




RBM38 in cancer: role and mechanism

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Abstract

Cancer is the second leading cause of death globally. Abnormality in gene expression regulation characterizes the trajectory of tumor development and progression. RNA-binding proteins (RBPs) are widely dysregulated, and thus implicated, in numerous human cancers. RBPs mainly regulate gene expression post-transcriptionally, but emerging studies suggest that many RBPs can impact transcription by acting on chromatin as transcription factors (TFs) or cofactors. Here, we review the evidence that RBM38, an intensively studied RBP, frequently plays a tumor-suppressive role in multiple human cancer types. Genetic studies in mice deficient in RBM38 on different p53 status also establish RBM38 as a tumor suppressor (TS). By uncovering a spectrum of transcripts bound by RBM38, we discuss the diversity in its mechanisms of action in distinct biological contexts. Examination of the genomic features and expression pattern of RBM38 in human tissues reveals that it is generally lost but rarely mutated, in cancers. By assessing future trends in the study of RBM38 in cancer, we signify the possibility of targeting RBM38 and its related pathways as therapeutic strategies against cancer.

Keywords Cancer · RBP · Tumor suppressor · Gene expression regulation · Cancer therapeutics

Introduction

Cancer, also known as a malignant tumor, is a generic term for a group of diseases that can affect any part of the body. It is a major public health problem and a leading cause of death globally. Based on the GLOBOCAN 2018 estimates of cancer incidence and mortality worldwide, there will be an estimated 18.1 million new cases and 9.6 million cancer deaths in 2018 [1]. In both sexes combined, lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death, closely followed by female breast, male prostate, and colorectal cancer for incidence and colorectal, stomach, and liver cancer for mortality [1]. Unfortunately,

the incidence and mortality are rapidly growing globally. In essence, cancer is the uncontrolled growth of abnormal cells in any tissues. Although it is conventionally believed that cancer is caused by genetic mutations, it is now clear that most human cancers are, in fact, induced by nongenetic factors [2], such as physical carcinogens (e.g., ultraviolet, ionizing radiation), chemical carcinogens (e.g., asbestos, components of tobacco smoke), and biological carcinogens (e.g., infections from viruses, bacteria, or parasites). Regardless of the origins in cancer initiation, these cancer-causing factors all converge, eventually, on gene expression regulation at versatile levels [3], in that gene expression is fundamentally the key determinant of cellular phenotypes.

RNA-binding proteins (RBPs) are a class of proteins that primarily bind to RNA to form ribonucleoprotein (RNP) complexes for the regulation of gene expression and exertion of their pleiotropic functions in physiological and pathological processes [4]. To date, over 1500 RBPs, representing ~7.5% of all protein-coding genes in the human genome, have been identified [4, 5], highlighting their functional diversity and importance. RBPs are virtually involved in all aspects of RNA metabolism, including pre-mRNA splicing, capping, and polyadenylation, as well as mRNA export, turnover, localization, and translation [6]. Mechanistically,

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many RBPs bind to sequence-specific motifs or RNA secondary structures, or a combination of both, through unique modular arrangements of individual RNA-binding domains (RBDs), together with an auxiliary module to mediate interplay between proteins [4, 7]. Currently, over 50 different RNA binding modules have been proposed, typified by RNA recognition motif (RRM), heterogeneous nuclear ribonucleoprotein (hnRNP) K-homology domain (KH), double-stranded RNA binding motif (dsRBM), zinc fingers (ZnF) of the CCHC/CCCH/ZZ types, arginine-glycine-glycine (RGG) motif, cold shock domain (CSD), and others [4, 5]. However, almost half of RBPs interact with RNA in the absence of specific motifs or structural domains [5], adding another layer of complexity within RNP interaction networks. Notably, and interestingly, previous studies have mainly focused RNPs on post-transcriptional events, a recent report showed that RBPs can prevalently exert their functions at the level of chromatin by regulating transcription as transcription factors (TFs) or cofactors [8]. Collectively, RBPs play pivotal roles in RNA biogenesis and metabolism and, therefore, perturbations in RBP–RNA network activities have been, not surprisingly, causally associated with tumorigenesis [4]. There is already ample experimental evidence that altered RBP function has a significant impact on cancer phenotypes (summarized in [4]). For instance, HNRNPA2B1 is characterized as a novel oncogene in glioblastoma in that it is overexpressed in tumor versus (vs.) normal tissues and predicts poor prognosis [9]. ESRP1, an epithelial cell-specific splicing regulatory protein, enhances lung colonization of metastatic cancer cell via splicing isoform switching tumor suppressive CD44s to oncogenic CD44v [10]. Moreover, ELAVL1 (best known as HuR) promotes the migration of tumor cells and lung cancer metastasis by stabilizing and

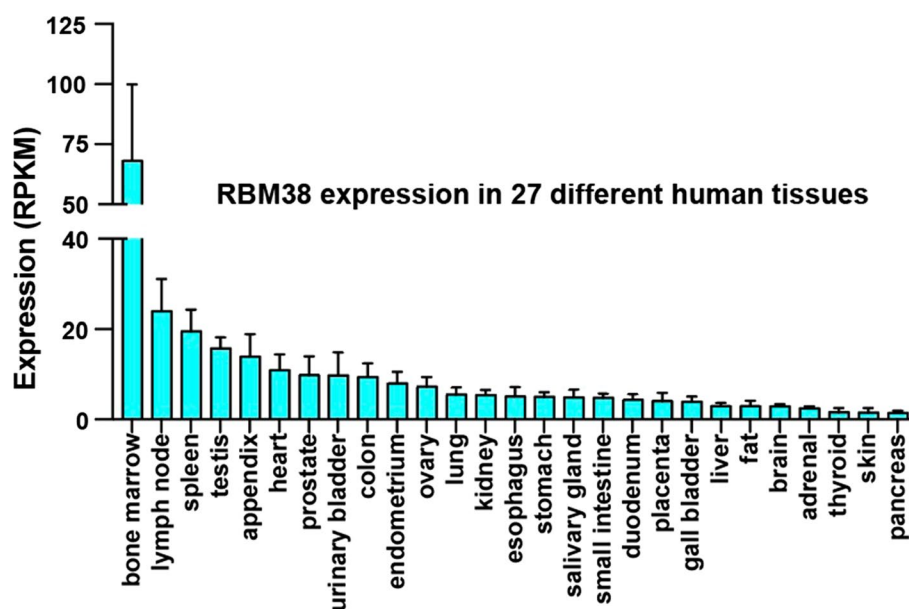
thus upregulating SNAIL (i.e., Snail), a marker of epithelial-mesenchymal transition (EMT) [11].

