RNA Binding Protein as an Emerging Therapeutic Target for Cancer Prevention and Treatment

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After transcription, RNAs are always associated with RNA binding proteins (RBPs) to perform biological activities. RBPs can interact with target RNAs in sequence- and structure-dependent manner through their unique RNA binding domains. In development and progression of carcinogenesis, RBPs are aberrantly dysregulated in many human cancers with various mechanisms, such as genetic alteration, epigenetic change, noncoding RNA-mediated regulation, and post-translational modifications. Upon deregulation in cancers, RBPs influence every step in the development and progression of cancer, including sustained cell proliferation, evasion of apoptosis, avoiding immune surveillance, inducing angiogenesis, and activating metastasis. To develop therapeutic strategies targeting RBPs, RNA interference-based oligonucleotides or small molecule inhibitors have been screened based on reduced RBP-RNA interaction and changed level of target RNAs. Identification of binding RNAs with high-throughput techniques and integral analysis of multiple datasets will help us develop new therapeutic drugs or prognostic biomarkers for human cancers.
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INTRODUCTION

After RNA is transcribed from genome, it is not present by itself in the cell. Many proteins interact with the transcribed RNAs to make huge complex, called ribonucleoproteins (RNPs). To form RNPs, RNA binding proteins (RBPs) participate as critical regulators for RNA metabolism. RBPs can modulate the fate of binding RNAs by regulating transcription, editing, splicing, polyadenylation, translocation, and turnover.[1] RBPs can also function as scaffold proteins for recruiting many factors and enzymes to modify their binding partners. By making different complexes with various combinations, RBPs can fine-tune target RNAs in a time- or space-specific manner. For exact work, RBPs are regulated by post-translational modifications (PTMs) such as acetylation, ubiquitination, and phosphorylation. For example, Src-associated protein in mitosis of 68 kDa (SAM68) is phosphorylated at tyrosine residue to mediate RNA binding activity and signal transduction.[2]

