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Review Article

RBFOX2 as a regulatory linchpin in cancer: insights from a comprehensive review of its roles in tumorigenesis

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Abstract: RNA-binding proteins (RBPs) are essential regulators of RNA expression during both transcriptional and post-transcriptional processes. Recent evidence indicates that dysregulation of RBPs is associated with cancer initiation and progression. Among these, RBFOX2 has been identified as exhibiting variable expression patterns across different cancers and is implicated in various malignant processes, including tumor growth, metastasis, ferroptosis, stemness, and chemoresistance. Despite these findings, the precise mechanisms by which RBFOX2 contributes to carcinogenesis remain largely unexplored. In this comprehensive review, we systematically examine the multifaceted functions of RBFOX2 in tumorigenesis, with a particular focus on its roles in alternative splicing, mRNA stability, and microRNA processing. Upon elucidating the specific roles of RBFOX2 in various cancers, targeted drugs can be devised to inhibit cancer development. Furthermore, we evaluate the specific roles of RBFOX2 in various cancer types, including pancreatic ductal adenocarcinoma, myeloid leukemia, and nasopharyngeal carcinoma. By providing an in-depth analysis, we aim to establish RBFOX2 as a potential diagnostic and therapeutic target in cancer biology and treatment, thereby offering new insights for future research.

Keywords: RBFOX2, tumorigenesis, RNA binding protein

Introduction

RNA-binding proteins (RBPs) are highly conserved across species and are indispensable regulators of gene expression [1, 2]. These proteins are crucial at nearly every stage of post-transcriptional regulation, influencing RNA synthesis, function, and maintaining cellular homeostasis. Mechanistically, RBPs interact with a variety of RNAs and proteins, governing essential processes such as RNA splicing, mRNA stability, localization and translation [3, 4]. Emerging studies further reveal that RBPs facilitate RNA modifications, significantly contributing to cancer progression by altering cellular proliferation and survival pathways [5].

Extensive evidence underscores the critical role of RBP dysregulation, particularly within the RBFOX family, in the initiation and development of various human cancers [6]. The RBFOX family comprises highly conserved RNA-binding proteins that specialize in the regulation of alternative splicing within specific tissues [7]. In mammals, this family includes Rbfox1 (A2BP1), RBFOX2 (RBM9), and Rbfox3 (NeuN) [8]. Among these, RBFOX2 is notable for its extensive tissue distribution, including neurons, muscles, stem cells, hematopoietic cells, and embryos [9]. In embryonic stem cells, RBFOX2 is uniquely expressed and plays a critical role in their proliferation [9, 10], underscoring its importance in early development. RBFOX2 is characterized by a single high-affinity RNA recognition motif (RRM) domain that predominantly binds to UGCAUG motifs [11]. These motifs are strategically located in various regulatory regions, such as pre-mRNA introns, mRNA 3' untranslated regions (UTRs), and pre-miRNA hairpin structures [12]. Through these binding sites, RBFOX2 ensures the precise expression of its target genes, thereby influencing vital biological pro-

cesses including epithelial-to-mesenchymal transition, development, differentiation, survival, invasion, and tumor suppression [13-21]. The ability of RBFOX2 to modulate such a wide array of processes highlights its versatile and pivotal role in cellular function. Moreover, RBFOX2 does not act in isolation. It interacts with other RBPs, such as hnRNPC, hnRNPM, and SRSF1, through unique sequences and motifs with distinct binding patterns [12, 22]. These interactions expand the regulatory capabilities of RBFOX2 by modulating alternative splicing events, thus broadening the spectrum of its functional impact on gene expression. Compare with other RBPs, RBFOX2's distinctive role as a master regulator of tissue-specific alternative splicing [16], its significant association with diseases like ovarian and breast cancer, and its involvement in the epithelial-mesenchymal transition (EMT) process crucial for cancer metastasis. Increasing evidence suggests a strong correlation between altered expression levels of RBFOX2 and the progression of various cancers, such as pancreatic ductal adenocarcinoma [23], myeloid leukemia [24], and nasopharyngeal carcinoma [25]. The role of RBFOX2 appears to be context-dependent, varying across different cancer types. For instance, RBFOX2 may act as a tumor suppressor in certain contexts while promoting tumorigenesis in others, depending on the cellular environment and interacting partners. This context-dependent behavior underscores the necessity for a nuanced understanding of RBFOX2's functions in cancer biology.

Given the complexity and significance of RBFOX2, this review aims to provide a comprehensive summary of its roles across different cancers. By examining the multifaceted functions of RBFOX2, we seek to offer valuable insights that could inform future research directions and therapeutic strategies. Understanding the diverse roles of RBFOX2 in tumorigenesis will not only enhance our knowledge of cancer biology but also pave the way for the development of targeted interventions, ultimately improving cancer treatment outcomes.