RNA-binding motif protein 38 (RBM38, also dubbed RNPC1) belongs to RRM-containing RBP family including NCL (i.e., nucleolin), U2AF56 and HuR [12, 13]. Since the first discovery of RBM38 as a p53 family target gene transcriptionally [14], later studies have unveiled pleiotropic roles of RBM38 in diverse pathological conditions, via frequently forming negative feedback loop with tumor suppressors (TS) such as p53 family (i.e., p53, p63, p73) [12, 15, 16]. Many well-known transcripts involved in tumor development and progression have been identified as RBM38 targets, rendering RBM38 a relatively extensively investigated RBP in the cancer research field. In this review, we describe the genomic features and expression pattern of RBM38 in human tissues, provide evidence for a tumor-suppressive role in various cancer types, and emphasize the diversity in its mechanisms of action in distinct biological contexts. By surveying the mutational landscape of RBM38 across the spectrum of human cancers, we also assess future trends in the study of RBM38 in cancer.

Molecular structure of RBM38

RBM38 is located on chromosome 20q13.31 and is highly expressed in a variety of human tissues (RPKM > 4 in 19 of 27 tissues; Fig. 1). Comparative phylogenetic analysis of *RBM38* at both mRNA and protein sequence levels reveals an evolutionary conservation across vertebrate species [13]. These results, together, signify a functional importance of *RBM38* in development. Previous studies have all discovered that *RBM38* has 4 exons and is expressed as two

Fig. 1 Expression of RBM38 in human tissues. Reads per kilobase million (RPKM) values, derived from RNA-seq analysis of tissue samples from 95 human individuals representing 27 different tissues, were extracted from NCBI with Gene ID: 55544 (accessed on Mar 18, 2020)



isoforms: RBM38a with 239 amino acids (aa) and RBM38b with 121aa identical to the N-terminal region of RBM38a (Fig. 2A). Genomically, *RBM38b* is the result of exon 4 skipping through alternative splicing. Interestingly, based on the recent NCBI annotation of Reference Sequences (RefSeq; updated on Mar 13, 2020), a new and the longest isoform *RBM38c* encoding 271aa is reported (Fig. 2A). Alignment of these three isoforms suggests the existence of an RRM domain consisting of two RNP sub-motifs (Fig. 2B). Notably, due to the inclusion of a cryptic short exon 2, the RNP1 motif is disrupted by an insertion of extra 32aa in RBM38c (Fig. 2B). Whether this novel isoform also functions normally, as does RBM38a, is unclear and requests a future investigation. Most of the previous studies have experimentally characterized isoforms a and b, with RBM38a being the predominant isoform that preserves the RBP properties in term of modulating mRNA post-transcriptionally [12, 14, 15]. Therefore, the evidence presented in this review is mainly attributed to RBM38a's function. Notably, a paralogue of *RBM38* located on chromosome 6p22.3, namely *RBM24*, is reported to preferentially express in striated muscles [17, 18]. *RBM24* gene encodes 236aa and shares a high degree of sequence similarity with that of RBM38a. Particularly, both of them have almost an identical RRM [17, 19], indicating functional similarity and the possible interplay between them (discussed below).

RBM38 mainly functions as a TS in diverse human cancers

Due to the earlier observations that chromosome 20q13 is often amplified in multiple cancers including breast [20], prostate [21], ovarian [22], and colorectal cancer [23, 24], and chronic lymphocytic leukemia [23], and that *RBM38* is overexpressed in dog lymphomas [12], human colorectal [24] and esophageal cancer [25], *RBM38* has, therefore, been proposed as a putative oncogene in these cancers. However, we performed a close examination of the aforementioned literature and found no direct evidence supporting the amplification of 20q13.31 region specifically, where *RBM38* resides, due to the low resolution of earlier mapping technologies. Consistently, little functional evidence was reported to implicate *RBM38* as an oncogenic factor. To address this discrepancy, we surveyed the mutational landscape of *RBM38* across 32 human cancer types offered by current The Cancer Genome Atlas (TCGA) DNA sequencing effort through cBioPortal [26]. Results clearly showed that, although amplification represents the main form of alterations in multiple cancers (e.g., colon, breast, ovary, sarcoma), the frequency is very low (generally $\leq 5.31\%$) (Fig. 3). Notably, the average mutation rate for *RBM38* in total is 2.4% (Fig. 3), suggesting that genomic amplification is a rare event at the population level and thus should not be perceived as a causal rationale for proposing *RBM38* for an oncogene. In fact, the vast majority of studies have established RBM38 as a TS in various human cancers (Table 1), including breast, hepatocellular, colorectal, renal, gastric, and other cancers.