Mammalian cells contain hundreds of genes encoding RBPs that are evolutionally conserved and are transcribed into thousands of splicing variants to make RBPs. Until now, over 1,500 RBPs have been identified through high-throughput screening and are validated as members of a unique database.[3,4] Due to large number of RBPs, they perform various functions to maintain the homeostasis of cellular physiology. RBPs can interact with cognate RNAs in sequence-dependent or structure-specific manner using RNA-binding domains (RBDs) containing 60-100 amino acids. RBPs can combine with different RBDs to provide specificity and affinity for binding partners (Fig. 1). However, half of known RBPs interact with RNA in the absence of specific motifs or structures.[5] They may interact with RNA through concentration levels, affinity distribution, or synergistic binding with other effectors. More than 40 RBDs have been reported to be able to orchestrate the role of RBPs, through RNA
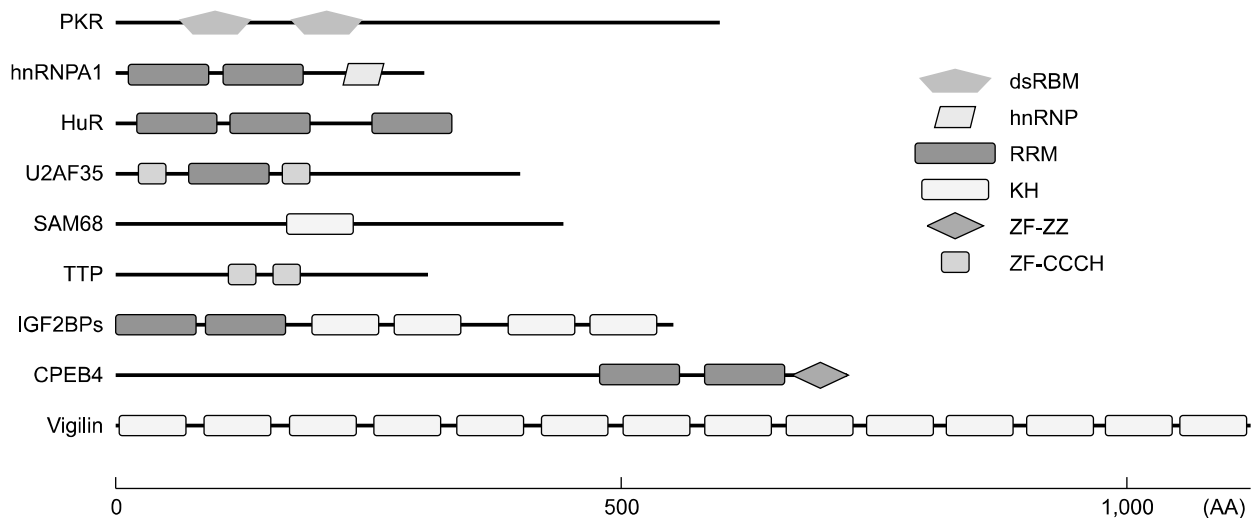
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Figure 1. Schematic diagram for various RNA binding domains of RNA binding proteins (RBPs). RBP interacts with target mRNAs using unique RNA binding domain (RBD) or a combination of different RBDs. Depending on RBDs, each RBP has specificity and affinity for its target RNAs. Each domain is schematically depicted with different shapes and colors. Each RBP is presented depending on its size. dsRBM, double-stranded RNA binding motiff; hnRNP, heterogeneous nuclear ribonucleoprotein; RRM, RNA recognition motif; KH, K-homology; ZF-ZZ, zinc finger binding with two zinc ions; ZF-CCCH, zinc finger C-x8-C-x5-C-x3-H type; PKR, protein kinase R; hnRNPA1, heterogeneous ribonucleoprotein A1; HuR, Hu-antigen R; U2AF35, U2 small nuclear RNA auxiliary factor 35; SAM68, Src-associated protein in mitosis of 68 kDa; TTP, tristetraprolin; IGF2BPs, Insulin-like growth factor 2 mRNA-binding proteins; CPEB4, cytoplasmic polyadenylation element binding protein 4; AA, amino acids.

recognition motif (RRM), K-homology (KH) domain, double-stranded RNA binding motif (dsRBM), Zinc finger (ZF) domain, and Piwi/Argonaute/ Zwille (PAZ) domain.[6] RBPs have been classified into different family members depending on compositions of RBD.

ABERRANT EXPRESSION OF RNA BINDING PROTEINS IN CANCERS

Many reports have suggested that deregulated expression of RBP is detected in various human diseases including cancer.[7-9] Altered expression of RBP causes wrong interactions with target RNAs to form incorrect RNP complex due to different affinity or concentration change. Such RNPs can affect the every post-transcriptional events in affected cells and modulate cell phenotype into pathological conditions. Neurodegenerative diseases are main representative pathological conditions caused by defected RBPs due to high expression of RBP in the brain.[8,10] Loss of RBP or expression of toxic RNA is involved in the development of many neurological disorders, including fragile X syndrome, paraneoplastic neurologic syndrome, and spinal muscular atrophy.

Based on genome-wide analysis, many RBPs have been identified as key players in development and progression of cancers. They can dramatically change cell growth and proliferation.[11-14] Aberrant expression of RBPs is also highly associated with survival rate of cancer patients.[11,15] Unexpectedly, expression levels in fold change of validated RBPs are very low in cancers.[16] Although expression levels of RBPs are not changed much in cancer cells, they can affect characteristics of cancer cells by targeting many target RNAs. Deregulation of RBPs in cancer is mainly induced by genomic alterations, epigenetic mechanism, noncoding RNA-mediated regulation, and PTMs.[17,18]