Characteristics of RBFOX2

The role of RBPs

Over 1,900 human RBPs have been identified, representing approximately 7.5% of protein-coding genes in the human genome [26]. These RBPs are crucial regulators of RNA processing stages, utilizing specific binding domains to interact with RNA molecules [27]. Typically, RBPs possess multiple modular domains, enhancing their RNA-binding efficiency [28]. This architecture enables RBPs to target a wide array of RNAs, including mRNA components (exons, introns, UTRs) and non-coding RNAs (miRNA, tRNA, siRNA, telomerase RNA, snoRNA, and snoRNA) [29]. By engaging with these RNA molecules, RBPs influence processes such as splicing, RNA modification, protein localization, secretion, chromosomal remodeling, and RNA degradation. This review selection of RBFOX2 within the RBP family as the focus of this article stems from its multifaceted merits, encompassing its ubiquitous intracellular functions and broad distribution, its correlations with various cancer types, as well as the novelty and feasibility of conducting research on this protein.

The structure of RBFOX2

RBFOX2 is a critical regulator of tissue-specific alternative splicing and the transcriptional activity of steroid receptors, significantly influencing various cellular processes [30-32]. The protein structure of RBFOX2 comprises three key domains: the C-terminal domain (CTD), the RNA recognition motif (RRM), and two alternative N-terminal domains [33], each contributing uniquely to its function and specificity.

Human RBFOX2 (hRBFOX2) is encoded by 15 exons and features two alternative promoters with distinct transcription start sites, along with two translation initiation codons (ATG1 and ATG2) [19]. Transcription initiation at exon 1 typically results in the exclusion of exon 3, forming the ATG1 isoform, while initiation at exon 3 produces the ATG2 isoform. Consequently, RBFOX2 exhibits two primary alternative N-terminal domains: domain 1, translated from exons 1 and 2 in the ATG1 isoform, and domain 2, translated from exon 3 in the ATG2 isoform.

The RRM domain, encoded by exons 5 through 7, is crucial for recognizing RNA sequences containing the UGCAUG motif, allowing RBFOX2 to precisely influence splicing decisions and other RNA processing events [34]. The CTD, encoded by the final five exons, is rich in alanine - a fea-

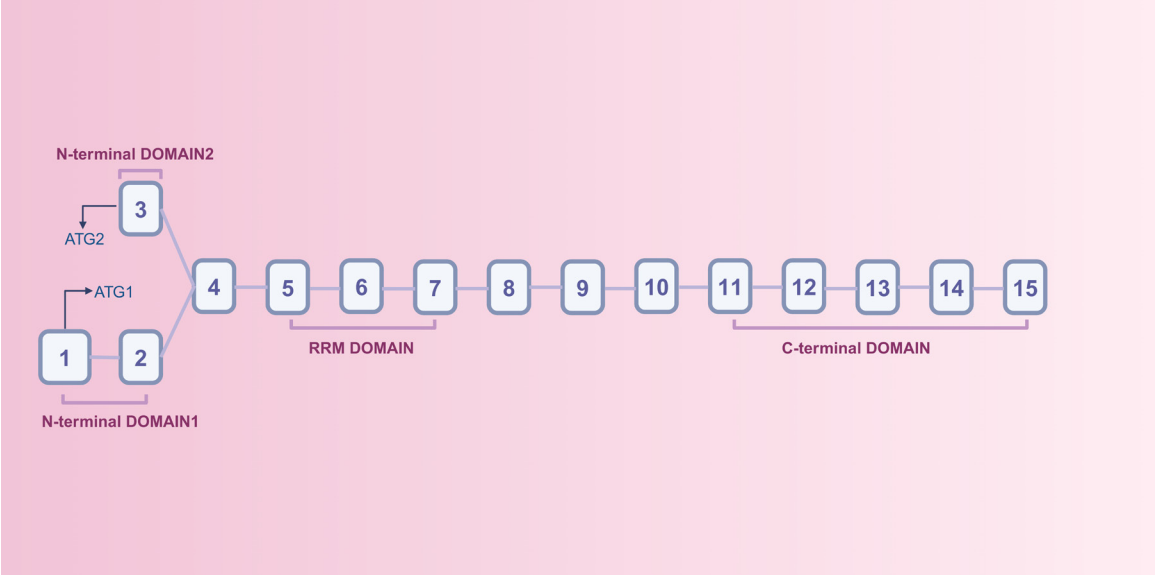

Figure 1. Detailed illustration of the structure of RBFOX2 protein.

ture often associated with transcriptional repressors-and includes glycine and arginine residues typical of RNA-binding protein CTDs [35]. The CTD is essential for RBFOX2's role in exon splicing, enhancing the recruitment of U1 snRNP to weak splice sites and thereby promoting exon inclusion [36]. This process is critical for the proper splicing of various exons, such as FGFR2 exon IIIb in epithelial cells and exon IIIc in mesenchymal cells [37]. Additionally, the CTD determines the subcellular localization of RBFOX2; constructs lacking the CTD fail to localize to nuclear speckles, underscoring its necessity for proper cellular localization [38]. Variations in CTD splicing can alter the nucleocytoplasmic distribution of RBFOX2, impacting its functional dynamics within the cell [39]. Notably, the skipping of exon 12 in RBFOX2, which significantly alters the sequence of the CTD, is elevated in breast cancer tissues compared to normal tissues [33]. This suggests a potential role of RBFOX2 splice variants in cancer development and progression. The detailed mechanisms of RBFOX2 are showed in **Figure 1**.