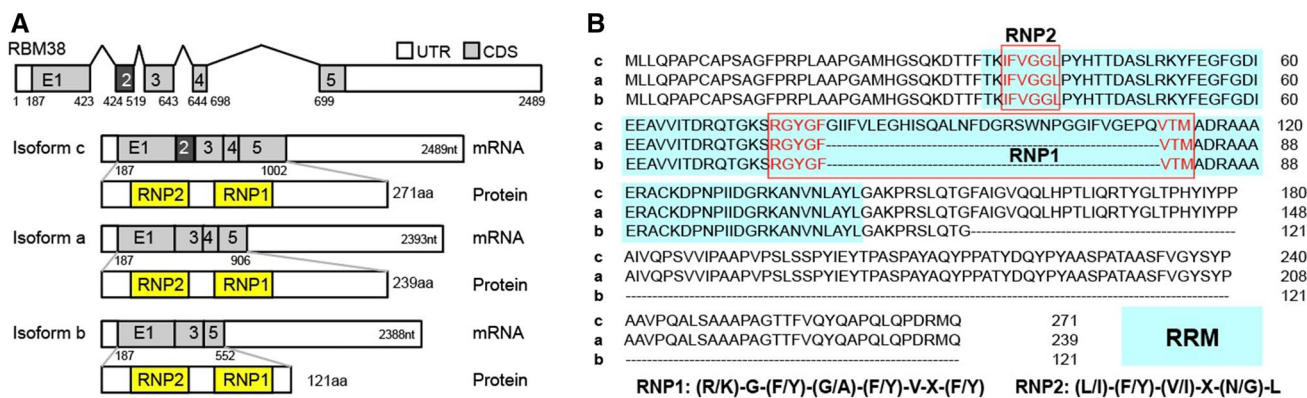


Fig. 2 Gene structure of RBM38. **A** Scheme depicting the central dogma (DNA/RNA/Protein) information of RBM38 locus. Previous studies have all discovered two isoforms (a, b) of RBM38 encoded by 4 exons (exon 1, 3, 4, 5). However, a novel and the longest isoform c is reported, due to an inclusion of cryptic exon 2, by recently updated NCBI RefSeq (Gene ID: 55544; accessed on Mar 18, 2020). The

numbers underneath denote genomic coordinates corresponding to either DNA or RNA sequences. **B** Alignment of three isoforms highlighting the RNA recognition motif (RRM) domain consisting of two ribonucleoprotein (RNP) motifs. The consensus sequence of RNP1 (8 aa) and RNP2 (6 aa) are shown. Please see more details in the text

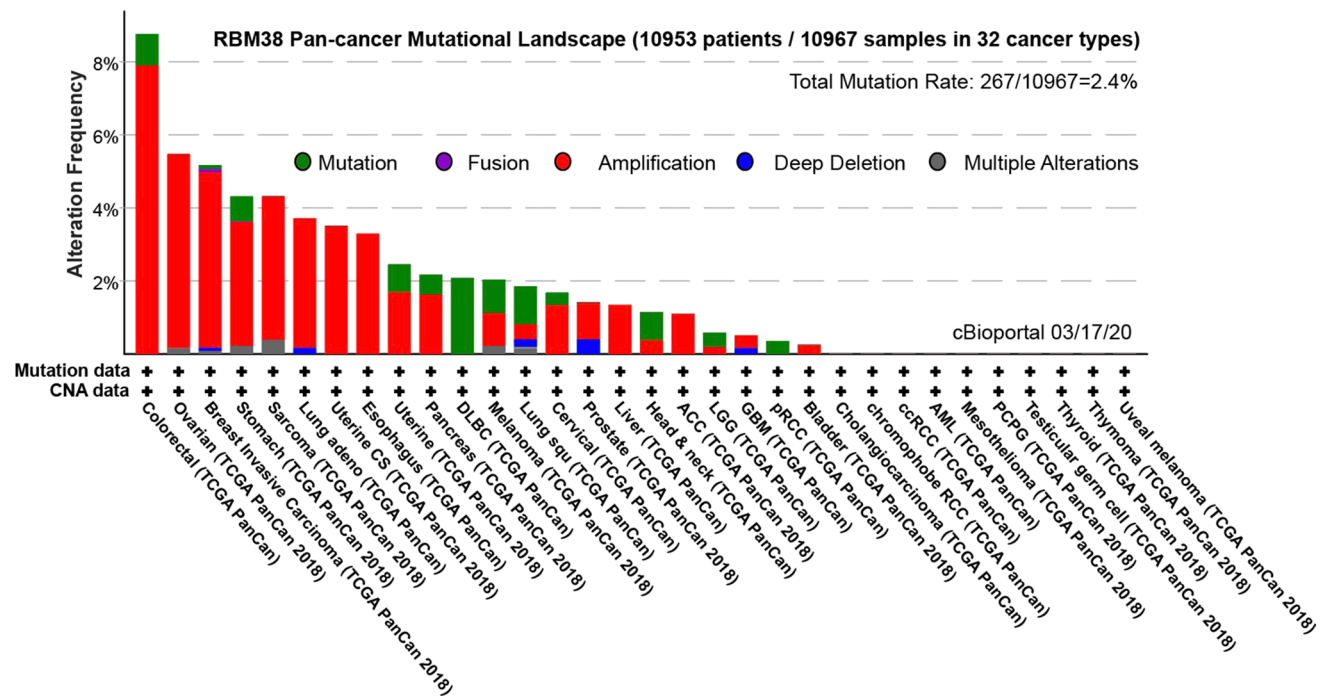


Fig. 3 Mutational landscape of RBM38 in 32 human cancers. Data derived from TCGA pan-cancer analysis was viewed through cBioPortal (accessed on Mar 17, 2020)

Table 1 Function of RBM38 in human cancer phenotypes

Cancer type	Tumorigenic potential	References
Breast	TS	[28, 29, 33–35]
Liver	TS	[38]
Colon	TS	[41]
Kidney	TS	[39]
Leukemia	TS	[43]
Stomach	TS	[40]
Lung	TS and Oncogene ^a	[42, 46]

^aUnder hypoxia of lung cancer cells in vitro, *HIF α* and *RBM38* are induced and the former upregulates SIRT1 to inhibits tumor suppressive miR-34a via suppression of p53 transcriptional activity [46]. This seemingly oncogenic potential of RBM38 is not experimentally validated

RBM38 in breast cancer

Breast cancer (BCa) is the most frequently diagnosed cancer and ranked as the second leading cause of death in women worldwide [27]. Study of *RBM38* in BCa is relatively intensive, we thus separate it from other cancer types for reviewing the role of RBM38 in cancers in detail. In 2014, Xue et al. first reported that RBM38 is downregulated in multiple BCa lines compared with non-transformed mammary epithelial cells (e.g., MCF-10A), as well as in 121 human BCa vs. adjacent normal tissues, at both mRNA (by qPCR) and protein (by western blot) levels [28].