Although genomic alterations are hallmarks of human cancer, mutations and copy number variations have been found in only 15.2% of all RBPs.[19] Due to alterations of RBPs, cancer cells can acquire differential splicing events, thus affecting various cancer hallmarks. Somatic mutations in spliceosome genes, such as serine arginine, SF3B1, U2AF1, and heterogeneous nuclear RNPs (hnRNPs) have been found in over 50% of myelodysplastic syndrome and acute myeloma leukemia patients.[20,21] However, small change in one RBP can also affect global gene expression to modulate the growth of cancers. For example, germline mutation of DICER1 gene has resulted in defect in processing of precursor microRNA (miRNA) followed by abnormal expression of target RNAs.[22,23] DICER1 defects are mainly found in patients of pleuropulmonary blastoma, cystic nephroma, cervical embryonal rhabdomyosarcoma, multinodular goiter, and Sertoli-Leydig cell tumors. Chromosomal translocation of the region containing RBP can also generate mutation. Fusion protein induced by rearrangement promotes transformation and progression of cancer

through both RNA binding and activation domains of different proteins.[24]

Aberrant expression of RBPs can also be induced by post-transcriptional mechanism through noncoding RNAs or other RBPs. Mature miR-328 interacts and sequesters PCBP4 and hnRNPK to enhance the expression of oncogenic activators such MYC and PIM1 in chronic myelogenous leukemia.[25] Tumor suppressor miRNAs, such as miR-34a, miR-101, miR-128, and miR-138 can suppress the expression of Musashi-1 (MSI-1) through translational repression in glioblastoma and medulloblastoma.[26] Long 3' untranslated region (UTR) containing several AU- and U-rich sequences of MSI-1 can be recognized by another RBP, Hu antigen R (HuR), thus protecting it from degradation to maintain high expression in glioblastoma.[27] In cancers, the function of RBPs can be deregulated by PTMs, including phosphorylation, methylation, acetylation, and ubiquitination.[28] By covalent incorporation of functional groups or proteins, the activity of RBPs is dramatically changed in many cancers. TGF-β/AKT2-dependent phosphorylation of hnRNPE1 can attenuate its suppressive activity on invasion and metastasis of breast cancer.[29]

ROLE OF RNA BINDING PROTEINS IN CANCER DEVELOPMENT

Because each RBP is associated with many target mRNAs and various biological processes, deregulation of RBP affects every step of cancer development, such as sustained cell proliferation, evasion of apoptosis, avoiding immune surveillance, inducing angiogenesis, and activating metastasis.[17] Representative roles of RBPs in cancer development are summarized in Table 1[13,27-60] depending on hallmarks of cancer.

The main function of RBPs in cancer development is sustaining cell proliferation through suppressing or enhancing expression levels of negative or positive regulators, respectively. SAM68 regulates gene expression at post-transcriptional level through alternative splicing of pre-mRNAs. Overexpression of SAM68 has been identified in many human cancers. It modulates alternative splicing of oncogenic genes.[11,39,40] For example, RAS/ERK-mediated phosphorylation of SAM68 promotes splicing of v5 exon of CD44 mRNA and stimulates cell proliferation.[61] SAM68 also mediates alternative splicing of cyclin D1 into D1b isoform by recruiting spliceosomal component in prostate cancer.[40] D1b

