178, 2022.
92. Boriack-Sjodin PA, Ribich S and Copeland RA: RNA-modifying proteins as anticancer drug targets. *Nat Rev Drug Discov* 17: 435-453, 2018.
93. Wei J, Harada BT, Lu D, Ma R, Gao B, Xu Y, Montauti E, Mani N, Chaudhuri SM, Gregory S, *et al*: HRD1-mediated METTL14 degradation regulates m(6)A mRNA modification to suppress ER proteotoxic liver disease. *Mol Cell* 81: 5052-5065.e6, 2021.
94. Chai J, Wang Q, Qiu Q, Han G, Chen Y, Li W and Zhang H: YBX1 regulates the survival of chronic myeloid leukemia stem cells by modulating m(6)A-mediated YWHAZ stability. *Cell Oncol (Dordr)* 46: 451-464, 2023.
95. Evans MK, Matsui Y, Xu B, Willis C, Loomer J, Milburn L, Fan Y, Pagala V and Peng JC: Ybx1 fine-tunes PRC2 activities to control embryonic brain development. *Nat Commun* 11: 4060, 2020.
96. Jiang WJ, Sun MH, Li XH, Lee SH, Heo G, Zhou D and Cui XS: Y-box binding protein 1 influences zygotic genome activation by regulating N6-methyladenosine in porcine embryos. *J Cell Physiol* 238: 1592-1604, 2023.
97. Peng J, He J, Lin L, Li Y and Xia Y: Neural stem cell extracellular vesicles carrying YBX1 inhibited neuronal pyroptosis through increasing m6A-modified GPR30 stability and expression in ischemic stroke. *Transl Stroke Res* 16: 262-279, 2025.
98. Huang H, Weng H, Sun W, Qin X, Shi H, Wu H, Zhao BS, Mesquita A, Liu C, Yuan CL, *et al*: Recognition of RNA N(6)-methyladenosine by IGF2BP proteins enhances mRNA stability and translation. *Nat Cell Biol* 20: 285-295, 2018.
99. Ramesh-Kumar D and Guil S: The IGF2BP family of RNA binding proteins links epitranscriptomics to cancer. *Semin Cancer Biol* 86(Pt 3): 18-31, 2022.
100. Ying Y, Wu Y, Zhang F, Tang Y, Yi J, Ma X, Li J, Chen D, Wang X, Liu X, *et al*: Co-transcriptional R-loops-mediated epigenetic regulation drives growth retardation and docetaxel chemosensitivity enhancement in advanced prostate cancer. *Mol Cancer* 23: 79, 2024.
101. Li W, Li W, Leng Y, Xu H, Xia Z and Wang Y: ALKBH5-Mediated M(6)A demethylation of G3BP1 attenuates ferroptosis via cytoplasmic retention of YBX1/p53 in diabetic myocardial ischemia-reperfusion injury. *Adv Sci (Weinh)* 12: e07254, 2025.
102. Wang C, Shen S, Kang J, Sugai-Munson A, Xiao X, Zhang Y, Zhu J, Liu Z, McKay TB, Akeju O, *et al*: METTL3 is essential for exercise benefits in diabetic cardiomyopathy. *Circulation* 152: 327-345, 2025.
103. Xi Q, Yang G, He X, Zhuang H, Li L, Lin B, Wang L, Wang X, Fang C, Chen Q, *et al*: M(6)A-mediated upregulation of lncRNA TUG1 in liver cancer cells regulates the antitumor response of CD8(+) T cells and phagocytosis of macrophages. *Adv Sci (Weinh)* 11: e2400695, 2024.
104. Yin H, Chen L, Piao S, Wang Y, Li Z, Lin Y, Tang X, Zhang H, Zhang H and Wang X: M6A RNA methylation-mediated RMRP stability renders proliferation and progression of non-small cell lung cancer through regulating TGFBR1/SMAD2/SMAD3 pathway. *Cell Death Differ* 30: 605-617, 2023.
105. Zhang H, Han Y, Wu C, Wang S, Chen M, Xu Q, Wei H, Zhou X and Wang G: m6A-modified LINC02418 induces transcriptional and post-transcriptional modification of CTNNB1 via interacting with YBX1 and IGF2BP1 in colorectal cancer. *Cell Death Discov* 11: 101, 2025.
106. Gunasekaran VP, Nishi K, Sivakumar D, Sivaraman T and Mathan G: Identification of 2,4-dihydroxy-5-pyrimidinyl imidothiocarbamate as a novel inhibitor to Y box binding protein-1 (YB-1) and its therapeutic actions against breast cancer. *Eur J Pharm Sci* 116: 2-14, 2018.

107. He M, Li T, Wang A, Liu Y, Wang X, Liu Z, Xie J, Wang Y, Wang Y, Ren Z, *et al*: MARCH8/NSUN6/ROS-mediated DNA damage positive feedback loop regulates cisplatin resistance in osteosarcoma. *Cell Death Differ*: Jul 19, 2025 (Epub ahead of print).
108. Huang H, Fang L, Zhu C, Lv J, Xu P, Chen Z, Zhang Z, Wang J, Wang W and Xu Z: YBX1 promotes 5-Fluorouracil resistance in gastric cancer via m<sup>5</sup>C-dependent ATG9A mRNA stabilization through autophagy. *Oncogene* 44: 2357-2371, 2025.
109. Li D, Chu X, Liu W, Ma Y, Tian X and Yang Y: The regulatory roles of RNA-binding proteins in the tumour immune microenvironment of gastrointestinal malignancies. *RNA Biol* 22: 1-14, 2025.
110. Ma L, Singh J and Schekman R: Two RNA-binding proteins mediate the sorting of miR223 from mitochondria into exosomes. *Elife* 12: e85878, 2023.
111. Dinh NTM, Nguyen TM, Park MK and Lee CH: Y-Box binding protein 1: Unraveling the multifaceted role in cancer development and therapeutic potential. *Int J Mol Sci* 25: 717, 2024.
112. Alkrekshi A, Wang W, Rana PS, Markovic V and Sossey-Alaoui K: A comprehensive review of the functions of YB-1 in cancer stemness, metastasis and drug resistance. *Cell Signal* 85: 110073, 2021.



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