Review

Role of N6-methyladenosine methyltransferase component RBM15 in cancer progression and its therapeutic potential

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Abstract

Cancer ranks as a primary cause of mortality globally, and the study of its molecular markers and regulatory mechanisms holds paramount importance. N6-methyladenosine (m⁶A) represents the predominant modification in messenger RNA (mRNA), influencing key biological processes including RNA stability, splicing, and translation. The dynamic modulation of m⁶A modification is mediated by an array of enzymes comprising methyltransferases ("writers"), demethylases ("erasers"), and m⁶A-binding proteins ("readers").As a pivotal member of the m⁶A "writer" family, RNA binding motif protein 15 (RBM15) facilitates the recruitment of the methyltransferase complex (MTC) to mRNA, thus orchestrating the addition of m⁶A modifications. Although prior research has underscored the critical role of m⁶A in oncogenesis, the precise mechanisms through which RBM15 operates in cancer are yet to be elucidated. This study endeavors to elucidate the structural characteristics and functional roles of RBM15, investigate its potential regulatory mechanisms across diverse tumors, uncover its distinct functions in tumor genesis, progression, and metastasis, and evaluate the therapeutic potential of targeting RBM15 in cancer treatment.

Keywords RBM15 · m⁶A · Oncogenesis · Therapeutic targets · Molecular regulation

1 Introduction

The m⁶A modification represents a dynamic process that encompasses multiple stages and associated enzymes, primarily categorized as "writers," "erasers," and "readers." The addition of m⁶A modifications is facilitated by specific methyltransferase complexes, termed "writers," including METTL3/14/16, RBM15/15B, ZC3H13, WTAP, and KIAA1429. The removal of m⁶A modifications is primarily mediated by demethylases, termed "erasers," such as FTO and ALKBH5.m⁶A modifications are recognized by m⁶A-binding proteins, including YTHDF1/2/3, YTHDC1/2, IGF2BP1/2/3, and HNRNPA2B1, collectively referred to as "readers" [1, 2]. Research suggests that m⁶A modifications play a role in nearly every stage of the RNA life cycle in eukaryotes, including the regulation of mRNA transcription, maturation, translation, degradation, and stability [3]. Recent studies have highlighted that m⁶A RNA modifications are pivotal in both physiological and pathological contexts, particularly in the onset and progression of human cancers [4, 5] (Fig. 1).

RBM15 is an evolutionarily conserved protein within the spen family, which plays a role in cell fate determination. Additionally, RBM15 is an RNA-binding protein encoded by the RBM15/OTT gene on chromosome 1 [3], which has been identified as a novel gene involved in specific chromosomal translocations in infant acute megakaryoblastic leukemia, particularly in children without Down syndrome [6]. A deficiency in and its paralog RBM15B disrupts XIST-mediated

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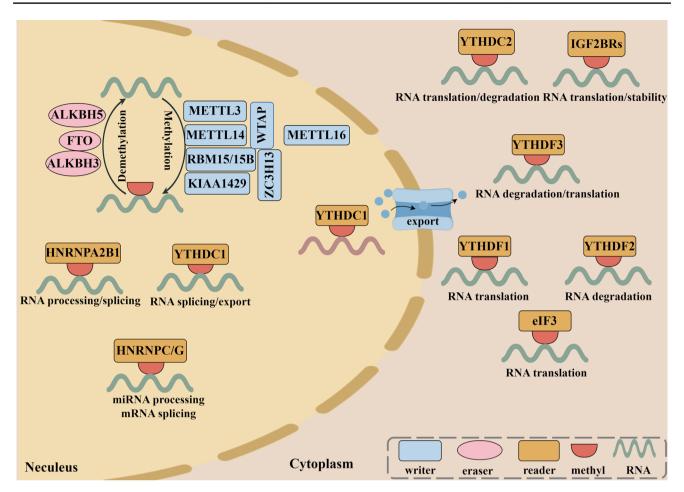


Fig. 1 m⁶A modification represents a vital chemical alteration in messenger RNA (mRNA), profoundly influencing the functionality and metabolic processes of RNA molecules, which encompasses aspects such as RNA stability, post-transcriptional modifications, translation efficiency, and degradation. The addition and removal of m⁶A are facilitated by the coordinated actions of multiple enzymes. Writer enzymes, or methyltransferases—primarily comprising the METTL3, METTL14, and METTL16 complex—add methyl groups to specific adenosine residues in RNA molecules, thereby forming m⁶A modifications. These enzymes collaborate synergistically with auxiliary factors including WTAP, VIRMA, ZC3H13, and RBM15B, enhancing their methylation activity and specificity. Primary erasers, or demethylases, such as FTO, ALKBH5, and ALKBH3, remove m⁶A modifications from RNA, thereby regulating RNA function and metabolic status, influencing the biological processes involved. Reader proteins, encompassing the YTHDF family (YTHDF1, YTHDF2, YTHDF3), YTHDC family (YTHDC1, YTHDC2), and others such as IGF2BP family proteins, HNRNPC/G, eIF3, etc., specifically recognize and bind to m⁶A sites, thus regulating RNA stability, translation, and additional biological functions

gene silencing on the X chromosome during female mammalian development [7]. RBM15 functions as a key component of the methyltransferase complex, interacting with METTL3 in a WTAP-dependent manner to direct transcript-specific methylation, thereby mediating methylation specificity [8]. RBM15 is a methylation regulator; however, despite its classification as an m⁶A methyltransferase, the addition of m⁶A is primarily carried out by METTL3, which has been identified as a WTAP interactor through proteomic analyses. Moreover, studies in Drosophila have demonstrated that the homolog Spenito (Nito) is crucial for m⁶A formation in these organisms [9]. Confocal microscopy observations indicate that RBM15 is predominantly localized at nuclear RNA splicing sites, suggesting its role in RNA splicing [10]. Furthermore, RBM15 is integral to both the physiological and pathological processes in organisms [11].

This review delineates the role and molecular mechanisms of RBM15 in oncogenesis, detailing the genetic and proteomic characteristics of RBM15 and its implications in cancer progression. By thoroughly examining extant studies, this review seeks to enhance the comprehension of RBM15's role in cancer biology.

RBM15 emerges as a pivotal regulator in m⁶A modifications, exhibiting extensive and complex biological functions. Although its central role in tumorigenesis has become increasingly evident, the specific mechanisms by which RBM15 exerts its effects remain largely unexplored. In this review, we aim to systematically elucidate the molecular characteristics



and functional mechanisms of RBM15, stimulating further research to facilitate its translation into cancer therapeutic strategies.

2 RBM15's biological functions

2.1 Structure and characteristics of RBM15

RBM15, an RNA-binding protein, is located on human chromosome 1p13.2 and comprises 19 exons and 18 introns. This protein was initially identified in infants diagnosed with acute megakaryoblastic leukemia, involving the t(1; 22)(p13; q13) translocation [12]. RBM15 exhibits a typical SPEN family protein-like structure, incorporating three highly conserved N-terminal RNA recognition motifs (RRM) and a SPEN paralogue and orthologue C-terminal (SPOC) domain. The RRM structural motif is composed of four antiparallel β -sheets and two α -helices. The RRM domain, prevalent in eukaryotes, plays a pivotal role in post-transcriptional splicing, translation, nuclear export, and mRNA stability. The SPOC domain, characterized by seven β -strands and four α -helices, plays a key role in the structural integrity of the protein [13–15]. The RRM and SPOC domains of RBM15 facilitate diverse protein–protein interactions, thus playing a crucial bridging role in the regulation of gene expression. (Fig. 2).