Table 1. Role of aberrantly deregulated RBPs in human cancers

Cancer Hallmark	RBP	Target mRNAs	Cancer types	Reference number
Sustained proliferation	ESRP1/2	CCND1, CDH1, CDKN1A, MYC, PKM2,	Colon	28, 29
	IGF2BP3	MYC, CDK6	Leukemia	30
	LIN28A/B	BMP4, HER2, HMGA1	Breast, ovary, liver, colon	31, 32
	QKI	CDKN1B, FOS, miR-20a, NUMB	Brain, colon, lung	33, 34
	HuR	CCNA2, CCNB1	Gastric, breast	35, 36
	SAM68	CD44, CCND1	Prostate, breast	37, 38
Evading apoptosis	hnRNPH	MADD, RON	Brain	39
	LARP4B	BCL2, BIK, BAX, XIAP	Brain	40, 41
	eIF4E	BCL2, BCL-XL	Lymphoma	42
	TIA1/TIAR	GADD45A, FAS, PDCD4	Multiple	43, 44
	CELF1	BAD, BAX, JunD	Oral	45
Inducing angiogenesis	RBP2	CDKI	Gastric	46
	HuR	VEGF, HIF-1α, THBS1	Breast, brain	47, 48
	LARP6	VEGF	Breast	49
	eIF4E	VEGF, FGF-2, PDGF	Multiple	50, 51
Activating EMT and metastasis	IGF2BPs	CD164, PDPN, CD44, IGF2, MMP9	Breast, colon, leukemia	52-54
	hnRNPE1	DAB2, ILE1	Breast, ovary	27
	UNR/CSDE1	VIM, RAC1	Melanoma	13
	RBM47	CUL3, DKK1, MDM4, MXI1, SLK	Breast, lung	55
Avoiding immune surveillance	IGF2BP3	ULPB2, MICB	Leukemia	56
	LIN28	Let-7	Leukemia	57, 58
	FXR1	PRKCI, ECT2	Lung	59, 60

RBP, RNA binding protein; EMT, epithelial-mesenchymal transition; ESRP1/2, epithelial splicing regulatory protein 1 and 2; IGF2BP3, insulin-like growth factor 2 mRNA-binding protein 3; QKI, protein quaking; HuR, Hu antigen R; SAM68, Src-associated protein in mitosis of 68 kDa; LARP4B, La ribonucleoprotein domain family member 4B; eIF4E, eukaryotic initiation factor 4E; TIA1, T cell intracellular antigen 1; CELF1, CUGBP, elav-like family member 1; RBP2, retinol binding protein 2; UNR/CSDE1, upstream of N-Ras/Cold shock domain-containing protein E1; RBM47, RNA binding motif protein 47; FXR1, fragile X-related 1.

isoform of cyclin D1 has higher oncogenic activity compared to D1a isoform. L1TD1, another RBP, can interact with LIN28 RNA and stabilize it to regulate the translation of OCT4.[62] Upregulated OCT4 positively regulates self-renewal and proliferation of cancer cells. Insulin-like growth factor 2 mRNA-binding protein 3 (IGF2BP3) interacts with 3'UTR of MYC and CDK6 mRNAs and stabilizes their transcripts to promote cell growth in B-acute lymphoblastic leukemia.[32] On the other hand, QKI protein is suppressed in glioblastomas and colorectal cancer to enhance cancer progression.[35,36] QKI inhibits cell growth by stabilizing p27 mRNA while degrading FOS mRNA.

Escaping apoptosis is one important mechanism to survive from extracellular stimuli and cytotoxic drugs in cancers. In this process, some RBPs play critical roles by regulating the expression of target mRNA at post-transcriptional level. Three-RRM containing HuR protein is overexpressed in many human cancers. It is closely correlated with prognosis of these patients.[49,63,64] HuR promotes cell growth by stabilizing many anti-apoptotic genes, such as SIRT1, p21, MDM2, PTMA, BCL2, and MCL1.[65-67] Eukaryotic initiation factor 4E (eIF4E) also regulates expression levels of proteins involved in cell survival, including BCL2 and BCL-XL.[44] LARP member protein also regulates cell growth by promoting the expression of pro-survival genes such as BCL2, BIK, BAX, MDM2, and XIAP.[42,43,68] CELF1 expression is increased in oral squamous cancer cells. It prevents programmed cell death and promotes cancer progression.[47] This RBP interacts with 3'UTR of BAD, BAX, and JunD and destabilizes these pro-apoptotic genes. As a tumor suppressor gene, T cell intracellular antigen 1 (TIA1) protein is decreased in human cancers. It promotes apoptosis by inducing alternative splicing of FAS mRNA or increasing the stability of PDCD4 and GADD45A.[45,46]