Regulatory mechanism of RBFOX2

The regulatory mechanisms of RBFOX2 mainly involves alternative splicing, microRNA biogenesis, and transcriptional regulation. The detailed mechanisms of RBFOX2 are showed in **Figure 2**.

The function of RBFOX2 in splicing: RBFOX2 is integral to RNA splicing, functioning through interactions with multiple protein partners in various binding modes [22]. These interactions include hnRNPC, hnRNPM, and SRSF1, enabling RBFOX2 to regulate splicing events via different sequence motifs and binding mechanisms [11]. RBFOX2 employs three distinct binding configurations in its regulatory roles: the single mode, where it targets splice sites through a canonical binding motif; the multiple mode, involving adjacent binding with at least one other RNA-binding protein partner; and the secondary mode, where RBFOX2 is indirectly recruited through interactions with a protein partner rather than binding RNA directly [22]. These dynamic binding modes associate with specific transcript sets at different positions and distances relative to alternative splice sites, contributing to the observed heterogeneity in RBFOX2 targets and splicing outcomes.

RBFOX2 regulate microRNA biogenesis: RBFOX2 is pivotal in the biogenesis of miRNAs, which are key post-transcriptional regulators of gene expression [40]. Its influence on miRNA biogenesis affects various cellular functions, and dysregulation, particularly of miR-20b and miR-107, is linked to cancer and neurodegenerative conditions [41]. RBFOX2 inhibits the maturation of miR-20b and miR-107 by interacting with their precursors and affecting nuclear processing steps [41]. Overexpression

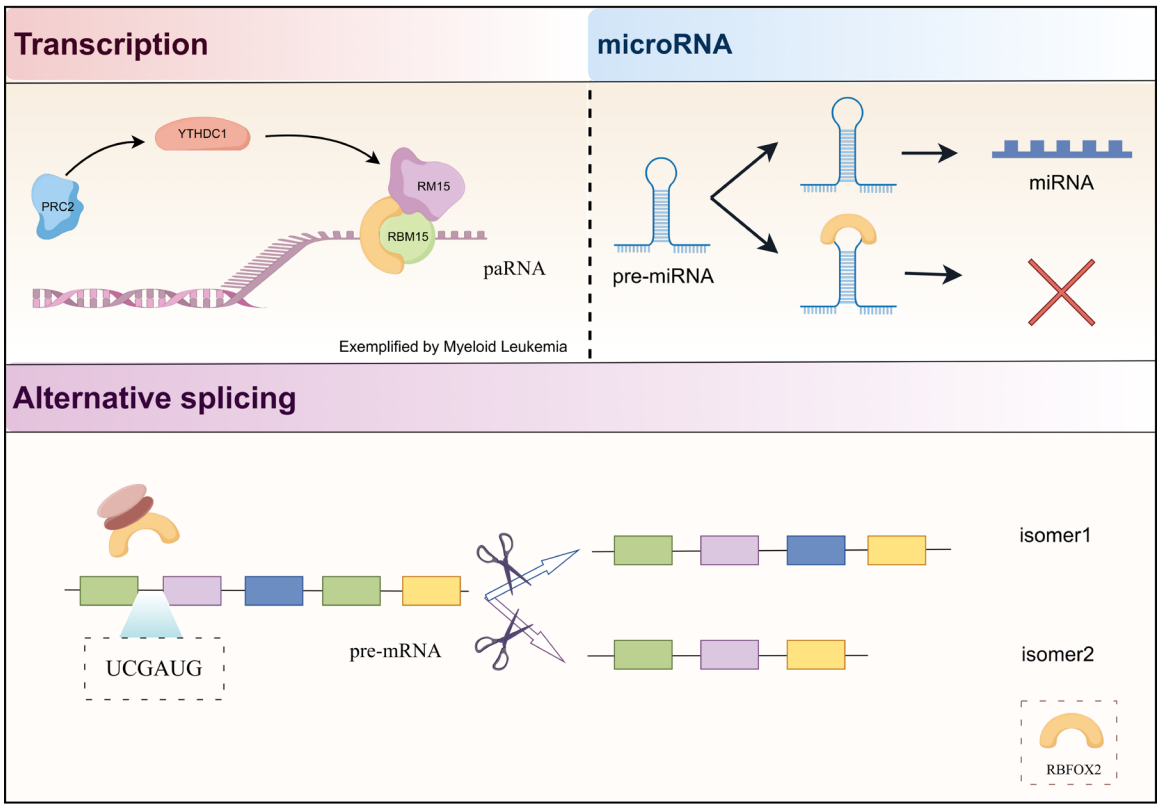

Figure 2. Comprehensive overview of the primary regulatory mechanism of RBFOX2.

of RBFOX2 leads to the upregulation of PTEN protein expression, a downstream target of miR-20b [42]. Conversely, downregulation of RBFOX2 decreases Dicer protein levels, highlighting its regulatory role in miR-107 expression and its association with the epithelial/mesenchymal characteristics of cancer cells [41]. In summary, RBFOX2 significantly influences the complex regulatory network of miRNA biogenesis, affecting downstream targets and contributing to cancer progression.