2.2 Role of RBM15 in m⁶A modification

RBM15 and RBM15B, though non-catalytic, bind to METTL3 and WTAP, directing these proteins to specific RNA sites for m⁶A modification. The interaction between RBM15/15B and METTL3 is WTAP-dependent, as documented in recent studies [7, 16]. RBM15 binds directly to target mRNA sequences abundant in uridine (U), thus recruiting the m⁶A methyltransferase complex, also known as the "writer," to catalyze the m⁶A modification [14]. Furthermore, proteomic analyses have recently identified RBM15 and RBM15B as high-confidence interactors with WTAP, which is a newly recognized component of the RNA processing machinery with significant roles in post-transcriptional control and cell cycle regulation [17]. The interaction between the METTL3-METTL14 complex and RBM15, which is dynamic and WTAP-level dependent, illustrates the complexity of these molecular relationships [7]. Recent studies have demonstrated that phosphorylation, especially of the N-terminal S14 of WTAP, influences the interaction between the RBM15 SPOC domain and WTAP.RBM15 exhibits a robust binding to WTAP through the SPOC domain, and mutational analyses have demonstrated that the R834 residue is critical for this interaction. Additionally, it has been shown that ZC3H13 does not directly bind to the RBM15 SPOC domain [14]. X-chromosome inactivation, a process in mammals that balances the expression levels of X-linked genes between XX females and XY males, is mediated by the long non-coding RNA known as X-inactive specific transcript (XIST). RBM15 participates in Xist-mediated chromosomal silencing by engaging with the METTL3/14 complex, thereby facilitating the deposition of m⁶A modifications within targeted regions of Xist RNA. While the role of RBM15 in the silencing process is considered minor, it potentially influences RNA folding, stability, and interactions with other relevant proteins, thereby contributing to its association with Xist function [18]. RBM15 and RBM15B constitute essential components of the m⁶A methylation complex, indispensable for XIST-mediated gene silencing. They initiate gene silencing mechanisms through their binding to XIST.RBM15 and RBB15B perform redundant functions; dual knockdown of these proteins significantly impairs XIST function, resulting in silencing defects. The binding of RBM15/15B dictates the methylation of specific DRACH sites, thereby influencing the transcriptional regulation of mRNA and XIST [7]. Further, super-resolution structured illumination microscopy studies have revealed that Rbm15, Wtap, and Spen co-localize

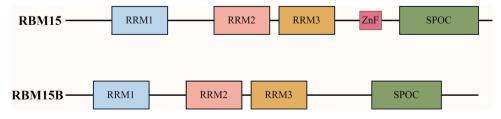


Fig. 2 Structural Comparison of RBM15 and RBM15B.Both proteins possess three RNA recognition motifs (RRMs) at the N-terminal region and a SPOC domain at the C-terminal region. RBM15 uniquely contains a zinc finger (ZnF) domain between the RRMs and the SPOC domain, which is absent in RBM15B



within the same nuclear subcompartment adjacent to Xist RNA, where these factors are likely to interact directly with XIST, facilitating transcriptional silencing of X chromosome genes [19].

RBM15 possesses highly conserved structural features and plays an essential role in RNA methylation processes. We propose that a deeper investigation into RBM15's context-specific interactions and regulatory mechanisms will enhance our understanding of the complex m⁶A modification network, particularly in pathological conditions, and thus guide targeted therapeutic development.

3 Expression and clinical significance of RBM15 in cancer

Bioinformatics analyses have revealed numerous instances of RBM15 overexpression at the transcriptional level in various cancers. Considering the pivotal role of RBM15 protein, elucidating its expression characteristics in cancer is imperative. Pan-cancer analysis investigates changes at the DNA, RNA, and protein levels across various human tumors to identify genes linked to tumor development, a critical aspect for advancing cancer prevention and patient survival rates [20]. Recent studies have examined the expression levels of RBM15 protein across a range of cancers. In pancreatic cancer, there is a noted overexpression of RBM15 protein in tumor tissues relative to adjacent normal tissues [21]. Inhibition of RBM15 suppresses pancreatic cancer development and modulates macrophage phagocytosis, potentially enhancing the efficacy of immunotherapy strategies for pancreatic cancer [22]. In colorectal cancer, an overexpression of RBM15 protein in tumor tissues compared to normal tissues has been associated negatively with overall and disease-free survival [23, 24]. In laryngeal cancer, a significant increase in RBM15 expression has been observed, which promotes in vivo tumor growth and correlates with a poor prognosis [25]. Upregulation of RBM15 in cervical cancer patients and cells has been observed, with higher levels correlating with poor clinical outcomes [26]. Further, investigations into breast cancer have demonstrated that patients with basal-like breast cancer exhibit significantly elevated RBM15 levels and poorer clinical outcomes compared to those with non-basal-like breast cancer [27]. Another study identified significant upregulation of METTL3 and RBM15 in bladder cancer specimens.METTL3 and RBM15 cooperatively enhance m⁶A modifications in long non-coding RNAs, contributing to the progression of bladder cancer [28]. RBM15 expression is elevated in various malignancies including stomach cancer [29], osteosarcoma [30], esophageal cancer [31], and kidney cancer [32]. Investigations by Zhao et al. reveal that mutations and copy number variations of RBM15 are prevalent across various human cancers. In numerous cancers, elevated RBM15 expression correlates with adverse prognosis and tumor immunity, particularly in pancreatic cancer [33]. This expression suggests mutations or copy number alterations in 25 cancer types, accompanied by aberrant upregulation of RBM15 mRNA. Prior research indicates that elevated RBM15 expression impacts the prognosis of patients with HBV-associated hepatocellular carcinoma [34]. Research has demonstrated that immune checkpoints are frequently upregulated in diverse malignancies, enhancing tumor growth and exhibiting high expression in dysfunctional CD8+T cells. This suggests that the association of RBM15 with immune checkpoint markers underscores its critical role in modulating tumor immunity [35]. Consequently, RBM15 may be regarded as a significant oncogenic gene. Notably, RBM15 protein exhibits reduced expression in certain benign tumors; for example, YTHDC1 and YTHDC2 display elevated levels in aortic dissection tissues relative to normal samples, whereas RBM15 shows decreased expression [36]. Given that RBM15 facilitates m⁶A modifications in numerous target transcripts, its overexpression augments total m⁶A modifications in cellular RNA. The overexpression of RBM15 and its association with poor prognosis in cancer patients imply that increased levels of RBM15 protein and m⁶A modifications actively contribute to tumorigenesis. However, it remains uncertain whether the overexpression of RBM15 and elevated m⁶A modifications can initiate tumorigenesis.

RBM15, functioning as an RNA-binding protein, influences mRNA stability and translation through the regulation of mRNA methylation levels, consequently affecting cell proliferation, invasion, and survival. These functions are pivotal in the progression of cancer, particularly in terms of cancer aggravation and resistance to treatment. In several malignancies, including pancreatic, colorectal, cervical, breast, and lung cancer, RBM15 expression inversely correlates with prognosis, underscoring its potential as a biomarker and therapeutic target.

In conclusion, as a multifaceted RNA-binding protein, RBM15 occupies a central position in the oncogenic development and progression. The potential application of RBM15 in oncological therapy merits additional research and development. These findings not only furnish a novel perspective on the molecular mechanisms underlying cancer but also propose potential targets for future oncological treatment strategies. The frequent overexpression of RBM15 across diverse cancers, coupled with its prognostic significance, highlights its broad clinical potential. Future studies should prioritize clinical validation of RBM15 as a robust cancer biomarker, facilitating its integration into precision diagnostics and prognostic evaluation to ultimately improve patient outcomes (Table 1).