Cancer tissues require generation of new blood vessels to supply nutrients and overcome hypoxia condition. In this process, histone demethylase retinoblastoma binding protein 2 (RBP2) can enhance the expression of VEGF through suppressing mRNA level of cyclin-dependent kinase inhibitor in gastric cancer.[48] In triple negative breast cancer and brain tumor, HuR also modulates angiogenesis program by targeting multiple genes such as VEGF, hypoxia-inducible factor-1α, and thromospondin 1.[49,50] For oncogenic activity of eIF4E, eIF4E controls the formation of blood vessel by targeting related genes, including VEGF, FGF-2, and platelet-derived growth factor.[52,53,69]

As a tumor promoter, RBP also enhances cancer progression by stimulating the invasion and metastasis. IGF2BPs are highly overexpressed in human cancers. It has been reported that they can stimulate the invasive activity of cancer cells through stabi-lization of CD44, CD164, MMP9, and podoplanin mRNAs.[54-56] Their target mRNAs can facilitate the process of epithe-lial-mesenchymal transition (EMT) and the formation of invadopodia to enhance the infiltration and degradation of extracellular matrix. It is known that hnRNPE1 can bind to the 3'UTR of disabled-2 and interleukin-like EMT inducer mRNAs and mediate TGF-β-induced EMT and metastasis.[29] UNR/CSDE1 can also promote the invasion and metastasis of melanoma by regulating VIM and RAC1 at post-transcriptional level.[13] In contrast, RBM47 can suppress the metastasis of breast cancer by stabilizing transcripts of dickkopf WNT signaling pathway inhibitor 1.[57]

Recent report has suggested that evading immune surveillance is one important hallmark of cancer.[70] IGF2BP3 induces immune escape by degrading ULPB2 and MICB, both of which are critical mediators in natural killer cells.[58] Although there is no direct evidence for the involvement of LIN28 in immune surveillance of carcinogenesis, regulation of immune system by LIN28 suggests that this RBP is highly associated with cancer induction.[59,60,71] Recent study also suggests that fragile X-related 1 (FXR1) protein is overexpressed in lung squamous cell carcinoma and associated with poor prognosis.[72] Aberrant expression of this RBP is nega-tively correlated with cancer surveillance by forming complex with protein kinase C iota and epithelial cell transforming 2 mRNAs.[73]

THERAPEUTIC APPROACH TARGETING RNA BINDING PROTEINS

Because deregulated RBP can affect many characteristics of cancer, it might be a good therapeutic target for cancer treatment. However, regulatory mechanism of RBP is mainly originated from stabilization or degradation of target mRNA, making it difficult to modulate its activity. There are several trials for regulating RBP's activity as cancer therapy using RNA interference-based appro-aches. Specific antisense oligonucleotide (ASO) against eIF4E can suppress tumor growth by repressing the translation of target mRNAs, such as VEGF, Survivin, c-Myc, Cyclin D1, and BCL-2.[74-76] Most importantly, intravenous injection of ASO can significantly inhibit tumor growth without showing any side effect in a mouse model. These data support clinical trials of using eIF4E-specific ASO against human cancers. In another study, treatment with folate or transferrin receptor-targeted liposomal nanoparticle-ba-sed HuR siRNA can efficiently reduce cell viability, migration, and invasion of lung cancer.[77,78] Conjugation of siRNAs against HuR with Cy3-labeled folic acid-coated DNA dendrimer nanocarrier

has shown dramatic anti-oncogenic activity in ovarian cancer.[79]