Transcriptional regulation: RBFOX2, a member of the RNA-binding FOX protein family, plays a crucial role in transcriptional regulation, particularly in the context of myeloid leukemia differentiation [24]. Recent research has illuminated its multifaceted functions, highlighting its involvement in a complex regulatory axis that includes the m6A methyltransferase complex (MTC), the m6A reader protein YTHDC1, and the RNA-binding protein RBM15 [43]. This intricate network underscores RBFOX2's significance in epigenetic and transcriptional control mechanisms.

One of the remarkable aspects of RBFOX2's function is its ability to selectively recognize N6-methyladenosine (m6A) modifications on chromatin-associated RNAs (caRNAs) [44, 45]. This specificity enables RBFOX2 to recruit RBM15, a vital component of the MTC. RBM15 facilitates the methylation of promoter-associated RNAs (paRNAs), a process essential for the regulation of gene expression [24]. This recruitment forms a regulatory axis known as RBFOX2/m6A/RBM15/YTHDC1/PRC2. Within this axis, RBM15 aids in attracting the polycomb repressive complex 2 (PRC2) to chromatin loci bound by RBFOX2 [24], leading to transcriptional suppression and chromatin silencing.

The role of RBFOX2 in this regulatory framework is critical for the differentiation and proliferation of myeloid cells. For instance, in acute myeloid leukemia (AML), the downregulation of RBFOX2 has been shown to inhibit the survival and proliferation of leukemia cells, highlighting its potential as a therapeutic target [46]. The RBFOX2-associated pathway's ability to modu-

late m6A modifications and recruit epigenetic silencing complexes underscores its pivotal role in maintaining cellular homeostasis and gene expression regulation.

The roles and mechanisms of RBFOX2 participating in cancers

Currently, RBFOX2 has been verified to be involved in the development and progression of various cancers. Given RBFOX2's pivotal role in RNA processing, specifically alternative splicing, its dysregulation has emerged as a crucial aspect in various malignancies. The observation that RBFOX2 exhibits diverse expression profiles across cancer types suggests a potential link to the heterogeneity and complexity of cancer biology. By exploring these varying patterns, the authors aim to gain insights into the mechanisms underlying cancer initiation, progression, and response to therapies, thereby contributing to the development of targeted therapeutic strategies. In the following section, we will show the detailed regulatory mechanisms of these malignant tumors (**Table 1**; **Figure 3**).

Pancreatic ductal adenocarcinoma (PDA)

PDA has a high mortality rate due to its aggressive local invasion and metastatic spread [47]. Recent studies have demonstrated that RBFOX2 significantly influences PDA metastasis. In a patient-derived xenograft metastatic PDA cell line, RBFOX2 overexpression markedly reduced the cells' metastatic potential both in vitro and in vivo [48]. Conversely, RBFOX2 reduction in primary pancreatic cancer cell lines enhanced their metastatic capability [23]. Further investigation of RBFOX2 target genes through RNA-sequencing and splicing analysis revealed a plethora of genes in the RHO GTPase pathways (RHOA, CDC42, and RAC1), which are essential for cellular processes such as actin cytoskeleton organization, cell polarity, microtubule dynamics, and vesicle trafficking [49]. The loss of RBFOX2 expression is associated with increased cellular motility [23]. Manipulation of RBFOX2-regulated splicing events, particularly through myosin phosphatase RHO-interacting protein, correlates with signaling pathway alterations, PDA metastasis, changes in cytoskeletal arrangement, and the initiation of focal adhesion formation [50]. RBFOX2 overexpression led to elevated expression of the longer isoform of MPRIP, characterized by the inclusion of exon 23 [23], while RBFOX2 silencing resulted in the generation of a shorter isoform with the exclusion of exon 23 in PDAC cells.

Additionally, analysis of two other RBFOX2 target genes, MYL6 and CLSTN1, indicated their critical roles in PDA progression and metastasis. Reintroducing the shorter isoforms of MPRIP, MYL6, and CLSTN1 into primary PDAC cells significantly amplified metastatic dissemination, particularly in the liver and lungs [23, 51]. These findings underscore RBFOX2's role as a robust metastatic suppressor in PDA and identify an RBFOX2-regulated alternative splicing signature in metastatic PDA. Moreover, RBFOX2 also impacts miRNA expression in PDA. It upregulates tumor suppressor miRNAs such as miR-20b and miR-107 while reducing the expression of the oncomiR-21 [52]. This regulation occurs through direct binding to miRNA sequences or indirectly by altering the expression of Dicer, an enzyme involved in miRNA processing [53-55]. The significance of miRNAs in pancreatic tumorigenesis is further highlighted by the rarity of mutations in the DICER gene in PDAC.

Overall, these findings highlight the crucial role of RBFOX2 in PDA metastasis and its impact on miRNA regulation, suggesting that RBFOX2 and its regulated pathways could serve as potential therapeutic targets for PDA.