4 The role of RBM15 in cancer

RBM15 exerts a crucial role in the oncogenesis, wherein it modulates the proliferation and viability of tumor cells. Research indicates that RBM15 orchestrates the expression of oncogenes through the control of RNA splicing and post-transcriptional modifications. For instance, it contributes to the regulation of genes linked to the cell cycle and apoptosis, which directly influence tumor growth and metastasis. The aberrant expression of RBM15 is strongly correlated with adverse prognoses in diverse cancers, positioning it as a potential biomarker and therapeutic target. The disruption of RBM15 is intricately linked to the malignant progression of a variety of human cancers. Herein, we systematically review the most recent developments concerning the role of RBM15 in human cancers (Figs. 3, 4, 5 and Table 2).

4.1 Pancreatic cancer

Pancreatic cancer ranks as the tenth most prevalent malignant neoplasm in China. It is the sixth and seventh leading cause of cancer-related mortality among men and women, respectively, exhibiting a 5-year survival rate of merely 7.2% to 9%. In the United States, the 5-year survival rate approximates 10%, with pancreatic cancer increasingly recognized as a common cause of cancer mortality [37]. Research indicates that RBM15 expression is elevated in patients with pancreatic cancer, correlating with adverse prognostic outcomes. Furthermore, RBM15 is instrumental in advancing tumor proliferation, invasion, and metastasis [21]. Additionally, studies demonstrate that elevated RBM15 expression across 25 cancer types is associated with unfavorable prognoses, especially in pancreatic cancer.RBM15 is implicated in tumor immune infiltration and checkpoint markers, potentially serving as a prognostic biomarker and immunotherapeutic target in pancreatic cancer [33]. Importantly, research has demonstrated that m⁶A modification influences immune cell infiltration in the pancreatic cancer microenvironment, with RBM15 playing a regulatory role in macrophage functions. Inhibition of RBM15 can suppress pancreatic cancer growth and augment macrophage phagocytosis, presenting novel strategies for pancreatic cancer immunotherapy [22].

4.2 Liver cancer

Liver cancer ranks among the most prevalent cancers globally, with hepatocellular carcinoma (HCC) as its dominant form. HCC constitutes the third most common cause of cancer mortality worldwide, exhibiting a relative five-year survival rate of approximately 18% [38]. High recurrence and metastasis rates characterize HCC, and the prognosis for affected patients is notably poor, particularly in advanced disease stages [39]. RBM15 facilitates the post-transcriptional activation of the YES proto-oncogene 1 (YES1) via m⁶A modification, dependent on insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1). Upon activation of YES1, RBM15 additionally advances HCC progression through the mitogen-activated protein kinase (MAPK) pathway. Consequently, RBM15 may function as a potential biomarker for prognosis prediction in HCC [40]. Furthermore, vascular endothelial growth factor A (VEGFA), a critical angiogenic factor, exhibits high expression in HCC. Recent research has identified high methylation levels of VEGFA in HCC, regulated by components of the m⁶A methyltransferase complex, including RBM15, reader YTHDF2, and IGF2BP3.RBM15 enhances the m⁶A modification-driven binding of IGF2BP3 or YTHDF2 to VEGFA mRNA, which stabilizes and increases its expression, thus promoting angiogenesis and tumor growth in HCC. Consequently, targeting RBM15, IGF2BP3, or YTHDF2 could represent a novel approach for anti-angiogenic therapy in HCC by inhibiting VEGFA[41].

4.3 Esophageal cancer

Esophageal cancer (ESCA) ranks as the sixth leading cause of cancer-related mortality globally [42]. ESCA is categorized into two primary histological subtypes: esophageal adenocarcinoma and esophageal squamous cell carcinoma (ESCC), each exhibiting distinct geographical and epidemiological profiles [43]. miR-3605-5p shows significant expression in ESCC, notably accompanied by reduced expression of KRT4.Overexpression of RBM15 induces cell proliferation and migration in ESCC. Subsequent research has demonstrated that RBM15 mediates the m⁶A modification of miR-3605-5p, facilitating the maturation of miR-3605-5p, which subsequently targets KRT4 to activate the p53 signaling pathway, thus enhancing cell proliferation and migration. The RBM15/miR-3605-5p/KRT4 axis presents a potential therapeutic target for ESCC in clinical applications[31].



Table 1 Expression and clinical significance of RBM15 in cancer

ימסופ באלוכיזיין מוומ כווו	ומסוב ו באטוכיזיסון מווס כיווויכמו זיפוווינמווכב טו זיסואויס ווו כמווכב	52.5	
Type of cancer	Expression level	Clinical/prognostic	References
Pancreatic cancer	High expression	Associated with poor prognosis, inhibition of RBM15 inhibits tumor development and improves immunotherapy [21, 22]	[21, 22]
Colorectal cancer	High expression	Negatively correlated with overall survival and disease-free survival	[23, 24]
Laryngeal cancer	High expression	High expression promotes tumor growth and associates with poor prognosis	[25]
Cervical cancer	Up-regulation	Poor clinical outcomes	[56]
Breast cancer	Significantly elevated in basal-like breast cancer	High RBM15 expression is associated with poorer clinical outcomes in patients with basal-like breast cancer	[27]
Bladder cancer	Significantly upregulated	Associated with cancer progression	[28]
Gastric cancer	High expression	Associated with tumor progression	[59]
Osteosarcoma	High expression	Associated with tumor progression	[30]
Esophageal cancer	High expression	Associated with tumor progression	[31]
Kidney cancer	High expression	Associated with tumor progression	[32]
Hepatocellular carcinoma	High expression	Poor prognosis in patients with hepatocellular carcinoma associated with high expression of HBV	[34]



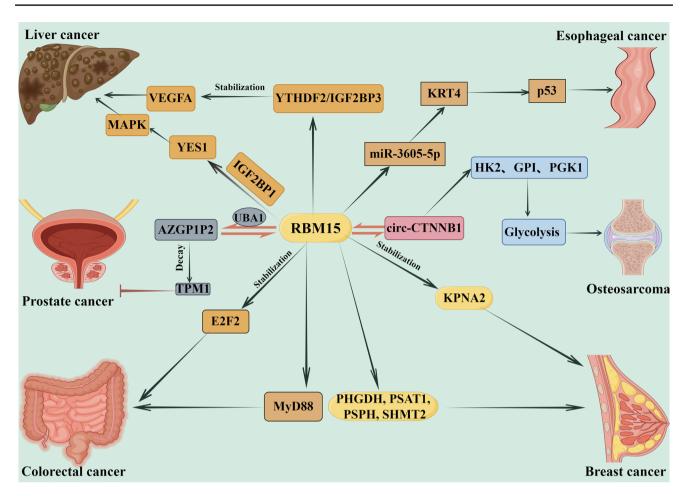


Fig. 3 The Role of RBM15 in Cancer

4.4 Prostate cancer

Prostate cancer is identified as the second leading cause of cancer-related mortality among men and remains the most frequently diagnosed cancer in males across a majority of countries globally [43]. AZGP1P2 is instrumental in regulating the stemness and apoptosis of prostate cancer stem cells (PCSCs) in castration-resistant prostate cancer (CRPC), thereby augmenting the therapeutic efficacy of docetaxel. Furthermore, AZGP1P2 collaborates with UBA1 and RBM15 to control the degradation of TPM1 mRNA, effectively inhibiting tumor proliferation and metastasis, thereby elucidating a novel molecular mechanism for treating CRPC[44].IGF2BPs attach to methylated DNA-RNA hybrids via KH domains and modulate gene expression through RBM15-mediated m⁶A modifications of R loops. Additionally, the trans-omics regulation of RBM15/IGF2BPs/DNMT1 unveils novel interactions between RNA and DNA methylation, identifying SEMA3F as a potential biomarker linked to the survival of prostate cancer patients[45].