Experimentally, overexpression of *RBM38a* inhibits cell proliferation and migration and invasion in both estrogen receptor positive (ER⁺) MCF7 and triple-negative MDA-MB-231 cells in vitro by arresting cells at G1 phase [28]. Consistently, exogenous *RBM38a* expression also dampens MDA-MB-231 tumor development in vivo [28]. Of clinical relevance, *RBM38* is positively correlated with the longer relapse-free and overall survival [29]. Furthermore, immunohistochemistry (IHC) analysis of 90 BCa samples revealed that RBM38a protein expression is significantly positively correlated with ER α [30] and progesterone receptor (PR) [31]. RBM38 increases the expression of *PR* [31] and *ER α* , but not *ER β* , by stabilizing their mRNAs in ER⁺/PR⁺ BCa cells; however, ER α reversely regulates the expression of *RBM38* in response to estrogen stimulation (Fig. 4A) [30]. MYC (i.e., c-Myc) is a notorious oncogenic TF that overexpresses in numerous human cancers and promotes G1/S cell cycle progression [32]. Interestingly, a recent report showed that, in a tissue microarray containing 162 BCa samples, RBM38 expression is negatively correlated with MYC at the protein level [33]. Although MYC is generally considered as a transcription activator, it binds to an E-box region in the promoter of *RBM38* to inhibit transcription and RBM38, in turn, binds to and destabilizes *MYC* mRNA in ER⁺ BCa cells [33]. PTEN is a well-characterized TS and an inhibitor of the phosphatidylinositol-3-kinase (PI3K)/AKT pathway, which is frequently overactivated in many cancers and is associated with metastasis and cancer stemness [34]. Another

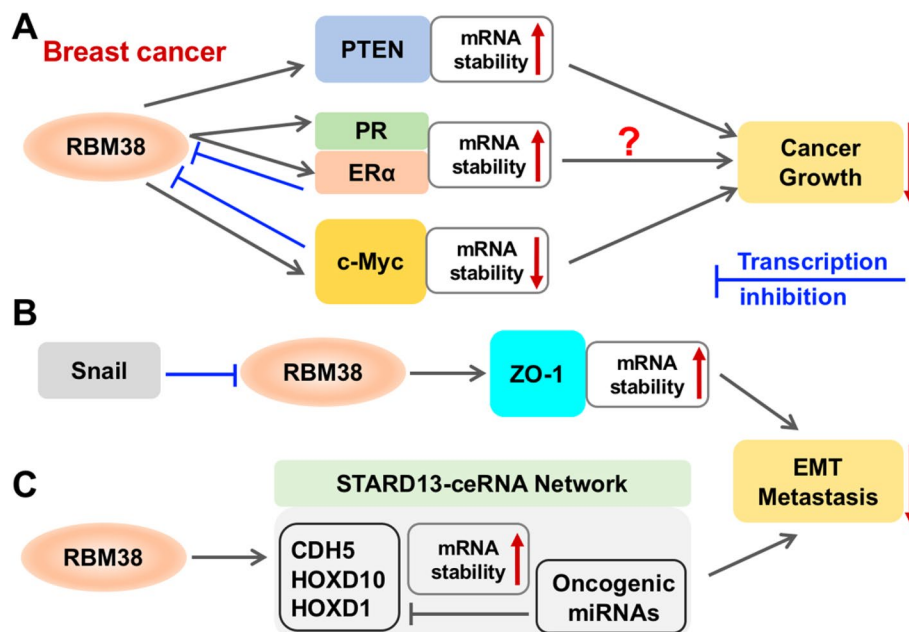


Fig. 4 Role and mechanism of RBM38 in inhibiting BCa cell growth and metastasis. **A** RBM38 suppresses cell proliferation via destabilizing oncogene *MYC* and stabilizing TS *PTEN* through AREs in their 3'-UTRs. It is currently unclear how RBM38 maintains its tumor suppressive function while enhancing the expression, and likely, function of *ER* and *PR*, both of which are oncogenic in BCa. Notably, both *MYC* and *ER* transcriptionally inhibits *RBM38*. **B** EMT-specific TF Snail halts *RBM38* transcription, leading to its loss during EMT. Functionally, ectopic expression of *RBM38* enhances *ZO-1* expres-

sion via mRNA stability, which eventually causes pause in metastatic process of BCa cells. **C** RBM38 binds to, and stabilizes, several ceRNAs for *STARD13*, thus avoiding it from degradation mediated by oncogenic miRNAs. *STARD13*-ceRNA network inhibits cancer cell metastatic properties. Lines with arrow and perpendicular denote a promotion or an inhibition effect, respectively. Please see more details in the text. *BCa* breast cancer, *AREs* AU/U-rich or CU-rich elements, *EMT* epithelial–mesenchymal transition, *TF* transcriptional factor

IHC examination of a cohort of 77 BCa revealed that the expression of RBM38 and PTEN are positively correlated [34]. Experimentally, RBM38 upregulates *PTEN* expression by stabilizing its mRNA in ER⁺/HER2⁺ BT474 and triple negative MDA-MB-453 cells (Fig. 4A) [34], underscoring a possible positive feedback loop between these two TSs.

EMT confers polarized epithelial cells with mobility and certain stem cell (SC) properties, aiding metastasis and drug resistance [6]. Interestingly, RBM38 is lost during TGF- β induced EMT in ER⁺ BCa cells via TF *SNAI1*-mediated transcriptional repression through the E-box elements in the promoter of *RBM38* [35]. Biologically, RBM38 blocks EMT via upregulation of an epithelial marker *ZO-1* by enhancing its mRNA stability (Fig. 4B) [35]. This observation has clinical implications because the expression of RBM38 and *ZO-1* is positively correlated in human BCa specimens by IHC staining [35]. Besides modulating EMT, RBM38 might halts metastasis by interfering the competing endogenous RNAs (ceRNAs) network. The ceRNA hypothesis postulates that RNA transcripts sharing common sequences called microRNA (miRNA) recognition elements (MREs) may crosstalk and indirectly regulate the expression of each other by competing for binding of the same pool of miRNAs [36]. This strategy has emerged as an important mechanism

of post-transcriptional gene expression regulation, and is proposed as a therapeutic target for treating cancers [36]. It was reported that *STARD13* and several other transcripts (i.e., *CDH5*, *HOXD10* and *HOXD1*) forms a ceRNA network to suppress BCa EMT and metastasis (Fig. 4C) [37]. Through binding to and stabilizing *CDH5* and *HOXD10* mRNAs, RBM38 facilitates *STARD13*-ceRNA network development in both ER⁺ and triple-negative BCa cell lines by alleviating the attack of metastasis-promoting miRNAs (i.e., miR-9, miR-10b, and miR-125b) to tumor suppressive *STARD13* [29].