After screening natural products against MSI-1, one group has identified (−)-gossypol from cottonseed as a potent anti-tumor agent.[80] This small molecule can suppress cell growth of colon and prostate cancers by directly interacting with RNA-binding pocket of MSI-1. Because HuR interacts with adenine- and uridine-rich elements in 3'UTR of target mRNAs, it will be good strategy to disrupt this interaction for cancer therapy. Wu et al.[81] has established a high-throughput screening system and identified several compounds as disruptors of HuR-mRNA interaction. These chemicals can block HuR-mRNA binding at nano-molar concentrations to inhibit the activity of HuR. Therefore, they can be used as cancer therapeutics for HuR-upregulated cancers. Interaction of LIN28 with Let-7 is also a therapeutic target for screening inhibitory chemicals using high-throughput system.[82] With fluorescence resonance energy transfer-based assay, dissociation of RBP/RNA interaction can be used as a marker for screening novel drugs.

Although many researchers have attempted to develop therapeutic strategies against RBPs, success is very limited due to difficulties in direct targeting of RBPs or in specific selection of interacting mRNAs. Alternatively, we can use downstream effectors of RBPs as therapeutic target. For example, MYC is a target of many RBPs. It reversely regulates the stability of many RBPs, such as Hu-antigen R (HuR), heterogeneous ribonu-cleoprotein A1 (hnRNPA1), and hnRNPH to modulate cancer progression.[83,84] Because MYC plays a pivotal role in many cancers, it will be a good approach to suppress the oncogenic activity of RBPs by targeting transcription or activity of MYC. As a first step, small molecule inhibitors, such as i-BET, JQ1, and MMS417 have been identified as transcriptional repressors of MYC. They can suppress cancer progression.[85-87] MYC is also suppressed at post-transcriptional level by ASOs, thus decreasing its translation or splicing events.[88,89] As alternative ways to block the activity of MYC, complex formation of MYC with its binding partners can be used as therapeutic target in cancer using mutant MYC or small molecule inhibitors.[90-92]

CONCLUSIONS

As mentioned above, RBPs play important roles in diverse biological processes. Many of them are found to be aberrantly dysregulated in various human cancers. Moreover, each RBP regulates a broad range of target mRNAs at the same time, thus leading to dramatic changes with important consequences for the development and progression of cancer. Nevertheless, expre-

ssion changes of RBPs are not as strong as other cancer-related genes based on genome-wide screening and bioinformatics analysis. This might be due to technical limitations for detecting small-scale changes of differential gene expression. We can overcome these bottlenecks using systems that are more sensitive for isolating novel cancer-related RBPs, such as next generation RNA sequencing and protein mass spectrometry.[4,93]

As targets for cancer therapy, binding partners of RBPs are good candidates. Therefore, it is important to identify the direct target of each RBP in various cancer types. Recent progress in bioin-formatics approaches and experimental techniques has improved our understanding of binding partners of RBPs involved in cancer progression. By introducing microarray and sequencing techni-ques, more RNAs can be identified as binding partners of proteins in diverse samples.[94] After immunoprecipitation with specific antibody, bound RNAs can be isolated followed by PCR and sequencing. To identify transient or weak interaction of RBP/RNA, crosslinking methodologies can be combined with sequencing techniques, such as crosslinking and immunoprecipitation (CLIP), photoactivatable-ribonucleoside-enhanced CLIP (PAR-CLIP), and individual-nucleotide resolution CLIP (iCLIP).[95-97] Another new technique called targets of RBPs identified by editing (TRIBE) has been developed to capture cell specific target of RBPs without antibody using small amounts of RNA.[98]

To support large-scale analysis of genome-wide data, analysis software should be developed to combine various datasets acquired from different cancers with multiple platforms. Data from genetically modified animal models or other physiological cellular models such as patient-derived tumor xenograft, tissue organoid, and microfluidic culture system can help us under-stand important functions of RBPs in human cancers. Then, identified RBPs or target mRNAs can be developed as therapeutic drugs for cancer therapy or are used as biomarkers for cancer progression or prognosis.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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