4.5 Osteosarcoma

Osteosarcoma (OS) represents the most frequent primary malignant bone tumor [46] and commonly affects individuals aged 10 to 30. The standard treatment for osteosarcoma involves surgical resection followed by adjuvant chemotherapy [47]. Approximately 60% of patients fall within the 10 to 20 age range, with osteosarcoma being the second most common cause of mortality in this demographic [48]. Studies have shown that the circular RNA circ-CTNNB1, which is highly expressed in OS tissues and cells, interacts with RBM15 to promote m⁶A modification, consequently enhancing the expression of HK2, GPI, and PGK1. This process stimulates glycolysis and fosters the growth, invasion, and metastasis of OS cells [30], presenting a potential therapeutic target for osteosarcoma.



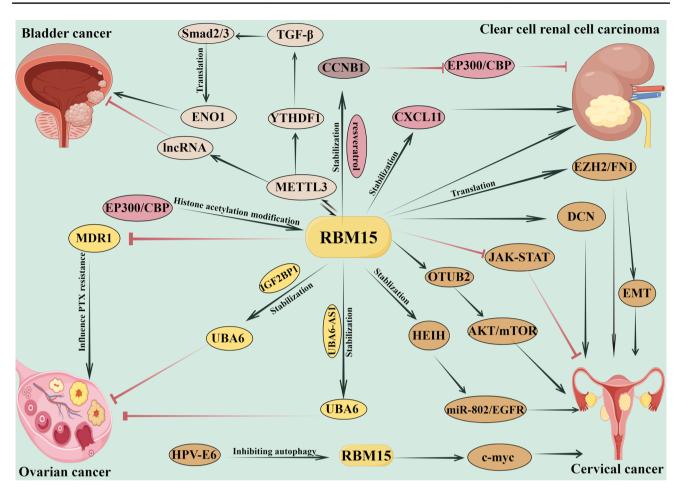


Fig. 4 The Role of RBM15 in Cancer

4.6 Colorectal cancer

Colorectal cancer represents the fourth most prevalent cancer in the United States and the second leading cause of cancer-related mortality, notably among men under 50 years of age [49]. Studies indicate that RBM15 facilitates CRC cell proliferation, invasion, and metastasis by mediating MyD88 mRNA methylation modifications via m⁶A in colorectal cancer. The silencing of RBM15 inhibits CRC cell proliferation and enhances apoptosis, demonstrating a negative correlation with the survival rates of CRC patients [24]. Recently, a growing body of research has concentrated on elucidating the mechanisms of RBM15 in CRC. Zhang et al. discovered that RBM15 exerts a carcinogenic effect on colorectal cancer by stabilizing E2F2 mRNA via binding to E2F2 and relying on m⁶A modification, thereby promoting the malignant phenotype of CRC cells. Furthermore, the silencing of RBM15 significantly reduces the proliferation and invasion of CRC cells, identifying the RBM15/E2F2 axis as a potential novel target for CRC therapy [23]. Additional research has investigated the role of RBM15 in colorectal cancer, analyzing its association with m⁶A modification and noting its elevated expression in CRC as linked to tumor progression. Via molecular typing and prognostic modeling, RBM15, as a crucial methylation regulator, significantly impacts the immune microenvironment and prognosis of CRC [50].

4.7 Breast cancer

Breast cancer represents a principal cause of cancer incidence, disability, and mortality globally among women, constituting the most frequently diagnosed malignancy [51]. Moreover, in the United States, breast cancer ranks as



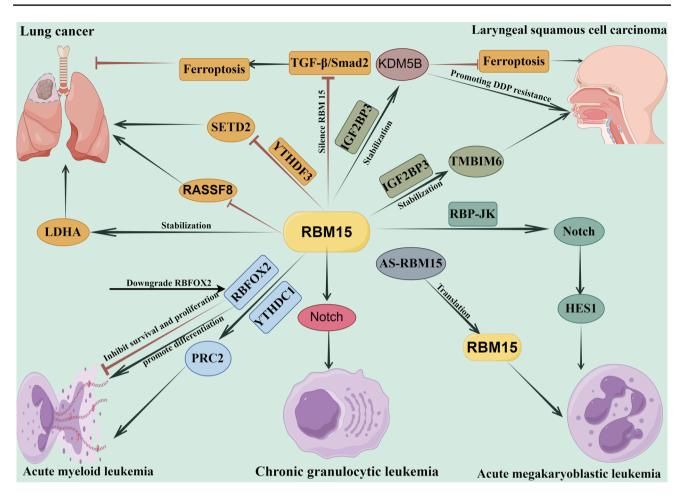


Fig. 5 The Role of RBM15 in Cancer

the second most prevalent cancer among women and the second leading cause of cancer mortality [52]. RBM15 is notably upregulated in basal-like breast cancer and correlates with an adverse clinical prognosis. The study indicates that RBM15 influences cancer cell growth through the regulation of m⁶A levels in genes involved in serine and glycine metabolism, including PHGDH, PSAT1, PSPH, SHMT2.RBM15 directly binds to the RNA of these genes and regulates their metabolic pathways, thus promoting cancer cell proliferation [27]. Furthermore, research demonstrates that elevated RBM15 expression is intimately associated with the malignant progression and immune evasion in breast cancer.RBM15 augments the stability and expression of KPNA2 mRNA via m⁶A methylation, thereby facilitating the progression of breast cancer and immune evasion [53].

4.8 Bladder cancer

Bladder cancer ranks ninth globally in terms of diagnosis frequency, with a markedly higher incidence and burden in males compared to females. It is the sixth most common cancer among women and the ninth leading cause of cancer-related mortality. Bladder cancer is frequently classified as one of the most aggressive malignancies within the urinary reproductive system [54]. Notable upregulation of METTL3 and RBM15 has been observed in specimens of bladder cancer. Knockdown of METTL3 and RBM15 led to marked reductions in tumor cell proliferation, invasion, and migration, accompanied by decreased m⁶A methylation levels in tumor cells. Subsequent research has pinpointed METTL3 and RBM15 as pivotal regulators of m⁶A-associated lncRNAs, noting that their upregulation corresponds with the overexpression of lncRNAs. This finding offers novel molecular targets for bladder cancer and enhances the understanding of m⁶A modifications, thereby facilitating clinical translation [28]. ENO1 functions as an oncogene and, in its capacity as a glycolytic enzyme, it promotes tumor proliferation while inhibiting apoptosis in cancer cells.