Collectively, RBM38 is a TS in BCa and can participate in either oncogenic or tumor-suppressive pathways to exert its anticancer functions (Fig. 4). In support, pharmacological targeting either *MYC* [33] or *PTEN* [34] attenuates RBM38-mediated growth suppression in cancer cells given that RBM38 negatively and positively regulates *MYC* and *PTEN*, respectively.

RBM38 in other cancer types

Similar to BCa, IHC analysis also revealed a common downregulation (vs. normal tissues) of RBM38 in hepatocellular carcinoma (HCC) [38], renal cell carcinoma (RCC)

[39], gastric cancer [40], colorectal cancer [41], lung cancer [42], and leukemia [43], highlighting potentially a tumor-suppressive role for RBM38 (Table 1). In support, the *RBM38* mRNA level is negatively correlated with the overall survival in patients with RCC [39], gastric [40] and colorectal cancer [13]. Biologically, forced expression of *RBM38* induces apoptosis, senescence, and cell cycle arrest, leading to inhibition of proliferation and invasion in vitro and tumorigenesis in vivo in multiple tumor systems [38, 39, 41, 42]. Mechanistically, overexpression of *RBM38* restores the expression of wild-type (WT), but not mutant, p53 via binding to, and thus destabilizing, the p53 inhibitor *MDM2* transcript in HCC [38, 44]. Notably, previous studies have established that RBM38 binds to and suppresses p53 mRNA translation [12] (see below). These seemingly opposite results signify the differential regulatory effect of RBM38 on p53 expression in a context-specific manner. Furthermore, RBM38 increases the expression of tumor-suppressive long non-coding RNA *CASC2* by competitively binding to its mRNA with oncogenic miR-181a in non-small cell lung cancer (NSCLC) cells [42]. RBM38 also upregulates *p21* and *DND1*, two TSs in leukemia [43]. In aggregate, these evidences, again, establish *RBM38* as a TS in a number of human cancers. Importantly, it is worth noting that there exist controversial results indicating that RBM38 might have oncogenic potential in certain cancer types, given the fact that *RBM38* is amplified (Fig. 3; albeit at low frequency) and might be overexpressed in particular pathological contexts. For example, it was reported that *RBM38a* is frequently overexpressed, along with downregulation of p53, in dog lymphoma, indicative of an oncogenic role in lymphomagenesis [12]. In NSCLC cells under hypoxic stress in vitro, RBM38 inhibits the expression of miR-34a (a well-known TS [45]), leading to upregulation of SIRT1 protein which deacetylates and inhibits the transcriptional activity of p53 [46]. Further characterization of RBM38 in a context-dependent manner is required to reconcile the discrepancy.

Targets of RBM38 unveil pleiotropic mechanisms

As one of intensively investigated RBPs, RBM38 is reported to bind to the AU/U- or CU-rich elements (AREs) in 3'-UTR of transcripts to eventually modulate cellular behavior through, mainly, three types of mechanisms (i.e., stabilization, or destabilization, and/or translational regulation, of its cargo mRNAs). For example, RBM38 targets transcripts of p53-related genes (e.g., *p21* [12, 14], *p73* [47], *GFD15* [48]), nuclear receptors (e.g., *ER* [30], *PR* [31]), RBP *ELAVL1* [49], TS *PTEN* [34], and metastasis-suppressive genes (e.g., *ZO-1* [35] and *STARD13*-ceRNAs (*CDH5* and *HOXD10*) [29]) for stabilization. Oppositely,

mRNAs encoding oncogene *MYC* [33] and *MDM2* [44] and, likely oncogenic, $\Delta Np63\alpha$ [15] are targeted for degradation. Besides the post-transcriptional regulation, RBM38 also modulates gene expression at the translation level. By preventing or recruiting the eIF4E, the translation initiation complex, from binding its targets, RBM38 reduces protein level of p53 [12] and oncogenic HIF α [50], but increases PPM1D synthesis [51]. Table 2 summarizes so far the reported targets of RBM38 with their-related pathways. Highlighted by these three mechanisms underpinning RBM38's actions, an intriguing, and obviously important, question is how and what determines the fate of a mRNA upon bound by RBM38.

The most well-characterized mechanism that explains the TS properties of RBM38 is the constitution of a negative feedback loop between RBM38 and multiple TSs (e.g., p53 family; Fig. 5) or oncogenes (e.g., *MYC* and *E2F1*), respectively. As a direct transcriptional target of the p53 family (but not the mutant R249S p53) in both normal and genotoxic conditions [14], RBM38 destabilizes *p63* (mainly the epithelium-expressing N-terminal truncated isoform $\Delta Np63\alpha$), and stabilizes *p73*, but minimally affects *p53* transcripts [12]. Instead, RBM38 represses *p53* translation by abolishing cap-binding protein eIF4E from binding its mRNA via its C-terminal domain for physical interaction with eIF4E and its N-terminal RRM domain for binding *p53* mRNA [12]. The full-length *TAp63\alpha* is tumor suppressive, but the $\Delta Np63\alpha$ is oncogenic in squamous cell carcinoma [52]. The functional consequence of RBM38's implication in p53 pathway is the upregulation of antiproliferative genes such as *p21* (an effector of p53) through RBM38-mediated mRNA stability, together with transcriptional output in both p53-dependent and -independent manner [14, 53, 54]. Notably, RBM38 and HuR coordinately regulate the stability of *p21* mRNA but have converse effects on *p53* translation [12, 55]. The E2F family of TFs plays a pivotal role in cell-cycle progression and is a critical downstream target of the TS pRB. The pRB/E2F pathway is defective in most human tumors [54]. Interestingly, *RBM38* is transcriptionally upregulated by E2F1 in an p53-independent manner and in turn restricts E2F1-mediated proliferation in ovarian cancer cells [54]. Alternatively, *MYC* decreases *RBM38* expression via binding to its promoter; RBM38 also abolishes *MYC* activity by destabilizing its transcript [33]. Similarly, ER negatively regulates *RBM38* transcription, but RBM38 stabilizes *ER* transcript in BCa cells [30].