Myeloid leukemia (AML)

Previous study showed that The RBFOX2/m6A/RBM15/YTHDC1/PRC2 axis plays a pivotal role in the pathophysiology of AML [44]. M6A is the most prevalent internal modification in mRNAs of mammalian cells [56], extending its influence on non-coding RNAs [45], including chromatin associated regulatory RNAs (carRNAs) [44]. The m6A modification is mediated by the methyltransferase complex, comprising METTL3/14 [57, 58], WTAP [59], RBM15/15B [60], ZC3H13 [61], and VIRMA [62]. This modification can be dynamically reversed by the demethylases FTO and ALKBH5 [63, 64]. Within this regulatory network, RBFOX2 functions as a chromatin factor that recognizes m6A modifications on carRNAs. It recruits RBM15, a component of the MTC, to promote the methylation

Table 1. The roles and mechanisms of RBFOX2 participating in 12 cancers

Type of the cancer	The functions of RBFOX2 overexpression in cancers	RBFOX2 in action	Regulate genes/network	Ref.
Pancreatic ductal adenocarcinoma (PDA)	↓	Regulate alternative splicing (as a metastatic suppressor), upregulates tumour suppressor miRNA	RHO GTPase pathways, MPRIP, MYL6, CLSTN1	[49-55]
Myeloid Leukaemia	↑	Regulate transcription	RBFOX2/m^{6}A/RBM15/YTHDC1/PRC2 axis	[44, 45, 56-62]
B-cell lymphoma	↑	Regulate alternative splicing	MALT1, CLSTN1, FMNL3, MYO9B	[67]
Nasopharyngeal carcinoma (NPC)	↑	Regulate alternative splicing	GOLIM4-L	[25, 69]
Hepatocellular carcinoma (HCC)	↑	Regulate alternative splicing	HIF-1α/METTL16/Lnc-CSMD1-7/RBFOX2 axis	[72, 74]
Mesenchymal glioblastoma (GBM)	↑	Regulate alternative splicing	FBXO7-Rbfox2 axis, FoxM1, Mta1, Postn	[76-80]
Endometrial cancer (EC)	↑	Regulate alternative splicing	TFRC	[84, 85]
Colorectal cancer (CRC)	↑	Regulate alternative splicing	Pre-mRNAs containing microexons	[87]
Gastric Cancer (GC)	↑	Regulate alternative splicing	p53/LINC00893/RBFOX2 axis	[90-91]
Laryngeal cancer (LC)	-	Regulate alternative splicing	Non-coding RNA ZFAS1, MENA gene	[93-97]
Breast cancer	↑	Regulate alternative splicing	FGFR2 and CD44, Bcl-x and MCL1, PI3K/AKT and MAPK pathway	[100-103]
Ovarian cancer	↑	Regulate alternative splicing	Long non-coding RNA MALAT1	[104-107]

*: "↑" means inhibiting the occurrence of the cancer, "↓" means promoting the occurrence of the cancer, "-" means the influence of cancer is insignificant.

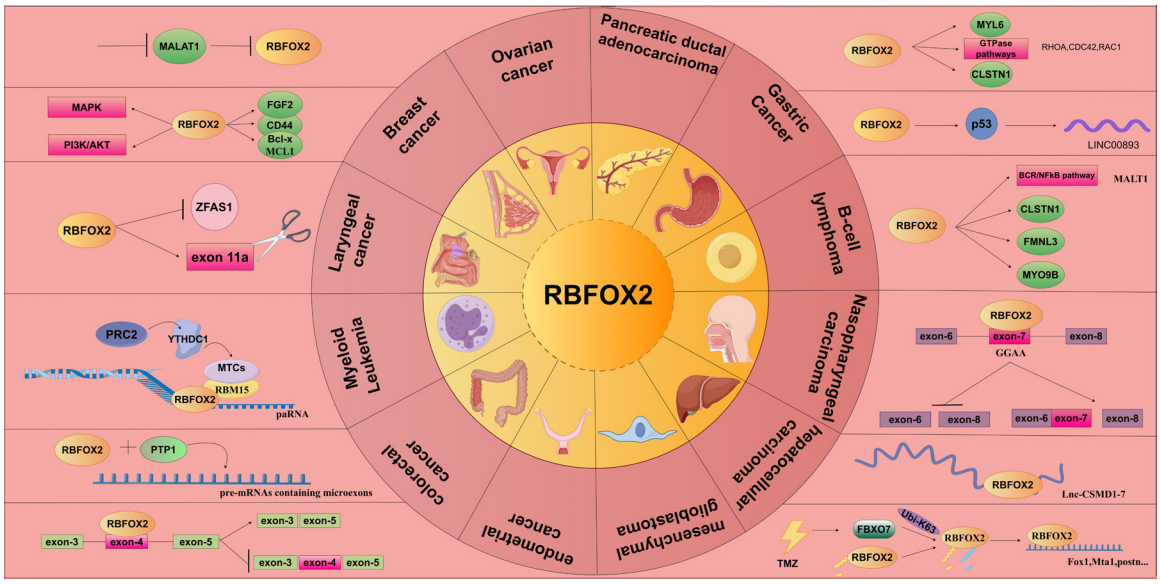

Figure 3. Roles and underlying mechanisms of RBFOX2 involvement in twelve types of cancer.

of promoter-associated RNAs [24]. RBM15, in turn, interacts physically with YTHDC1, facilitating the recruitment of the PRC2 to RBFOX2-bound loci [24]. This recruitment leads to chromatin silencing and transcriptional repression. RBFOX2 is integral to this axis; its depletion significantly compromises the survival and proliferation of AML cells while promoting their differentiation towards the myeloid lineage. Furthermore, RBFOX2 is essential for the self-renewal of leukemia stem/inception cells and the maintenance of AML [65], highlighting its critical role in the disease's pathogenesis.