References [22] [74] [7] [75] [73] [40] [41] **64**] [36] [68] [28] **6**2 [66] **63** [30] [77] [25] [88] Promote glycolysis, promote cell growth, inva-Promote proliferation, invasion, migration and Promoting megakaryocyte differentiation and Promotes proliferation, migration and tumor Promotes angiogenesis and promotes tumor Inhibit ferroptosis, promote DDP resistance, Promote the malignant transformation and Promoting leukemogenesis through fusion Promote malignant behavior and enhance Regulating cell proliferation and migration Inhibiting cell proliferation, migration and promote tumor proliferation and inhibit IGF-β increases m⁶A modification via Smad2/3 Promote the expression of ENO1 protein, Promote cell growth and enhance mRNA Inhibiting cell proliferation and invasion Affecting myeloid cell differentiation nhibition of RASSF8 protein levels affects m⁶A Promote cell invasion and migration Promotes cell proliferation and EMT inhibit apoptosis of LSCC cells Promote cellular ferroptosis **Enhanced LDHA expression** growth and metastasis sion and metastasis progression of HCC Promote apoptosis **Biological effects** modification signaling invasion proteins circ-CTNNB1 interacts with RBM15 to enhance RBM15 co-regulates m⁶A levels with METTL3, translation, and activate signaling pathways and upregulation promotes IncRNA expres-Mediated m⁶A modification of OTUB2 mRNA GF2BP1-dependent promotion of post-tran-Enhance m⁶A modification, enhance protein Affects DNA repair and histone modification upregulates AKT/mTOR signaling and pro-HPV-E6 accumulates RBM15 through inhibiilencing RBM15 reduces TGF-β and Smad2 nhibitory pathway inhibits tumorigenesis Stabilizing HEIH affects cell stemness and Promote m⁶A modification and enhance metastasis via miR-802/EGFR pathway Enhanced TMBIM6 stability via IGF2BP3 mproving KDM5B Stability by IGF2BP3 Regulation of HES1 activity by RBP-JK Enhanced RBM15 protein translation glycolysis-related gene expression Affects the stability of DCN mRNA VEGFA stability and expression Influence epigenetic regulation scriptional activation of YES1 motes malignant behavior **Enhanced mRNA stability Molecular mechanisms** tion of autophagy dependence modification expression OTUB2, AKT/mTOR signaling pathway m⁶A-associated IncRNA, METTL3 ENO1, TGF-β, Smad2/3 Pathway HEIH, miR-802/EGFR pathway VEGFA/YTHDF2/IGF2BP3 Target gene or pathway RBM15-MKL1, Setd1b JAK-STAT pathway AS-RBM15 series SETD2, YTHDF3 HPV-E6, c-myc HK2, GPI, PGK1 TGF-β/Smad2 Notch signal **DCN Series** EZH2/FN1 RASSF8 TMBIM6 KDM5B LDHA MAPK Acute megakaryocytic leukemia Acute megakaryocytic leukemia Acute megakaryocytic leukemia Lung adenocarcinoma Lung adenocarcinoma Lung adenocarcinoma Laryngeal cancer Laryngeal cancer Cervical cancer Cervical cancer Cervical cancer Cervical cancer Cervical cancer Bladder cancer Cervical cancer ype of cancer Bladder cancer Osteosarcoma Lung cancer Liver cancer Liver cancer



The Role of RBM15 in Cancer

Type of cancer	Target gene or pathway	Molecular mechanisms	Biological effects	References
Acute myeloid leukemia	RBFOX2, YTHDC1, PRC2	m ⁶ A methylation of promoter-associated RNA and chromatin silencing	RBFOX2 down-regulation inhibits proliferation and promotes differentiation of leukemia cells	[81]
Colorectal cancer	MyD88	Promotes MyD88 mRNA methylation	Promote CRC cell proliferation, invasion and metastasis, and inhibit apoptosis	[24]
Colorectal cancer	E2F2	Binding to E2F2 stabilizes E2F2 mRNA	Promoting malignant phenotype, targeted therapy	[23]
Ovarian cancer	Immune gene marker	High expression is associated with metastasis and immune cell infiltration	Promote metastasis and reduce drug resistance	[09]
Ovarian cancer	MDR1, TGF-β signaling pathway	Inhibition of RBM15 expression by m ⁶ A meth- ylation levels and Smad2	Influence PTX resistance	[61]
Ovarian cancer	UBA6 mRNA, IGF2BP1	Enhanced RNA stability	Inhibiting cell proliferation, migration and invasion	[62]
Chronic myelogenous leukemia	Notch signal	Affects Notch signaling	Inhibit cell growth and induce apoptosis	[84]
Prostate cancer	AZGP1P2/UBA1/TPM1	Modulating TPM1 mRNA decay and enhancing chemotherapeutic effects	Inhibition of tumor growth and metastasis	[44]
Prostate cancer	IGF2BPs/DNMT1/RBM15	Mediates m ⁶ A modification of the R loop	Gene expression regulation affects patient survival rate	[45]
Breast cancer	PHGDH, PSAT1, PSPH, SHMT2	Affects metabolic pathways and promotes cancer cell proliferation	Associated with poor prognosis of basal-like breast cancer, promoting cancer cell growth	[27]
Breast cancer	KPNA2	m ⁶ A modification to improve mRNA stability	Facilitating progression and immune escape	[23]
Esophageal squamous cell carcinoma	niR-3605-5p/KRT4/p53 pathway	Promote miR-3605-5p maturation and activate the p53 signaling pathway	Promote cell proliferation and migration	[31]
Clear cell renal cell carcinoma	CXCL11	Stabilizes CXCL11 mRNA and promotes CXCL11 secretion in exosomes	Enhance tumor immune escape and promote tumor invasiveness and metastasis	[32]
Clear cell renal cell carcinoma	EP300/CBP	Induced histone acetylation modification	Promotes tumor cell proliferation, migration, invasion, and epithelial-mesenchymal transition	[32]
Clear cell renal cell carcinoma	CCNB1	Affects CCNB1 mRNA stability and inhibits EP300/CBP expression	Induces cell senescence and inhibits tumor progression	[57]
Pancreatic cancer	I	High expression affects tumor immune infiltration and checkpoint markers	Promote proliferation, invasion and metastasis	[33]
Pancreatic cancer	I	Regulating macrophage function and affecting the immune environment	Inhibit cancer growth and enhance macrophage phagocytosis	[22]



Recent research has demonstrated that the RBM15/METTL3 complex augments m⁶A modification of ENO1 mRNA in bladder cancer cells via YTHDF1 dependency, thereby enhancing ENO1 protein translation. Significantly, TGF-β enhances its m⁶A modification via the Smad2/3 pathway, consequently boosting ENO1 expression [55]. In conclusion, targeting RBM15 offers a novel strategy for the treatment of bladder cancer.

4.9 Clear cell renal cell carcinoma

Renal cell carcinoma (RCC) arises from the epithelium of renal tubules and ranks among the top ten malignancies affecting both genders. RCC comprises several pathological variants, with clear cell renal cell carcinoma (ccRCC) being the predominant subtype [32]. Furthermore, it represents the most prevalent and aggressive form of urinary system cancer, characterized by a poor prognosis and high mortality [56]. Upregulation of RBM15 in clear cell renal cell carcinoma (ccRCC) facilitates increased ccRCC cell proliferation, migration, invasion, and epithelial-mesenchymal transition, thus impacting tumor progression.EP300/CBP-induced histone acetylation modifications drive the upregulation of RBM15.RBM15 stabilizes CXCL11 mRNA via m⁶A-dependent mechanisms, promoting CXCL11 secretion in exosomes, which further induces macrophage infiltration and M2 polarization. This research elucidates the pivotal role of the EP300/CBP-RBM15-CXCL11 signaling axis in ccRCC, providing novel insights into ccRCC treatment [32]. Additionally, studies have investigated the therapeutic effects of resveratrol on clear cell renal cell carcinoma. Results demonstrate that resveratrol impedes tumor progression by impacting the stability of RBM15-mediated CCNB1 mRNA, reducing EP300/CBP expression, and promoting cellular senescence, thereby introducing a novel mechanism for treating ccRCC with resveratrol [57].