How does RBM38 promote the stability of one transcript over the other? An area of interest is that RBM38 can restrict the accessibility of a selective set of miRNAs to its targets. For example, RBM38 can block miRNA-mediated repression of p53 target genes such as *RBM38* itself, *p21*, *DDIT4* and *LATS2* [56]. By loading into the RNA-induced silencing complex (RISC), miRNAs usually interact with mRNAs to

Table 2 List of reported targets of RBM38

Mechanism	Gene	Function	References
RNA Stabilization	<i>p21</i>	A cell cycle inhibitor that promotes senescence	[12, 14]
	<i>p73</i>	TAp73 and p21 mediate the functions of RBM38-induced growth inhibition and premature senescence	[47]
	<i>GDF15</i> (i.e., <i>MIC-1</i>)	A direct target of WT p53 and a divergent member of the TGF- β family. Its knock-down reduces RBM38-induced cell growth suppression	[48]
	<i>ELAVL1</i> (i.e., <i>HuR</i>)	A well-studied RBP with context-dependent roles such as repressing c-Myc expression and thus facilitating RBM38-mediated cell growth suppression	[49]
	<i>PTEN</i>	A TS that inhibits oncogenic PI3K/AKT signaling	[34, 58]
	<i>ER</i>	An oncogene in BCa that transcriptionally decreases RBM38 expression	[30]
	<i>PR</i>	A nuclear receptor that mediates the mitogenic effects of progesterone on the mammary gland	[31]
	<i>ZO1</i>	An epithelial cell marker that inhibits EMT	[35]
	<i>CDH5, HOXD10</i>	Members involved in STARD13-correlated ceRNA network to halt EMT and BCa cell invasion in vitro	[29]
RNA Destabilization	<i>p63</i>	A SC factor that maintains epithelial cell stemness and inhibits keratinocyte differentiation	[15]
	<i>MDM2</i>	An E3 ubiquitin ligase that degrades p53	[44]
	<i>MYC</i>	A prevalently upregulated oncogene in many cancers that promotes proliferation, stemness and drug resistance	[33]
Translation	<i>p53</i>	A TS that promotes cell cycle arrest and senescence. RBM38 inhibits p53 translation by preventing eIF4E from binding to its mRNA	[59]
	<i>HIF1α</i>	A hypoxia responsive TF important for cell survival. RBM38 inhibits HIF1 α translation by preventing eIF4E from binding to its mRNA	[50]
	<i>PPM1D</i>	A p53 target with reported oncogenic activities. RBM38 promotes PPM1D expression via mRNA translation	[51]

TS tumor suppressor, BCa breast cancer, EMT epithelial-mesenchymal transition, SC stem cell, TF transcriptional factor

induce degradation and/or translational repression [45, 56]. Ago2, an essential RISC component, possesses the endonuclease activity. Interestingly, RBM38 interacts with Ago2 to protect *p21* 3'-UTR from miR17-mediated decay [56], but conversely, to recruit miR-203 to target *p63* mRNA for degradation [57]. Intriguingly, the RBM38-Ago2 interplay is disrupted by its Serine-195 (S195) phosphorylation (see below), yielding reduced accessibility of miR-203 to, and thus upregulation of, *p63* mRNA [57]. The difference in selectivity of targets and their corresponding miRNAs by RBM38 for miRNA-mediated decay not only highlights the complexity of RBM38-centered regulatory network but also signifies a future research direction.

S195 phosphorylation rewires RBM38's biological activity

Post-translational modifications greatly impact protein functions, and phosphorylation is the most prevalent one [57, 59]. Inspired by an observation that RBM38 appears as two bands in SDS-PAGE gels, Dr. Chen's group has made a significant discovery that RBM38 can be phosphorylated by GSK3 β kinase at Serine-195 (S195) and this phosphorylation converts

RBM38 from a repressor to an activator of *p53* mRNA translation via altered interaction with eIF4E [59]. Similarly, they recently reported that S195 phosphorylation can turn RBM38 from a repressor to an activator of *p63* mRNA stability by disassociating with Ago-miR203 complex (also see above) [57]. Subsequently, in a search for phosphatases that regulate RBM38, Zhang et al. found that PPM1D phosphatase, a target of p53 and RBM38, interacts directly with and dephosphorylates RBM38 at S195, leading to suppression of *p53* translation and thus p53-dependent growth inhibition [51]. An oncogenic activity has been observed for PPM1D [51]. Leveraging the large-scale DNA sequencing data, we examined the S195-site mutation across the TCGA 32 human cancer types (Fig. 3) and revealed only 2 out of 10,967 samples bearing a non-phosphorylatable S195L mutation, indicating the importance of GSK3 β -mediated S195 phosphorylation in balancing RBM38's functions.

Genetic evidence for a tumor-inhibiting role

To definitively establish RBM38 as a TS (or an oncogene), a systematic *RBM38-null* or -knockout (KO) mouse model has been generated by Dr. Chen's group (Table 3). Based