B-cell lymphoma

The annual incidence of lymphoma in Western countries is approximately 20 new cases per 100,000 individuals [66]. The majority of these lymphomas, around 95%, originate from B-cells, with the remaining cases comprising T-cell malignancies [66]. RBFOX2 has been implicated in B-cell non-Hodgkin lymphoma (B-NHL) by modulating the splicing of key target genes, including MALT1, CLSTN1, FMNL3, and MYO9B [67]. The expression of full-length variants of these genes positively correlates with RBFOX2 levels in both B-NHL cell lines and primary B-NHL tissue samples [67]. Knockdown experiments further corroborate the role of RBFOX2 in the splicing of these targets, particularly MALT1, which is crucial for the BCR/NF-κB signaling pathway [67]. These findings underscore RBFOX2 as a critical regulator of splicing in B-NHL, highlighting its potential involvement in the pathogenesis of this lymphoma.

Nasopharyngeal carcinoma (NPC)

NPC is an epithelial carcinoma originating from the mucosal lining of the nasopharynx [68]. In NPC, RBFOX2 functions as a splicing regulator of GOLIM4-L, a variant highly expressed and linked to poor prognosis [25]. RBFOX2 recognizes GGAA motifs to facilitate the generation of GOLIM4-L, which promotes cell proliferation and migration in NPC cells, mirroring the effects of GOLIM4-L expression [25]. Additionally, RBFOX2 is involved in the downregulation of RAB26, a critical regulator of Golgi apparatus organization in NPC cells [69]. GOLIM4-L interacts with and recruits RAB26 to the Golgi apparatus, thereby mediating vesicular transport [25]. These findings underscore the crucial functional relationship between GOLIM4-L and RAB26, highlighting their essential roles in maintaining Golgi apparatus integrity and facilitating vesicle-mediated transport in NPC.

Hepatocellular carcinoma (HCC)

HCC is a prevalent malignancy and the third leading cause of cancer-related mortality worldwide [70]. Hypoxia, a common condition in HCC, plays a critical role in promoting metastatic pro-

gression [71]. This process is mediated by the HIF-1α/METTL16/Lnc-CSMD1-7/RBFOX2 axis [72]. HIF-1α is a key player in this pathway, induced under low oxygen conditions and contributing to the aggressive behavior of HCC [73]. Research indicates a significant reduction in the expression of Lnc-CSMD1-7, a long non-coding RNA in HCC, which correlates with poor patient prognosis [72]. Functionally, Lnc-CSMD1-7 suppresses HCC cell migration and invasion in vitro and inhibits lung metastasis in vivo [74]. Mechanistically, Lnc-CSMD1-7 binds directly to RBFOX2 affecting RBFOX2-regulated alternative splicing events crucial for EMT [72]. These findings elucidate the molecular underpinnings of hypoxia-induced metastasis in HCC, highlighting potential therapeutic targets.

Glioblastoma (GBM)

GBM represents the most aggressive central nervous system tumor, demonstrating significant resistance to radiotherapy and chemotherapy, resulting in suboptimal therapeutic outcomes [75]. Within the Skp1-cullin1-F-box protein ubiquitin E3 ligase complex, FBXO7 functions as a substrate recognition component [76]. Additionally, FBXO7 mediates substrate ubiquitination via an SCF-independent mechanism [77]. In GBM, FBXO7 induces mesenchymal characteristics and chemoresistance by modulating RBFOX2-mediated alternative splicing [78]. Specifically, FBXO7 ubiquitinates RBFOX2 at Lys249 with K63-linked ubiquitin chains following arginine demethylation at Arg341 and Arg441 by PRMT5, leading to RBFOX2 stabilization [78, 79]. This stabilization regulates the splicing of mesenchymal genes such as FoxM1, Mta1, and Postn [16, 80]. Consequently, this splicing mechanism promotes the mesenchymal transformation and tumorigenesis of GBM. Targeting the FBXO7-RBFOX2 axis may represent a promising therapeutic strategy for combating this aggressive brain cancer.

Endometrial cancer (EC)

EC is among the most common gynecological malignancies, impacting over 280,000 individuals globally each year [81, 82]. Circular RNAs are increasingly recognized for their roles in cancer progression, although their impact on ferroptosis in EC remains to be fully elucidated [83]. Recent study has demonstrated that circRAPGEF5 binds with RBFOX2 to influence the alternative splicing of TFRC pre-mRNA in EC [84]. Notably, circRAPGEF5 induces exon-4 skipping in TFRC, a modification that confers resistance to ferroptosis by diminishing the levels of labile iron within EC cells [84]. Ferroptosis is a form of cell death recently characterized by the accumulation of iron and lipid peroxides, which prompt lipid peroxidation and oxidative stress, often resulting from decreased activity of antioxidant enzymes [85]. This circRNA-protein interaction underscores a novel pathway by which EC cells may evade ferroptosis, suggesting potential targets for therapeutic intervention in managing resistance to this iron-dependent form of cell death.