4.10 Ovarian cancer

Ovarian cancer (OC) ranks as the second leading cause of mortality from gynecological cancers globally [58]. Despite substantial advancements in the rapeutic approaches, approximately 80% of OC patients are diagnosed at an advanced stage, resulting in a high mortality rate. The five-year survival rate for OC patients remains below 45% [59]. Research indicates that RBM15 expression is elevated in OC tissues compared to normal tissues, and this upregulation is correlated with the metastasis of ovarian cancer cells. Furthermore, the degree of immune cell infiltration and the expression of diverse immune gene markers exhibit a close association with RBM15 expression [60]. RBM15 is overexpressed in ovarian cancer (OC) and in paclitaxel (PTX)-resistant cells, which correlates with a poor prognosis in patients. Overexpression of RBM15 augments cell vitality and colony formation, concurrently diminishing sensitivity to PTX, whereas its knockdown inhibits cell proliferation and heightens sensitivity to PTX. Additionally, silencing of RBM15 can reduce MDR1 expression by decreasing the m⁶A methylation level of MDR1 mRNA, thus influencing PTX resistance. Subsequent studies have determined that the TGF-β signaling pathway suppresses RBM15 expression through Smad2 activation, offering a novel strategy for addressing PTX-resistant OC [61]. Significantly, RBM15 interacts with IncRNA ubiquitin-like modifier activating enzyme 6 antisense RNA 1 (UBA6-AS1), facilitating the m⁶A methylation of UBA6 mRNA, thereby enhancing its stability. In conjunction with factors like IGF2BP1, RBM15 enhances the stability of UBA6 mRNA, thereby inhibiting the proliferation, migration, and invasion of ovarian cancer cells [62].

4.11 Cervical cancer

Cervical cancer ranks as the fourth most prevalent cancer among women worldwide, predominantly attributable to the human papillomavirus (HPV). Although vaccination and screening are effective preventive measures, the limited coverage in low-income countries leads to a disproportionate burden of cervical cancer. The World Health Organization advocates the eradication of cervical cancer via a tripartite strategy encompassing vaccination, screening, and treatment of precancerous lesions [37]. Recent research has primarily concentrated on elucidating the specific regulatory mechanisms of RBM15 in cervical cancer.RBM15, an N6-methyladenosine (m⁶A) methylation writer protein, plays a crucial role in the development of cervical cancer. Knockdown of RBM15 significantly reduces the proliferation, migration, and invasion of cervical cancer cells, affecting tumorigenesis by inhibiting the JAK-STAT pathway [63]. Additionally, studies have demonstrated that RBM15-mediated m⁶A modification of OTUB2 mRNA primarily contributes to the upregulation of OTUB2 expression in cervical cancer cells.OTUB2 amplifies the activation of the AKT/mTOR signaling pathway, thereby facilitating the malignant behavior of cervical cancer cells [64]. Significantly, HEIH, a carcinogenic long non-coding RNA, can promote the proliferation, migration, and tumor growth of cervical cancer cells.RBM15 can affect tumor cell proliferation, metastasis, and stemness by stabilizing HEIH expression, with further mechanistic studies suggesting mediation through



the miR-802/EGFR pathway [65]. RBM15 controls the stability of DCN mRNA via m⁶A methylation, thereby promoting tumor cell proliferation, migration, and progression. Further research has indicated that RBM15 knockout can inhibit the malignant traits of cervical cancer, with its antitumor effects achieved through enhanced DCN expression [66]. The human papillomavirus genome comprises eight protein-coding genes, with HPV-E6 and HPV-E7 extensively examined regarding their roles in the onset and progression of cervical cancer. Recent studies have discovered that HPV-E6 facilitates the accumulation of RBM15 protein by inhibiting autophagy, elevates m⁶A modification on c-myc mRNA, and boosts c-myc protein expression, thereby advancing cervical cancer cell growth [67]. RBM15 enhances the m⁶A modification of EZH2, amplifying its protein translation, which in turn activates the EZH2/FN1 signaling pathway, fostering tumor cell proliferation and epithelial-mesenchymal transition (EMT) [26].

4.12 Lung cancer

Lung cancer ranks as one of the top three most common cancers globally among both men and women, and it is the foremost cause of cancer-related mortality, exhibiting a five-year survival rate of approximately 10%-20% [37]. Owing to the often indistinct symptoms of lung cancer in its early stages, more than two-thirds of cases are identified at an advanced and inoperable stage. The five-year survival rate for patients with metastatic stage IV lung cancer is a mere 4.7%, in contrast to 56.3% for those with stage I cancer [68]. Lung adenocarcinoma (LUAD) represents the predominant subtype of lung cancer globally [69]. Research has demonstrated that RBM15 is upregulated in LUAD tissues and cells, correlating with reduced patient survival rates. Further exploration of the relationship between RBM15 and cellular characteristics indicated that RBM15 knockdown led to reduced mRNA methylation levels, decreased cell proliferation, increased apoptosis, and inhibited tumor growth [70]. However, the potential downstream molecular mechanisms underlying RBM15 activity in LUAD and m⁶A modification necessitate further investigation. Recent studies indicate that RBM15 modulates cell invasion and migration in LUAD via m⁶A modification, facilitating invasion by suppressing RASSF8 protein levels, thus proposing the RBM15-m⁶A-RASSF8 axis as a viable therapeutic target [71] Additional research revealed that RBM15-mediated m⁶A modification of LDHA mRNA enhances its stability, thereby playing an oncogenic role in LUAD and identifying the RBM15/LDHA axis as an innovative and promising therapeutic target for LUAD[72].SETD2 serves as an epigenetic biomarker linked to radiosensitivity in lung adenocarcinoma, impacting DNA repair and histone modifications by enhancing chromatin accessibility and gene transcription, thereby promoting LUAD cell apoptosis. This process is adversely affected by RBM15 and YTHDF3, contributing to precision medicine [73]. Additionally, silencing RBM15 via the TGF- β /Smad2 pathway diminishes the expression of TGF- β and Smad2, thereby enhancing ferroptosis in lung cancer cells [74]. RBM15 could represent a potential target for lung cancer treatment, providing new avenues for therapeutic interventions.

4.13 Laryngeal cancer

Laryngeal cancer represents approximately 20% of all head and neck malignancies [75] and ranks as the second most prevalent malignant tumor in the upper respiratory and digestive tracts after lung cancer. An estimated 85%-95% of cases are diagnosed as squamous cell carcinoma (LSCC) [76]. In patients with LSCC, the overall mRNA m⁶A methylation level is significantly elevated, and levels of RBM15 are notably higher. Knockout of RBM15 results in reduced proliferation, invasion, migration, and apoptosis of LSCC cells both in vitro and in vivo. Recent studies have shown that RBM15 and IGF2BP3, functioning as oncogenes in LSCC, are implicated in the m⁶A methylation modification of TMBIM6.RBM15 enhances TMBIM6 stability through dependence on IGF2BP3.Moreover, the downregulation of IGF2BP3 or RBM15 significantly reduces both the levels and stability of TMBIM6 [77]. Other studies indicate that RBM15 enhances the stability of KDM5B via IGF2BP3 dependency, consequently promoting KDM5B expression. Upregulation of KDM5B modulates gene expression by downregulating FER1L4 and upregulating GPX4, and by upregulating KCNQ1OT1 and inhibiting ACSL4, which affects the KDM5B/FER1L4/KCNQ1OT1 axis' influence on GPX4/ACSL4 expression, thereby inhibiting ferroptosis and enhancing DDP resistance in LC cells. Notably, the silencing of RBM15 suppresses tumor growth in vivo[25].