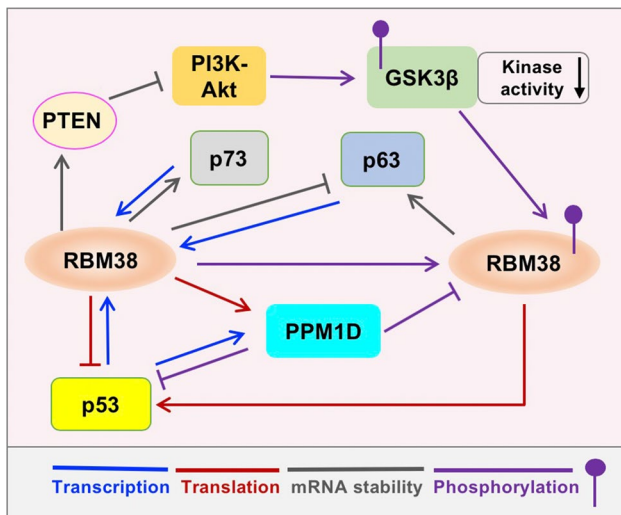


Fig. 5 Intricate RBM38-p53 family regulatory network. Transcriptionally targeted by p53 family, RBM38 in turn destabilizes *p63* but stabilizes *p73*, and suppresses *p53* translation. GSK3 β phosphorylates RBM38 at S195, which converts RBM38 from a repressor to an activator of *p63* mRNA degradation and *p53* translation. Notably, genetic PTEN loss-mediated PI3K-Akt hyperactivation in cancers can phosphorylates GSK3 β , leading to attenuated kinase activity and thus RBM38 phosphorylation. RBM38 stabilizes *PTEN* transcript in *PTEN*-expressing cancer cells. PPM1D, a target of p53 and RBM38 via transcription and mRNA translation, respectively, dephosphorylates RBM38 at S195 to restrain p53 upregulation and thus exerts oncogenic function in many cancers. Moreover, it has also been reported that PPM1D can dephosphorylates p53 at S15 to impair p53's function in cell cycle suppression [70]. Lines with arrow and perpendicular denote a promotion or an inhibition effect, respectively

on the evidence that mice deficient in *RBM38* exhibit signs of accelerated aging, via partial upregulation of p53, and are prone to hematopoietic defects and spontaneous tumors [60], a TS-like property has been proposed for RBM38. Interestingly, the young *RBM38*^{-/-} mice (< 12 months)

were largely fine but elder ones (~ 18 months) developed a broad spectrum of tumors, including lymphoma, hemangiosarcoma, and HCC [60]. Consistent with the hematopoietic defects, *RBM38* is highly expressed in mature blood cell types (Fig. 1) and has been reported to promote erythroid differentiation [61], with its loss of expression often observed in acute myeloid leukemia [43]. Importantly, *RBM38* deficiency markedly decreases the tumor penetrance in heterozygous *p53*^{+/-} mice via enhanced p53 expression. In *p53*-null mice, loss of *RBM38* shortens the animal lifespan and accelerates lymphomagenesis due to ineffectiveness of *RBM38*-KO mediated p53 upregulation [60], consistent with its tumor-suppressive role. Interestingly, the overall tumor burden was markedly reduced in *RBM38*^{-/-}; *p53*^{-/-} mice compared with *p53*^{-/-} mice [60]. This is seemingly counterintuitive as one would expect an accelerated tumorigenesis in double-KO of TSs [60]. The discrepancy could be potentially explained by the p53-independent functions of RBM38 and the possibility that tumor development in double KO mice takes longer but the hosts possess a shorter lifespan compared with single KO mice. Also, a “intergenic suppression” effect might exist (see below). Besides the genetic loss, *p53* is frequently altered as missense mutations, typified by hotspot mutations (e.g., R175H, R248W, and R273H) in human cancers [62]. These mutations often confer gain-of-functions to convert p53 to an oncogenic driver of metastasis [58, 62]. To determine the role of RBM38-mutant p53 axis in tumorigenesis in vivo, mutant *p53* knock-in (KI) mice were generated and crossed with *RBM38*-KO mice. Results showed that ablation of *RBM38* shortens the lifespan of, and alters tumor incidence in, both *p53*^{R270H/-} and *p53*^{R172H/-} (equivalent to human R273H and R175H, respectively) mice [58], again establishing RBM38 as a TS. Although the overall tumor spectrum remained similar, the incidence of T cell lymphomas was

Table 3 Tumor phenotype in *RBM38*-deficient mice on different genetic backgrounds

Genotype	Phenotype	References
<i>RBM38</i> ^{-/-}	Aging via partial p53 upregulation, hematopoietic defects, and development of spontaneous tumors compared with WT mice	[60]
<i>RBM38</i> ^{-/-} ; <i>p53</i> ^{+/-}	Longer survival time and reduced tumor penetrance compared with <i>p53</i> ^{+/-} mice	[60]
<i>RBM38</i> ^{-/-} ; <i>p53</i> ^{-/-}	Shorter survival time, difference in tumor spectrum (increase in lymphomas incidence and decrease in hemangioma and sarcoma incidence), reduced tumor burden, and no difference in tumor penetrance compared with <i>p53</i> ^{-/-} mice	[60]
<i>RBM38</i> ^{-/-a} ; <i>p53</i> ^{R270H/-}	Short lifespan with altered tumor incidence (increase in T-cell lymphomas and decrease in sarcomas) compared with <i>p53</i> ^{R270H/-} mice	[58]
<i>RBM38</i> ^{-/-a} ; <i>p53</i> ^{R172H/-}	Short lifespan with similar tumor spectrum and altered tumor incidence (increase in T-cell lymphomas and decrease in B-cell lymphoma) compared with <i>p53</i> ^{R172H/-} mice	[58]
<i>RBM38</i> ^{-/-} ; <i>TAp63</i> ^{+/-}	Longer lifespan with reduced tumor penetrance and liver steatosis, alleviated aging-related phenotypes (e.g., senescence) compared with <i>p63</i> ^{+/-} mice	[16]

^a*p53* mutations R270H and R172H in mouse are equivalent to human R273H and R175H, respectively. Note that both mutations are oncogenic

significantly higher in *RBM38*^{-/-}; *p53*^{K1/-} mice than that in *p53*^{K1/-} mice, along with increased mutant *p53* translation and decreased stability of *PTEN* [58].

RBM38 and p63 also form a negative feedback loop [15] and mice deficient in *TAp63* are prone to enhanced aging and spontaneous tumors [63]. Similar to *RBM38*^{-/-}; *p53*^{+/-} mice, *RBM38*-KO extends the lifespan, reduces tumor penetrance and liver steatosis in *TAp63*^{+/-} mice, probably due to upregulation of tumor-suppressive *TAp63* [16]. Biologically, loss of *RBM38* or *TAp63* alone results in an increase in cellular senescence, but their combined loss reduces, surprisingly, senescence, as seen in *RBM38*^{-/-}; *TAp63*^{+/-} mice [16]. The “intergenic suppression” is proposed for the effect of *RBM38*-null in a *p53*^{-/-} or *TAp63*^{+/-} background [16]. Intergenic suppression denotes a second mutation that relieves or reverts the phenotypic effects of an already existing mutation within the genome. Altogether, the negative feedback loops between RBM38 and p53, p63, and likely other cancer drivers, are not linear but rather intricate, especially in tumors with diverse genetics backgrounds. Future investigation is warranted to uncover the detailed molecular mechanisms.