Colorectal cancer (CRC)

CRC ranks as the fourth leading cause of cancer-related deaths worldwide, claiming nearly 700,000 lives annually [86]. Recent studies have revealed that alternative splicing of microexons, mediated by splicing factors RBFOX2 and PTBP1, plays a pivotal role in CRC metastasis [87]. Microexons, defined as small exons ranging from 3 to 30 nucleotides, are critical components in the regulation of gene expression [88]. In CRC cells, RBFOX2 and PTBP1 specifically interact with pre-mRNAs that contain microexons, thereby influencing their splicing patterns [87]. Notably, alterations in the expression levels of these splicing factors between CRC and normal tissue have been associated with differential splicing outcomes [87]. These variations in microexon splicing have been linked to the metastatic progression of CRC, suggesting a significant impact on the disease's prognosis [89]. Thus, the modulation of microexon splicing by RBFOX2 and PTBP1 highlights a crucial molecular mechanism underlying CRC metastasis, underscoring potential targets for therapeutic intervention in one of the gravest cancer challenges globally.

Gastric cancer (GC)

GC remains a major cause of cancer-related mortality globally, ranking as the fourth leading cause of such deaths in 2020 [71]. Recent study found that LINC00893 is regulated by p53 and plays a pivotal role in curtailing the proliferation, migration, and invasion of gastric cancer cells [90]. It achieves this by binding to RBFOX2, which facilitates the ubiquitin-mediat-

ed degradation of RBFOX2, thus inhibiting EMT and associated functions in GC [91]. Further, p53 indirectly modulates the expression of LINC00893, reinforcing its integral role in impeding GC advancement [91]. In essence, LINC00893, activated by p53, serves as a tumor-suppressive lncRNA in gastric cancer, offering a valuable experimental basis for clinical interventions. The p53/LINC00893/RBFOX2 regulatory axis emerges as a potential target for enhancing diagnostic and therapeutic strategies in gastric cancer management.

Laryngeal cancer (LC)

LC is a significant form of malignancy that characteristically invades the head and neck region [92]. The non-coding RNA ZFAS1, implicated in oncogenic processes in head and neck squamous cell carcinoma, remains a subject of ongoing research [93, 94].

Studies indicate that ZFAS1 exhibits higher expression levels in LC tissues and cells compared to normal counterparts, with increased expression associated with advanced lymph node metastasis and clinical progression [93, 95]. Functionally, elevated ZFAS1 levels enhance cellular proliferation, aggressive tumor behavior, and the modulation of adhesive and mesenchymal markers including N-cadherin, Vimentin, and E-cadherin [95]. A key mechanism involves ZFAS1's interaction with RBFOX2 protein, which stabilizes the latter's expression. This interaction is pivotal as overexpression of RBFOX2 can mitigate the suppressive effects of ZFAS1 silencing on cellular activities. Additionally, increased RBFOX2 levels promote the exclusion of exon 11a from the MENA gene transcript, giving rise to a pro-invasive splice variant known as MENAINV [96]. This splice variant counteracts the tumor-suppressive effects of RBFOX2 downregulation [95, 97]. These findings underscore the therapeutic relevance of targeting ZFAS1 to inhibit laryngeal cancer progression through the modulation of RBFOX2-mediated MENA splicing, presenting a novel intervention strategy.

Breast cancer

RBFOX2 also significantly influences breast cancer progression through its role in alternative splicing. Dysregulation of RBFOX2 alters splicing events, leading to the production of oncogenic splice variants that drive tumorigenesis and metastasis [71]. For instance, RBFOX2-mediated splicing of FGFR2 and CD44 enhances EMT [98], promoting cancer cell invasiveness [99]. RBFOX2 also affects apoptosis by regulating the splicing of genes like Bcl-x and MCL1, favoring anti-apoptotic isoforms that support cancer cell survival under therapeutic stress [100]. Additionally, RBFOX2 interacts with crucial signaling pathways, such as PI3K/AKT and MAPK, modulating oncogenic signals and contributing to breast cancer pathophysiology [101-103]. Given its central role in splicing regulation and cancer progression, RBFOX2 is a promising therapeutic target. Modulating RBFOX2 activity or correcting its splicing defects could provide new treatment strategies. Moreover, RBFOX2 expression and splicing activity could serve as biomarkers for prognosis and treatment response, aiding in personalized breast cancer therapy.