4.14 Acute myeloid leukemia

Acute myeloid leukemia (AML) constitutes a clonal disorder of hematopoietic stem and progenitor cells (HSPCs), marked by abnormal proliferation, impaired differentiation, and accumulation of immature myeloid cells. This disease



manifests as aggressive malignant proliferation of bone marrow stem cells, frequently accompanied by infections, anemia, and bleeding [78]. It represents the predominant form of acute leukemia in adults, with a higher incidence in the elderly population [79, 80]. Recent studies have demonstrated that RBM15, a component of the MTC complex, facilitates m⁶A methylation of promoter-associated RNA through interactions with RBFOX2.Furthermore, RBM15 engages in physical interactions with YTHDC1 to enlist the Polycomb Repressive Complex 2 (PRC2) at the RBFOX2binding gene loci. This interaction not only assists in chromatin silencing but also contributes to transcriptional repression. The RBFOX2/m⁶A/RBM15/YTHDC1/PRC2 axis plays a critical role in the pathogenesis of myeloid leukemia. Additionally, the downregulation of RBFOX2 markedly reduces the survival and proliferation of acute myeloid leukemia cells, while promoting their differentiation into myeloid lineages, thus providing novel potential targets and strategies for leukemia therapy [81].

4.15 Chronic myeloid leukemia

Chronic myeloid leukemia (CML) represents a rare malignancy of the hematopoietic system [82], characterized by the presence of the Philadelphia chromosome t(9;22)(q34;q11.2), resulting in the BCR-ABL1 fusion gene [83]. Investigations have revealed that RBM15 expression is significantly elevated in patients experiencing the blast crisis phase of CML, and inhibition of its expression can arrest CML cell growth and proliferation, induce apoptosis, and facilitate myeloid differentiation. Subsequent research suggests that the function of RBM15 may be mediated via its effects on Notch signaling pathways, playing a pivotal role in the survival of CML cells [84]. This indicates the potential utility of RBM15 as a molecular target for CML treatment.

4.16 Acute megakaryoblastic leukemia

Acute megakaryoblastic leukemia (AMKL) represents a subtype of acute myeloid leukemia (AML) that impacts megakaryocytes [85], characterized by the accumulation of immature megakaryocytes in the bone marrow and thrombocytopenia [86]. Non-Down syndrome-associated pediatric acute megakaryoblastic leukemia (non-DS AMKL) is a rare disorder with a poor prognosis, approximately 15% of cases are linked to the fusion oncogene RBM15-MKL1 due to chromosomal translocation t(1;22), typically manifesting during the fetal period. Research has demonstrated enhanced expression of RBM15-MKL1 target genes in two human pluripotent stem cell lines continuously expressing the RBM15-MKL1 gene [87]. The RBM15-MKL1 fusion protein is implicated in the initiation of AMKL. Investigations reveal that Rbm15 and its fusion protein directly interact with the histone methyltransferase Setd1b, necessitating Rbm15's SPOC domain and Setd1b's LSD motif, altering the Setd1b complex's function, resulting in epigenetic regulatory modifications, potential oncogenic mechanisms in AMKL [88]. Additionally, research has indicated that RBM15, through fusion with MKL1, influences disease progression in AMKL. This research suggests that RBM15 is highly expressed in hematopoietic stem cells, impacting myeloid cell differentiation. Reducing its expression promotes differentiation, whereas overexpression inhibits it.RBM15 regulates Notch signaling via RBP-JK, mediating HES1 activity and playing a cell-type-specific role [89]. The antisense RNA AS-RBM15, by enhancing RBM15 protein translation, facilitates megakaryocyte differentiation. Transcription of AS-RBM15 is activated by RUNX1 and repressed by RUNX1-ETO, potentially playing a role in leukemia. Downregulation of AS-RBM15 may contribute to leukemia induced by AML1-ETO and RBM15-MKL1. Nevertheless, these findings and their connection to the pathogenesis of AMKL warrant further investigation [90].

4.17 RBM15 in cancer drug resistance

RBM15, a critical regulator involved in m⁶A RNA modification, has recently attracted attention for its pivotal roles in cancer therapeutic resistance. Increasing evidence has indicated that RBM15 influences drug resistance in cancer cells by modulating the m⁶A-dependent expression of various resistance-related genes and pathways, highlighting its significance as a potential therapeutic target for overcoming cancer resistance.

Recent studies have demonstrated RBM15 significantly contributes to osimertinib resistance in lung adenocarcinoma through enhancing m⁶A-mediated SPOCK1 expression, promoting epithelial-mesenchymal transition (EMT). This RBM15-SPOCK1 axis was confirmed in osimertinib-resistant H1975 cells and patient-derived organoids, suggesting early RBM15 targeting could enhance responses to EGFR-TKIs [91]. Additionally, RBM15 induces radiotherapy



resistance in NSCLC by elevating IncRNA CBR3-AS1 via m⁶A-IGF2BP3, subsequently increasing CXCL1 expression, recruiting MDSCs, and suppressing anti-tumor immunity [92]. Clinically, elevated RBM15 correlates with radioresistance in NSCLC patients. Furthermore, RBM15 mediates paclitaxel resistance in ovarian cancer by stabilizing MDR1 mRNA [61] and confers cisplatin resistance in laryngeal carcinoma by modulating ferroptosis-related genes (GPX4, ACSL4) [25]. These findings underscore RBM15's broad involvement in therapeutic resistance across diverse cancers.

In summary, RBM15 emerges as a central player in cancer resistance through its regulatory effects on m⁶A modifications, influencing the expression of drug-resistance-related genes, cellular ferroptosis, and immunosuppressive remodeling of the tumor microenvironment. Targeting RBM15 thus holds promising therapeutic potential for reversing resistance and improving cancer treatment outcomes.

Although RBM15 demonstrates common regulatory mechanisms across various cancer types, distinct tissue-specific roles have also been identified. We emphasize the need for in-depth analysis of these unique mechanisms, advocating the development of RBM15-specific therapeutic agents tailored to individual cancer types to advance personalized cancer treatment.

5 Molecular mechanisms of RBM15 in cancer

RBM15, characterized as a multifunctional RNA-binding protein, exerts a critical molecular regulatory function across diverse cancers. It predominantly impacts the biological behavior of cancer cells via mechanisms including the regulation of RNA splicing, m⁶A methylation modification, gene expression, and signaling pathways. Below are six principal molecular mechanisms by which RBM15 functions in cancer.

5.1 Oncogene and signaling pathway regulation

RBM15 functions as an oncogene across multiple cancer types, primarily by promoting cancer cell proliferation and metastasis via modulation of signaling pathways. In hepatocellular carcinoma, RBM15 induces the expression of the YES1 gene via m⁶A modification mediated by IGF2BP1, thereby advancing cancer progression through the MAPK signaling pathway [40]. In esophageal carcinoma, RBM15 augments p53 signaling by facilitating the maturation of miR-3605-5p, consequently promoting the proliferation and migration of cancer cells [31]. Moreover, in chronic granulocytic leukemia, RBM15 influences the survival and differentiation of cancer cells via the Notch signaling pathway [84]. These instances illustrate how RBM15 contributes to the onset and progression of cancer through regulation of pivotal oncogenes and signaling pathways.

5.2 Post-transcriptional modifications and m⁶A methylation

RBM15 plays a significant role in the regulation of m⁶A methylation modifications across various cancers, consequently affecting RNA stability and translation efficiency. In colorectal cancer, RBM15 stabilizes E2F2 mRNA via binding with E2F2 and its dependency on m⁶A modification, thereby enhancing the malignant phenotype of cancer cells [23]. In bladder cancer, RBM15 collaborates with METTL3 to elevate m⁶A modification of ENO1, which promotes protein expression and augments glycolytic activity in cancer cells [55]. In acute myeloid leukemia, RBM15 engages with YTHDC1 to recruit the Polycomb Repressive Complex 2 to specific loci, thereby facilitating chromatin silencing [81]. These post-transcriptional modifications underscore the critical role of RBM15 in cancer regulation via m⁶A methylation.