RBM38 as a therapeutic target

RBPs control many, if not all, biological processes and their dysregulation is prevalent in human cancers, and thus have been emerged as a novel class of therapeutic targets for cancer prevention and treatment [4, 5]. In light of being a TS in numerous cancers by often forming negative feedback loops with cancer drivers, *RBM38* presents itself as a promising therapeutic target. Restoration of WT *p53* has been shown in animal models to be an effective avenue to suppress tumor growth [64]. As a p53 target, RBM38 inhibits, but its S195 phosphorylation enhances, *p53* translation via interaction with eIF4E [12]. Therefore, blocking RBM38-mediated translational suppression would be a strategy to restore p53 protein expression in *p53*-WT and *RBM38*-expressing tumors. In support, it was recently reported that a synthetic 8aa peptide (Pep8), derived from RBM38 and corresponding to the binding interface between RBM38 and eIF4E, is effective in relieving RBM38-mediated repression of p53 [65]. Functionally, Pep8 alone or together with a low dose of doxorubicin potently induces *p53* expression and impedes tumor growth in vitro and in vivo in a RBM38- and p53-dependent manner [65], establishing therapeutic potential for modulation of the RBM38-eIF4E complex in cancers carrying WT *p53*. Alternatively, the PI3K/AKT pathway is often overactivated in a number of cancers and it phosphorylates GSK3β at S9 to inhibit its kinase activity [66]. The GSK3β can phosphorylate and promote degradation of oncogenic CCND1 and MYC [66]. In this regard, blocking PI3K/AKT activity to de-phosphorylate GSK3β might

represent a way to enhance S195 phosphorylation of RBM38 and thus upregulate p53 translation in tumors positive for both RBM38 and p53. Encouragingly, treatment with AKT kinase inhibitor, MK2206, increases the level of phosphorylated RBM38 and p53 (via a RBM38-dependent manner) in a dose-dependent manner [59]. Clinically, *p53* is frequently lost genomically and *RBM38* is rarely mutated in human cancers (Fig. 3). We thus postulate that the loss of RBM38 expression is largely attributed to epigenetic mechanisms, and in such scenarios, epigenetic modulation may convey an approach to boost *RBM38* expression. In support, RBM38 is silenced in BCa due to, at least partially, hypermethylation of its promoter CpG island [56]. Treatment with DNA demethylating agents such as 5-aza-2'-deoxycytidine (5-Aza or Decitabine) induces upregulation of *RBM38* in triple negative BCa cells and thus inhibition of cell proliferation [56].

Conclusions and future perspectives

The involvement of RBM38 in multiple key cancer-related pathways (Table 2) has placed RBM38 in a hub position within the RBP-RNA regulatory networks. In vitro studies have revealed a limited number of transcripts targeted by RBM38 for mRNA stability and translation modulations. However, to uncover the full picture of RBM38's function as an RBP, the identification of its targets on a global scale via high throughput techniques is necessary. Mechanistically, it would be interesting to examine how RBM38 recruits other partners to fulfill pleiotropic impacts on mRNA fate in diverse contexts. Could one of them be HuR? It was reported that RBM38 interacts and cooperates with HuR to regulate *p21* mRNA stability [53], but RBM38 and HuR have opposite effects on (i.e., RBM38 decreases [12] while HuR stimulates [55]) *p53* mRNA translation. As a RBM38 closely related protein, *RBM24* is also reported to be a p53 target and positively regulate *p21* mRNA stability [17]. Interestingly, RBM24 binds to the same regions of *p63* transcript as that of RBM38 (likely due to their identical RRM), and it can negatively regulate *p63* expression in the absence of RBM38 [19], suggesting possible cooperative or antagonistic mechanisms between these two RBPs in regulating the similar set of transcripts. Like RBM38, RBM24 also forms a negative feedback loop with p53 by suppressing its mRNA translation [67]. In the context of cancer development, RBM24 was found frequently downregulated in human nasopharyngeal carcinoma, with its overexpression inhibiting cell proliferation and invasion in vitro and metastatic colonization in vivo [68]. Collectively, it appears that RBM38 and RBM24 function similarly in terms of RBP properties and tumor suppressive role in human cancers. The detailed interplay between them remains to be elucidated. RBM38 localizes in both nucleus and, largely, cytosol [14,

34]. Therefore, besides the post-transcriptional regulation, another emerging question is whether RBM38 also regulates transcription, like other RBPs reported recently [8].

Animal studies have uncovered differential effects of *RBM38* deficiency on tumorigenesis depending on *p53* status [58, 60], signifying a consideration of *p53* when exploring *RBM38* as a target for cancer treatment. However, both *p53*-dependent and -independent mechanisms have been reported to downregulate *RBM38* in a spectrum of human cancers bearing diverse genetic backgrounds [14, 54]. It is, therefore, necessary to investigate that whether *RBM38* is also transcriptionally regulated by other driver TFs. Based on a simple motif analysis of *RBM38* promoter sequence, several TFs (e.g., *SOX5*, *RUNX3*, *CUTL1*, *PPAR γ 2*, *ATF6*) are identified to potentially regulate *RBM38* expression [13], likely in distinct cancer contexts.

RBM38 is obviously a splicing regulator. However, such an RBP property has been overlooked in previous cancer studies. Currently, there is only one report that has examined the role of *RBM38* in alternative splicing during human erythropoiesis [61]. Using a splicing-detecting microarray, Heinicke et al. has identified a subset of *RBM38*-regulated splicing events and determined that *RBM38* regulates activation of *EPB41* exon-16 during late erythroid differentiation [61]. In our recent work, we discovered that *RBM38* might function as a splicing inhibitor in aggressive prostate cancer [69]. Subsequently, we are now characterizing the roles and mechanisms of *RBM38* in human prostate tumorigenesis and leukemia. In aggregate, further understanding of detailed *RBM38* biology will shed fresh lights on the aetiology of, and developing novel therapeutic strategies against, human cancers.

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