Ovarian cancer

Increasing studies found that RBFOX2 also participated in the progression of ovarian cancer. Research highlights that the long non-coding RNA MALAT1 is upregulated in anoikic-resistant ovarian cancer cells, promoting survival and metastasis [104]. MALAT1 enhances a pro-metastatic phenotype by regulating apoptosis and epithelial-to-mesenchymal transition (EMT) genes [105]. Suppression of MALAT1 reduces RBFOX2 expression, leading to the pro-apoptotic splicing of the gene KIF1B, thereby increasing cell death and reducing metastasis [106]. Another study examines RBFOX2's impact on alternative splicing in epithelial and mesenchymal tissues. Using high-throughput RT-PCR, researchers observed significant splicing differences in normal and cancerous ovarian tissues [107]. RBFOX2 was identified as a key driver of mesenchymal-specific splicing patterns essential for the invasive and metastatic behavior of ovarian cancer cells. Knocking down potential splicing factors confirmed RBFOX2's critical role in maintaining the mesenchymal characteristics of cancer cells.

In summary, RBFOX2 influences ovarian cancer progression by regulating alternative splicing, affecting cell survival and EMT. Understanding RBFOX2's mechanisms offers potential therapeutic targets for reducing ovarian cancer metastasis.

Conclusion and future prospective

RBPs are pivotal in the post-transcriptional regulation of gene expression, influencing processes such as alternative splicing, mRNA stability, translation, and microRNA processing. Among these, RBFOX2 has garnered attention for its profound impact on tumorigenesis across various cancer types, affecting tumor growth, metastasis, EMT, ferroptosis, cancer stem cell maintenance, and chemoresistance. The widespread expression of RBFOX2 in diverse tissues and its central role in RNA metabolism underscore its immense potential as a therapeutically relevant target.

RBFOX2's regulation of alternative splicing significantly impacts cancer progression, operating in a context-dependent manner to either promote or inhibit tumorigenesis. It is instrumental in EMT [108], a crucial process enabling cancer cell invasion and metastasis. Recent studies have elucidated RBFOX2's role in controlling the splicing of pre-mRNA, which affects the expression of genes critical to cell motility, invasion, and resistance to cell death. Furthermore, RBFOX2 is implicated in the regulation of apoptosis and cellular differentiation, reinforcing its potential as a multifaceted target in cancer therapy.

The differential expression patterns of RBFOX2 among various cancer types highlight its value as a diagnostic and prognostic biomarker. For instance, aberrant RBFOX2 expression has been linked to adverse clinical outcomes in cancers such as breast, lung, and ovarian cancer. This association underscores the need for a deeper exploration of RBFOX2's mechanistic roles and their clinical correlations, which could pave the way for novel, personalized therapeutic strategies. Moreover, emerging evidence suggests that RBFOX2 might also play roles in other post-transcriptional regulatory mechanisms, including its impact on translation and RNA stability. Investigating these areas could unveil new dimensions of RBFOX2's influence in cancer biology, potentially opening up novel therapeutic avenues.

Future research should aim to elucidate the intricate molecular mechanisms by which RBFOX2 influences cancer and other cellular processes. Key areas of focus include:

Comprehensive Mechanistic Studies: Detailed investigations into the molecular pathways regulated by RBFOX2, including its interactions with other RBPs and splicing factors, are essential. Understanding how RBFOX2 modulates signaling pathways and cellular processes will provide deeper insights into its role in tumorigenesis.

Clinical Correlations: Large-scale clinical studies are needed to explore the association between RBFOX2 expression levels and patient outcomes across various cancer types. This will help to establish RBFOX2 as a reliable biomarker for cancer diagnosis, prognosis, and treatment response.

Therapeutic Interventions: The development of specific modulators, such as inhibitors or enhancers of RBFOX2's activity, holds promise for cancer therapy. Currently, the scientific literature lacks definitive reports on RBFOX2-specific inhibitors. Nonetheless, published studies have highlighted the potential application of microRNAs as inhibitors of RBFOX2 expression in the context of heart disease therapeutics, emphasizing the pressing need for the development of targeted drugs directed against RBFOX2. Preclinical and clinical trials should assess the efficacy and safety of these potential therapeutic agents.

Translational Research: Bridging the gap between basic research and clinical application is crucial. Through current laboratory research, we've identified regulators that impact RBFOX2 expression. For example, in glioblastoma, SON protein promotes oncogenic splicing while inhibiting RBFOX2-mediated splicing [109]. In heart failure, miRNAs like Let-7, miR-16, and miR-200b decrease RBFOX2 levels [110]. RBFOX2 gene methylation also affects its expression, and its levels correlate with immune checkpoint blockade (ICB) treatment response [111]. Our future focus is on developing RBFOX2 inhibitors for clinical applications. Translational studies should focus on integrating RBFOX2-based diagnostics and therapeutics into clinical practice, including the development of personalized treatment regimens based on RBFOX2 expression profiles.

In conclusion, the burgeoning understanding of RBFOX2's multifaceted roles in cancer underscores its potential as a critical therapeutic tar-

get. While curing cancer solely through RBFOX2 modulation might be an ambitious goal, advancements in targeting RBFOX2 can significantly enhance existing treatment paradigms. Ongoing and future studies are anticipated to expedite the clinical translation of RBFOX2-based diagnostics and therapies, ultimately aiming to improve patient outcomes and enrich the landscape of cancer treatment. The path forward necessitates a concerted effort from the research community to explore and exploit the full therapeutic potential of RBFOX2 in combating cancer.

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Disclosure of conflict of interest

None.

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