5.3 Glycolysis and metabolic reprogramming

RBM15 further promotes cancer progression by regulating cellular metabolic pathways, particularly glycolysis. In breast cancer, RBM15 modulates the m⁶A levels of key glycolytic enzymes, including PHGDH and PSAT1, thus regulating metabolic pathways and augmenting the proliferative capabilities of cancer cells [27]. In bladder cancer, this metabolic effect arises from the activity of the RBM15 and METTL3 complex, which enhances the translation of ENO1, thereby promoting intracellular glycolysis [28]. In osteosarcoma, RBM15, by interacting with the circular RNA circ-CTNNB1, enhances the expression of HK2, GPI, and PGK1, thereby augmenting glycolysis and facilitating tumor growth [30]. These studies elucidate RBM15's function as a metabolic regulator within the context of tumor metabolic reprogramming.



5.4 Immunoregulation and tumor microenvironment intervention

RBM15 exerts a pivotal role in cancer immunoregulation, particularly in modulating the tumor microenvironment. In pancreatic cancer, elevated expression of RBM15 facilitates the development of an immunosuppressive microenvironment, which results in macrophage dysfunction and consequently supports tumor proliferation [22]. In clear cell renal cell carcinoma, RBM15 stabilizes CXCL11 mRNA and augments its secretion in exosomes, thereby promoting macrophage infiltration and M2 polarization, thus modifying the tumor microenvironment [32]. This immunoregulatory effect implies a critical role for RBM15 in facilitating cancer immune escape and the remodeling of the tumor microenvironment.

5.5 Ferroptosis and programmed cell death

RBM15 exerts a significant role in various cancers by influencing programmed cell death modalities, including ferroptosis. In lung cancer, the silencing of RBM15 enhances ferroptosis by inhibiting the TGF-β/Smad2 pathway [74]. In laryngeal squamous cell carcinoma, RBM15 downregulation increases chemotherapy resistance through regulation of ferroptosisrelated genes, including GPX4 and ACSL4 [25]. Additionally, in acute myeloid leukemia, RBM15 demonstrates its capacity to regulate the apoptosis pathway, affecting the survival and differentiation of myeloid cells [81]. These investigations reveal that RBM15 modulates the balance of cell life and death through diverse pathways, suggesting potential therapeutic significance in cancer treatment.

5.6 Gene fusion and hematopoietic regulation

RBM15 is implicated in the oncogenesis of specific leukemia types via gene fusion. In non-Down syndrome-associated pediatric acute megakaryoblastic leukemia, the RBM15-MKL1 fusion protein, formed by the fusion of RBM15 with MKL1, exhibits increased expression correlated with the progression of the disease [87]. Recent studies highlight the oncogenic role of RBM15-MKL1 fusion protein in leukemogenesis via RNA-binding and m⁶A methylation inherited from RBM15. RBM15-MKL1 selectively activates Wnt signaling by targeting key genes like Frizzled (Fzd), promoting acute megakaryoblastic leukemia (AMKL) pathogenesis. Inhibition of METTL3 by the novel inhibitor STM3675 disrupted m⁶A modification, induced apoptosis in RM-AMKL cells, and prolonged mouse survival, suggesting targeting these pathways as a promising therapeutic strategy [93]. Additionally, in acute myeloid leukemia, RBM15 modulates the Notch signaling pathway, thereby influencing the differentiation and hematopoietic processes of myeloid cells [89]. These mechanisms demonstrate RBM15's significant influence on hematopoietic cell development, indicating its potential therapeutic value in leukemia treatment. These mechanisms elucidate RBM15's complex role in cancer as an essential molecular node that regulates RNA metabolism, signal transduction, and cellular life and death, consistently revealing its potential as a therapeutic target and offering novel perspectives for innovative treatment strategies.

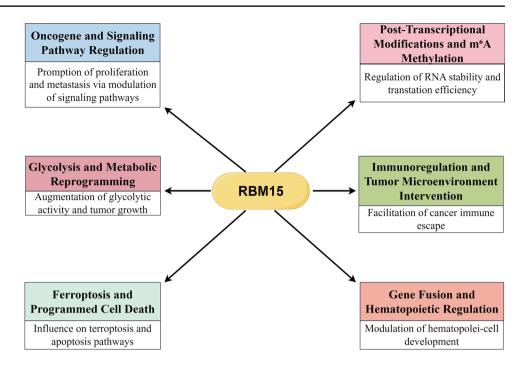
RBM15 influences cancer cell proliferation, metabolic reprogramming, immune evasion, and programmed cell death through multiple pathways, underscoring its central role in m⁶A-mediated cancer regulation. We assert that further delineation of RBM15 interactions within the broader m⁶A regulatory network, along with its role in tumor heterogeneity and microenvironment dynamics, represents a significant direction for future research (Fig. 6).

6 Conclusion and perspectives

Accumulating evidence underscores RBM15 as a pivotal regulator within the dynamic landscape of m⁶A RNA methylation, playing significant roles in tumorigenesis, progression, metastasis, and therapeutic resistance across diverse cancer types. By orchestrating m⁶A modifications, RBM15 modulates critical biological processes, including RNA splicing, stability, translation efficiency, and metabolic reprogramming, thus fundamentally impacting cancer cell behavior and the tumor microenvironment. Current research indicates the therapeutic potential of targeting RBM15 in cancer treatment. Specifically, inhibiting RBM15-driven pathways may sensitize resistant tumors to conventional therapies, as evidenced in lung adenocarcinoma, ovarian cancer, and laryngeal carcinoma, among others. Early intervention targeting RBM15 could disrupt drug-tolerant persistent states, enhance ferroptosis, and reverse immunosuppressive microenvironment remodeling, thereby improving the efficacy and outcomes of existing therapeutic regimens.



Fig. 6 Molecular Mechanisms of RBM15 in Cancer



However, several critical knowledge gaps remain unresolved. First, despite extensive documentation of RBM15 dysregulation across cancers, the precise context-dependent molecular mechanisms underlying its diverse regulatory roles remain incompletely characterized. Second, detailed structural analyses to elucidate RBM15's interactions with other m⁶A methylation complex components and downstream effectors are limited, hindering rational drug design targeting these interactions. Third, although correlations between RBM15 overexpression and poor prognosis have been robustly observed, the direct causal relationships and mechanisms linking RBM15-driven m⁶A modifications with tumor initiation and progression require deeper mechanistic validation. Moreover, current studies exhibit certain inherent limitations. Predominantly, these include reliance on cell-line models and retrospective clinical correlations, with a paucity of prospective clinical trials validating RBM15 as a predictive biomarker or therapeutic target. Additionally, existing research largely overlooks the heterogeneity of tumor microenvironments and the influence of diverse genetic and epigenetic backgrounds on RBM15's function, emphasizing the necessity for broader, multidimensional omics studies and patient-derived models.

Future studies should prioritize addressing these limitations through comprehensive functional genomics, single-cell sequencing, and spatial transcriptomics approaches. Additionally, systematic investigation into the tumor-specific roles of RBM15 and its potential crosstalk with other epitranscriptomic regulators could unveil novel therapeutic vulnerabilities. Rigorous preclinical evaluations combined with prospective clinical studies will be indispensable for validating RBM15-targeted therapeutic strategies, ensuring their safety, efficacy, and eventual translation into clinical practice.

In conclusion, this review synthesizes current insights into RBM15-mediated regulatory mechanisms in cancer biology, emphasizing its therapeutic potential and identifying critical avenues for future investigation. By bridging existing knowledge gaps and overcoming methodological constraints, research into RBM15 could significantly enhance precision oncology, providing novel diagnostic markers and effective therapeutic interventions tailored to individual tumor profiles.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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